Statin Use Is Associated With Reduced Mortality On Mechanically Ventilated Patients: A Retrospective Propensity-Matched Analysis Of MIMIC-III Database

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Research

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Abstract

Objective: Mechanical ventilation can cause injury and inflammatory disorders in the lungs of critically ill patients. We sought to determine whether statin treatment has a protective effect on the outcome of these patients.

Methods: A retrospective observational study of ICU patients from the Medical Information Mart for Intensive Care III (MIMIC-III) database. Information on ventilated patients was analyzed using data from the MIMIC-III database. The non-statin cohort was selected using 1:1 propensity matching with the statin cohort by age, sex, severity scores and 29 other variables. Compared with nonusers, the use of statins was associated with improved 28-day survival in the unmatched cohort (HR 0.85 95% CI 0.80~0.90) and matched cohort (HR 0.72 95% CI 0.67~0.77). Statin use was also associated with improved in-hospital survival in both the unmatched cohort (HR 0.90, 95% CI 0.85~0.95) and the matched cohort (HR 0.75 95% CI 0.70~0.80). In the multivariate Cox model, the use of statins was also associated with an improvement in 28-day survival in the unmatched cohort (HR 0.73 95% CI 0.68□0.77) and in the matched cohort (HR 0.73 95% CI 0.68~0.78). The use of statins was associated with longer ICU length of stay (LOS), shorter ventilator-free days (VFDs) and fewer model for end-stage liver disease score (MELD) in the matched cohort. The subgroup analysis results showed improved 28-day survival, but this improvement was not observed in patients with pneumonia, obesity, septicemia or acute respiratory failure.

Conclusions: In a population of mechanically ventilated patients, the use of statins may be associated with reduced mortality.

Background

Ventilation is a key life-saving treatment measure for critically ill patients, including patients with acute respiratory distress syndrome (ARDS), trauma, shock and other life-threatening conditions. Epidemiological data have shown that there were an estimated 790,257 hospitalizations involving mechanical ventilation in 2005 in the USA, representing 2.7 cases of mechanical ventilation per 1000 people. The estimated national associated cost was $27 billion, representing 12% of hospital costs, which accounts for a large amount of resources in the critical care department [1]. Furthermore, ventilation can cause lung injury and lead to ventilator-associated pneumonia (VAP) and other severe complications, which may increase the mortality of critically ill patients [2]. Lung injury remains one of the major complications of mechanical ventilation in the intensive care unit (ICU). This lung injury could result from an altered host immune response after mechanical stretch. A shift toward a proinflammatory state occurs within lungs subjected to ventilation, especially if ventilation is applied to infected lungs [3]. It is greatly important to identify a medication that can modulate the altered inflammatory state after mechanical ventilation is performed on critically ill patients. Statins might have a latent capacity for lung protection.

Statins, also known as 3-hydroxy-3 methylblycel coenzyme A (HMG-CoA) reductase inhibitors, exert pleiotropic effects in addition to their lipid-lowering effects in the context of coronary artery disease [4] and ischemic stroke [5] prophylaxes. Studies in vitro and in vivo have shown that statins can provide additional protective effects, including the reduction in inflammation, immunomodulation, antimicrobial effects, improved endothelial cell function and antithrombotic actions [6–10]. In pneumonia patients, current statin use was associated with decreased mortality [11]. Statin use or prior use may have decreased the mortality of septic patients in some observational studies [12–14]. Preliminary data from animal models have shown the protective effect on lung injury induced by sepsis [15]. Two other animal models of lung injury induced by mechanical ventilation also support these approaches [16, 17].

This evidence greatly increased interest in utilizing statins as a treatment and for the prevention of mechanically induced lung injury. Whether the use of statins may decrease lung injury caused by ventilation in humans is not clear. Therefore, we designed this observational study to research the potential protective effect of statin use among ventilated patients.

Methods

Study design and data source

This is a retrospective observational study. We analyzed data from a large database: Medical Information Mart for Intensive Care (MIMIC-III). The MIMIC-III database is an openly available dataset developed by the MIT Laboratory for Computational Physiology, comprising deidentified health data associated with nearly 54,000 intensive care unit admissions [18]. The data in the MIMIC-III database are composed of comprehensive clinical datasets from patients admitted to the ICUs of Beth Israel Deaconess Medical Center in Boston, MA, from June 1, 2001 to October 31, 2012. The requirement for institutional review board (IRB) approval from our institution was exempted because MIMIC-III is a third-party anonymized publicly available database with pre-existing IRB approval.

Participants

Patients who underwent mechanical ventilation were selected from the MIMIC-III database. The ventilation data were extracted from the chartvcents table. Statin usage information was extracted from the prescription table. We selected those who had taken statins before or during ventilation as the statin cohort and those who underwent ventilation without statins as the control cohort. Those who took statin medicine after extubation were excluded from this study. We included only adults in this study, so those under 18 years old were excluded. A total of 3999 patients were selected for the statin cohort. Then, we performed propensity matching by age, sex, Simplified Acute Physiology Score II (SAPSII), and 29 other variables. Each statin-exposed patient was matched with the closest corresponding nonexposed patient (that is, a patient who was not exposed to statins) at a 1:1 fixed ratio (nearest match cohort). Finally, 3717 patients were matched and included in each cohort. Detailed Postgresql and R codecs about the ventilation and statin use data are provided in the supplemental materials.

Medication exposure

Patients who had taken statins before or during ventilation were selected as the statin cohort, and those who underwent ventilation without statins were selected as the control cohort. Patients taking statin medicine after extubation were excluded from this study. Atorvastatin, pravastatin, rosuvastatin and simvastatin were the 4 most common statin types. A total of 187 patients received atorvastatin plus simvastatin.

Statistical methods

The primary outcome was 28-day and in-hospital all-cause mortality. The primary statistical method of comparison for the time-to-event end points was the log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio (HR) of 28-day mortality and its associated 95% confidence interval (CI). We included several variables in the model to adjust the 28-day survival (age, SAPSII score, sex, liver disease, diabetes, obesity, hypertension, etc.). The APACHE III score was not recorded for every patient, so we could not extract all APACHE III scores. The SAPSII was chosen to represent the severity of illness. The secondary outcome analyses also included ICU LOS, hospital LOS, VFDs at 28 days and model for MELD score. Eight plasma biomarkers were extracted and studied to measure the host responses during the first 10 days after intubation. R.3.6.0 and Rstudio1.2.1335 were used to perform the statistical analyses. Some studies have reported different potencies between statins; for example, simvastatin exerted better antibacterial effects than rosuvastatin, and the latter was found to have a more potent lipid-lowering capacity [19, 20]. Therefore, we analyzed the difference in 28-day survival among statin types in the Cox regression model. To test the efficiency of statins on patients with different profiles, we performed a subgroup analysis. Patient categorical data are presented as percentages, and continuous data are listed as means with standard deviations (SDs). We used Student's t tests for continuous variables and chi-square or Fisher's exact tests for dichotomous variables.

Results

Baseline results

All 53432 cases in the MIMIC-III database were screened. A total of 24,769 individuals who had undergone ventilation met the inclusion criteria. A total of 17065 patients who had not received statin treatment were included in the nonstatin cohort. There were 3999 patients who received statin treatment before or during the ventilation time. After matching, there were 3717 patients in each cohort. They were similarities in age, sex, SAPSII and 29 more variables. The characteristics of the patients are presented in Table 1. There were 2145 cases of atorvastatin, 200 pravastatin, 171 rosuvastatin, 1284 simvastatin and 149 cases received both atorvastatin and simvastatin in the unmatched cohort. In the matched cohort, there were 1998 cases of atorvastatin, 181 pravastatin, 158 rosuvastatin, 1198 simvastatin and 135 cases received both atorvastatin plus simvastatin.

Table 1

Baseline characteristics of the unmatched and the propensity score matched cohort

	Unmatched cohort			Matched cohort		
Variables	No Statin N = 17452	Statin N = 3999	p-value	No Statin N = 3717	Statin N = 3717	p-value
Demographics						
Age* (mean (SD))	62.06 (17.63)	69.96 (11.92)	< 0.001	70.48 (13.42)	69.68 (12.02)	0.007
OASIS(mean (SD))	36.61 (8.39)	35.59 (8.22)	< 0.001	36.57 (8.45)	35.69 (8.23)	< 0.001
SOFA(mean (SD))	5.31 (3.57)	5.35 (3.02)	0.554	5.44 (3.15)	5.29 (3.02)	0.047
SAPSII* (mean (SD))	39.73 (15.68)	41.04 (13.39)	< 0.001	41.25 (14.42)	40.93 (13.47)	0.333
Gender* = Male (%)	9967 (57.1)	2485 (62.1)	< 0.001	2201 (59.2)	2284 (61.4)	0.052
Statin name (%)						
Atorvastatin		2145 (53.6)			1998 (53.8)	
Atorvastatin + Simvastatin		149 (3.7)			135 (3.6)	
Pravastatin		200 (5.0)			181 (4.9)	
Rosuvastatin		171 (4.3)			158 (4.3)	
Simvastatin		1284 (32.1)			1198 (32.2)	
Commobidities						
Congestive heart failure * (%)	4573 (26.2)	1718 (43.0)	< 0.001	1633 (43.9)	1545 (41.6)	0.041
Cardiac arrhythmias * (%)	5011 (28.7)	1849 (46.2)	< 0.001	1709 (46.0)	1672 (45.0)	0.402

Continuous variables are presented as mean (standard deviation), categorical as frequency (percentage). T-test was used to compare statin recipients vs non-statin for continuous variables, Fisher´s exact test for categorical variables. Standardized differences (SD) are defined as the difference in means, proportions or ranks divided by the mutual standard deviation.

(*)variables were used for the calculation of propensity scores.

Abbreviations:LOS: length of stay; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SAPSII: Simplified Acute Physiology Score II.

	Unmatched cohort			Matched cohort		
Valvular disease * (%)	2561 (14.7)	1251 (31.3)	< 0.001	1128 (30.3)	1092 (29.4)	0.375
Pulmonary circulation * (%)	1253 (7.2)	395 (9.9)	< 0.001	355 (9.6)	346 (9.3)	0.751
Peripheral vascular * (%)	1659 (9.5)	775 (19.4)	< 0.001	665 (17.9)	659 (17.7)	0.88
Other neurological * (%)	2551 (14.6)	482 (12.1)	< 0.001	435 (11.7)	463 (12.5)	0.337
Chronic pulmonary * (%)	3629 (20.8)	962 (24.1)	< 0.001	923 (24.8)	882 (23.7)	0.279
Diabetes uncomplicated * (%)	3184 (18.2)	1195 (29.9)	< 0.001	1063 (28.6)	1054 (28.4)	0.837
Diabetes complicated * (%)	922 (5.3)	415 (10.4)	< 0.001	378 (10.2)	364 (9.8)	0.615
Hypertension * (%)	8219 (47.1)	2949 (73.7)	< 0.001	2657 (71.5)	2675 (72.0)	0.662
Paralysis * (%)	735 (4.2)	193 (4.8)	0.093	180 (4.8)	181 (4.9)	1
Hypothyroidism * (%)	1538 (8.8)	469 (11.7)	< 0.001	449 (12.1)	426 (11.5)	0.428
Renal failure * (%)	2112 (12.1)	800 (20.0)	< 0.001	699 (18.8)	696 (18.7)	0.953
Liver disease * (%)	1843 (10.6)	108 (2.7)	< 0.001	87 (2.3)	108 (2.9)	0.147
Peptic ulcer * (%)	16 (0.1)	1 (0.0)	0.298	0 (0.0)	1 (0.0)	1
Lymphoma * (%)	339 (1.9)	39 (1.0)	< 0.001	36 (1.0)	38 (1.0)	0.907
Metastatic cancer * (%)	1092 (6.3)	78 (2.0)	< 0.001	72 (1.9)	78 (2.1)	0.68
Solid tumor * (%)	990 (5.7)	111 (2.8)	< 0.001	107 (2.9)	106 (2.9)	1

Continuous variables are presented as mean (standard deviation), categorical as frequency (percentage). T-test was used to compare statin recipients vs non-statin for continuous variables, Fisher´s exact test for categorical variables. Standardized differences (SD) are defined as the difference in means, proportions or ranks divided by the mutual standard deviation.

(*)variables were used for the calculation of propensity scores.

Abbreviations:LOS: length of stay; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SAPSII: Simplified Acute Physiology Score II.

	Unmatched cohort			Matched cohort		
Rheumatoid arthritis * (%)	459 (2.6)	103 (2.6)	0.889	123 (3.3)	101 (2.7)	0.154
Coagulopathy * (%)	2499 (14.3)	520 (13.0)	0.033	447 (12.0)	458 (12.3)	0.723
Obesity * (%)	1033 (5.9)	448 (11.2)	< 0.001	363 (9.8)	374 (10.1)	0.698
Weight loss * (%)	957 (5.5)	122 (3.1)	< 0.001	120 (3.2)	119 (3.2)	1
Fluid electrolyte * (%)	5840 (33.5)	1230 (30.8)	0.001	1116 (30.0)	1140 (30.7)	0.562
Blood loss anemia * (%)	353 (2.0)	60 (1.5)	0.035	66 (1.8)	56 (1.5)	0.411
Deficiency anemias * (%)	2907 (16.7)	968 (24.2)	< 0.001	820 (22.1)	834 (22.4)	0.717
Alcohol abuse * (%)	1732 (9.9)	135 (3.4)	< 0.001	109 (2.9)	133 (3.6)	0.133
Drug abuse * (%)	803 (4.6)	50 (1.3)	< 0.001	40 (1.1)	50 (1.3)	0.34
Psychoses * (%)	756 (4.3)	126 (3.2)	0.001	107 (2.9)	119 (3.2)	0.457
Depression * (%)	1354 (7.8)	315 (7.9)	0.826	272 (7.3)	291 (7.8)	0.43
Top diagnoses* (%)			< 0.001			0.992
Bone Fracture	1173 (6.7)	78 (2.0)		76 (2.0)	78 (2.1)	
Cerebral infarction	206 (1.2)	129 (3.2)		121 (3.3)	121 (3.3)	
Coronary Artery Disorder	944 (5.4)	865 (21.6)		712 (19.2)	744 (20.0)	
Heart Failure	423 (2.4)	171 (4.3)		192 (5.2)	167 (4.5)	
Hemorrhage	881 (5.0)	93 (2.3)		94 (2.5)	93 (2.5)	
Infection	487 (2.8)	74 (1.9)		69 (1.9)	74 (2.0)	

Continuous variables are presented as mean (standard deviation), categorical as frequency (percentage). T-test was used to compare statin recipients vs non-statin for continuous variables, Fisher´s exact test for categorical variables. Standardized differences (SD) are defined as the difference in means, proportions or ranks divided by the mutual standard deviation.

(*)variables were used for the calculation of propensity scores.

Abbreviations:LOS: length of stay; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SAPSII: Simplified Acute Physiology Score II.

	Unmatched cohort		Matched cohort	
Intracranial Hemorrhage	791 (4.5)	79 (2.0)	85 (2.3)	79 (2.1)
Kidney Failure	109 (0.6)	22 (0.6)	24 (0.6)	22 (0.6)
Liver Disease	606 (3.5)	6 (0.2)	4 (0.1)	6 (0.2)
Misc	6920 (39.7)	761 (19.0)	790 (21.3)	761 (20.5)
Myocardial Infarction	635 (3.6)	551 (13.8)	448 (12.1)	464 (12.5)
Nalignant Neoplasm	94 (0.5)	9 (0.2)	5 (0.1)	9 (0.2)
Pancreatitis	166 (1.0)	10 (0.3)	8 (0.2)	10 (0.3)
Pneumonia	691 (4.0)	97 (2.4)	95 (2.6)	97 (2.6)
Respiratory Failure	991 (5.7)	238 (6.0)	243 (6.5)	237 (6.4)
Sepsis	1409 (8.1)	249 (6.2)	261 (7.0)	249 (6.7)
Tachycardia	48 (0.3)	23 (0.6)	22 (0.6)	22 (0.6)
Vavular Disease	878 (5.0)	544 (13.6)	468 (12.6)	484 (13.0)
Continuous variables are presented as mean (standard deviation), categorical as frequency (percentage). T-test was used to compare statin recipients vs non-statin for continuous variables, Fisher´s exact test for categorical variables. Standardized differences (SD) are defined as the difference in means, proportions or ranks divided by the mutual standard deviation.				
(*)variables were used for the calculation of propensity scores.				
Abbreviations:LOS: length of stay; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SAPSII: Simplified Acute Physiology Score II.				

The primary outcome

The Kaplan-Meier analysis showed that statin users had a better 28-day and in hospital survival curve than the non-users in unmatched and matched cohorts. The Cox model showed that the use of statins before or during ventilation was associated with an improved 28-day survival in both the overall cohort (HR 0.85 95% CI 0.80 ~ 0.90 Fig. 2A) and the matched cohort (HR 0.72 95% CI 0.67 ~ 0.77 Fig. 2B). Statin use was also associated with improved in-hospital survival in the overall cohort (HR 0.90, 95% CI 0.85 ~ 0.95 Fig. 2C) and the matched cohort (HR 0.72 95% CI 0.67 ~ 0.77 Fig. 2D). In the multivariate Cox model, the use of statins was associated with a beneficial effect on 28-day survival in the unmatched cohort (HR 0.73 95% CI 0.68 ~ 0.77 Table 2) and the matched cohort (HR 0.73 95% CI 0.68 ~ 0.78 Table 2).

Table 2

Cox regression model of 28 days mortality in the unmatched and matched cohorts

	Unmatched cohort		Matched cohort	
Variables	HR [95% CI]	p-value	HR [95% CI]	p-value
Statin Use	0.73 [0.68, 0.77]	< 0.001	0.73 [0.68, 0.79]	< 0.001
Age	1.03 [1.02, 1.03]	< 0.001	1.03 [1.02, 1.03]	< 0.001
Gender = Male	1.00 [0.96, 1.04]	0.978	1.00 [0.93, 1.08]	0.923
SAPSII	1.01 [1.01, 1.01]	< 0.001	1.01 [1.01, 1.01]	< 0.001
Liver disease	1.02 [0.95, 1.10]	0.567	1.11 [0.90, 1.38]	0.322
Renal failure	0.99 [0.93, 1.05]	0.75	1.02 [0.93, 1.12]	0.639
Diabetes uncomplicated	1.10 [1.04, 1.15]	0.001	1.15 [1.06, 1.24]	0.001
Diabetes complicated	1.08 [0.99, 1.17]	0.077	1.10 [0.98, 1.25]	0.106
Coronary	0.99 [0.92, 1.06]	0.79	1.01 [0.93, 1.10]	0.818
Obesity	0.75 [0.68, 0.83]	< 0.001	0.77 [0.67, 0.89]	< 0.001
Cerebral Infarction	1.68 [1.47, 1.93]	< 0.001	1.50 [1.26, 1.78]	< 0.001
Hypertension	0.98 [0.93, 1.02]	0.294	0.94 [0.87, 1.02]	0.136
Congestive heart failure	0.97 [0.93, 1.02]	0.217	1.04 [0.96, 1.12]	0.343
Cardiac arrhythmias	0.83 [0.80, 0.87]	< 0.001	0.85 [0.79, 0.92]	< 0.001
Other neurological	1.07 [1.01, 1.13]	0.02	1.05 [0.94, 1.16]	0.378
Chronic pulmonary	1.24 [1.18, 1.30]	< 0.001	1.29 [1.19, 1.40]	< 0.001
Alcohol abuse	0.89 [0.81, 0.97]	0.012	0.97 [0.78, 1.21]	0.811

An HR value less than 1 indicates that the presence of a variable or increase in a continuous variable is associated with lower probability of mortality. After adjusted to potential confounders, statin use was still associated to decreased HR of 0.73 (95%CI 0.68 ~ 0.78, p < 0.01)

Secondary outcomes and plasma biomarkers

The secondary outcomes included ICU LOS, hospital LOS, VFDs and MELD score. After matching, statin use was associated with longer ICU LOS (6.83 ± 8.40 vs 6.04 ± 7.57), shorter hospital LOS (12.37 ± 10.96 vs. 12.46 ± 11.91), fewer VFDs (24.34 ± 5.94 vs 24.84 ± 5.53) and lower MELD score (14.25 ± 6.91 vs. 15.34 ± 7.79). We compared users of different types of statins to nonusers by Cox regression model. In the Cox model, all statins improved the survival of ventilated patients. Atorvastatin + simvastatin seemed to be associated with the best outcome (HR 0.42 95% CI 0.30 ~ 0.60), followed by rosuvastatin (HR 0.52 95% CI 0.36 ~ 0.73), pravastatin (HR 0.65 95% CI 0.50 ~ 0.84) and simvastatin (HR 0.66 95% CI 0.59 ~

0.74). The least-effective statin was atorvastatin, which was associated with a decreased 28-day mortality (HR 0.81 95% CI 0.74 ~ 0.88). After adjusting for confounders, all the statins still resulted in significant improvement in survival compared to nonuse based on this survival function.

Regarding the biomarkers, we found no large differences in the matched cohort. Additionally, we found that statin use was not associated with higher aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels after matching (Fig. 3).

Subgroup analysis

In the subgroup analysis, we found that statins had a protective effect in most of the subgroups but not in individuals with liver disease or obesity. More importantly, statin use showed no effect in inflammation-related groups, such as the septicemia, respiratory failure and pneumonia subgroups (Fig. 4). In the current study, patients with coronary disease accounted for a large proportion of the sample. However, in the noncoronary artery disease subgroup, we also found that statin use was associated with reduced mortality.

Discussion

Lung injury remains one of the major complications of mechanical ventilation in the ICU. This injury could result from an altered host immune response after mechanical stretch [3]. Using statin therapy to protect patients with lung injury could therefore be a reasonable strategy, as these drugs could abate the host inflammatory response to infection [21], especially within the lungs [6]. This study revealed that statin use was associated with improved 28-day survival and in-hospital survival. All kinds of statins showed reduced HRs. This evidence might indicate the protective effect of statins in ventilation patients. In the subgroup analyses, we found that statins had a protective effect in most of the subgroups but not in the septicemia, acute respiratory failure or pneumonia subgroups. All these results might explain the protective effect of statins.

In addition to lowering cholesterol, statins exert pleiotropic effects [6–9] such as anti-inflammatory, antioxidant, and immunomodulatory effects, especially in the context of pulmonary disorders [22]. Statins may reduce COPD exacerbation [23]. Statins have also been suggested to be effective in patients with acute lung injury or acute respiratory distress syndrome in some observational studies [24, 25]. These clinical effects may be mediated by a reduction in pulmonary and systemic inflammation. Simvastatin decreased bronchoalveolar lavage IL-8 by 2.5-fold (P = 0.04) [26]. Statins also showed a protective effect against sepsis. When compared with nonusers, simvastatin (HR, 0.72; 95% CI, 0.58–0.90) and atorvastatin (HR, 0.78; 95% CI, 0.68–0.90) users had improved 30-day survival [13]. The current study examined the anti-inflammatory effect of statins from a ventilation patient cohort, which has not been previously reported. A recent study showed that infections in older adults were associated with prolonged, impaired neutrophil migration. Simvastatin improves neutrophil migration in vivo in healthy

individuals and in vitro in milder infective events but not in severe sepsis, supporting its potential utility as an early intervention during pulmonary infections [27, 28].

Animal models may have further explained the protective effect of statins against lung injury. Statins increase glucocorticoid receptor expression in alveolar macrophages and downregulate NF-κB activation associated with the increased number of alveolar macrophages [15]. Two other animal models of lung injury induced by mechanical ventilation also support these findings [16, 17]. The protective effect may be due to the anti-inflammatory effect of statins. Prior statin use was associated with a lower baseline IL-6 concentration, and continuation of atorvastatin treatment in this cohort was associated with improved survival [29]. Statins have been shown to reduce vascular leakage and inflammation in animal models of lung injury [30]. Statins may also attenuate lung injury by downregulating the expression of inflammatory cytokines [31, 32]. Our previous study revealed the lung-protective effect of statins caused by the reduction of inflammatory cell infiltration [33]. Additionally, statins may have direct antibacterial effects and modulate bacterial virulence [34–36]. Sarah et al. showed that prior exposure to physiological nanomolar serum concentrations of simvastatin confers significant cellular resistance to the cytotoxicity of pneumolysin, which revealed how statins contribute to the reduced pathology observed in the context of pneumonia and other bacterial infections [37].

The subgroup analyses showed that statins had no efficacy in the context of pneumonia, septicemia or acute respiratory failure. However, this difference might be explained by the fact that statins may exert an inflammatory protective effect only for mild-to-moderate pulmonary infectious disease. From this point of view, the subgroup analyses explained why evidence of the efficacy of statins against sepsis and ARDS is controversial. In a randomized controlled trial (RCT) with a follow-up of over one year, there was no significant difference in cumulative survival between the rosuvastatin and placebo groups (58% vs 61%; p = 0.377) [38]. Simvastatin therapy was not significantly associated with the difference between the study groups in mortality at 28 days (22.0% and 26.8%; P = 0.23) among patients with ARDS [39]. However, the effect of statins on ventilation-induced lung injury was minimal. Recently, a group of “hyperinflammatory” ARDS patients showed a benefit from statin treatment [40]. Sapey stated that statins may improve neutrophil migration and may have protective effects in milder infective events but not in severe sepsis or ARDS [27]. The underlying reason for this controversial evidence might be that statins may have immune modulatory effects in only milder diseases instead of in intensive inflammatory diseases such as ARDS. However, we might need new RCTs exploring the effects on mild infectious diseases such as ventilation-induced lung injury to prove this hypothesis.

Several limitations must be disclosed in the current study. The main limitation of this study was that the observational nature without randomization precludes a definite conclusion regarding statin benefits. However, a randomized controlled trial on the effect of long-term statin treatment on the outcome of patients on ventilation would require many participants. To explore the effect of statins on patients on ventilation, observational data may currently remain the best available evidence. Second, because of the retrospective design of this study, patient selection bias may be inevitable. Third, the missing data of potential confounders was a limitation that could not be overcome. Our findings should thus be

interpreted with caution. Additionally, only white blood cell (WBC) measurements were analyzed for inflammation assessment. Regarding the host response, the assessment of inflammatory cytokines might provide different insights. The relationships of the dose and treatment duration of statins with survival were not analyzed here because we included different types of statins, and the doses of the different statins were not comparable. Finally, we included ventilation patients with different diagnoses. Even with subgroup analyses, we cannot conclude that statins are specifically effective in a specific population.

Conclusion

Our study suggests that the use of statins may be associated with reduced mortality in ventilated patients. The favorable effects of statins correlate with their anti-inflammatory effects. Further studies in different populations or RCTs are needed to validate our findings.

Abbreviations

MIMIC-III:Medical Information Mart for Intensive Care III ; LOS:length of stay; length of stay; VFDs:ventilator-free days; MELD:model for end-stage liver disease score; ARDS:acute respiratory distress syndrome; VAP:ventilator-associated pneumonia; ICU:intensive care unit ; IRB:institutional review board; SAPSII:Simplified Acute Physiology Score II; CI:confidence interval (CI); SDs:standard deviations ; HR:Hazard Ratio; AST:aminotransferase; ALT:alanine aminotransferase; RCT:randomized controlled trial; WBC:white blood cell.

Declarations

Ethics approval and consent to participate:

The requirement for institutional review board (IRB) approval from our institution was exempted because MIMIC-III is a third-party anonymized publicly available database with pre-existing IRB approval.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed 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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Authors' contributions

LQ write the manuscript and collect the data from database. CD collect the data from MIMIC database, washed the data and did the statistical analysis. MC contributed to data collecting and data analysis of this work. XY contributed to the data collecting and analysis of this work. HY contributed to the data collecting work. WL contributed to the data collecting work. GF contributed to the data collecting work. XJ contributed to the data collecting and literature research of this work. KM contributed to the statistic work of this study. TR contributed to the study design and paper revising. ZY contributed to the data collecting of this work. ZH contributed to the data collecting of this work. WR designed this research, revised the manuscript and analyzed the data. Du, Jiang designed this research, write the manuscript, analyzed the data and drew all the figures in this study. All authors read and approved the final manuscript.

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Figures

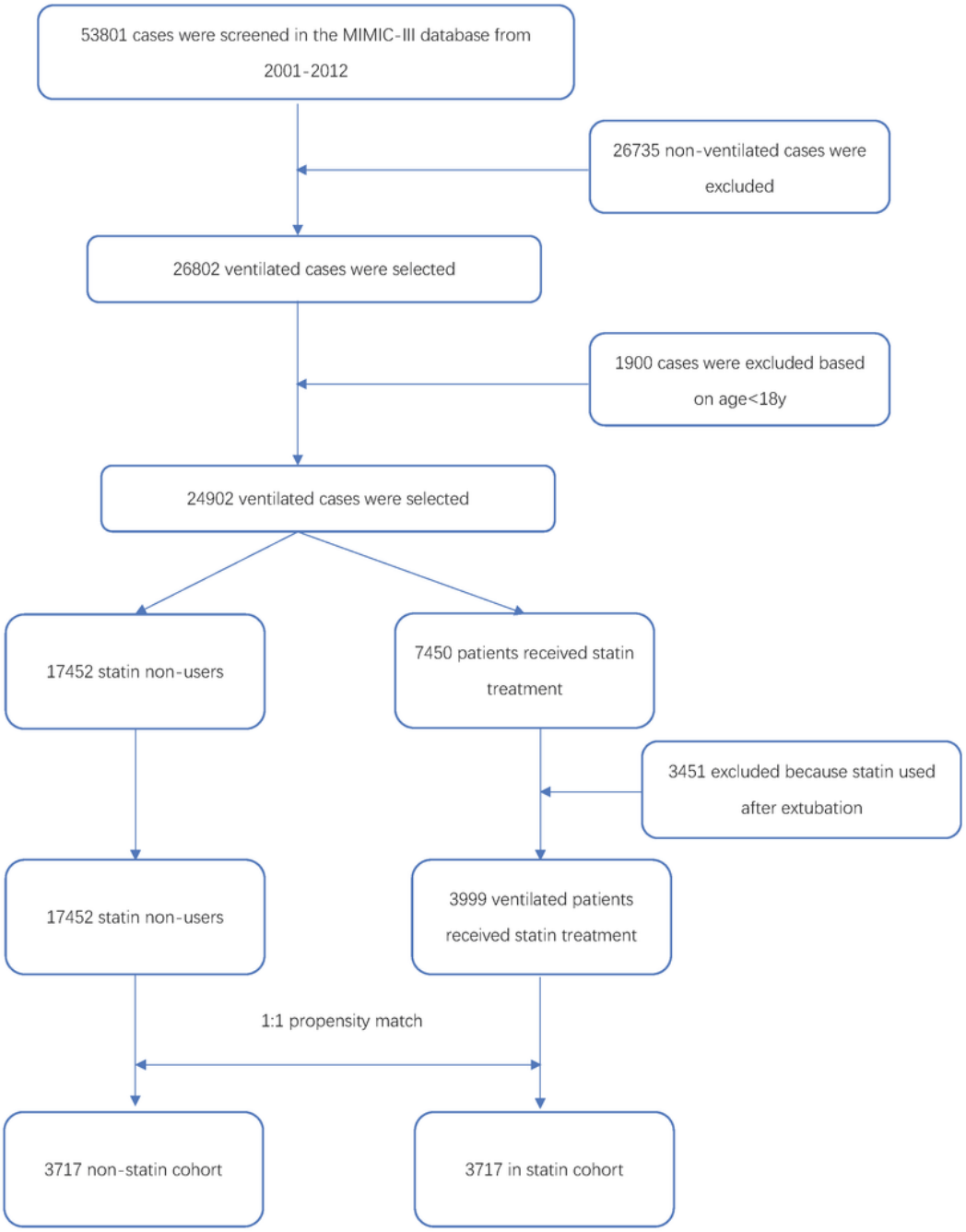

Figure 1

Flowchart of cohort building.

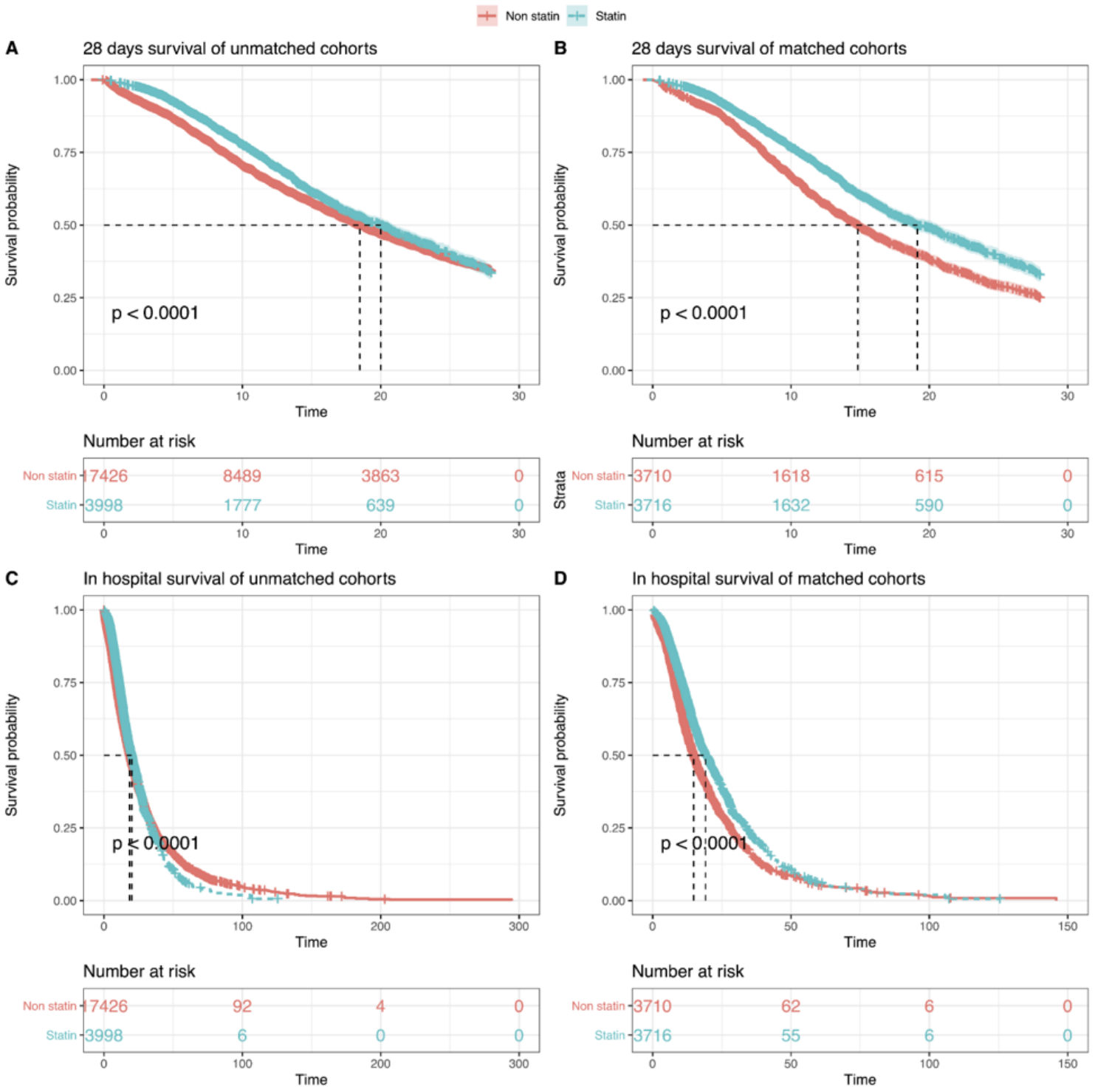

Figure 2

Kaplan-Meier curves for all-cause mortality in statin recipients vs. nonrecipients in the unmatched cohorts and propensity score-matched cohorts. A: Statin use was associated with improved 28-day survival in the unmatched cohort (HR 0.85 95% CI 0.80~0.90); B: Statin use was associated with improved 28-day survival in the matched cohort (HR 0.72 95% CI 0.67~0.77); C: Statin use was associated with improved in-hospital survival in the unmatched cohort (HR 0.90, 95% CI 0.85~0.95); D: Statin use was associated with improved in-hospital survival in the matched cohort (HR 0.75 95% CI 0.70~0.80).

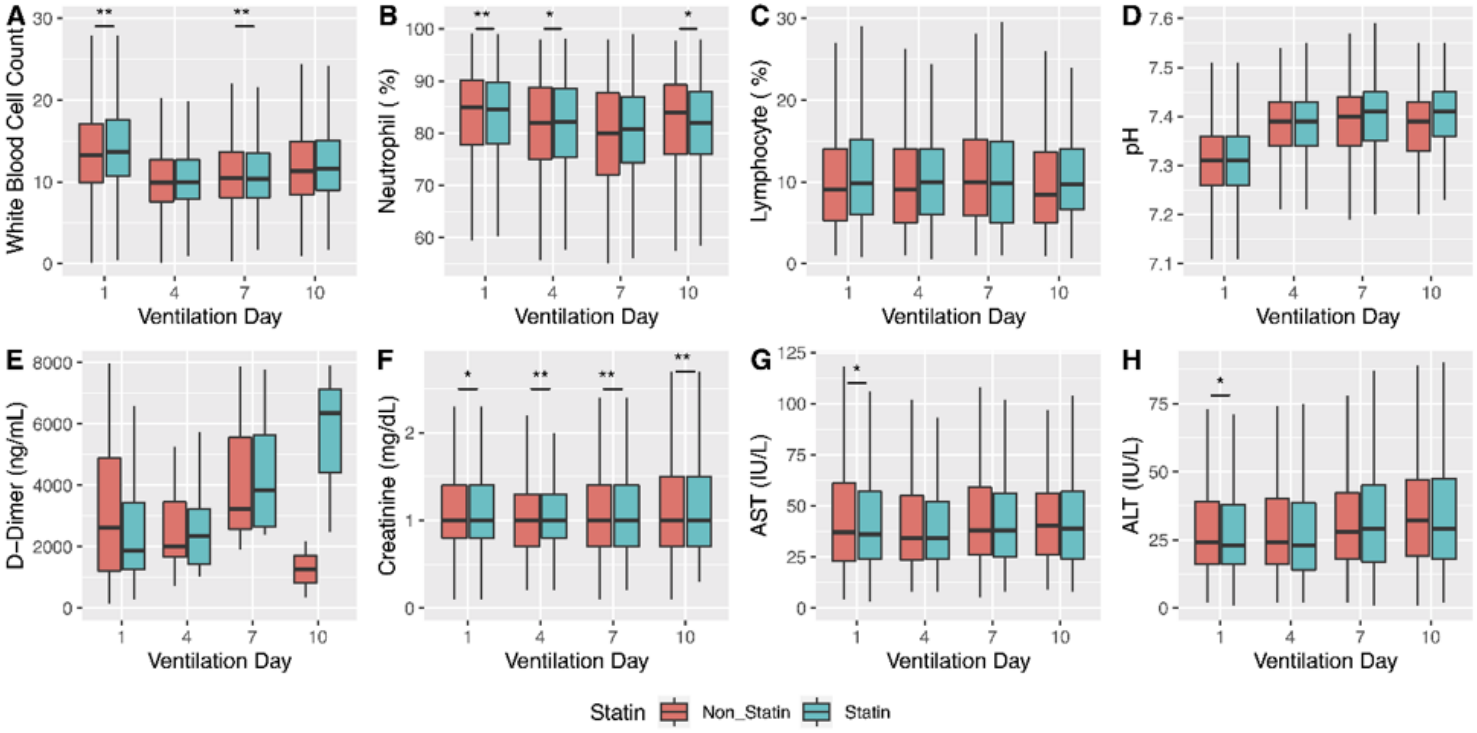

Figure 3

The plasma biomarkers during the first ten ventilation days. Day 1 was the first day of ventilation; *: p<0.05; **: p<0.01.

Subgroups	Sample Size	HR	95% CI lower	95% CI upper	p–value
Age>65 YES	4961	0.76	0.71	0.82	<0.01
NO	2469	0.83	0.72	0.96	0.01
Pneumonia YES	209	0.99	0.71	1.38	0.97
NO	7221	0.76	0.71	0.81	<0.01
Sepsis YES	517	1.05	0.85	1.3	0.63
NO	6913	0.74	0.69	0.8	<0.01
Resfailure YES	478	1.21	0.97	1.51	0.09
NO	6952	0.73	0.68	0.79	<0.01
Coronary disease YES	2357	0.55	0.47	0.64	<0.01
NO	5073	0.84	0.78	0.91	<0.01
Ischemic stroke YES	238	0.59	0.43	0.81	<0.01
NO	7192	0.78	0.72	0.83	<0.01
Congestive heart failure YES	3153	0.82	0.75	0.9	<0.01
NO	4277	0.7	0.64	0.78	<0.01
Valvular disease YES	2198	0.64	0.56	0.73	<0.01
NO	5232	0.81	0.75	0.88	<0.01
Chronic pulmonary YES	1812	0.82	0.73	0.93	<0.01
NO	5618	0.75	0.69	0.81	<0.01
Diabetes uncomplicated YES	2152	0.74	0.65	0.84	<0.01
NO	5278	0.78	0.72	0.85	<0.01
Diabetes complicated YES	721	0.77	0.64	0.94	<0.01
NO	6709	0.77	0.71	0.82	<0.01
Hypertension YES	5360	0.72	0.67	0.78	<0.01
NO	2070	0.87	0.77	0.98	0.02
Renal failure YES	1400	0.87	0.76	1	0.04
NO	6030	0.74	0.68	0.8	<0.01
Liver disease YES	209	0.66	0.46	0.94	0.02
NO	7221	0.77	0.72	0.83	<0.01
Obesity YES	730	0.79	0.61	1.02	0.07
NO	6700	0.77	0.71	0.82	<0.01
Total	**7430**	**0.77**	**0.72**	**0.82**	**<0.01**

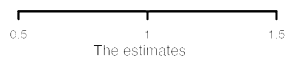

Figure 4

The forest plot of statins in the 28-day survival subgroup analyses.