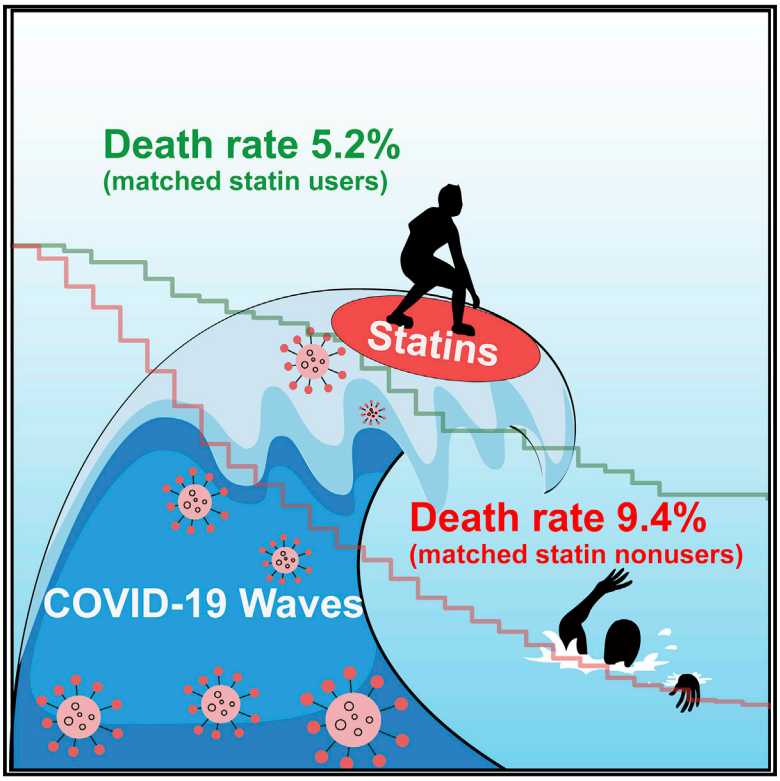
Cell Metabolism
Clinical and Translational Report

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

Graphical Abstract



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.

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Clinical and Translational Report

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

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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

Context and Significance

Statins, potent lipid-lowering agents with anti-inflammatory effects, have been suggested as a therapeutic option for COVID-19. However, these drugs may increase the expression of ACE2, the receptor for the virus that causes COVID-19, and thus may exacerbate pathology. Here, Zhang et al. report that among 13,981 cases of COVID-19, in-hospital use of statins compared to non-statin use is significantly associated with a lower risk of death and a less inflammatory response during the entire hospitalization period. These findings support the notion that the potential benefits of statin therapy for COVID-19 might outweigh the risks. And they call for further prospective studies and randomized controlled clinical trials to more definitively determine the overall clinical benefits of statin treatment for COVID-19-related pathologies.

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Clinical and Translational Report

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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 coronoviral infections, including for SARS-CoV-2 (Castiglione et al., 2020; Dashti-Khavidaki and Khalili, 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; Pertzov 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 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 Gazzerro, 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.

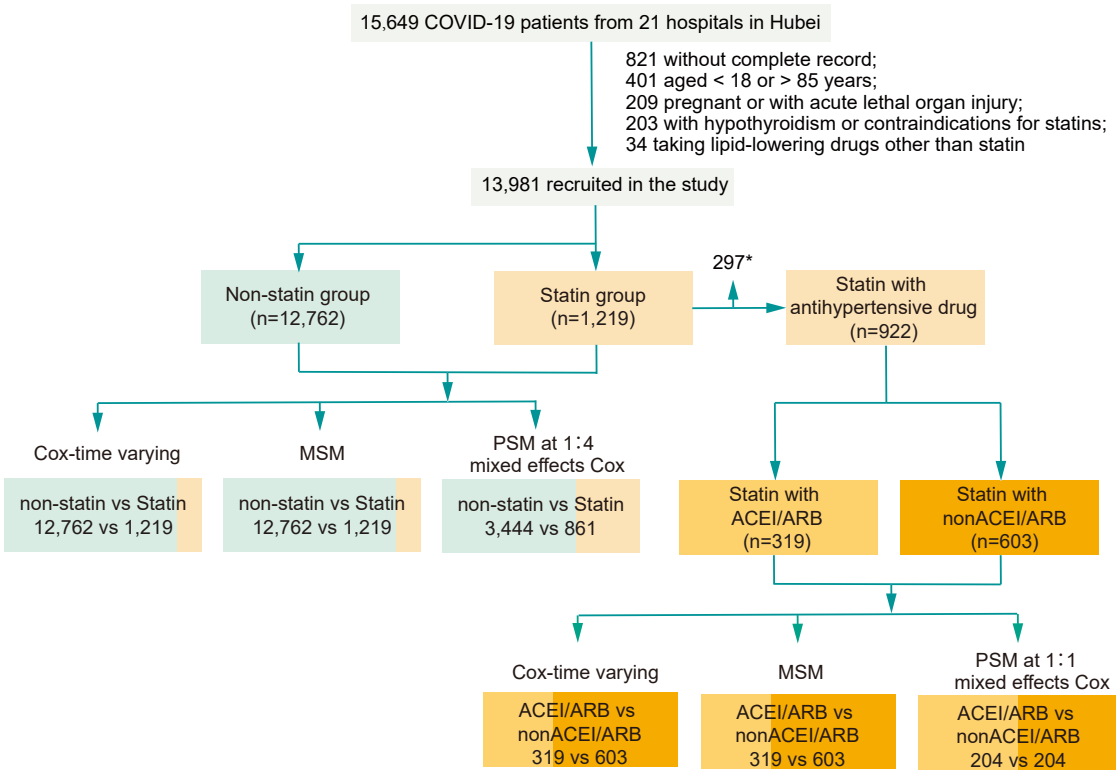


Figure 1. The Flowchart Showing the Strategy of Participant Enrollment

A schematic overview illustrating participant enrollment and the exclusion and inclusion criteria.

*297 participants without a medical history of hypertension or with hypertension but not taking antihypertensive medication were excluded from subgroup analyses.

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

Table 1. Characteristics of Patients in Statin and Non-statin Groups

Parameters	Statin (N = 1,219)	Non-statin (N = 12,762)	p Value[b]
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/m^2	24.3 (22.7–25.6)	23.9 (22.3–25.3)	0.501
Days from symptom to hospital, median (IQR)	14.0 (8.0–23.0)	11.0 (6.0–20.0)	<0.001
Days from symptom to medical treatment in hospitalization, median (IQR)	14.0 (8.0–23.0)	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 > ULN[a], n/N (%)	349/717 (48.7%)	3,435/6,892 (49.8%)	0.579
Procalcitonin > ULN[a], 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 > ULN[a], n/N (%)	649/1,112 (58.4%)	4,721/10,425 (45.3%)	<0.001
LDL-c > ULN[a], n/N (%)	194/1,007 (19.3%)	1,147/8,308 (13.8%)	<0.001
TC > ULN[a], n/N (%)	198/1,093 (18.1%)	1,089/9,257 (11.8%)	<0.001
CK > ULN[a], 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.

[a]Upper limit of normal (ULN) was defined according to criteria in each hospital

[b]p values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or $\chi 2$ test for categorical variables

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 2. In-Hospital Application of Statin and ACEi/ARB in Statin and Non-statin Groups

	Unmatched			Matched			
Parameters	Statin (n = 1,219)	Non-statin (n = 12,762)	p Value[b]	Statin (n = 861)	Non-statin (n = 3,444)	SD	p Value[b]
Atorvastatin, n (%)	1,014 (83.2%)	0 (0.0%)	<0.001	730 (84.8%)	0 (0.0%)	3.338	<0.001
Rosuvastatin, n (%)	190 (15.6%)	0 (0.0%)	<0.001	113 (13.1%)	0 (0.0%)	0.550	<0.001
Simvastatin, n (%)	22 (1.8%)	0 (0.0%)	<0.001	16 (1.9%)	0 (0.0%)	0.195	<0.001
Pravastatin, n (%)	16 (1.3%)	0 (0.0%)	<0.001	11 (1.3%)	0 (0.0%)	0.161	<0.001
Fluvastatin, n (%)	1 (0.1%)	0 (0.0%)	0.087	0 (0.0%)	0 (0.0%)	0.000	1.000
Pitavastatin, n (%)	10 (0.8%)	0 (0.0%)	<0.001	7 (0.8%)	0 (0.0%)	0.128	<0.001
ACEi/ARB, n (%)	319 (26.2%)	848 (6.6%)	<0.001	154 (17.9%)	653 (19.0%)	−0.028	0.501
Statin initial day after admission, median (IQR), days	0.0 (0.0–0.0)	–	–	0.0 (0.0–0.0)	–	–	–
Statin therapeutic duration, median (IQR), days	22.0 (14.0–28.0)	–	–	21.0 (14.0–28.0)	–	–	–
Daily equivalent dose of statin[a], median (IQR), mg	20.0 (18.9–20.0)	–	–	20.0 (17.1–20.0)	–	–	–

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; IQR, interquartile range; SD, standardized difference.
[a]Daily equivalent dose of statin was converted to an equivalent dose of atorvastatin according to Hu et al. (2015)
[b]p values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or $\chi 2$ 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+ACEi/ARB group were matched at a 1:1 ratio to 204 individuals in the statin+nonACEi/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 (Tables 2 and S7) (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 at 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 also associated with a decreased incidence of death (aHR, 0.58, 95% CI, 0.43–0.80; p = 0.001) (Table 3; Figure 2).

To adjust for the potential bias from the competing medical issues caused by a delayed start or discontinued use of statin therapy, we performed analysis using marginal structural model analysis in the individuals with and without statin treatment. In this model, the use of statins was maintained to be associated

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

	Unmatched							Matched				
	Crude Incidence			Cox Model Time-Varying Exposure		Marginal Structural Model		Crude Incidence after PSM			Mixed Cox Model	
	IR	IRR (95%CI)	p Value[c]	aHR (95%CI)	p Value	aHR (95%CI)	p Value	IR	IRR (95%CI)	p Value[c]	aHR (95%CI)	p Value
Statin versus non-statin[a]	0.21 versus 0.27	0.78 (0.61–0.996)	0.046	0.63 (0.48–0.84)[d]	0.001	0.72 (0.54–0.97)[f]	0.032	0.20 versus 0.37	0.53 (0.39–0.72)	<0.001	0.58 (0.43–0.80)[h]	0.001
Statin+ACEi/ARB versus statin+nonACEi/ARB[b]	0.16 versus 0.26	0.62 (0.34–1.14)	0.119	0.48 (0.21–1.07)[e]	0.074	1.20 (0.63–2.24)[g]	0.587	0.13 versus 0.38	0.34 (0.14–0.81)	0.010	0.32 (0.12–0.82)[i]	0.018

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.

[a]There were 1,219 and 12,762 participants in unmatched statin and non-statin groups, respectively. After PSM with a 1:4 ratio, there were 861 and 3,444 participants in the matched statin and non-statin groups, respectively.

[b]There were 319 and 603 participants in unmatched statin+ACEi/ARB and statin+nonACEi/ARB groups, respectively. After PSM with a 1:1 ratio, there were 204 and 204 participants in the matched statin+ACEi/ARB and statin+nonACEi/ARB groups, respectively.

[c]p values were calculated by R package "fmsb"; the significant probability of the result of null-hypothesis testing.

[d]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, ALT 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.

[e]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.

[f]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.

[g]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.

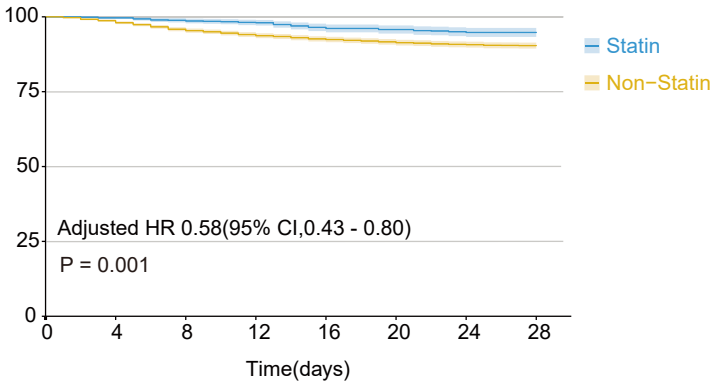
[h]aHR was calculated based on mixed-effect Cox model with adjustment of age, gender, and SpO2 at admission.

[i]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.

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 confounders, it is unlikely that unmeasured confounders would overcome the conclusion that statin use is not associated with increased 28-day all-cause mortality among individuals with COVID-19.

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 (Calfee 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.



		0	4	8	12	16	20	24	28
No.at risk	Statin	861	858	845	835	806	790	776	770
	Non-Statin	3444	3389	3253	3152	3015	2943	2892	2856
No.death	Statin	0	3	10	16	30	36	42	45
	Non-Statin	0	44	142	202	250	282	309	325
No.discharge	Statin	0	1	26	91	197	295	394	506
	Non-Statin	0	27	197	561	991	1383	1795	2204
No.loss of follow-up	Statin	0	0	6	10	25	35	43	46
	Non-Statin	0	11	49	90	179	219	243	263

Figure 2. Survival Curves of the Statin Group versus the Non-statin Group after PSM

Adjusted HR was calculated based on the mixed-effect Cox model with adjustment of age, gender, and SpO2 at admission. The 95% confidence intervals were represented by shaded regions. The association between statin usage and 28-day all-cause death was calculated with an adjusted HR of 0.58 (95%CI, 0.43–0.80; p = 0.001) compared to non-statin group. The table below the graph indicates accumulated numbers at risk, death, discharge, and loss of follow-up at each indicated time point. The number of "at-risk" was defined as the total number of individuals subtracting the number of "death" and the number of "loss of follow-up." Participants in the "loss of follow-up" group were those still in the hospital, but who did not meet the criteria for 28-day follow-up at the end of our study follow-up day.

To minimize the potential bias in our study, we conducted various models and sensitivity tests to evaluate the reliability of our study results. Individual accessibility of medical resources, survivor treatment selection bias (Glesby and Hoover, 1996), and competing medical issues (Redelmeier et al., 1998) are three potential causes for bias in observational studies of treatment efficacy. In our study, individuals who received statins did not have earlier initiation of medical therapy or hospital admission than statin nonusers (14.0 days in the statin group versus 11.0 days in the non-statin group), implying unlikely imbalanced access to the health system-related lower risk of COVID-19 mortality in the statin group. In addition, the COVID-19-associated medical expenses were covered by the Chinese government during the pandemic, which largely reduced the impact of the socio-economic level on in-hospital treatment. Regarding the potential bias from survivor treatment selection, we performed a Cox model with time-varying exposure to adjust for potential bias caused by differences in the initial time of treatment. Meanwhile, we calculated the average hospitalization period for individuals discharged in the statin and the non-statin groups, which were similar (15.0 days versus 16.0 days), indicating unlikely prolonged benefit from hospital treatment in the statin group. Competing medical issues, such as clinicians being more likely to arrange urgent therapy in critically ill patients versus those less critically ill, could lead to a bias resulting in an association between not using statins with poor outcomes. Therefore, we conducted an MSM analysis and adjusted time-varying confounders that simultaneously influence the time of statin initiation and risk of mortality. Cox models with and without time-varying exposure and MSM analysis were also performed in the patient populations excluding those who were admitted to the ICU or died within 48 h after admission.

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 (NCT04407273, 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). Although a mixed-effect Cox model in PSM cohorts showed ACEi/ARB therapy treatment was associated with decreased incidence of death (3.4% in the statin+ACEi/ARB group versus 9.8% in statin+nonACEi/ARB group; aHR, 0.32, 95% CI, 0.12–0.82; p = 0.018) (Table 3), the significant association did not appear in a marginal structure model (aHR, 1.20; 95% CI, 0.64–2.25; p = 0.576) (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

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

	Statin versus Non-statin					Statin+ACEi/ARB versus Statin+nonACEi/ARB				
	IR	IRR (95% CI)	p Value[a]	aHR[b] (95% CI)	p Value[c]	IR	IRR (95% CI)	p Value[a]	aHR[d] (95% CI)	p Value[c]
Secondary Outcome										
Invasive mechanical ventilation	0.11 versus 0.22	0.50 (0.33–0.76)	0.001	0.51 (0.34–0.78)	0.002	0.13 versus 0.15	0.85 (0.31–2.35)	0.755	1.11 (0.35–3.51)	0.854
ICU admission	0.29 versus 0.40	0.71 (0.55–0.93)	0.012	0.80 (0.62–1.05)	0.110	0.38 versus 0.47	0.82 (0.46–1.46)	0.494	0.78 (0.42–1.45)	0.427
ARDS	0.65 versus 0.81	0.80 (0.67–0.96)	0.016	0.88 (0.73–1.05)	0.159	0.64 versus 1.13	0.57 (0.37–0.86)	0.007	0.59 (0.37–0.92)	0.020
Septic shock	0.12 versus 0.13	0.92 (0.60–1.39)	0.684	0.93 (0.61–1.43)	0.744	0.11 versus 0.24	0.45 (0.17–1.18)	0.096	0.35 (0.12–1.07)	0.065
Acute liver injury	0.30 versus 0.28	1.06 (0.81–1.39)	0.653	1.17 (0.89–1.54)	0.253	0.27 versus 0.43	0.63 (0.33–1.22)	0.167	0.85 (0.42–1.74)	0.657
Acute kidney injury	0.13 versus 0.17	0.78 (0.53–1.16)	0.217	0.86 (0.58–1.28)	0.454	0.13 versus 0.23	0.57 (0.22–1.44)	0.227	0.57 (0.21–1.55)	0.268
Acute cardiac injury	0.51 versus 0.49	1.03 (0.84–1.26)	0.793	1.22 (0.99–1.50)	0.063	0.60 versus 1.05	0.57 (0.37–0.88)	0.010	0.61 (0.38–0.97)	0.038
CK and Transaminase Elevation										
CK > ULN	0.40 versus 0.46	0.87 (0.69–1.09)	0.219	0.98 (0.78–1.24)	0.896	0.42 versus 0.53	0.80 (0.46–1.39)	0.424	0.91 (0.51–1.64)	0.765
ALT > 3ULN	0.23 versus 0.23	1.00 (0.74–1.36)	0.983	1.10 (0.81–1.49)	0.554	0.16 versus 0.41	0.40 (0.18–0.86)	0.016	0.60 (0.26–1.37)	0.223

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.
[a]p values were calculated by R package "fmsb"; the significant probability of the result of null-hypothesis testing.
[b]Adjusted HR was calculated based on mixed-effect Cox model with adjustment of age, gender, and SpO2 on admission.
[c]p values were calculated based on mixed-effect Cox model.
[d]Adjusted 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.

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, 0.26–0.53, $p < 0.001$), 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, $p = 0.002$) (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 associations between statin+ACEi/ARB treatment and lower incidences of ARDS (aHR, 0.59; 95% CI, 0.37–0.92; $p = 0.020$) and cardiac injury (aHR, 0.61; 95% CI, 0.38–0.97; $p = 0.038$) compared to the statin+nonACEi/ARB group were shown in a mixed-effect Cox model (Table 4). There were no significant associations between the co-treatment of statin with ACEi/ARB and other secondary outcomes or the raised serum CK or transaminase levels (Table 4).

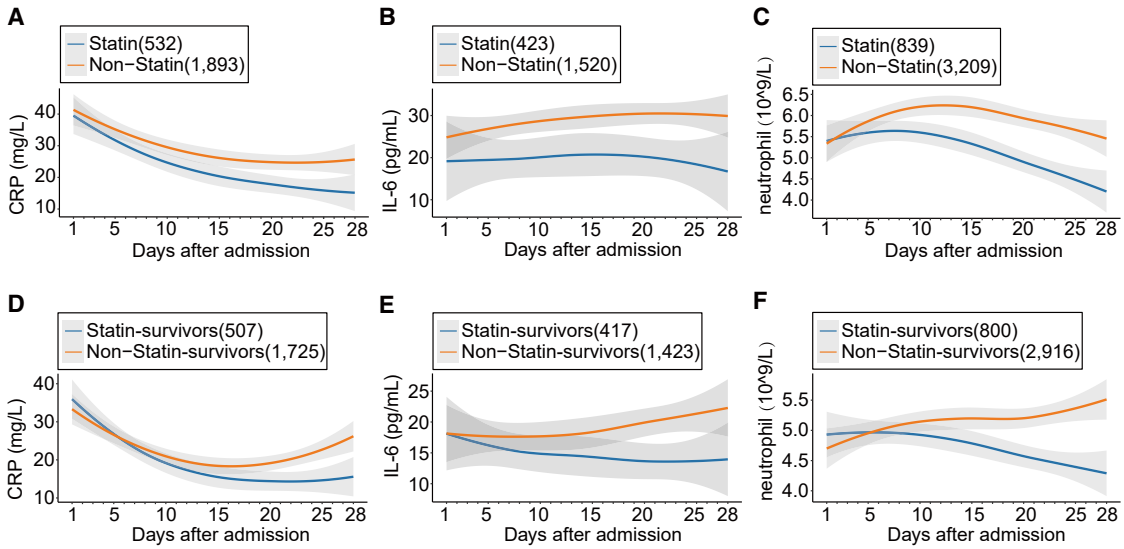


Figure 3. Dynamic Change of Inflammatory Factors in Statin and Non-statin Groups during Hospitalization

(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; Dashti-Khavidaki and Khalili, 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 nonusers before PSM and found to show similar patterns to those after PSM analysis (Figure S3). Because individuals on statins 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 (Henriksbo 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 function (i.e., NETosis and chemotaxis) (Sapey et al., 2019). 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

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead Contact
  - Materials Availability
  - Data and Code Availability
- METHOD DETAILS
  - Study Design and Participants
  - Data Collection
  - Definition
  - Association of Statin Use with COVID-19 Mortality
  - Propensity Score-Matched Analysis
  - Mixed-Effects Cox Model
  - Cox Model with Time-Varying Exposure
  - Marginal Structural Cox Proportional Hazards Model
  - Sensitivity Analysis
  - Missing Data and Imputation
- QUANTIFICATION AND STATISTICAL ANALYSIS

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

X.-J.Z., J.-J.Q., X.C., L.S., and Y.-C.Z. designed the study, collected and analyzed data, and wrote the manuscript. Y. Yuan, H.Y., L.B., X.S., L. Lin, M.X., P.Y., G.C., L. Liu, W.M., Y. Yan, B.X., Z.L., G.P., M.L., Jun Yang, L.Y., H. Lu., X.X., D.W., X.L., X.W., B.-H.Z., X.Z., Juan Yang, G.-N.Z., P.Z., and Y.-X.J. collected and revised clinical, laboratory, and radiological data. F.L. and F.Z. performed the statistical analysis. M.-M.C., J.Z., L.Z., and C.Z. reviewed, interpreted, and checked clinical data. Z.-G.S., X.M., Q.X., P.P.L., and R.L. edited manuscript and provided valuable suggestions for study design and data analysis. J.X., Y.W., J.C., J.G., and H. Li. contributed equally, designed the project, edited the manuscript, and supervised the study. All authors have approved the final version of this paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and Algorithms		
R-3.6.3	R Foundation for Statistical Computing	https://www.r-project.org/
SPSS statistics 23.0	IBM Corporation	http://www.spss.com.hk/software/statistics/
Coxme-2.2.16	Therneau et al.	https://cran.r-project.org/web/packages/coxme/index.html
Matchit-3.0.2	Daniel et al.	https://cran.r-project.org/web/packages/MatchIt/index.html
Matching-4.9-7	Sekhon et al.	https://cran.r-project.org/web/packages/Matching/
Tableone-0.11.1	Kazuki Yoshida	https://github.com/kaz-yos/tableone
DoBy-4.6.6	Søren Højsgaard	https://cran.r-project.org/web/packages/doBy/index.html
Survival-3.1-12	Therneau et al.	https://cran.r-project.org/web/packages/survival/index.html
Rms-6.0-0	Frank E Harrell Jr	https://cran.r-project.org/web/packages/rms/index.html
Nnet-7.3-14	Ripley et al.	https://cran.r-project.org/web/packages/nnet/index.html
Car-3.0-8	Fox et al.	https://cran.r-project.org/web/packages/car/index.html
Mgcv-1.8-31	Wood	https://cran.r-project.org/web/packages/mgcv/index.html
Hmisc-4.4-0	Harrell et al.	https://cran.r-project.org/web/packages/Hmisc/index.html
Survey-4.0	Lumley	https://cran.r-project.org/web/packages/survey/index.html
MASS-7.3-51.6	Venables et al.	https://cran.r-project.org/web/packages/MASS/index.html
Landest-1.0	Parast	https://cran.r-project.org/web/packages/landest/index.html
Matrix-1.2-18	Bates et al.	https://cran.r-project.org/web/packages/Matrix/index.html

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, therapeutic interventions, 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 $\geq$26.5μmmol/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 ULN (Marrone et al., 2017). The adverse effect of statin was determined by CK to increase above ULN or ALT increase above 3-folds of 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 m^2) 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

decrease) and LDL-c increase, TC increase, numbers of antihypertensive drugs, and SpO2. Pre-existing coronary heart disease, CRP increase, LDL-c increase, and D-dimer increase were remaining imbalanced variables after PSM and were further adjusted in the Cox regression model.

We used nonparametric missing value imputation, based on the missForest procedure in the R, to account for the missing data on the laboratory variables of increased CRP, LDL-c, eGFR, ALT, CK, BUN, D-dimer and cholesterol as well as decreased lymphocyte counts (Waljee et al., 2013). A random forest model using the remaining variables in the dataset was performed to predict the missing values for chest CT lesions and decreased SpO2. The internally cross-validated errors were also estimated. Statin users and non-users were paired according to the propensity scores using exact matching with a caliper size of 0.05. The balance of covariates was evaluated by estimating standardized differences before and after matching, and a small absolute value of less than 0.1 was considered qualified balancing between the two groups. For the mixed Cox analysis, the statin versus non-statin group ratio was paired at 1:4. In subgroup analysis, ratio was paired at 1:1 for statin+ACEi/ARB versus statin+nonACEi/ARB group. The caliper size in the subgroup cohort was 0.05 according to the propensity scores.

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 documented. 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 standardized 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, LDL-c, and D-dimer were adjusted when analyzing the association between ACEi/ARB treatment and clinical outcomes in subjects with statin treatment. We modeled the site as a random effect in the mixed-effect Cox model. The proportional hazard assumptions 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, cerebral 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 increase, TC increase, medications at admission, using invasive mechanical ventilation support, and days from symptom onset to hospitalization 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 mortality in participants with COVID-19, time-varying confounders are factors that influence the statin therapy initiation and correlated with the risk of mortality. In this analysis, CURB-65 pneumonia severity score (including confusion, blood urea nitrogen, respiratory rate, SBP, and age) (Table S12), serum ALT levels and CK levels were considered as time-varying confounders, which reflected the patient conditions that might impact clinical decision on initiating statin therapy. Baseline characteristic, including 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 counts increase, procalcitonin increase, D-dimer increase, AST increase, creatine increase, and SpO2), LDL-c increase, TC increase, medications at admission, using invasive mechanical ventilation support, and days from symptom onset to hospitalization were adjusted in the model. ALT level, CK level, and CRUB-65 score in days with missing values were imputed by the last-observation-carried-forward approach through the linear mixed-effects model. Before imputation, ALT and CK levels were standardized through dividing by the upper limit of the reference value of the corresponding institution.

When analyzing the association between ACEi/ARB use and mortality in the statin treated patients, time-varying confounders were factors that could influence the ACEi/ARB therapy initiation and correlated with the risk of mortality. In this analysis, CURB-65 pneumonia severity score, serum creatinine, and ALT levels were considered as time-varying confounders, which reflected the patient conditions that could impact clinical decision on initiating ACEi/ARB therapy. The gender, pre-existing COPD and DM, medication

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 α 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).

Cell Metabolism, Volume *32*

Supplemental Information

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

Xiao-Jing Zhang, Juan-Juan Qin, Xu Cheng, Lijun Shen, Yan-Ci Zhao, Yufeng Yuan, Fang Lei, Ming-Ming Chen, Huilin Yang, Liangjie Bai, Xiaohui Song, Lijin Lin, Meng Xia, Feng Zhou, Jianghua Zhou, Zhi-Gang She, Lihua Zhu, Xinliang Ma, Qingbo Xu, Ping Ye, Guohua Chen, Liming Liu, Weiming Mao, Youqin Yan, Bing Xiao, Zhigang Lu, Gang Peng, Mingyu Liu, Jun Yang, Luyu Yang, Changjiang Zhang, Haofeng Lu, Xigang Xia, Daihong Wang, Xiaofeng Liao, Xiang Wei, Bing-Hong Zhang, Xin Zhang, Juan Yang, Guang-Nian Zhao, Peng Zhang, Peter P. Liu, Rohit Loomba, Yan-Xiao Ji, Jiahong Xia, Yibin Wang, Jingjing Cai, Jiao Guo, and Hongliang Li

In-hospital Use of Statins is Associated with a Reduced Risk of Mortality among Individuals with COVID-19

By Zhang et al.

Supplemental Information

Figure S1. Dynamics profiles of TG, TC, LDL-c, and HDL-c in statin and non-statin groups before PSM during hospitalization

Figure S2. Dynamics profiles of TG, TC, LDL-c, and HDL-c in statin and non-statin groups after PSM during hospitalization

Figure S3. Dynamic change of inflammatory factors in statin and non-statin groups before PSM during hospitalization

Table S1. Absolute values of laboratory indicators on admission in statin and non-statin groups before and after PSM

Table S2. The reference range of laboratory indicators in study hospitals

Table S3. Characteristics of patients in statin and non-statin groups after PSM

Table S4. Characteristics of patients in statin+ACEi/ARB and statin+nonACEi/ARB groups

Table S5. Absolute values of laboratory indicators on admission in statin+ACEi/ARB and statin+nonACEi/ARB groups before and after PSM

Table S6. Characteristics of patients in statin+ACEi/ARB and statin+nonACEi/ARB groups after PSM

Table S7. Statin dose conversion

Table S8. In-hospital application of statin and ACEi/ARB in statin+ACEi/ARB and statin+nonACEi/ARB groups

Table S9. Hazard ratios for 28-day all-cause mortality before PSM in study cohorts excluding participants with ICU admission or death within 48 hours after admission.

Table S10. 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 before PSM

Table S11. The number of patients in each hospital and statin users for each hospital

Table S12. CURB-65 scale of the community-acquired pneumonia

Supplemental Figures

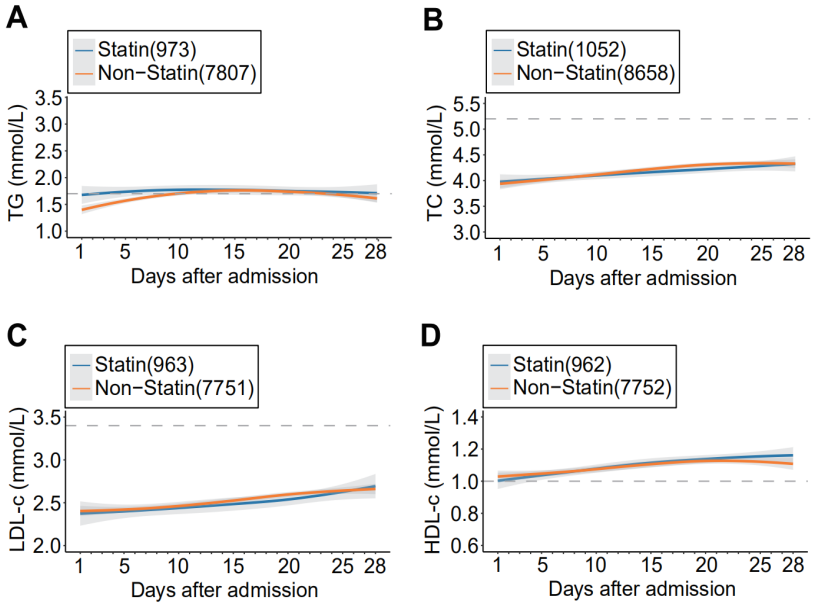

Figure S1. Dynamics profiles of TG, TC, LDL-c, and HDL-c in the statin and the non-statin groups before PSM during hospitalization, related to Table 1.

(A-D) Dynamic trajectories of TG, TC, LDL-c, and HDL-c levels during 28-day follow-up duration with 95% confidence interval represented by shaded regions. The sample sizes for each parameter in each group were labeled in the parentheses of legends.

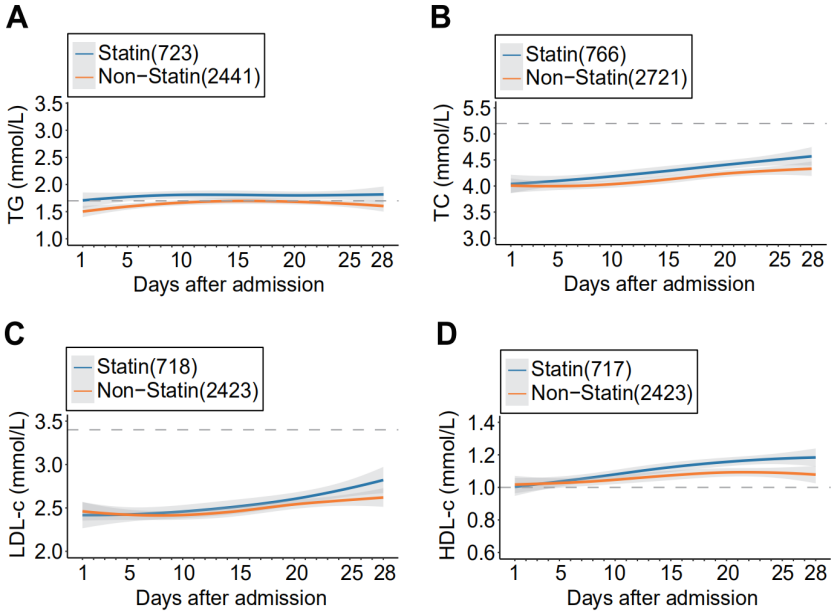

Figure S2. Dynamics profiles of TG, TC, LDL-c, and HDL-c in the statin and the non-statin groups after PSM during hospitalization, related to Table 1.

(A)-(D) Dynamic trajectories of TG, TC, LDL-c, and HDL-c levels during 28-day follow-up duration with 95% confidence interval represented by shaded regions. The sample sizes for each parameter in each group were labeled in the parentheses of legends.

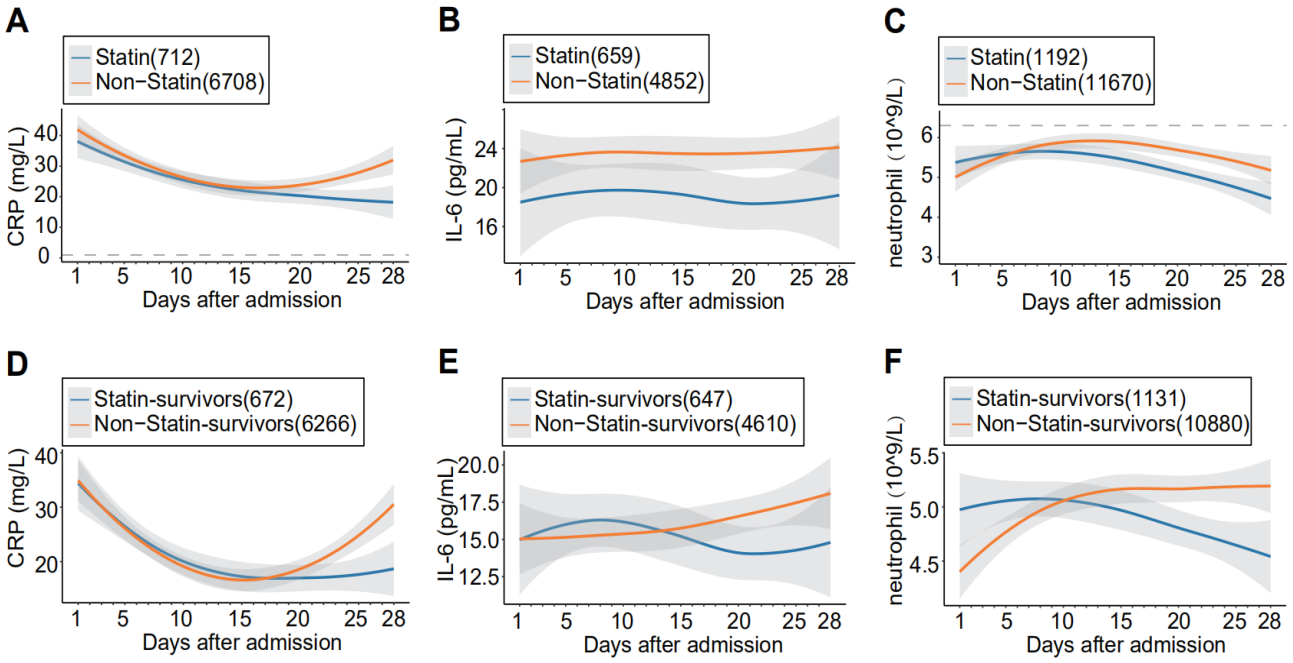

Figure S3. Dynamic change of inflammatory factors in the statin and the non-statin groups before PSM during hospitalization, related to Figure 3.

(A-C) showed the dynamic profiles of CRP, IL-6, and neutrophil count levels in all participants in the statin and non-statin groups.

(D-F) showed the dynamic profiles of CRP, IL-6, and neutrophil count levels in survivors of the statin and non-statin groups. The 95% confidence interval was represented by shaded regions. The sample sizes for each parameter in each group were labeled in the parentheses of legends.

Table S1. Absolute values of laboratory indicators on admission in statin and non-statin groups before and after PSM, related to Table 1.

Parameters	Unmatched			Matched			
	Statin (N=1219)	Non-statin (N=12762)	P value	Statin (N=861)	Non-statin (N=3444)	SD	P value
Leukocyte count, median(IQR), 10^9/L	6.0(4.7-7.5)	5.5(4.3-7.1)	<0.001	5.9(4.7-7.4)	5.8(4.6-7.5)	-0.026	0.283
Neutrophil count, median(IQR), 10^9/L	3.9(2.9-5.5)	3.5(2.5-5.0)	<0.001	3.8(2.8-5.4)	3.7(2.7-5.4)	-0.036	0.473
Lymphocyte count, median(IQR), 10^9/L	1.2(0.9-1.7)	1.2(0.8-1.7)	0.680	1.2(0.9-1.7)	1.2(0.8-1.6)	0.056	0.321
C-reactive protein, median(IQR), mg/L	5.8(1.9-36.2)	6.6(3.0-36.8)	0.029	5.8(1.9-38.2)	5.5(2.6-37.9)	-0.019	0.510
Procalcitonin, median(IQR), ng/mL	0.1(0.0-0.1)	0.1(0.0-0.1)	0.211	0.1(0.0-0.1)	0.1(0.0-0.1)	-0.092	0.040
ALT, median(IQR), U/L	26.0(17.0-42.0)	24.0(15.0-39.4)	<0.001	25.0(17.0-41.0)	25.0(16.0-42.0)	0.008	0.592
AST, median(IQR), U/L	25.0(18.4-37.0)	24.0(18.0-36.0)	0.046	24.0(18.0-36.0)	25.0(18.0-37.0)	-0.018	0.359
eGFR, median(IQR), mL/min	96.9(79.8-109.5)	105.4(90.0-122.2)	<0.001	99.5(82.7-113.2)	98.1(81.2-111.8)	0.038	0.185
D-dimer, median(IQR),mg/L	0.8(0.4-2.1)	0.7(0.3-2.7)	0.065	0.8(0.3-2.3)	0.8(0.3-2.6)	0.023	0.654
LDL-c, median(IQR), mmol/L	2.3(1.7-3.0)	2.4(1.9-3.0)	0.007	2.4(1.8-3.0)	2.5(2.0-3.2)	-0.127	<0.001
TC, median(IQR), mmol/L	3.9(3.2-4.8)	4.0(3.4-4.7)	0.042	4.0(3.3-4.8)	4.2(3.5-5.0)	-0.115	<0.001
CK, median(IQR), U/L	63.0(42.0-106.0)	64.0(43.0-104.0)	0.890	61.9(41.0-98.0)	64.0(43.0-106.0)	-0.047	0.085

ALT, alanine transaminase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; LDL-c, low density lipoprotein cholesterol; TC, total cholesterol; CK, creatine kinase; IQR, interquartile range; SD, standardized difference.

Table S2. The Reference Range of laboratory indicators in Study Hospitals, related to Table 1.

Hospital site	CRP (mg/L)	Procalcitonin (ng/ml)	D-Dimer (mg/L)	LDL-c (mmol/L)	TC (mmol/L)	CK (U/L)
1	[0,10]	[0,0.05]	[0,0.5]	[0,3.37)	[0,5.18)	[0,171)/[0,145)
2	[0,10]	[0,0.1]	[0,0.55]	[0,3.4)	[0,5.2)	[40,200]/[50,310]
3	[0,5]	[0,0.05]	[0,0.5]	[2.2,3.1]	[3.1,5.7]	[30,180]
4	[0,3]	[0,0.5]	[0,1]	[0,3.12]	[2.9,5.68]	[40,200]/[50,310]
5	[0,10]	[0,0.5]/[0,0.046]	[0,1]	[0,3.37)	[0,5.18)	[38,174]/[0,190]
6	[0,10]	[0,0.1]	[0,0.243]	[1,3.35]	[2.8,5.2]	[40,200]/[50,310]
7	[0,4]	[0,0.05]	[0,0.55]	[0,3.37]	[0,5.18]	[0,145]/[0,174]
8	[0,5]	[0,0.5]	[0,0.55]	[2.07,3.10]	[3.38,5.17]	[0,171]/[30,170]
9	[0,10]/[0,5]	[0,0.1]/[0,0.5]	[0,0.243]	[1.5,3.10]	[0,5.71]	[0,190]
10	[0,8]	[0,0.5]	[0,2]	[0,3.12]	[3,5.7]	[0,170]/[0,190]
11	[0,6]	[0,0.5]	[0,1]	[0,3.36)	[0,5.2)	[26,140]/[38,174]
12	[0,10]	[0,0.5]	[0,0.243]	[0,3.12]	[3,5.2]	[24,195]
13	[0,10]	[0,0.05]	[0,0.5]	[2.07,3.10]	[2.8,6]	[40,200]
14	[0,10]	[0,0.5]	[0,0.55]	[0,3.37]	[2.8,5.2]	[40,200]/[50,310]
15	[0,10]	[0,0.5]	[0,0.55]	[0.5,3.2]	[3.1,6.2]	[0,160]
16	[0,10]	[0,0.046]	[0,0.5]	[0,3.7]	[2.8,5.2]	[50,310]
17	[0,8]	[0,0.5]	[0,0.55]	[0,3.4]	[2.8,5.2]	[0.171]/[0,145]
18	[0,10]	[0,0.25]	[0,0.5]	[2.07,3.10]	[2.33,5.69]	[40,200]/[50,310]
19	[0,10]	[0,0.5]	[0,0.232]	[0,2.84)/ [0,3.37)	[3.12,5.20]/ [3.63,5.17]	[0,167]/[0,190]
20	[0,10]	[0,0.05]	[0,0.5]	[0,3.37]	[0,5.18]	[0,170]/[0,190]
21	[0,10]	[0,0.05]/[0,0.5]	[0,0.5]	[0,3.12]/ [0,3.37)	[0,5.2]	[26,140]/[24,194]

CRP, C-reactive protein; LDL-c, low density lipoprotein cholesterol; TC, total cholesterol; CK, creatine kinase. “[” indicates an interval that includes the endpoints; “(” indicates an interval that does not include the endpoints

Table S3. Characteristics of patients in statin and non-statin groups after PSM[b], related to Table 1.				
Parameters	**Statin (N=861)**	**Non-statin (N=3444)**	**SD**	**P value[c]**
Clinical characteristics on admission				
Age, median(IQR)	65.0(57.0-71.0)	65.0(57.0-72.0)	-0.025	0.225
Male gender, n(%)	411(47.7%)	1652(48.0%)	-0.005	0.933
Heart rate, median(IQR), bpm	84.0(76.0-96.0)	85.0(78.0-97.0)	-0.041	0.229
Respiratory rate, median(IQR), bpm	20.0(19.0-21.0)	20.0(19.0-21.0)	-0.061	0.236
SBP, median(IQR), mmHg	131.0(120.0-145.0)	133.0(121.0-146.0)	-0.073	0.069
DBP, median(IQR), mmHg	80.0(72.0-89.0)	80.0(73.0-89.0)	-0.047	0.377
BMI, median(IQR), kg/m^2	24.0(22.6-25.7)	24.2(22.7-25.5)	-0.080	0.435
Days from symptom to hospital, median(IQR)	14.0(8.0-23.0)	13.0(7.0-22.0)	0.041	0.058
Days from symptom to medical treatment in hospitalization, median(IQR)	14.0(8.0-23.0)	13.0(7.0-22.0)	0.036	0.091
Follow-up days, median(IQR)	22.0(15.0,28.0)	18.0(12.0,27.0)	0.329	<0.001
Comorbidities on admission				
COPD, n(%)	9(1.1%)	44(1.3%)	-0.022	0.704
Hypertension, n(%)	637(74.0%)	2545(73.9%)	0.002	0.993
Diabetes, n(%)	265(30.8%)	997(29.0%)	0.040	0.311
Coronary heart disease, n(%)	157(18.2%)	597(17.3%)	0.024	0.568
Cerebrovascular disease, n(%)	67(7.8%)	234(6.8%)	0.038	0.347
Chronic liver disease, n(%)	13(1.5%)	50(1.5%)	-0.005	1.000
Chronic renal disease, n(%)	43(5.0%)	167(4.9%)	0.007	0.930
Chest CT on admission				
Bilateral lesions, n/N (%)	715/803(89.0%)	2801/3218(87.0%)	0.062	0.142
Laboratory examination on admission				
Leukocyte count > 9.5, 10^9/L, n/N(%)	78/829(9.4%)	361/3203(11.3%)	-0.061	0.141
Neutrophil count > 6.3, 10^9/L, n/N(%)	135/829(16.3%)	538/3202(16.8%)	-0.014	0.761
Lymphocyte count < 1.1, 10^9/L, n/N(%)	329/829(39.7%)	1280/3202(40.0%)	-0.006	0.911
C-reactive protein >ULN[a], n/N(%)	259/533(48.6%)	940/1933(48.6%)	-0.001	1.000
Procalcitonin > ULN[a], n/N(%)	297/722(41.1%)	1190/2624(45.4%)	-0.085	0.048
ALT > 40 U/L, n/N(%)	188/825(22.8%)	783/3134(25.0%)	-0.052	0.208
AST > 40 U/L, n/N(%)	181/825(21.9%)	701/3135(22.4%)	-0.010	0.832
eGFR < 90 mL/min, n/N(%)	270/820(32.9%)	1101/3149(35.0%)	-0.043	0.293
D-dimer > ULN[a], n/N(%)	435/771(56.4%)	1537/2899(53.0%)	0.068	0.100
LDL-c > ULN[a], n/N(%)	125/711(17.6%)	510/2424(21.0%)	-0.088	0.049
TC > ULN[a], n/N(%)	133/755(17.6%)	548/2708(20.2%)	-0.067	0.121
CK > ULN[a], n/N(%)	68/732(9.3%)	319/2688(11.9%)	-0.084	0.059
SpO2 < 95%, n/N(%)	247/861(28.7%)	1224/3444(35.5%)	-0.147	<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; SD, standardized difference.

[a] Upper limit of normal (ULN) was defined according to criteria in each hospital.

[b] The statin and non-statin groups were matched based on variables including age, gender, pre-existing comorbidities (COPD, DM, hypertension, coronary heart disease, cerebral arterial disease, chronic liver disease, and chronic renal disease), indicators of disease severity and organ injuries (neutrophil counts increase, lymphocyte counts decrease, CRP level increase, ALT increase, creatine kinase [CK] increase, eGFR decrease) and LDL-c increase, TC increase, and use of ACEi/ARB.

[c] P values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or $\chi 2$ test for categorical variables.

Table S4. Characteristics of patients in statin+ACEi/ARB and statin+nonACEi/ARB groups, related to Table 1

Parameters	Statin+ACEi/ARB (N=319)	Statin-nonACEi/ ARB (N=603)	P value[b]
Clinical characteristics on admission			
Age, median(IQR)	67.0(62.0-73.0)	67.0(61.0-73.0)	0.724
Male gender, n(%)	172(53.9%)	294(48.8%)	0.155
Heart rate, median(IQR), bpm	84.0(77.0-97.0)	84.5(77.0-97.0)	0.782
Respiratory rate, median(IQR), bpm	20.0(19.8-21.0)	20.0(19.0-21.0)	0.408
SBP, median(IQR), mmHg	138.0(125.0-152.0)	133.0(120.0-146.0)	0.002
DBP, median(IQR), mmHg	80.0(72.0-90.0)	80.0(71.0-89.0)	0.238
BMI, median(IQR), kg/m^2	24.5(23.1-25.8)	24.3(22.8-26.0)	0.739
Days from symptom to hospital, median(IQR)	13.0(7.0-19.5)	14.0(8.0-21.0)	0.290
Days from symptom to medical treatment in hospitalization, median(IQR)	13.0(7.0-20.0)	14.0(8.0-21.0)	0.109
Follow-up days, median(IQR)	22.0(15.0-28.0)	22.0(14.0-28.0)	0.345
Comorbidities on admission			
COPD, n(%)	0(0.0%)	14(2.3%)	0.003
Hypertension, n(%)	319(100.0%)	603(100.0%)	-
Diabetes, n(%)	140(43.9%)	195(32.3%)	0.001
Coronary heart disease, n(%)	151(47.3%)	250(41.5%)	0.101
Cerebrovascular disease, n(%)	29(9.1%)	51(8.5%)	0.840
Chronic liver disease, n(%)	9(2.8%)	6(1.0%)	0.070
Chronic kidney disease, n(%)	18(5.7%)	39(6.5%)	0.726
Chest CT on admission			
Bilateral lesions, n/N (%)	272/303(89.8%)	514/565(91.0%)	0.648
Laboratory examination on admission			
Leukocyte count > 9.5, 10^9/L, n/N(%)	42/312(13.5%)	73/588(12.4%)	0.732
Neutrophil count > 6.3, 10^9/L, n/N(%)	61/312(19.6%)	119/588(20.2%)	0.875
Lymphocyte count < 1.1, 10^9/L, n/N(%)	139/312(44.6%)	256/588(43.5%)	0.825
C-reactive protein >ULN[a], n/N(%)	88/176(50.0%)	191/357(53.5%)	0.504
Procalcitonin > ULN[a], n/N(%)	141/269(52.4%)	267/517(51.6%)	0.896
ALT > 40 U/L, n/N(%)	84/309(27.2%)	138/587(23.5%)	0.259
AST > 40 U/L, n/N(%)	76/309(24.6%)	140/587(23.9%)	0.868
eGFR < 90 mL/min, n/N(%)	130/307(42.4%)	257/587(43.8%)	0.733
D-dimer > ULN[a], n/N(%)	167/296(56.4%)	352/555(63.4%)	0.055
LDL-c > ULN[a], n/N(%)	41/259(15.8%)	79/497(15.9%)	1.000
TC > ULN[a], n/N(%)	37/287(12.9%)	72/540(13.3%)	0.944
CK > ULN[a], n/N(%)	38/260(14.6%)	62/524(11.8%)	0.324
SpO2 < 95%, n/N(%)	99/319(31.0%)	202/603(33.5%)	0.493

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.

[a]Upper limit of normal (ULN) was defined according to criteria in each hospital.

[b]P values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or $\chi 2$ test for categorical variables.

Table S5. Absolute values of laboratory indicators on admission in statin+ACEi/ARB and Statin+nonACEi/ARB groups before and after PSM, related to Table 1.

Parameters	Unmatched			Matched			
	Statin+ACEi/ARB (N=319)	Statin+nonACEi/ARB (N=603)	P value[a]	Statin+ACEi/ARB (N=204)	Statin+nonACEi/ARB (N=204)	SD	P value[a]
Leukocyte count, median(IQR), 10^9/L	6.0(4.8-7.8)	6.1(4.8-7.7)	0.838	5.9(4.7-7.9)	6.3(4.9-7.9)	-0.060	0.314
Neutrophil count, median(IQR), 10^9/L	4.0(2.9-5.6)	4.1(3.0-5.9)	0.760	3.9(2.9-5.5)	4.5(3.2-6.1)	-0.124	0.065
Lymphocyte count, median(IQR), 10^9/L	1.2(0.8-1.6)	1.1(0.8-1.6)	0.447	1.2(0.9-1.7)	1.1(0.8-1.6)	0.191	0.133
C-reactive protein, median(IQR), mg/L	5.9(2.8-29.7)	8.3(2.2-41.3)	0.393	6.4(3.1-32.2)	9.4(1.7-62.5)	-0.201	0.470
Procalcitonin, median(IQR), ng/mL	0.1(0.0-0.1)	0.1(0.0-0.1)	0.144	0.1(0.0-0.1)	0.1(0.0-0.1)	-0.013	0.128
ALT, median(IQR), U/L	26.0(16.0-44.0)	25.0(17.0-40.0)	0.654	26.0(15.5-45.0)	26.0(17.1-41.5)	0.022	0.732
AST, median(IQR), U/L	26.0(19.0-37.0)	25.0(18.0-38.0)	0.834	25.0(18.0-36.4)	26.0(18.0-39.0)	-0.119	0.599
eGFR, median(IQR), mL/min	94.4(77.8-105.1)	93.9(75.4-107.5)	0.992	94.5(80.2-103.8)	96.4(77.5-109.8)	-0.062	0.325
D-dimer, median(IQR), mg/L	0.8(0.4-2.0)	1.0(0.4-2.8)	0.038	0.7(0.4-2.7)	0.9(0.4-2.4)	0.100	0.440
LDL-c, median(IQR), mmol/L	2.1(1.6-2.9)	2.2(1.6-2.9)	0.749	2.1(1.6-2.8)	2.2(1.6-2.9)	-0.091	0.589
TC, median(IQR), mmol/L	3.7(3.1-4.5)	3.8(3.1-4.7)	0.375	3.7(3.1-4.4)	3.7(3.0-4.6)	-0.073	0.620
CK, median(IQR), U/L	68.0(46.8-110.3)	64.0(41.0-107.3)	0.145	62.5(45.0-102.8)	66.0(43.3-105.8)	-0.089	0.810

ALT, alanine transaminase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; LDL-c, low density lipoprotein cholesterol; TC, total cholesterol; CK, creatine kinase; IQR, interquartile range; SD, standardized difference.

[a] P values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or χ^2 test for categorical variables.

Table S6. Characteristics of patients in statin+ACEi/ARB and statin+nonACEi/ARB groups after PSM[b], related to Table 1.

Parameters	Statin+ACEi/ARB (N=204)	Statin+nonACEi/ ARB (N=204)	SD	P value[c]
Clinical characteristics on admission				
Age, median(IQR)	67.0(62.0-73.0)	68.0(62.0-73.0)	0.031	0.915
Male gender, n(%)	111(54.4%)	107(52.5%)	0.039	0.766
Heart rate, median(IQR), bpm	84.0(76.0-98.0)	86.0(78.0-99.5)	-0.053	0.543
Respiratory rate, median(IQR), bpm	20.0(20.0-21.0)	20.0(19.8-21.0)	-0.131	0.729
SBP, median(IQR), mmHg	136.0(125.0-152.0)	135.0(122.0-150.0)	0.067	0.520
DBP, median(IQR), mmHg	80.5(73.0-90.0)	80.0(70.0-88.5)	0.051	0.336
BMI, median(IQR), kg/m^2	24.5(23.1-25.8)	24.0(22.0-25.4)	0.074	0.752
Days from symptom to hospital, median(IQR)	12.0(7.0-18.5)	13.0(8.0-21.0)	-0.129	0.166
Days from symptom to medical treatment in hospitalization, median(IQR)	12.0(7.0-18.3)	13.0(8.0-21.0)	-0.130	0.160
Follow-up days, median(IQR)	22.0(15.0-28.0)	24.0(15.8-28.0)	0.151	0.359
Comorbidities on admission				
COPD, n(%)	0(0.0%)	0(0.0%)	0.000	1.000
Hypertension, n(%)	204(100.0%)	204(100.0%)	0.000	1.000
Diabetes, n(%)	79(38.7%)	79(38.7%)	0.000	1.000
Coronary heart disease, n(%)	84(41.2%)	96(47.1%)	-0.119	0.273
Cerebrovascular disease, n(%)	20(9.8%)	16(7.8%)	0.069	0.601
Chronic liver disease, n(%)	4(2.0%)	3(1.5%)	0.038	1.000
Chronic renal disease, n(%)	11(5.4%)	12(5.9%)	-0.021	1.000
Chest CT on admission				
Bilateral lesions, n/N (%)	176/196(89.8%)	170/186(91.4%)	-0.055	0.719
Laboratory examination on admission				
Leukocyte count > 9.5, 10^9/L, n/N(%)	26/198(13.1%)	30/199(15.1%)	-0.056	0.680
Neutrophil count > 6.3, 10^9/L, n/N(%)	40/198(20.2%)	45/199(22.6%)	-0.059	0.643
Lymphocyte count < 1.1, 10^9/L, n/N(%)	83/198(41.9%)	87/199(43.7%)	-0.036	0.794
C-reactive protein >ULN[a], n/N(%)	57/116(49.1%)	73/126(57.9%)	-0.177	0.214
Procalcitonin > ULN[a], n/N(%)	85/174(48.9%)	94/180(52.2%)	-0.067	0.598
ALT > 40 U/L, n/N(%)	52/195(26.7%)	47/199(23.6%)	0.070	0.561
AST > 40 U/L, n/N (%)	47/195(24.1%)	51/199(25.6%)	-0.035	0.815
eGFR < 90 mL/min, n/N (%)	82/193(42.5%)	77/198(38.9%)	0.073	0.534
D-dimer > ULN[a], n/N(%)	103/185(55.7%)	122/191(63.9%)	-0.168	0.130
LDL-c > ULN[a], n/N(%)	21/160(13.1%)	32/175(18.3%)	-0.142	0.253
TC > ULN[a], n/N(%)	23/176(13.1%)	28/186(15.1%)	-0.057	0.695
CK > ULN[a], n/N(%)	22/164(13.4%)	23/182(12.6%)	0.023	0.956
SpO2 < 95%, n/N(%)	62/204(30.4%)	69/204(33.8%)	-0.074	0.525

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; SD, standardized difference.

[a] Upper limit of normal (ULN) was defined according to criteria in each hospital.

[b] The statin+ACEi/ARB and statin+nonACEi/ARB groups were matched based on variables including age, gender, blood pressure (SBP and DBP), pre-existing comorbidities (COPD, DM, coronary heart disease, cerebral arterial disease, chronic liver disease, and chronic renal disease), indicators of disease severity and organ injuries (neutrophil counts increase, lymphocyte counts decrease, CRP level increase, eGFR decrease) and LDL-c increase, TC increase and numbers of antihypertensive drugs, and SpO2.

[c] P values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or $\chi 2$ test for categorical variables.

Table S7. Statin dose conversion[a], related to Table 2.

Atorvastatin	Fluvastatin	Pitavastatin	lovastatin	Pravastatin	Rosuvastatin	Simvastatin	Lowers LDL-c(%)
	40 mg	1 mg	20 mg	20 mg		10 mg	30
10 mg	80 mg	2 mg	40 or 80 mg	40 mg		20 mg	38
20 mg		4 mg	80 mg	80 mg	5 mg	40 mg	41
40 mg					10 mg	80 mg	47
80 mg					20 mg		55

[a]Statin dose conversion was based on "Chinese expert consensus on the use of statins in elderly with dyslipidemia in 2015"

Table S8. In-hospital application of statin and ACEi/ARB in statin+ACEi/ARB and statin+nonACEi/ARB groups, related to Table 2.

Parameters	Unmatched			Matched			
	Statin+ ACEi/ARB (N=319)	Statin+non ACEi/ARB (N=603)	P value[b]	Statin+ ACEi/ARB (N=204)	Statin+non ACEi/ARB (N=204)	SD	P value[b]
Atorvastatin, n(%)	259(81.2%)	496(82.3%)	0.757	159(77.9%)	160(78.4%)	-0.012	1.000
Rosuvastatin, n(%)	57(17.9%)	99(16.4%)	0.641	39(19.1%)	37(18.1%)	0.025	0.899
Simvastatin, n(%)	10(3.1%)	8(1.3%)	0.102	9(4.4%)	3(1.5%)	0.175	0.143
Pravastatin, n(%)	5(1.6%)	8 (1.3%)	0.774	4(2.0%)	6(2.9%)	-0.063	0.749
Fluvastatin, n(%)	0(0.0%)	1 (0.2%)	1.000	0(0.0%)	0(0.0%)	0.000	1.000
Pitavastatin, n(%)	4(1.3%)	3 (0.5%)	0.243	4(2.0%)	2(1.0%)	0.082	0.685
ACEi/ARB, n(%)	319(100.0%)	0 (0.0%)	<0.001	204(100.0%)	0(0.0%)	-	<0.001
Statin initial day after admission, median(IQR), Days	0.0(0.0,0.0)	0.0(0.0,0.0)	-	0.0(0.0,0.0)	0.0(0.0,0.0)	-0.085	0.308
Statin therapeutic duration, median(IQR), Days	22.0(15.0-28.0)	23.0(15.0-28.0)	0.749	22.0(15.0-28.0)	24.0(15.0-28.0)	0.113	0.166
Daily equivalent dose of statin[a], median(IQR), mg	20.0(20.0-20.0)	20.0(19.8-20.0)	0.166	20.0(19.8-20.0)	20.0(19.7-20.0)	0.092	0.478
ACEi/ARB initial day after admission, median(IQR), Days	3.0(0.0-9.0)	-	-	4.0(0.0-10.0)	-	-	-
ACEi/ARB therapeutic duration, median(IQR), Days	17.0(9.5-25.0)	-	-	16.0(9.0-23.3)	-	-	-

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; IQR, interquartile range; SD, standardized difference.
[a]Daily equivalent dose of statin were converted to an equivalent dose of atorvastatin according to the "Chinese expert consensus on the use of statins in elderly with dyslipidemia in 2015"
[b]P values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or $\chi 2$ test for categorical variables.

Table S9. Hazard ratios for 28-day all-cause mortality in study cohorts excluding participants with ICU admission or death within 48 hours after admission, related to Table 3.

	Cox model-time varying		Marginal structural model		Mixed-effect Cox model	
	aHR (95%CI)	**P value**	**aHR (95%CI)**	**P value**	**aHR (95%CI)**	**P value**
Statin vs. Non-statin	0.74(0.55-0.99)[a]	0.044	0.73(0.53-0.99)[c]	0.046	0.59(0.44-0.78)[e]	<0.001
Statin+ACEi/ARB vs. Statin+nonACEi/ARB	0.52(0.22-1.22)[b]	0.132	1.21(0.63-2.33)[d]	0.568	0.55(0.29-1.07)[f]	0.079

aHR, adjusted hazard ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

[a] Adjusted for age, gender, blood pressure (SBP and DBP), pre-existing comorbidities (DM, hypertension, coronary heart disease, cerebrovascular disease, and chronic renal disease), indicators of disease severity and organ injuries (lesions in chest CT, WBC increase, neutrophil counts increase, procalcitonin increase, D-dimer increase, ALT increase, AST increase, creatinine increase, SpO2, LDL-c increase, TC increase, medications at admission, using invasive mechanical ventilation support, and days from symptom onset to hospitalization support covariates with statin therapy as time-varying exposures.

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

[c] CURB-65 pneumonia severity score, serum ALT levels, and CK levels were considered as time-varying confounders. Additionally, the adjustment factors included gender, blood pressure (SBP and DBP), pre-existing comorbidities (DM, coronary heart disease, cerebrovascular disease, and chronic renal disease), indicators of disease severity and organ injuries (lesions in chest CT, WBC increase, neutrophil counts 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.

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

[e] aHR was calculated based on mixed-effect Cox model with adjustment of age, gender, blood pressure (SBP and DBP), pre-existing comorbidities (DM, hypertension, coronary heart disease, cerebrovascular disease, and chronic renal disease), indicators of disease severity and organ injuries (lesions in chest CT, the incidence of increased WBC, neutrophil counts, ALT, AST, procalcitonin, D-dimer and SpO2, decreased eGFR), LDL-c increase, TC increase.

[f] aHR was calculated based on mixed-effect Cox model with adjustment of age, gender, blood pressure (SBP), pre-existing COPD and DM.

Table S10. 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 before PSM, related to Table 4.

	Statin vs. Non-statin					Statin+ACEi/ARB vs. Statin+nonACEi/ARB				
	IR	IRR (95%CI)	P value[a]	aHR[b] (95%CI)	P value[c]	IR	IRR (95%CI)	P value[a]	aHR[d] (95%CI)	P value[c]
Secondary outcome										
Invasive mechanical ventilation	0.10 vs 0.15	0.68 (0.48-0.96)	0.029	0.37 (0.26-0.53)	<0.001	0.12 vs 0.13	0.93 (0.44-1.99)	0.854	0.82 (0.37-1.81)	0.626
ICU admission	0.34 vs 0.32	1.06 (0.87-1.30)	0.538	0.69 (0.56-0.85)	0.001	0.41 vs 0.43	0.96 (0.64-1.44)	0.840	0.81 (0.53-1.24)	0.330
ARDS	0.73 vs 0.60	1.22 (1.06-1.39)	0.004	0.83 (0.72-0.97)	0.015	0.76 vs 0.90	0.85 (0.63-1.14)	0.266	0.75 (0.55-1.01)	0.057
Septic shock	0.12 vs 0.11	1.13 (0.81-1.57)	0.483	0.73 (0.51-1.04)	0.083	0.13 vs 0.16	0.82 (0.40-1.67)	0.582	0.53 (0.25-1.12)	0.095
Acute liver injury	0.30 vs 0.29	1.03 (0.83-1.27)	0.801	1.05 (0.84-1.33)	0.653	0.28 vs 0.30	0.93 (0.57-1.52)	0.776	0.88 (0.53-1.45)	0.608
Acute kidney injury	0.13 vs 0.12	1.08 (0.78-1.48)	0.648	0.72 (0.51-1.01)	0.060	0.17 vs 0.15	1.16 (0.61-2.22)	0.644	0.91 (0.47-1.8)	0.796
Acute cardiac injury	0.61 vs 0.31	1.99 (1.71-2.31)	<0.001	1.16 (0.98-1.37)	0.089	0.77 vs 0.73	1.05 (0.78-1.42)	0.747	0.89 (0.65-1.21)	0.46
CK and transaminase elevation										
CK > ULN	0.43 vs 0.39	1.12 (0.94-1.33)	0.210	0.97 (0.8-1.17)	0.715	0.47 vs 0.48	0.98 (0.67-1.44)	0.919	1.09 (0.73-1.62)	0.679
ALT > 3ULN	0.25 vs 0.24	1.04 (0.83-1.31)	0.730	0.98 (0.76-1.26)	0.852	0.17 vs 0.29	0.61 (0.34-1.09)	0.090	0.58 (0.32-1.05)	0.074

IR(100 person-days), incidence rate; IRR, incidence rate 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.

[a] P values were calculated by R package"fmsb". The significant probability of the result of null-hypothesis testing.

[b] aHR was calculated based on mixed-effect Cox model with adjustment of age, gender, blood pressure (SBP and DBP), pre-existing comorbidities (DM, hypertension, coronary heart disease, cerebrovascular disease, and chronic renal disease), indicators of disease severity and organ injuries (lesions in lung CT, the incidence of increased neutrophil counts, ALT, AST, procalcitonin, D-dimer and SpO2, decreased eGFR), LDL-c increase, TC increase.

[c] P values were calculated based on mixed-effect Cox model.

[d] aHR was calculated based on mixed-effect Cox model with adjustment of age, gender, blood pressure (SBP), pre-existing COPD and DM.

Table S11. The number of patients in each hospital and statin users for each hospital, related to Table 1.

Hospital code	Statin users (N)	Non-statin users (N)	Total (N)
1	29	570	599
2	130	1232	1362
3	27	437	464
4	25	1029	1054
5	42	567	609
6	29	345	374
7	223	1669	1892
8	25	331	356
9	42	831	873
10	0	17	17
11	12	301	313
12	0	33	33
13	0	42	42
14	5	132	137
15	0	44	44
16	0	37	37
17	6	267	273
18	8	102	110
19	10	177	187
20	335	2664	2999
21	271	1935	2206
Total	**1219**	**12762**	**13981**

Table S12. CURB-65 scale of community-acquired pneumonia, related to Table 3.

Clinical indicator	Score	
Confusion	1	
Urea>7mmol/L	1	
Respiratory rate≥30/min	1	
Low BP (SBP<90 or DBP≤60 mmHg)	1	
Age≥65	1	
Total scores		
CURB-65 scale	**Mortality (%)[a]**	**Suggestion[b]**
0	0.6	Low risk, out-of-hospital treatment.
1	2.7	Low risk, out-of-hospital treatment.
2	6.8	Short-term hospitalization or out-of-hospital treatment with close observation.
3	14	Severe pneumonia, hospitalization or ICU treatment
4 or 5	27.8	Severe pneumonia, hospitalization or ICU treatment

CURB-65= Confusion, Urea>7mmol/L, Respiratory rate≥30/min, Low BP(SBP<90 or DBP≤60 mmHg), Age≥65

[a] Data on mortality rate were from valid studies.

[b] Consistent with the British Thoracic Society guidelines, but the clinical judgment is prior to the guidelines.