Statin Therapy May Be Associated with Reduced Mortality Risk of Sepsis Patients: A Retrospective Study from the MIMIC-IV Database

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Abstract

Background

It is controversial whether statin therapy is beneficial for sepsis patients. A large retrospective cohort study was conducted to evaluate the association between statin therapy and mortality in sepsis patients.

Methods

Adult (≥18 years) sepsis patients were enrolled and divided into two groups: the statin group and the no-statin group. Data including demographic features, vital signs, laboratory tests, and comorbidities from MIMIC-IV v1.0 were extracted. Delirium was assessed via the Confusion Assessment Method for the ICU (CAM-ICU). Ninety-day mortality, 28-day mortality and the incidence of delirium after statin therapy were evaluated using multivariable logistic analysis, the PSM model and subgroup analysis based on univariate analysis.

Results

In univariate analysis and multivariable logistic analysis, statin therapy showed a significant association with both reduced 28-day and 90-day mortality (90-day mortality: OR 0.58, 95% CI: 0.46-0.72, p<0.001; 28-day mortality: OR 0.47, 95% CI: 0.37-0.60, p<0.001), while no relationship was found between statin therapy and delirium (OR 0.92, 95% CI: 0.49-1.72, p=0.787). In further PSM model and subgroup analyses or sensitivity analysis, consistent results were shown.

Conclusion

Statin therapy is significantly associated with 28-day and 90-day mortality without decrease in the incidence of delirium.

Background

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Sepsis-3)[1]. It is a major challenge worldwide due to its high morbidity and mortality. The incidence of sepsis continued to increase, although the total in-hospital mortality fell in the United States from 1979 through 2000[2]. Epidemiological studies of Spain showed a similar tendency from 2008 to 2017[3]. In China, a recent clinical study of secondary analysis of a population-based database revealed that the standardized mortality rate was 67 cases per 100,000 population per year[4].

It is prevalently recognized that the inflammatory response plays a vital role in the progression of sepsis[5-7]. However, agents used to regulate the inflammatory cascade are rare, and most of them lack convincing evidence[8-10]. Since sepsis may cause an inflammatory and hypercoagulable state of endothelial cells[5], statins, well-known hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase

inhibitors[11], were studied in the sepsis population to explore their potential role in the prevention and treatment of sepsis[12, 13].

Over 20 million Americans, and millions more worldwide, take statins, such as atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin, fluvastatin, and lovastatin, to lower cholesterol synthesis[14, 15]. Interestingly, statins also have complex pleiotropic effects[12], which include multiple anti-inflammatory actions by inhibiting macrophages and neutrophils as well as endothelial cell activation via changes in the inflammatory signaling pathway[16]. Therefore, several studies have focused on whether statin therapy may affect sepsis mortality. In 2009, two observational studies reported that statin therapy was associated with reduced mortality in patients with infection or sepsis[17, 18]. Some meta-analyses also revealed a protective role of statins in sepsis patients[19, 20]. However, a small randomized clinical study failed to confirm a significant association between statin therapy and decreased sepsis mortality[21].

Of note, statins were reported to prevent delirium in critically ill patients [23], and the possible mechanism by which satins protect against delirium includes suppressing upregulated toll-like receptors (TLRs), reducing the expression of tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β), and decreasing leukocyte adhesion[22]. In contrast, the MoDUS study established that early administration of statins did not attenuate the duration of delirium or coma in critically ill patients on mechanical ventilation[24].

Therefore, it remains controversial whether statin therapy is beneficial for sepsis patients. Here, we conducted a single-center, retrospective cohort study from the MIMIC- IV database to mainly evaluate the impact of statin therapy on mortality and delirium in patients with sepsis.

Methods

Data source

We performed a retrospective study using records from the Multiparameter Intelligent Motoring in Intensive Care Database IV (MIMIC-IV)[25]. MIMIC-IV is a large single-center critical care database with electronic data from the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center from 2008 to 2019. Access to the MIMIC-IV database was approved by the institutional review boards of both Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. Content was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived. One of the authors (SY) obtained access (Certification number 35931520) and extracted the data.

Inclusion and exclusion criteria

Adult (age≥18 years old) patients diagnosed with sepsis using International Classification of Disease, 10th Revision (ICD-10) according to the definition of sepsis [1] and receiving statin therapy for more than 7 days were considered to be eligible for the study cohort. The exclusion criteria were as follows: (1)

repeated admission to the ICU, (2) receiving statin therapy before ICU admission, and (3) patients whose baseline creatine kinase level was 10 times or ALT level was 8 times higher than the upper normal range.

Sample size

The sample size was constrained by the number of patients meeting the inclusion criteria and receiving one of the statins for more than 7 days.

Definitions

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Sepsis 3.0). That is, infectious patients with a SOFA score of 2 points or more are diagnosed with sepsis[1]. Statins include atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin, fluvastatin, and lovastatin[15].

Data collection

Demographics, vital signs, disease severity, laboratory tests, comorbidities, medicines, and clinical outcomes, such as follow-up records were extracted from the database. The severity of sepsis was represented by the Simplified Acute Physiology Score II (SAPS II)[26] and Sequential Organ Failure Assessment (SOFA) score[27]. Comorbidities were defined using ICD-10 codes[28]. Medicines mainly collected included some cardiovascular system related drugs, such as calcium channel blockers (CCBs), beta blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), thiazides, spironolactone, clopidogrel and aspirin.

Outcomes

The primary outcome was the association between statin therapy and 28-day mortality for sepsis patients. The secondary outcomes were 90-day mortality and the incidence of delirium.

Statistical analysis

Baseline characteristics for continuous variables are described as the median and interquartile range (IQR). Categorical variables are presented as the count and percentage (%). The Mann-Whitney U test, chi-square test, or Fisher's exact test was used for comparisons between the statin and no-statin groups.

Univariate and multivariable logistic analyses were conducted to explore the association between statin use and outcomes with odd ratios (ORs) and 95% confidence intervals (CIs). Adjustment confounders included the baseline characteristics listed in Table 1. In addition, we applied propensity score matching (PSM) to balance the baseline variables between groups. The propensity score revealed the likelihood of receiving statin therapy with a condition of prespecified confounders (Table 1). We matched patients based on their propensity score with a caliper less than 0.02, and the matching ratio was 1:1. After matching, the standard mean difference (SMD) for each covariate was calculated, and an SMD less than 0.1 was an indicator for balance.

In subgroup analyses, we examined the association of statin use and 90-day mortality stratified by age, use of cardiovascular-related drugs, SOFA scores, and mechanical ventilation. A prespecified sensitivity analysis was performed under the following conditions: patients who died in the first 24 h after ICU admission.

All p values (two-sided) less than 0.05 indicated statistical significance. All analyses were performed using SAS 9.4 and R Version 4.1.0.

Results

Patient characteristics

An initial cohort of 35010 patients was eligible for the study. Among them, 7871 patients were repeatedly admitted to the ICU, 4694 had received statin therapy before ICU admission, and 1125 had baseline creatine kinase levels 10 times or ALT levels 8 times higher than the upper normal range. Finally, 21320 patients were included in our study. A total of 2158 (10.2%) patients received statin therapy for more than 7 days (statin group), and 19162 (89.8%) patients did not receive statins or had received statins for less than 7 days (no-statin group). Figure 1 is a flow chart describing the procedure for the selection of subjects.

For patients receiving statins therapy, age, weight, insurance, admitted type, SOFA score, SAPS II, mean arterial pressure (MAP), lactate level, platelets, urine output, blood urea nitrogen (BUN), creatine level, heart rate, fluid input within 24 h, AST, ALT, total bilirubin, acute kidney injury (AKI), and comorbidities such as malignancy, diabetes, renal disease, cerebrovascular disease, liver disease, cardiovascular disease and cardiovascular-related drugs, except for spironolactone differed significantly compared with patients in the no-statin group. However, ethnicity, sex, first GCS assessment, hemoglobin (Hb), white blood cells (WBCs), respiratory rate, temperature, SpO_2, albumin level, positive blood culture, vasopressor use, mechanical ventilation, CRRT, RASS evaluation, and comorbidities such as hypertension showed no significant difference between the two groups (Table 1).

Table 1 Summary of the baseline characteristics

characteristics	statin (2158)	no-statin (19162)	Total (21320)	P
Age (yr)	72.0(64.0-81.0)	66.0(54.0-78.0)	67.0(55.0-78.0)	<0.001
Weight (kg)	79.8(66.7-95.3)	77.6(65.0-93.0)	77.9(65.0-93.2)	0.001
Non-white, %	763(35.4)	6390(33.3)	7153(33.6)	0.061
Insurance, %	1316(61.0)	10017(52.3)	11333(53.2)	<0.001
Male, %	1198(55.5)	10748(56.1)	11946(56.0)	0.609
Admitted type, %		<0.001		
Surgical department	208(9.6)	1914(10.0)	2122(10.0)	
Medical department	362(16.8)	2226(11.6)	2588(12.1)	
Emergency treatment	1231(57.0)	11261(58.8)	12492(58.6)	
Others	357(16.5)	3761(19.6)	4118(19.3)	
GCS	15.0(14.0-15.0)	15.0(14.0-15.0)	15.0(14.0-15.0)	0.959
SOFA	6.0(4.0-9.0)	5.0(4.0-8.0)	6.0(4.0-8.0)	<0.001
SAPS-II	40.0(33.0-49.0)	37.0(29.0-47.0)	38.0(29.0-47.0)	<0.001
MAP (mmHg)	48.0(38.5-57.7)	51.9(42.0-60.2)	51.6(41.5-60.0)	<0.001
Lactate (mmol/L)	1.5(1.1-2.2)	1.7(1.2-2.5)	1.7(1.2-2.4)	<0.001
Hb (mg/dL)	10.4(9.0-12.0)	10.5(9.2-12.1)	10.5(9.2-12.1)	0.127
Platelets ($\times 10^{12}$)	195.3(144.0-259.5)	182.7(127.8-252.4)	184.0(129.5-253.0)	<0.001
WBC ($\times 10^{9}$)	11.9(8.9-15.9)	11.7(8.4-15.7)	11.7(8.4-15.8)	0.357
Urine output (L)	1415.0(840.0-2170.0)	1530.0(918.0-2375.0)	1520.0(910.0-2360.0)	<0.001
BUN (mg/dl)	25.0(16.5-40.0)	20.0(13.5-33.3)	20.5(14.0-34.0)	<0.001
Creatinine (mg/dL)	1.2(0.9-1.9)	1.0(0.8-1.5)	1.0(0.8-1.6)	<0.001
Heart rate (bpm)	83.0(73.8-94.6)	86.3(75.8-98.5)	86.0(75.6-98.2)	<0.001
Respiratory rate (/min)	19.5(17.1-22.2)	19.1(16.7-22.1)	19.1(16.8-22.2)	0.052
Temperature (°C)	36.9(36.7-37.2)	36.9(36.7-37.2)	36.9(36.7-37.2)	0.081
SpO_2, %	97.0(95.6-98.4)	97.2(95.7-98.5)	97.2(95.7-98.5)	0.779
Albumin (mg/dl)	3.0(2.6-3.4)	3.0(2.5-3.5)	3.0(2.6-3.5)	0.480
Fluid input in 24h (l)	3.6(2.0-6.4)	4.6(2.6-7.5)	4.5(2.5-7.4)	<0.001

AST (U/L)	34.0(23.0-63.3)	42.5(25.0-91.0)	41.0(25.0-87.5)	<0.001
ALT (U/L)	23.0(15.0-43.5)	28.0(17.0-58.5)	27.5(17.0-56.5)	<0.001
TBIL (mg/dL)	0.6(0.4-0.9)	0.7(0.4-1.7)	0.7(0.4-1.5)	<0.001
Positive blood culture, %	169(7.8)	1370(7.1)	1539(7.2)	0.246
Vasopressor use, %	871(40.4)	7375(38.5)	8246(38.7)	0.090
Ventilation, %	643(29.8)	6022(31.4)	6665(31.3)	0.121
AKI, %	1240(57.5)	9830(51.3)	11070(51.9)	<0.001
CRRT, %	29(1.3)	301(1.6)	330(1.5)	0.418
AKI stage, %				<0.001
3	59(2.7)	400(2.1)	459(2.2)	
2	378(17.5)	3024(15.8)	3402(16.0)	
1	1304(60.4)	9706(50.7)	11010(51.6)	
0	417(19.3)	6032(31.5)	6449(30.2)	
RASS≤-2, %	794(40.7)	6439(39.8)	7233(39.9)	0.422
CAM-ICU, %	626(29.0)	3801(19.8)	4427(20.8)	<0.001
Comorbidity, %				
Malignant	231(10.7)	2926(15.3)	3157(14.8)	<0.001
Hypertension	884(41.0)	7862(41.0)	8746(41.0)	0.953
Diabetes	972(45.0)	5016(26.2)	5988(28.1)	<0.001
Renal disease	748(34.7)	3682(19.2)	4430(20.8)	<0.001
Cerebrovascular disease	529(24.5)	2548(13.3)	3077(14.4)	<0.001
Cerebral infarction	300(13.9)	965(5.0)	1265(5.9)	<0.001
Liver disease	158(7.3)	3002(15.7)	3160(14.8)	<0.001
Cardiovascular disease	1088(50.4)	6320(33.0)	7408(34.7)	<0.001
Coronary heart disease	520(24.1)	1388(7.2)	1908(8.9)	<0.001
Myocardial infarction	668(31.0)	2331(12.2)	2999(14.1)	<0.001
Cardiovascular related drugs, %	2051(95.0)	14725(76.8)	16776(78.7)	<0.001
CCB	468(22.4)	2316(15.1)	2784(16.0)	<0.001
β blockers	1631(78.2)	10577(68.9)	12208(70.0)	<0.001

ACEI	196(9.4)	732(4.8)	928(5.3)	<0.001
ARB	137(6.6)	566(3.7)	703(4.0)	<0.001
Thiazides	127(6.1)	845(5.5)	972(5.6)	0.271
Furosemide	1567(75.2)	10756(70.0)	12323(70.6)	<0.001
Spironolactone	120(5.8)	1032(6.7)	1152(6.6)	0.096
Clopidogrel	389(18.7)	1108(7.2)	1497(8.6)	<0.001
Aspirin	1562(74.9)	7641(49.8)	9203(52.8)	<0.001

Abbreviations: GCS: Glasgow Coma Score; SOFA: Sequential Organ Failure Assessment, SAPS II: Simplified Acute Physiology Score II, MAP: mean arterial pressure, Hb: Hemoglobin, WBC: white blood cell, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TBI: total bilirubin, AKI: acute kidney injury, CRRT: continuous renal replacement therapy, RASS: Richmond Agitation-Sedation Scale, CAM-ICU: Confusion Assessment Method for the Intensive Care Unit, CCB: calcium channel blocker, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker.

Clinical outcomes under univariate analysis

In our univariate analysis, statin treatment for more than 7 days was significantly associated with reduced 90-day mortality (12.4% vs. 17.5%, p<0.001) and 28-day mortality (9.0% vs. 15.5%, p<0.001) but prolonged length of stay (LOS) in the ICU (5.1 days vs. 2.9 days, p<0.001) and hospital (14.0 days vs. 8.0 days, p<0.001). No significant difference was found between the two groups regarding delirium (1.3% vs. 1.0%, p=0.080) (Table 2).

Table 2 Clinical outcomes under univariate analysis

Outcomes	Statin (2158)	No-statin (19162)	p
28-day mortality	268(12.4)	3460(18.1)	<0.001
90-day mortality	195(9.0)	3104(16.2)	<0.001
Delirium	29(1.3)	182(0.9)	0.080
LOS Hospital	5.1(2.5-10.0)	2.7(1.5-5.6)	<0.001
LOS ICU	14.0(10.0-21.0)	7.0(5.0-14.0)	<0.001

Clinical outcomes with multivariable logistic analysis adjusted for confounders or after PSM

When adjusted for confounders, such as age, weight, insurance, admitted type, SOFA score, SAPS II, MAP, lactate level, platelets, urine output, BUN, creatine, heart rate, fluid input within 24 h, AST, ALT, TBIL, AKI,

and various comorbidities, statin therapy remained significantly associated with both reduced 28-day and 90-day mortality (28-day mortality: OR 0.47, 95% CI: 0.37-0.60, p<0.001; 90-day mortality: OR 0.58, 95% CI: 0.46-0.72, p<0.001) and there was still no association between statin therapy and delirium (OR 0.92, 95% CI: 0.49-1.72, p=0.787). In our further PSM model, consistent results are shown in Figure 2. The SMD of each baseline variable is shown in Table 3.

Table 3 Standard mean difference of each baseline variable.

	statin	no-statin	SMD
N	2126	2126	
Age (SD)	71.73 (12.16)	72.09 (14.13)	0.027
Weight (SD)	82.83 (24.12)	83.16 (28.84)	0.013
Non-white (%)	1382 (65.0)	1400 (65.9)	0.018
Insurance (%)	1296 (61.0)	1302 (61.2)	0.006
Male (%)	1179 (55.5)	1206 (56.7)	0.026
Admitted type (%)			0.027
Surgical department	1220 (57.4)	1228 (57.8)	
Medical department	348 (16.4)	332 (15.6)	
Emergency treatment	354 (16.7)	350 (16.5)	
Other	204 (9.6)	216 (10.2)	
GCS (SD)	14.22 (1.85)	14.23 (1.91)	0.005
SOFA (SD)	6.60 (3.47)	6.54 (3.38)	0.020
SAPS-II (SD)	41.47 (12.03)	41.45 (13.04)	0.002
MAP (SD)	48.53 (13.50)	48.53 (13.96)	<0.001
Lactate (SD)	1.73 (0.90)	1.74 (0.94)	0.015
Hb (SD)	10.60 (2.07)	10.62 (2.01)	0.009
Platelets (SD)	213.59 (106.45)	219.92 (118.71)	0.056
WBC ($\times 10^9$/L)	13.31 (8.02)	13.55 (10.05)	0.026
Urine output (SD)	1635.48 (1145.70)	1613.86 (1167.26)	0.019
BUN (SD)	32.50 (24.18)	32.32 (23.75)	0.007
Creatinine (SD)	1.76 (1.70)	1.72 (1.62)	0.021
Heart rate (SD)	84.75 (15.47)	84.79 (15.53)	0.003
Respiratory rate (SD)	19.89 (3.82)	19.97 (3.86)	0.021
Temperature (SD)	36.91 (0.57)	36.91 (0.59)	0.005
SpO_2 (SD)	96.86 (2.04)	96.88 (2.23)	0.009
Albumin (SD)	3.01 (0.61)	3.00 (0.63)	0.02
Fluid input in 24h (SD)	4.79 (4.06)	4.81 (4.04)	0.005

AST (SD)	97.43 (845.54)	100.06 (796.80)	0.003
ALT (SD)	56.81 (317.87)	56.37 (213.86)	0.002
TBIL (mg/dL)	0.84 (0.97)	0.80 (0.89)	0.039
Positive blood culture (%)	167 (7.9)	167 (7.9)	<0.001
Vasopressor use (%)	860 (40.5)	858 (40.4)	0.002
Ventilation (%)	638 (30.0)	618 (29.1)	0.021
AKI at baseline (%)	1218 (57.3)	1248 (58.7)	0.029
CRRT (%)	29 (1.4)	24 (1.1)	0.021
AKI stage (%)			0.053
3	416 (19.6)	379 (17.8)	
2	1282 (60.3)	1314 (61.8)	
1	373 (17.5)	386 (18.2)	
0	55 (2.6)	47 (2.2)	
RAS≤-2 (%)	776 (36.5)	792 (37.3)	0.020
CAM-ICU (%)	605 (28.5)	592 (27.8)	0.014
comorbidity (%)			
Malignant	230 (10.8)	238 (11.2)	0.012
Hypertension	880 (41.4)	891 (41.9)	0.010
Diabetes	943 (44.4)	945 (44.4)	0.002
Renal disease	721 (33.9)	722 (34.0)	0.001
Cerebrovascular disease	509 (23.9)	499 (23.5)	0.011
Cerebral infarction	282 (13.3)	282 (13.3)	<0.001
Liver diseases	157 (7.4)	157 (7.4)	<0.001
Cardiovascular disease	1066 (50.1)	1067 (50.2)	0.001
Coronary heart disease	491 (23.1)	443 (20.8)	0.055
Myocardial infarction	642 (30.2)	618 (29.1)	0.025
Cardiovascular-related drugs (%)	2019 (95.0)	2034 (95.7)	0.033

Subgroup analysis of the association between statin therapy and 28-day mortality

In our subgroup analysis stratified by age, SOFA score and ventilation, the OR (95% CI) values in univariate analysis (crude OR [95% CI]), multivariable logistic analysis adjusted for confounders (aOR [95% CI]) and PSM (OR_{PSM} [95% CI]) were all statistically significant (all p<0.05). For cardiovascular-related drugs, only when patients received cardiovascular-related drug did the OR_{PSM} value show no difference (p=0.087). Overall, the subgroup analysis further illuminated that statin therapy was significantly associated with reduced 90-day mortality (Table 4).

Table 4 Subgroup analysis of the association between statin therapy and 28-day mortality

		unadjusted	p	adjusted	p	PSM	p
age	≥65	0.50(0.43-0.59)	<0.001	0.51(0.39-0.68)	<0.001	0.54(0.44-0.66)	<0.001
	<65	0.30(0.20-0.46)	<0.001	0.27(0.14-0.51)	<0.001	0.24(0.15-0.40)	<0.001
Cardiovascular-related drugs	Y	0.60(0.52-0.70)	<0.001	0.48(0.37-0.61)	<0.001	0.48(0.40-0.59)	<0.001
	N	0.11(0.03-0.34)	<0.001	0.14(0.02-1.17)	0.070	0.31(0.08-1.12)	0.087
SOFA	≤6	0.40(0.30-0.52)	0.059	0.46(0.31-0.70)	<0.001	0.53(0.39-0.72)	<0.001
	>6	0.34(0.28-0.42)	<0.001	0.46(0.34-0.63)	<0.001	0.40(0.31-0.51)	<0.001
ventilation	Y	0.40(0.30-0.52)	<0.001	0.34(0.22-0.53)	<0.001	0.35(0.25-0.50)	<0.001
	N	0.59(0.49-0.71)	<0.001	0.57(0.42-0.77)	<0.001	0.55(0.44-0.69)	<0.001

Sensitivity analysis

When specially excluding patients who died in the first 24 h after ICU admission (379 patients excluded), we determined that statin therapy exhibited significant association with both decreased 28-day and 90-day mortality and no association with the incidence of delirium (Table 5).

Table 5 Sensitivity analysis for the association of statin use and outcomes with sepsis patients who died in the first 24 h after ICU admission exclusion.

Outcomes	OR	LOW	UP	P
28-day mortality	0.59	0.50	0.68	0.000
90-day mortality	0.72	0.63	0.83	0.000
Delirium	1.39	0.94	2.07	0.100
28-day mortality	0.49	0.38	0.62	0.000
90-day mortality	0.59	0.47	0.74	0.000
Delirium	0.90	0.48	1.69	0.744
28-day mortality	0.53	0.43	0.63	0.000
90-day mortality	0.65	0.55	0.77	0.000
Delirium	1.08	0.63	1.84	0.784

Discussion

In this retrospective cohort study, we found that statin therapy more than 7 days was significantly associated with decreased 28- and 90-day mortality compared with patients who did not receive statins or had received statins for less than 7 days.

Statins are widely used in elderly people to reduce cholesterol, and drugs may soon become even more popular[14]. However, statins are not common prescriptions for patients with critically ill conditions, such as sepsis. In an early observational study, the authors found that 33% of sepsis patients were treated with statins before ICU admission[29], while only 26% of sepsis patients received statins after ICU admission [30]. In our study, we reported that only 2158 patients, which accounted for 10.1% of all eligible patients, received statin treatment more than 7 days, which indicates that most sepsis patients in the ICU did not or could not receive statins due to various subjective and objective reasons. For example, sepsis patients with unstable hemodynamics or undergoing abdominal surgery might have to prohibit eating and drinking, and clinicians may neglect or disregard prescribing statins for patients due to their undetermined effects.

In addition to inhibiting cholesterol and isoprenoids, statins have also been proven to have antioxidant effects via inhibition of isoprenoid formation and nicotinamide adenine dinucleotide phosphate oxidase[31] and anti-inflammatory properties with reduction of C-reactive protein and nuclear factor-kappa B[32], which might be beneficial to sepsis prognosis. Other pleiotropic effects include immunomodulation, normalization of sympathetic outflow, plaque stabilization and suppression of the coagulation cascade or platelet aggregation[12]. The powerful effects of statins independent of lowering lipids and lipoproteins have piqued the interest of clinicians. In our study, we found that statin therapy for more than 7 days was greatly associated with reduced 28-day and 90-day mortality, which was consistent with several prospective observational studies[33, 34] and a meta-analysis[19]. In our

subgroup analysis of this study, we also reported that sepsis patients who received statins for more than 7 days had an improved prognosis regardless of age, severity of the disease (SOFA), whether taking cardiovascular-related drugs or receiving mechanical ventilation at the same time. The sensitivity analysis showed a consistent tendency, which indicated that our results were relatively stable and reliable. However, there are also some meta-analysis reports that included randomized clinical trials and concluded that statin therapy did not improve the survival of sepsis patients [35-37]. In addition, researchers demonstrated that there was no difference in changes in interleukin-6 (IL-6) with statin therapy in a randomized trial[38]. Previous studies included fewer subjects or populations without sepsis[19, 33, 34]. Some studies concentrated on the impact of prior statin therapy before ICU admission[39-41], which constrained the clinical guiding role of stains, since we could not predict whether and when one person would be hospitalized in the ICU. Unfortunately, there are no records on some inflammatory mediators, such as C-reactive protein (CRP), procalcitonin (PCT), IL-6 and IL-1 in the MIMIC-IV database, and we could not further analyze the relationship between statins and inflammatory cytokines to explore the potential anti-inflammatory effects of statins on mortality reduction. Specifically, we included patients taking statins for more than 7 days after ICU admission to avoid accidental results. Further large randomized controlled trial and mechanistic experiments are needed to unveil the mystery of statins in the sepsis population.

In this study, we did not find any significant association between statin therapy and delirium. Delirium occurs early in critically ill patients, and there are multiple etiologies of delirium, including sepsis, electrolyte disturbance, kidney injury, exposure to sedation and analgesia[24]. Mechanistically, sepsis-associated delirium (SAD) occurs when a combination of neuroinflammation and disturbances in cerebral perfusion, blood brain barrier (BBB) and neurotransmission exist[42]. Consistent with our research, the MoDUS study, a prospective, randomized, double-blind and placebo-controlled trial, also found no evidence that statins attenuate delirium and coma in critically ill patients[24]. By analyzing serum CRP concentrations, the authors revealed that no difference was found between the statin therapy group and the placebo group. In addition, it is possible that the pleiotropic effects of statins were overwhelmed by other potential confounding factors[43]. The timing, duration, and dosage of statin administration in sepsis patients remain unknown, and require further research.

Our study has several limitations. First, we did not focus on the specific kinds or dosages of statins. Different kinds of statins may have different effects in patients with sepsis. Some previous studies have shown that simvastatin at doses as high as 80 mg daily maintained a high therapeutic range, and the median dose was 40 mg[23]. Second, limited by retrospective study of a database, we had no access to learn about the prior statin therapy of our included subjects. Therefore, the survival advantage of continued statin therapy in prior statin users may cause type I error. The influence of the duration of previous statin use or cessation time is uncertain in sepsis conditions.

Conclusions

Statin therapy is significantly associated with 28- and 90-day mortality, without reducing the incidence of delirium. More high-quality laboratory experiments and multicenter clinical trials are needed to confirm the benefits of statin administration for sepsis treatment.

Abbreviations

Multiparameter Intelligent Monitoring in Intensive Care Database IV	MIMIC-IV
Confusion Assessment Method for the ICU	CAM-ICU
hydroxymethyl glutaryl coenzyme A	HMG-CoA
toll-like receptors	TLRs
tumor necrosis factor-α	TNF-α
interleukin 1β	IL-1β
Simplified Acute Physiology Score II	SAPS II
Sequential Organ Failure Assessment	SOFA
calcium channel blockers	CCBs
angiotensin converting enzyme inhibitors	ACEIs
angiotensin II receptor blockers	ARBs
odd ratios	ORs
confidence intervals	CIs
propensity score matching	PSM
standard mean difference	SMD
mean arterial pressure	MAP
blood urea nitrogen	BUN
acute kidney injury	AKI
hemoglobin	Hb
white blood cells	WBCs
length of stay	LOS
continuous renal replacement therapy	CRRT
alanine transaminase	ALT
aspartate transaminase	AST
interleukin-6	IL-6
C reactive protein	CRP
procalcitonin	PCT
sepsis-associated delirium	SAD
blood brain barrier	BBB

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from

the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

ZZ and JS designed the work, SY and SL record and summarized the patient of MIMIC features, LL, KC, FW, and SY analyzed datasets. ZZ, JS, and LL wrote this paper. XD and ZQ revised the article and explained some of the results. All authors read and approved the final manuscript.

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References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM *et al*: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**. *Jama* 2016, **315**(8):801.

2. Martin GS, Mannino DM, Eaton S, Moss M: **The epidemiology of sepsis in the United States from 1979 through 2000**. *The New England journal of medicine* 2003, **348**(16):1546-1554.

3. Darbà J, Marsà A: **Epidemiology, management and costs of sepsis in Spain (2008-2017): a retrospective multicentre study**. *Current medical research and opinion* 2020, **36**(7):1089-1095.

4. Tian HC, Zhou JF, Weng L, Hu XY, Peng JM, Wang CY, Jiang W, Du XP, Xi XM, An YZ *et al*: **Epidemiology of Sepsis-3 in a sub-district of Beijing: secondary analysis of a population-based database**. *Chinese medical journal* 2019, **132**(17):2039-2045.

5. Almog Y: **Statins, inflammation, and sepsis: hypothesis**. *Chest* 2003, **124**(2):740-743.

6. Huang M, Cai S, Su J: **The Pathogenesis of Sepsis and Potential Therapeutic Targets**. *Int J Mol Sci* 2019, **20**(21).

7. Cecconi M, Evans L, Levy M, Rhodes A: **Sepsis and septic shock**. *Lancet (London, England)* 2018, **392**(10141):75-87.

8. Dhainaut JF, Tenaillon A, Hemmer M, Damas P, Le Tulzo Y, Radermacher P, Schaller MD, Sollet JP, Wolff M, Holzapfel L *et al*: **Confirmatory platelet-activating factor receptor antagonist trial in patients with severe gram-negative bacterial sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. BN 52021 Sepsis Investigator Group**. *Crit Care Med* 1998, **26**(12):1963-1971.

9. O'Brien JM, Jr., Abraham E: **Human models of endotoxemia and recombinant human activated protein C**. *Crit Care Med* 2004, **32**(5 Suppl):S202-208.

10. Xiao SH, Luo L, Liu XH, Zhou YM, Liu HM, Huang ZF: **Curative efficacy and safety of traditional Chinese medicine xuebijing injections combined with ulinastatin for treating sepsis in the Chinese population: A meta-analysis**. *Medicine* 2018, **97**(23):e10971.

11. Kwak B, Mulhaupt F, Myit S, Mach F: **Statins as a newly recognized type of immunomodulator**. *Nature medicine* 2000, **6**(12):1399-1402.

12. Liao JK, Laufs U: **Pleiotropic effects of statins**. *Annual review of pharmacology and toxicology* 2005, **45**:89-118.

13. Jain MK, Ridker PM: **Anti-inflammatory effects of statins: clinical evidence and basic mechanisms**. *Nature reviews Drug discovery* 2005, **4**(12):977-987.

14. Wenner Moyer M: **The search beyond statins**. *Nature medicine* 2010, **16**(2):150-153.

15. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM *et al*: **2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American**

Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* 2014, **63**(25 Pt B):2889-2934.

16. Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG: **Statins and sepsis: multiple modifications at multiple levels**. *The Lancet Infectious Diseases* 2007, **7**(5):358-368.

17. Donnino MW, Cocchi MN, Howell M, Clardy P, Talmor D, Cataldo L, Chase M, Al-Marshad A, Ngo L, Shapiro NI: **Statin therapy is associated with decreased mortality in patients with infection**. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 2009, **16**(3):230-234.

18. Dobesh PP, Klepser DG, McGuire TR, Morgan CW, Olsen KM: **Reduction in mortality associated with statin therapy in patients with severe sepsis**. *Pharmacotherapy* 2009, **29**(6):621-630.

19. Janda S, Young A, Fitzgerald JM, Etminan M, Swiston J: **The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis**. *Journal of critical care* 2010, **25**(4):656.e657-622.

20. Tleyjeh IM, Kashour T, Hakim FA, Zimmerman VA, Erwin PJ, Sutton AJ, Ibrahim T: **Statins for the prevention and treatment of infections: a systematic review and meta-analysis**. *Archives of internal medicine* 2009, **169**(18):1658-1667.

21. Patel JM, Snaith C, Thickett DR, Linhartova L, Melody T, Hawkey P, Barnett AH, Jones A, Hong T, Cooke MW *et al*: **Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial)**. *Crit Care* 2012, **16**(6):R231.

22. Niessner A, Steiner S, Speidl WS, Pleiner J, Seidinger D, Maurer G, Goronzy JJ, Weyand CM, Kopp CW, Huber K *et al*: **Simvastatin suppresses endotoxin-induced upregulation of toll-like receptors 4 and 2 in vivo**. *Atherosclerosis* 2006, **189**(2):408-413.

23. Morandi A, Hughes CG, Thompson JL, Pandharipande PP, Shintani AK, Vasilevskis EE, Han JH, Jackson JC, Laskowitz DT, Bernard GR *et al*: **Statins and delirium during critical illness: a multicenter, prospective cohort study**. *Crit Care Med* 2014, **42**(8):1899-1909.

24. Page VJ, Casarin A, Ely EW, Zhao XB, McDowell C, Murphy L, McAuley DF: **Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial**. *The Lancet Respiratory Medicine* 2017, **5**(9):727-737.

25. **MIMIC-IV v1.0** [https://mimic.physionet. org/]

26. Khwannimit B, Bhurayanontachai R, Vattanavanit V: **Validation of the Sepsis Severity Score Compared with Updated Severity Scores in Predicting Hospital Mortality in Sepsis Patients**. *Shock* 2017, **47**(6):720-725.

27. Liu Z, Meng Z, Li Y, Zhao J, Wu S, Gou S, Wu H: **Prognostic accuracy of the serum lactate level, the SOFA score and the qSOFA score for mortality among adults with Sepsis**. *Scandinavian journal of trauma, resuscitation and emergency medicine* 2019, **27**(1):51.

28. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA: **Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data**. *Medical care* 2005, **43**(11):1130-1139.

29. Wiewel MA, Scicluna BP, van Vught LA, Hoogendijk AJ, Zwinderman AH, Lutter R, Horn J, Cremer OL, Bonten MJ, Schultz MJ *et al*: **The host response in critically ill sepsis patients on statin therapy: a prospective observational study**. *Annals of intensive care* 2018, **8**(1):9.

30. Mansur A, Steinau M, Popov AF, Ghadimi M, Beissbarth T, Bauer M, Hinz J: **Impact of statin therapy on mortality in patients with sepsis-associated acute respiratory distress syndrome (ARDS) depends on ARDS severity: a prospective observational cohort study**. *BMC medicine* 2015, **13**:128.

31. Aznaouridis K, Masoura C, Vlachopoulos C, Tousoulis D: **Statins in Stroke**. *Curr Med Chem* 2019, **26**(33):6174-6185.

32. Li J, Li JJ, He JG, Nan JL, Guo YL, Xiong CM: **Atorvastatin decreases C-reactive protein-induced inflammatory response in pulmonary artery smooth muscle cells by inhibiting nuclear factor-kappaB pathway**. *Cardiovascular therapeutics* 2010, **28**(1):8-14.

33. Hackam DG, Mamdani M, Li P, Redelmeier DA: **Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis**. *Lancet (London, England)* 2006, **367**(9508):413-418.

34. Almog Y, Novack V, Eisinger M, Porath A, Novack L, Gilutz H: **The effect of statin therapy on infection-related mortality in patients with atherosclerotic diseases**. *Crit Care Med* 2007, **35**(2):372-378.

35. Pertzov B, Eliakim-Raz N, Atamna H, Trestioreanu AZ, Yahav D, Leibovici L: **Hydroxymethylglutaryl-CoA reductase inhibitors (statins) for the treatment of sepsis in adults - A systematic review and meta-analysis**. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2019, **25**(3):280-289.

36. Chen M, Ji M, Si X: **The effects of statin therapy on mortality in patients with sepsis: A meta-analysis of randomized trials**. *Medicine* 2018, **97**(31):e11578.

37. Thomas G, Hraiech S, Loundou A, Truwit J, Kruger P, McAuley DF, Papazian L, Roch A: **Statin therapy in critically-ill patients with severe sepsis: a review and meta-analysis of randomized clinical trials**. *Minerva anestesiologica* 2015, **81**(8):921-930.

38. Kruger PS, Harward ML, Jones MA, Joyce CJ, Kostner KM, Roberts MS, Venkatesh B: **Continuation of statin therapy in patients with presumed infection: a randomized controlled trial**. *Am J Respir Crit Care Med* 2011, **183**(6):774-781.

39. Oh TK, Song IA, Choi S: **Prior statin therapy and mortality among critically ill patients: a systemic review and meta-analysis of cohort studies**. *Annals of translational medicine* 2020, **8**(6):396.

40. Almog Y, Shefer A, Novack V, Maimon N, Barski L, Eizinger M, Friger M, Zeller L, Danon A: **Prior statin therapy is associated with a decreased rate of severe sepsis**. *Circulation* 2004, **110**(7):880-885.

41. Kruger P, Fitzsimmons K, Cook D, Jones M, Nimmo G: **Statin therapy is associated with fewer deaths in patients with bacteraemia**. *Intensive Care Med* 2006, **32**(1):75-79.

42. Atterton B, Paulino MC, Povoa P, Martin-Loeches I: **Sepsis Associated Delirium**. *Medicina (Kaunas, Lithuania)* 2020, **56**(5).

43. Ebersoldt M, Sharshar T, Annane D: **Sepsis-associated delirium**. *Intensive Care Med* 2007, **33**(6):941-950.

Figures

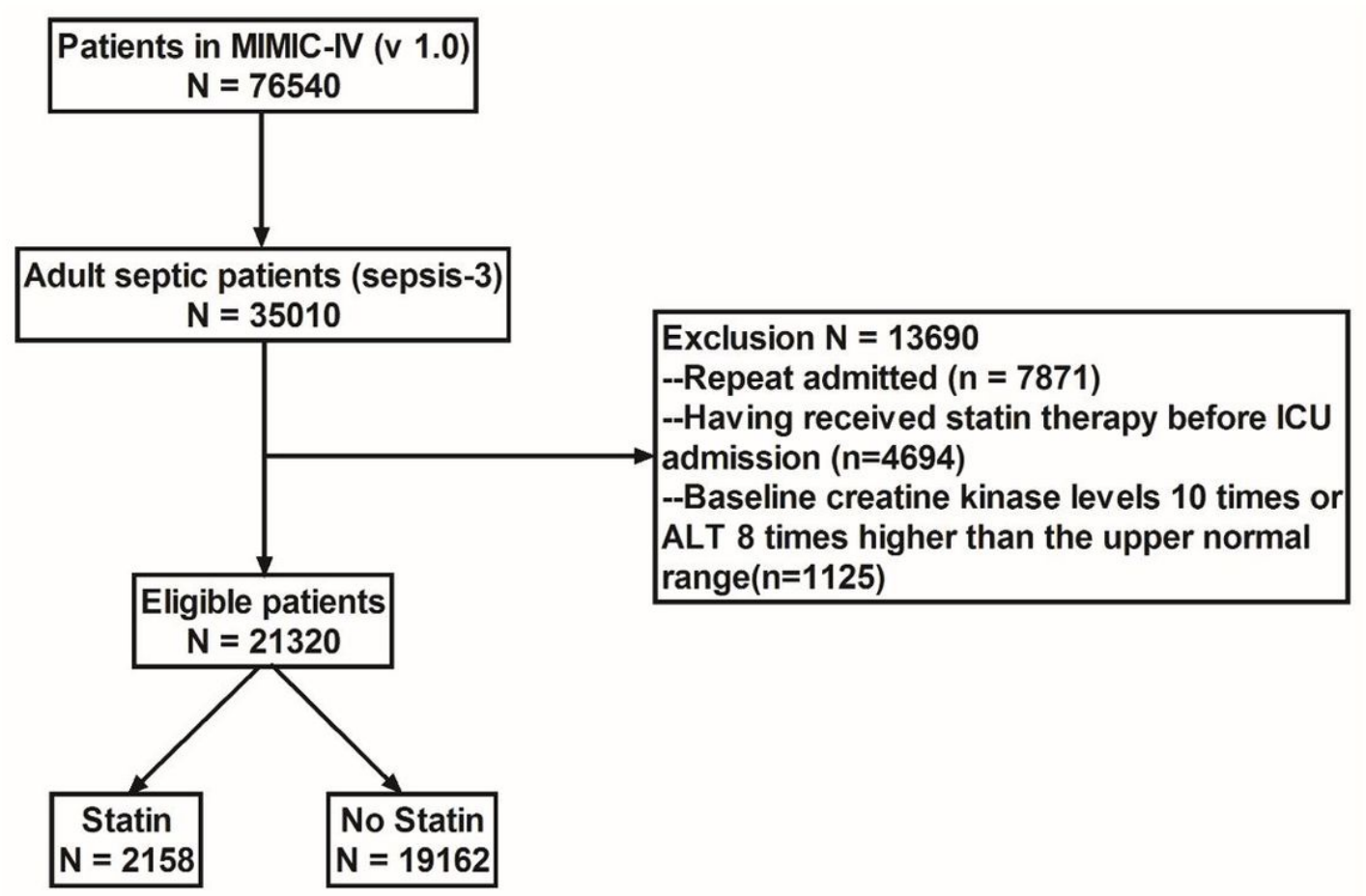

Figure 1

Flow chart describing the procedure for the selection of subjects

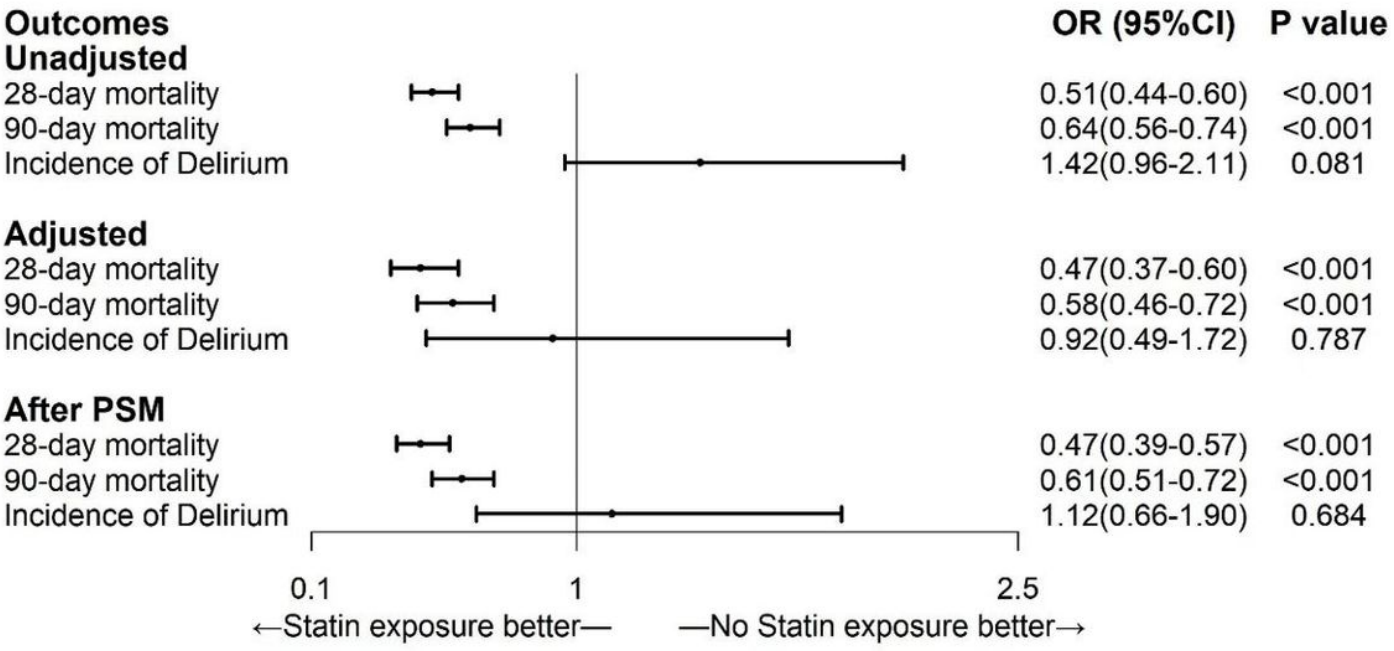

Figure 2

Clinical outcomes adjusted for confounders or after PSM.