

# Is rosuvastatin protective against sepsis associated encephalopathy? A secondary analysis of the SAILS trial

**Shiyuan Yu**

Peking Union Medical College Hospital

**Zengzheng Ge**

Peking Union Medical College Hospital

**Yanxia Gao**

Zhengzhou University First Affiliated Hospital

**Joseph Harold Walline**

Hong Kong University: University of Hong Kong

**Huadong Zhu**

Peking Union Medical College Hospital

**Yi Li (✉ [billiyi@126.com](mailto:billiyi@126.com))**

Emergency Department, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences

<https://orcid.org/0000-0002-7158-3624>

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## Research

**Keywords:** Rosuvastatin Calcium, Sepsis-Associated Encephalopathy, Anti-Inflammatory Agents, Sepsis, Drug-Related Side Effects and Adverse Reactions

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# Abstract

## Background

Sepsis is a common cause of death in emergency departments and sepsis associated encephalopathy is a major complication of sepsis. Rosuvastatin may have a cerebral protective role based on its vascular endothelial protective and anti-inflammatory functions. Our study aims to explore the potential for a protective function of rosuvastatin against sepsis associated encephalopathy.

## Methods

Sepsis patients without any neurological dysfunction on admission were prospectively enrolled in the 'Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome' study (SAILS trial, ClinicalTrials.gov number, NCT00979121). Patients were divided into rosuvastatin and placebo groups. This is a secondary analysis of this dataset. Baseline characteristics, therapy outcomes and adverse drug events were reported between groups.

## Outcomes:

86 patients were eligible for our study. 51 of them were treated with rosuvastatin. There were significantly fewer cases of sepsis associated encephalopathy in the rosuvastatin group than in the placebo group (32.1% vs 57.1%,  $p = 0.028$ ). However, the highest CK level was significantly higher in the rosuvastatin group than in the placebo group ( $204.8 \pm 425.31$  vs  $89.3 \pm 78.29$ ,  $p = 0.034$ ).

## Conclusions

Rosuvastatin is likely to have a protective role against sepsis associated encephalopathy, but may result in higher adverse events. Future large, multicenter randomized controlled trials are still needed to determine if rosuvastatin is appropriate for preventing sepsis associated encephalopathy.

## Introduction

Sepsis is a life-threatening disease, defined as organ dysfunction caused by intense systemic inflammatory and coagulation cascade reactions arising from severe infection(s) [1]. Sepsis associated encephalopathy (SAE), a transient and reversible encephalopathy caused by infection outside of the brain [5–7], occurs in 25%-50% of sepsis patients [2, 3, 4]. However, SAE is closely related to mortality rates of sepsis patients and long-term rates of disability [8, 9]. Therefore, early diagnosis and prevention of SAE may be of vital importance to reducing the mortality, disability and public health burden of sepsis.

Rosuvastatin is a 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor, which can control high cholesterol disorders, helping prevent cerebrovascular diseases [10, 11]. Apart from its cholesterol control function, rosuvastatin has also been shown to suppress proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) [12]. These three cytokines are theorized to play important roles in SAE initiation [6–10]. An in-vivo study revealed that statin drugs can increase the expression of endothelial nitric oxide (NO) synthase and down-regulating inducible NO synthase, attenuating the dysfunction of endothelium in sepsis patients [13]. Furthermore, statins also show antioxidant [14] and antiapoptotic [15] functions, both of which contribute to depressing the inflammatory cascade during sepsis.

A 2010 meta-analysis demonstrated statin drugs were able to reduce all-cause mortality in sepsis induced ARDS patients [16]. In recent years, a series of studies were carried out to investigate the role of statins on different types and locations of infections, with varying results. A randomized controlled trial (RCT) consisting of 745 participants showed that rosuvastatin does not reduce mortality rate in sepsis associated acute respiratory dysfunction syndrome (ARDS) patients [17]. Regarding the effect of statin drugs on SAE patients specifically, there were no clinical trials focusing on just this issue. Therefore, our team looked at a secondary analysis of related study data to investigate any protective role of rosuvastatin for SAE patients. We hypothesized that rosuvastatin can reduce the rate of SAE among sepsis patients.

## Methods

### Study population

Our study is a secondary analysis of the Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome ('SAILS' study, ClinicalTrials.gov number, NCT00979121). This study was a RCT consisting of 745 patients, investigating any protective effect of rosuvastatin on sepsis patients. The patients were enrolled if their chest radiography showed pulmonary edema and acute respiratory failure. The detailed research methodology of the RCT was shown in the SAILS report [18]. Access to the full database of the original RCT can be requested at the website of the National Institutes of Health (NIH): <https://biolincc.nhlbi.nih.gov/studies/rocprimed/?q=primed>. Our research team was authenticated by the NIH and was able to download the full database from the NIH website.

### Patient enrollment

Patients were enrolled in the original study if they were receiving positive-pressure mechanical ventilation through an endotracheal tube, had a ratio of the partial pressure of arterial oxygen (PaO<sub>2</sub>) to the fraction of inspired oxygen (FIO<sub>2</sub>) of 300 or less, and had bilateral infiltrates on chest radiography that were consistent with pulmonary edema, without evidence of left atrial hypertension [19].

### *Inclusion criteria*

- 1) Patients greater than 18 years old,
- 2) Patients diagnosed with sepsis [patients with an infection and sepsis-related organ failure assessment (SOFA) score  $\geq 2$ ],
- 3) Patients with a completed informed consent form.

#### *Exclusion criteria*

- 1) Pregnancy,
- 2) Patients with any psychiatric disorders,
- 3) Patients diagnosed with or suspected of having an intracranial infection,
- 4) Patients with cerebral injuries,
- 5) Patients with acute cerebral vascular disease,
- 6) Patients with underlying intracranial diseases.

#### **Exposures**

Patients received a 40mg loading dose of rosuvastatin in the SAILS study, within four hours after randomization. Maintenance doses of 20mg rosuvastatin were administered daily at 10 a.m. ( $\pm 4$  hours). For patients with a morning serum creatinine level of 2.8 mg per deciliter (250  $\mu\text{mol}$  per liter) or more who were not receiving renal-replacement therapy, the daily dose was reduced to 10mg. Rosuvastatin drug administration terminated on the third day after discharge from the intensive care unit (ICU), study day 28, hospital discharge, or death. The study drug was suspended for safety reasons if the creatine kinase (CK) level exceeded 10 times the upper limit of the normal range or level of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) exceeded eight times the upper limit of the normal range.

#### **Study outcomes**

In our study, SAE was defined as a Glasgow coma scale (GCS) or intensive care unit - confusion assessment method (ICU-CAM) scores lower than on admission, excluding central nervous system infections, cerebrovascular accident, central nervous system organic diseases or patients undergoing cardiopulmonary cerebral resuscitation.

Primary outcome of this analysis was the rate of SAE. Secondary outcomes included: 28-day all-cause mortality, duration of hospital stay, length of ICU stay, and adverse drug events. Adverse drug events were described using the highest level of CK, ALT and AST during the patient's hospitalization period, (symptoms such as muscle pain were not available in the current data set).

#### **Statistical analysis**

Baseline characteristics were compared between the rosuvastatin group and the placebo group. Continuous data were described as medians with standard differences (SD), and categorical data were described using absolute numbers with percentages. All statistical calculations were performed using the statistical program SPSS 20.0 (IBM Inc., Armonk, NY, USA). Chi-square tests were used for percentage statistics and t-tests were used for continuous statistics. Kaplan-Meier curves were drawn with time since randomization in the SAILS study. A p-value less than 0.05 was interpreted as statistically significant.

## Results

### Baseline characteristics

Our analysis enrolled 86 sepsis patients in total from the original RCT. Please see Figure 1 for the study flow diagram. Fifty-one patients received rosuvastatin treatment while 31 received placebo. SOFA scores in the rosuvastatin group were  $4.6 \pm 3.2$  and  $5.1 \pm 4.6$  in placebo group ( $p=0.061$ ). The use of antibiotic, vasoactive, narcotic, and paralytic medications was comparable between the rosuvastatin and placebo groups.

Other baseline characteristics were also comparable between rosuvastatin and placebo group. Complete baseline characteristics are shown in Table 1.

### Patient outcomes

Regarding the rate of SAE, 17 of 51 patients in the rosuvastatin group developed SAE while 20 of 35 patients in placebo group developed SAE (33.3% vs 57.1%,  $p=0.028$ ). No patient died in either group during the seven-day observation period. There was no significant difference between the rosuvastatin or placebo groups in 28-day all-cause mortality (27.5% vs 11.4%,  $p=0.106$ ), hospital length of stay ( $11.2 \pm 8.97$  vs  $11.7 \pm 9.72$ ,  $p=0.811$ ), or length of ICU stay ( $5.5 \pm 4.41$  vs  $5.7 \pm 3.72$ ,  $p=0.815$ ). SAE incidence curves are shown in Figure 2.

### Safety outcomes

In our analysis, the highest level of CK was significantly higher in the rosuvastatin group than in the placebo group ( $204.8 \pm 425.31$  vs  $89.3 \pm 78.29$ ,  $p=0.034$ ). There was no significant difference between the rosuvastatin or placebo groups' ALT levels ( $35.1 \pm 29.95$  vs  $32.1 \pm 57.7$ ,  $p=0.747$ ) or AST levels ( $33.6 \pm 119.82$  vs  $14.8 \pm 25.30$ ,  $p=1.000$ ). Patient outcomes and safety outcomes are shown in Table 2.

## Discussion

In this study comparing SAE incidence in sepsis patients with or without rosuvastatin in a secondary analysis of a prospective RCT, we found that the rosuvastatin group had a statistically significant lower incidence of SAE, although at a statistically significant higher risk of adverse drug effects. Like in the

original SAILS study, our study did not show that rosuvastatin was associated with a shortened length of hospital or ICU stay.

In recent years, a series of observational studies and randomized trials showed a beneficial effect of statins on patients suffering from severe infections [19]. A 2006 retrospective study showed that, regardless of infection site, administration of statins at the time of bacteremia diagnosed was associated with a lower all-cause mortality rate in bacteremic patients, and further administration of statins led to even lower mortality [20].

Concerning the severity of sepsis, the protective effect of statin drugs was also recently highlighted [21]. Yaniv Almog and his colleagues conducted a prospective cohort study in 2004, finding that prior therapy with statins was associated with a lower rate of severe sepsis [22]. In the long term, statin also showed a protective effect on bacteremic patients, reducing the 180-day mortality rate in one study [23]. These results were consistent with our findings that found a beneficial effect of statin drugs for SAE patients. Nevertheless, the original study did not perform dose-effect research, which is awaiting further investigation.

Another prospective cohort study with 470 ICU patients illustrated that statin drugs were capable of increasing delirium-free ICU days, although the rate of delirium decrease did not show a significant difference between groups (40% in statin group VS 33% in statin free group) [24]. Like our findings, this other study also reported a decreased SAE rate (32.1% in the statin group vs. 57.1% in the placebo group). Another multicenter prospective cohort study, including 763 ICU patients (263 of which were septic or ARDS patients), showed that in-hospital statin use was associated with a reduced delirium rate while statin use prior to hospitalization did not show a benefit [25].

However, there are also some studies challenging the use of statins for patients with sepsis. A retrospective cohort consisting of 438 septic participants showed worse outcomes in the statin group, with a significantly higher in-hospital mortality rate [26]. Specifically, statins may not attenuate lung injury during sepsis, and the ARDS rate was not significantly reduced in sepsis patients when statins were administered [27]. In our study, we still found that rosuvastatin was protective against SAE, while the mortality rate was not significantly elevated in patients receiving rosuvastatin.

SAE is a central nervous system dysfunction in sepsis caused by an inflammatory cascade [28]. Rosuvastatin is widely used in cardiovascular and cerebral vascular disease patients to lower blood cholesterol levels and rates of disease recurrence [29]. In recent decades, statins such as rosuvastatin were found to possess pleiotropic pharmacologic effects, including anti-inflammatory and immunomodulatory functions [30]. The immunomodulatory effects in particular may contribute to cerebral protection for sepsis patients suffering from an inflammatory cascade.

Up-regulation of IL-1 and IL-6 is associated with reduced inter-endothelial junction proteins [31], leading to BBB disruption, which may also cause SAE in sepsis patients [32]. Statins can reduce the expression of pro-inflammatory factors such as IL-1, IL-6, IL-10, IL-17, IL-18, intracellular adhesion molecule (ICAM) and

TNF- $\alpha$  [33], which are closely related to the severity of sepsis in animal models [34]. Similar outcomes were also shown in burn patients treated with statins [35]. Also, statin drugs inhibit the prenylation of Rac and Rho proteins [36], upgrading the expression of endothelium-derived nitric oxide synthetase (eNOS). In turn, eNOS increases NO expression, maintaining endothelial cell function, attenuating BBB damage in sepsis patients [37], thereby reducing the rate of SAE among sepsis patients through an anti-inflammatory pathway. However, the exact pharmacological mechanism of immunomodulation caused by statins has not clearly been demonstrated yet.

Although rare, adverse drug events from statins include myopathy, hepatic function damage and rhabdomyolysis [38]. The original SAILS study selected rosuvastatin due to fewer drug interactions than other statins [39]. Symptoms of statins' adverse effects include muscle pain, nausea, and vomiting, among others. Unfortunately, in our current study, these symptomatic descriptions were not included in the original data set. We could only assess adverse drug events by comparing the levels of CK, AST and ALT between the rosuvastatin and placebo groups. Our study showed the rosuvastatin group has a statistically significant higher CK level, which may be related to a higher risk of myopathy in the rosuvastatin group than placebo.

Our study still has some limitations. First, bilirubin levels are an important laboratory test for evaluating hepatic function, which may be affected by rosuvastatin. However, bilirubin levels were absent from the SAILS study. Second, regarding baseline drug administration, detailed information such as the type of narcotics and antibiotics was not fully reported in the original study, which could interfere with the SAE outcomes. Statin outcomes may also vary among different types of pathogens.

## Conclusions

Rosuvastatin may possess a protective function against SAE in sepsis patients, but at a higher rate of adverse drug events. A future RCT involving varying doses of rosuvastatin may help confirm our findings and identify future treatment recommendations.

## Declarations

### **Ethics approval and consent to participate**

Not applicable

### **Consent for publication**

Not applicable

### **Availability of data and materials**

Access to the full database of the original RCT can be requested at the website of the National Institutes of Health (NIH): <https://biolincc.nhlbi.nih.gov/studies/rocprimed/?q=primed>.

**Competing of interest:**

The authors declare that they have no competing interests.

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**Authors' contributions**

YL and HZ brought up the research idea. SY and ZG collected and analyzed the data. SY and YG prepared the manuscript. JW and YL revised the manuscript. All author agreed with the final version of the manuscript.

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**Abbreviations**

SAE, Sepsis associated encephalopathy

BBB, blood-brain barrier

HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA

IL, interleukin

TNF, tumor necrosis factor

NO, nitric oxide

RCT, randomized controlled trial

ARDS, acute respiratory dysfunction syndrome

NIH, National Institutes of Health

SOFA, sepsis-related organ failure assessment

ICU-CAM, intensive care unit - confusion assessment method

ALT, alanine aminotransferase

AST, aspartate aminotransferase

SD, standard difference

CK, creatine kinase

ICAM, intracellular adhesion molecule

eNOS, nitric oxide synthetase

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## Tables

### Table 1. Baseline characteristics

	Rosuvastatin group	Placebo group	<i>P</i> value
Number of subjects	51	35	-
Male sex/n(%)	30(58%)	13(37%)	0.078
Age	54.5±17.80	53.3±15.31	0.737
Heart rate*	112±24	98±19	0.201
Mean arterial pressure*	76±6.2	78±9.8	0.312
Respiratory rate*	29±9.2	25±10.5	0.197
SOFA score	4.6±3.2	5.1±4.6	0.061
Apache II score	16.2±8.12	18.9±8.49	0.243
Glasgow score	10.1±3.40	9.5±3.38	0.515
<b>Infection site</b>			
Thorax/n(%)	44(86%)	31(88%)	0.754
Abdomen/n(%)	6(12%)	5(15%)	0.317
Skin or soft tissue/n(%)	2(3.9%)	1(2.8%)	0.792
Urinary tract/n(%)	3(5.8%)	1(2.8%)	0.500
Other/n(%)	4(7.8%)	3(8.4%)	0.903
<b>Underlying disease</b>			
Diabetes Mellitus/n(%)	13(25%)	9(26%)	0.981
Hypertension/n(%)	30(58%)	17(49%)	0.348
Myocardial infarction/n(%)	3(5.8%)	2(5.6%)	0.974
Requiring renal replacement therapy/n(%)	0	1(2.8%)	0.178
Hepatic failure/n(%)	1(1.9%)	0	0.405
Chronic pulmonary disease/n(%)	5(9.5%)	6(17%)	0.317
<b>Laboratory tests/n(%)</b>			
PLT/μL*	1.62±0.24×10 <sup>5</sup>	1.21±0.51×10 <sup>5</sup>	0.212
WBC/μL*	15.2±6.25×10 <sup>3</sup>	13.9±5.11×10 <sup>3</sup>	0.381
Hb(g/dL)*	11.2±2.2	12.5±3.5	0.765
Cr(μmol/L)*	133±26	125±19	0.625
BUN(mmol/L)*	9.28±5.6	8.56±4.2	0.286
CK(U/L)	198.1±300.91	251.5±924.5	0.701
ALT(U/L)	36.6±33.74	32.5±37.22	0.599
AST(U/L)	50.3±40.72	39.9±36.04	0.221
<b>Antibiotics n(%)</b>			

Daptomycin	3(5.8%)	1(2.8%)	0.643
Atazanavir	1(1.9%)	1(2.8%)	0.659
Ritonavir	1(1.9%)	0	0.593
<b>Vasoactive drugs n(%)</b>			
Dobutamine	4(7.8%)	3(8.5%)	0.481
Dopamine	2(3.9%)	3(8.5%)	0.385
Epinepherine	0	0	1.000
Norepinepherine	2(3.9%)	1(2.8%)	0.640
<b>Other Medications n(%)</b>			
Narcotics	28(55%)	19(54%)	0.833
Paralytics	2(3.9%)	2(5.6%)	0.833

\* Initial data at admission

PLT=platelet, WBC=white blood cell, Hb=hemoglobin, Cr=creatinine, BUN=blood urea nitrogen, CK=creatine kinase, ALT=alanine aminotransferase, AST=aspartate aminotransferase

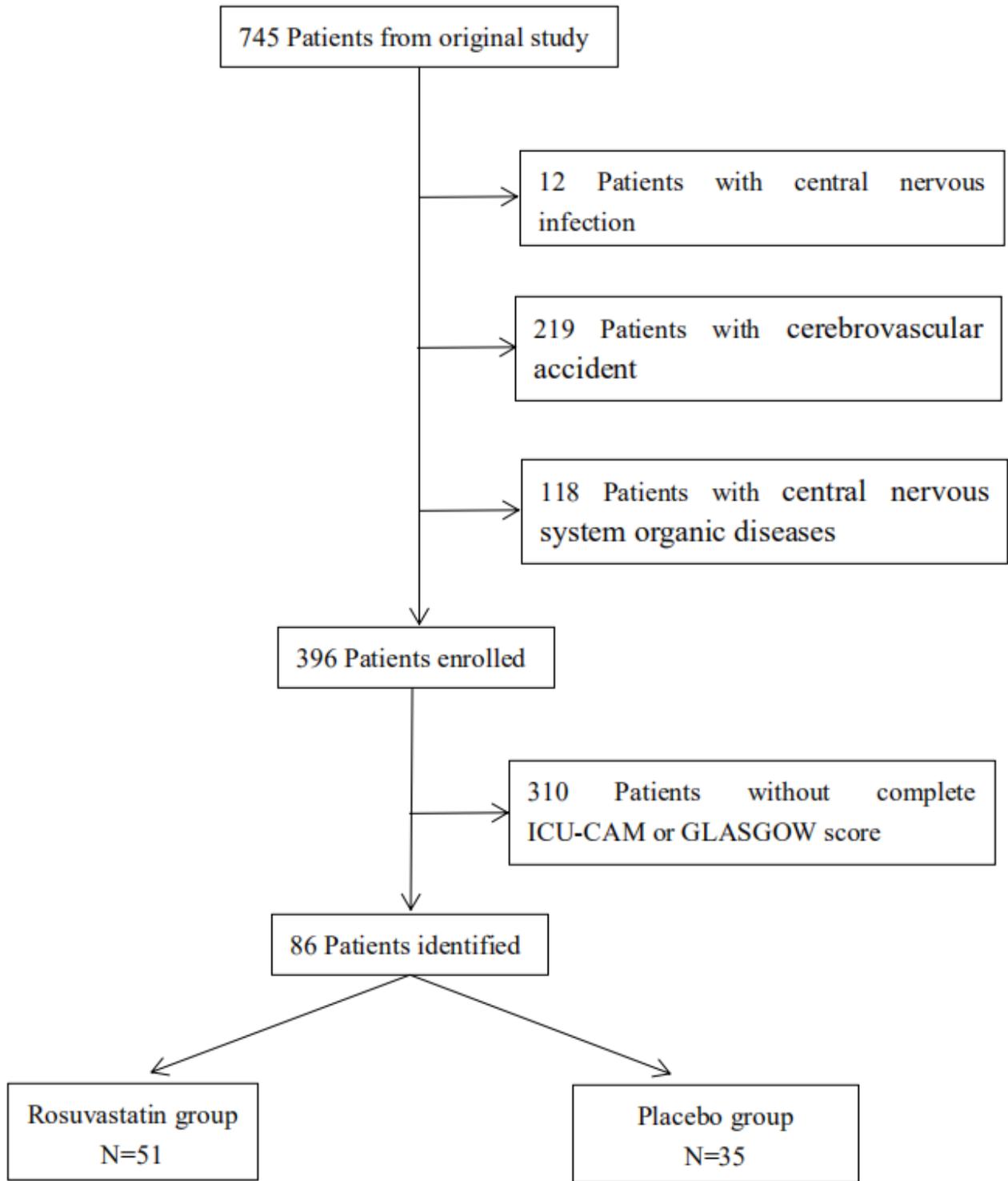
**Table 2. Outcomes between rosuvastatin and placebo groups**

	Rosuvastatin (n=51)	Placebo (n=35)	<i>P</i> value
SAE/n(%)	17(33.3%)	20(57.1%)	0.028*
Death/n(%)	14(27.5%)	4(11.3%)	0.106
Hospital stay/day	11.2±8.97	11.7±9.72	0.811
ICU stay/day	5.5±4.41	5.7±3.72	0.815
Adverse drug events			
CK(U/L)	204.8±425.31	89.3±78.29	0.034*
ALT(U/L)	35.1±29.95	32.1±57.7	0.747
AST(U/L)	33.6±119.82	14.8±25.30	1.000

\* *P* value < 0.05

SAE=sepsis associated encephalopathy, CK=creatine kinase, ALT=alanine aminotransferase, AST=aspartate aminotransferase

## Figures



**Figure 1**

Flow diagram

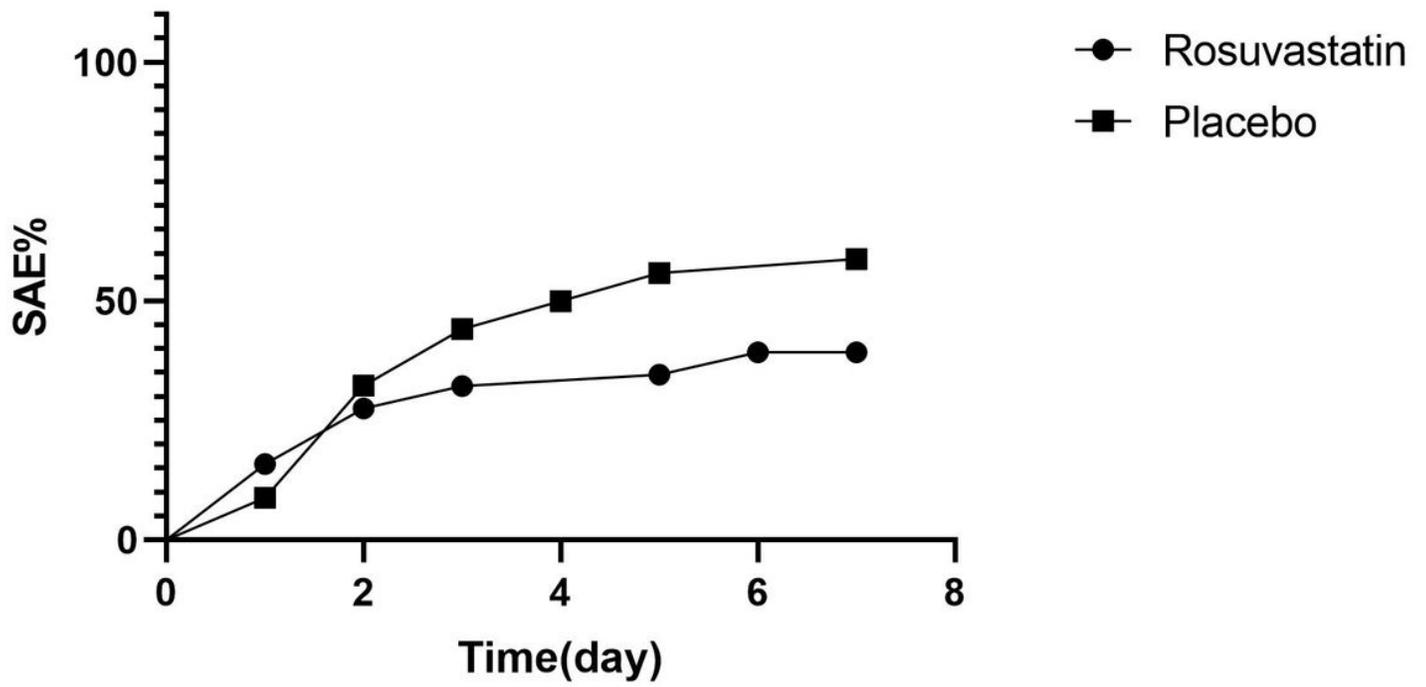


Figure 2

SAE incidence curve

## Supplementary Files

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