The Relationship Between Delirium and Statin Use According To Disease Severity in Patients in the Intensive Care Unit

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Abstract

Background

There have been few earlier studies on the efficacy of statins in the prevention of delirium. However, the results were controversial. The aim of this study was to investigate the association between the use of statins and the occurrence of delirium in a large cohort of patients in the intensive care unit (ICU), considering disease severity and statin properties, which were not sufficiently considered in the previous works.

Methods

We obtained clinical and demographical information from 3604 patients admitted to the ICU of Gangnam Severance Hospital from January 2013 to April 2020. This included information on daily statin use and delirium state, as assessed by the Confusion Assessment Method for ICU. We used inverse probability of treatment weighting and categorized the ICU patients into four groups based on the Acute Physiology and Chronic Health Evaluation II score (group 1: 0-10 - mild; group 2: 11-20 – mild to moderate; group 3: 21-30 – moderate to severe; group 4: > 30 - severe). We analyzed the association between the use of statin and the occurrence of delirium in each group, while taking into account the properties of statins.

Results

Comparisons between statin and non-statin patient groups revealed that only in group 2, patients who were administered statin showed significantly higher occurrence of delirium (p=0.004, odds ratio [OR]=1.58) compared to the patients who did not receive statin. Regardless of whether statins were lipophilic (p=0.036, OR=1.47) or hydrophilic (p=0.032, OR=1.84), the occurrence of delirium was higher only in patients from group 2. Although both lipophilic and hydrophilic statins in group 2 were associated with delirium, neither showed a greater association than the other.

Conclusions

The use of statins may be associated with the increases in the risk of delirium occurrence in patients with mild to moderate disease severity, irrespective of statin properties, as revealed by results from a large cohort study.

Background

Delirium is commonly defined as a disturbance in attention and awareness, and it is characterized by an acute onset and a fluctuating course [1]. As the occurrence of delirium is known to be associated with increased morbidity, mortality, extended hospitalization, and long-term cognitive impairment [2–4], studies on both pharmacologic and non-pharmacologic interventions to prevent delirium have been actively conducted [5–9]. However, contrary to results showing that non-pharmacological interventions are effective for the prevention of delirium, reproducible findings on the efficacies of pharmacological interventions have not been reported [10]. Recently, a meta-analysis of randomized, controlled trials showed limited evidence that atypical antipsychotics may reduce postoperative delirium [5]. However, till date, side effects associated with the use of medication in treating delirium have outweighed the benefits.

One of the reasons why optimal medications to prevent or mitigate delirium have not been discovered might be that the pathophysiology of delirium has not yet been clearly identified [10, 11]. Recently, studies have suggested that neuroinflammation may cause oxidative damage and apoptosis, which in turn may contribute to the occurrence of delirium, although the exact mechanism has not been elucidated yet [11–13]. However, based on such theoretical assumptions, several medications which could reduce neuroinflammation have been investigated [6, 7].

Statin, or 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor, is mainly prescribed for patients with cardiovascular diseases because it can reduce the synthesis of cholesterol in the body [14]. In addition to its cholesterol-reducing ability, statin has pleiotropic effects; these include anti-inflammatory, immunomodulatory, endothelial function-enhancing, and anticoagulant effects [15–17]. The pleiotropic effects of statin are expected to prevent the occurrence of delirium, in line with the neuroinflammation theory [18, 19].

There have been few earlier studies on the efficacy of statins in the prevention of delirium [20–24]. However, the results were controversial. Supporting the neuroinflammation theory, some large cohort, propensity-matched studies suggested that statins are associated with a lower risk of delirium, and their anti-inflammatory effect may contribute to the prevention of delirium [21–23]. However, one retrospective large cohort study which is restricted to relatively homogeneous patients older than 65 years undergoing elective surgery showed findings, suggesting that statin treatment may induce delirium [24]. It was hypothesized that the endothelial function-enhancing effect of statin may induce delirium by leading the brain into a state of hypoperfusion [24, 25].

This inconsistency may be explained by the lack of analyses on the types of statins used in previous studies. In other words, previous studies did not investigate the possible differences between hydrophilic and lipophilic statins, and their possibly distinct effects on delirium. It is known that lipophilic statins can cross the blood brain barrier [26], and lower the level of cholesterol in the brain, below the level required for normal cognitive functioning [27]. Consequently, it is possible that the risk of delirium may be higher with lipophilic statins than with hydrophilic statins.

Disease severity, which could be a major risk factor for the onset of delirium [28, 29], was controlled in previous studies, which was advantageous because the overall association between the use of statin and the occurrence of delirium could be investigated [21–23]. However, we considered it useful to explore whether the effects of statins (prevention or triggering the onset of delirium) varied according to the disease severity, considering the two-sided effects of statin on delirium in the previous investigations [21–25].

In this observational study, we aimed to investigate the relationship between the use of statin and the occurrence of delirium in a large cohort of patients admitted to the intensive care unit (ICU), considering the type of statin and the disease severity. We used a large cohort, grouping patients according to the disease severity, and examined the associations between the uses of two types of statins (lipophilic and hydrophilic) and delirium within each group. We aimed to reveal which type of statin was able to prevent delirium depending on the disease severity. Additionally, we only included patients who had already been using statins before being admitted to the ICU, since previous research did not clearly mention whether statin administration had been started during ICU admission or before it [21–23].

Methods

This observational study was carried out from January 2013 to April 2020 at the Gangnam Severance Hospital (South Korea) and included critically ill patients admitted to either the medical or surgical ICU (23 beds). The study was a part of the ongoing ICU Distress and Delirium Management project for monitoring delirium and distress among

the ICU patients [30]. We obtained ethical approval to conduct our study and for the waiver of informed consent from the institutional review board at Gangnam Severance Hospital (IRB No. 3-2014-0041).

The following information was obtained from each patient, on the day of ICU admission: age, sex, the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score, and medication use including statin. The evaluation of delirium state was performed daily by trained psychiatrists and nurses working in the ICU, using the Confusion Assessment Method for ICU (CAM-ICU) [31], and Richmond Agitation-Sedation Scale (RASS) [32]. Nurses conducted a few assessments daily, after which the trained psychiatrists made the final decision as to the patient's daily condition. Patients were divided into three groups: (1) "comatose" (RASS score-4 or -5), (2) "delirious" (Confusion Assessment Method for ICU positive), and (3) "non-delirious, non-comatose".

Initially, 9151 patients were considered for the study. However, some patients could not be assessed due to the short length of their stay (<24 hours) or their young age (<6 years) (n=2868). Of the remaining 6283 patients, those who were missing admission data (e.g., APACHE-II score was not assessed or recorded) were additionally excluded (n= 2027). Finally, patients who were in a comatose state during their ICU stay were also excluded (n= 652). The final study population consisted of 3604 patients who were assessed as "delirious" or "non-delirious, non-comatose" at least once by the psychiatrists during their entire ICU stay (Fig. 1). The disease severity of all patients was estimated based on the APACHE-II score, the most widely used evaluation test in such scenarios [33, 34]. Patients were classified into four sub-groups as follows: group 1: APACHE 0-10 - mild, group 2: APACHE 11-20 – mild to moderate, group 3: APACHE 21-30 – moderate to severe, group 4: APACHE > 30 - severe).

The patients were further divided into statin and non-statin groups depending on whether they had been administered statins before being admitted to the ICU. The statin group was further subclassified into hydrophilic and lipophilic statin groups, in accordance with the statin type which was administered to them. The ICU patients were taking a total of six different statins: atorvastatin, pitavastatin, simvastatin, pravastatin, rosuvastatin, and fluvastatin. Among them, patients who took pravastatin, rosuvastatin were included in the hydrophilic statin group and those under atorvastatin, pitavastatin, and simvastatin were included in the lipophilic statin group. Because fluvastatin is neither hydrophilic nor lipophilic, patients who were administered fluvastatin were excluded from further analyses on the statin type.

We used inverse probability of treatment weighting [35] that was based on propensity scores to construct sub-groups of patients who differed with respect to statin use but were similar with respect to age and sex [36]. Patients who had not used statin were assigned a weight of $\frac{1-\text{propensity score}}{\text{propensity score}}$ and those who had used statin were assigned a weight of 1 [37]. Subsequently, inverse probability of treatment weighting was repeatedly applied whenever additional comparisons (between non-statin group and lipophilic statin group, non-statin group and hydrophilic statin group, and lipophilic statin group and hydrophilic statin group) were performed. After each process, to determine whether the matchings were successful, independent sample t-tests were performed to check the mean difference in age before and after matching. Additionally, to check the sex ratio of each group (i.e., statin and non-statin), chi-square tests were performed when less than 20% of cells in a contingency table had expected frequencies of ≤ 5; otherwise, Fisher's exact test was performed.

In the propensity-score-weighted cohort that was divided into four groups according to the APACHE-II score, we compared how the delirium occurrence varied between statin and non-statin subgroups, at each level of disease severity, by using chi-square tests. We also compared the delirium occurrence between non-statin and lipophilic statin groups, non-statin and hydrophilic statin groups, and lipophilic and hydrophilic statin groups. All statistical analyses

were performed using SAS version 9.4 (SAS institute INC., Cary, NC, USA), R package, version 4.0.2 (http://www.R-project.org).

Table 1
Demographics and clinical patient characteristics (n = 3604)

	Total	Group 1[a] (N = 678)	Group 2[a] (N= 1708)	Group 3[a] (N = 934)	Group 4[a] (N = 284)
Age (y), mean (SD)	69.1 (15.9)	58.6 (16.3)	70.9 (15.3)	71.6 (14.1)	75.7 (12.8)
Male sex, no (%)	2142 (59.4)	460 (67.9)	987 (57.8)	537 (57.5)	158 (55.6)
Admission for medical problem, no. (%)	1179 (32.7)	247 (36.4)	585 (34.3)	297 (31.8)	50 (17.6)
Length of hospital stay (d), median(range)/mean (SD)	21 (1-1848) /41.3 (70.2)	16 (2-571) /31.9 (51.9)	21 (1-1848) /41.0 (77.9)	24 (2-738) /45.8 (70.4)	32 (3-479) /50.8 (54.8)
Length of ICU stay (d), median(range)/mean (SD)	4 (1-343) /8.4 (13.6)	3 (1-141) /5.3 (9.0)	4 (1-157) /7.0 (10.8)	5 (1-343) /10.7 (17.4)	10 (1-154) /16.8 (18.3)
Mortality at the end of ICU stay, no. (%)	461 (12.8)	38 (5.6)	207 (12.1)	152 (16.3)	64 (22.5)
Emergent admission, no. (%)	2299 (63.8)	430 (63.4)	1043 (61.1)	594 (63.6)	232 (81.7)
Surgery prior to ICU admission, no. (%)	2181 (60.5)	350 (51.6)	1001 (58.6)	603 (64.6)	227 (79.9)
Emergent surgery prior to ICU admission, no. (%)	1018 (28.2)	115 (17.0)	413 (24.2)	314 (33.6)	176 (62.0)

Notes: [a] Group 1: APACHE 1-10, Group 2: APACHE 11-20, Group 3: APACHE 21-30, Group 4: APACHE 31-40

Results

The demographics and clinical characteristics of the patients are shown in Table 1. The mean [standard deviation(SD)] age of the patients was 69.1 [15.9] years, 2142 patients (59.4%) were male patients, and 1184 patients (32.9%) were admitted for medical (i.e. not surgical) problems. The median and mean [SD] hospital stays were 21 days and 41.3 [70.2] days, respectively. In addition, the length of stay in the ICU ranged from 1 to 343 days, and the median and mean [SD] lengths of stay in the ICU were 4 days and 8.4 [13.6], respectively. Of the total number of patients, 461 (12.8%) died at the end of their ICU stay, 2299 (63.8%) were admitted via the emergency department, 2181 (60.5%) underwent surgery prior to ICU admission, and 1018 (28.2%) underwent emergency surgery prior to ICU admission. Additional data on the subdivisions regarding hospitalization is available in Supplementary Table 1.

Table 2

Selected demographics and clinical characteristics of the patients who were admitted to the ICU, according to the use of statin, before and after inverse probability of treatment weighting

APACHE Group	Variable	Cohort before Inverse probability of Treatment Weighting				Cohort after Inverse probability of Treatment Weighting			
		All	Non-statin	Statin	P-value	All	Non-statin	Statin	P-value
		Mean ± Standard deviation or Number (%)				Weighted mean (Standard Error) or Weighted Number (%)			
1	Patients (n)	678	618	60		120.1	60.1	60.0	
	Age	58.6 ± 16.3	58.0 ± 16.3	64.5 ± 14.9	0.003 [a]	64.6 (1.0)	64.6 (0.7)	64.5 (1.9)	0.956
	Male (%)	460 (67.9)	416 (67.3)	44 (73.3)	0.341	88.3 (73.6)	44.3 (73.8)	44.0 (73.3)	0.942
	Delirium (%)	114 (16.8)	101 (16.3)	13 (21.7)	0.293	31.8 (26.5)	15.8 (26.2)	16.0 (26.7)	0.528
2	Patients (n)	1708	1509	199		398.7	199.7	199.0	
	Age	70.9 ± 15.3	70. 1 ± 15.6	76.6 ± 11.4	<.001 [a]	76.7 (0.4)	76.8 (0.3)	76.6 (0.8)	0.841
	Male (%)	987 (57.8)	865 (57.3)	122 (61.3)	0.285	244.9 (61.4)	122.9 (61.6)	122.0 (61.3)	0.946
	Delirium (%)	509 (29.8)	427 (28.3)	82 (41.2)	0.002 [a]	143.5 (36.0)	61.5 (30.8)	82.0 (41.2)	0.004 [a]
3	Patients (n)	934	779	155		310.2	155.2	155.0	
	Age	71.6 ± 14.1	70.7 ± 14.3	76.2 ± 12.1	<.001 [a]	76.22 (0.53)	76.2 (0.4)	76.2 (1.0)	0.968
	Male (%)	537 (57.5)	446 (57.3)	91 (58.7)	0.738	182.8 (58.9)	91.8 (59.2)	91.0 (58.7)	0.919

Notes: [a] $p<0.05$

	Delirium (%)	418 (44.8)	334 (42.9)	84 (54.2)	0.010 [a]	156.9 (50.6)	72.9 (47.0)	84.0 (54.2)	0.106
4	Patients (n)	284	239	45		90.0	45.0	45.0	
	Age	75.7 ± 12.8	75.4 ± 13.2	77.3 ± 10.5	0.373	77.3 (0.9)	77.3 (0.8)	77.3 (1.6)	0.972
	Male (%)	158 (55.6)	132 (55.2)	26 (57.8)	0.752	52.0 (57.8)	26.0 (57.7)	26.00 (57.8)	0.996
	Delirium (%)	178 (62.7)	144 (60.3)	34 (75.6)	0.052	62.2 (69.1)	28.2 (62.6)	34.0 (75.6)	0.098

Notes: [a] $p<0.05$

Table 2 summarizes the demographical and clinical characteristics of the study population before and after propensity-score weighting. In the patient population prior to propensity-score weighting, 459 patients (12.7%) had been taking statin before they were admitted to the ICU (Group 1: n=60, group 2: n=199, group 3: n=155, group 4: n=45). A further 1219 patients (33.8%) were diagnosed with delirium during the ICU stay, of which 314 patients (25.8%) were hyperactive, 526 patients (43.2%) were hypoactive, and 379 (31.1%) were classified as a mixed motor subtype. The median and mean [SD] duration of delirium was 3 days and 5.6 [7.9] days. In each severity group (groups 1 to 4), 114, 509, 418, and 178 patients were diagnosed with delirium, respectively. Details about delirium in each group is available in Supplementary Table 1.

As shown in Table 2, the mean ages between non-statin and statin groups were significantly different, except for group 4, indicating that the mean age of patients undergoing statin treatment was higher. The sex ratio was not statistically different between the statin and non-statin groups. After applying the propensity-score weighting, the corrected mean ages were not different between the non-statin and statin groups. Likewise, the weighted sex ratios did not show significant differences between the non-statin and statin groups.

In the group comparison analysis, the occurrence of delirium was not significantly different between the two statin groups, except in group 2. Here, the occurrence of delirium and the use of statin showed a significant relationship ($p=0.004$, with the odds ratio [OR] of 1.58). Specifically, in the statin group, the proportion of delirium occurrence was significantly higher than in the non-statin group.

Table 3
Statin types administered to the patients in the statin treatment group

		Lipophilic			Hydrophilic		Intermediate
		atorvastatin	pitavastatin	simvastatin	pravastatin	rosuvastatin	fluvastatin
GROUP	Total	310	12	23	3	106	5
	1 (n = 60) (APACHE 1-10)	36	1	4	0	18	1
	2 (n = 199) (APACHE 11-20)	124	5	14	2	51	3
	3 (n = 155) (APACHE 21-30)	115	6	4	1	28	1
	4 (n = 45) (APACHE 31-40)	35	0	1	0	9	0

When the statin group was further classified into lipophilic and hydrophilic statin groups, 345 patients (75.2%) were shown to take lipophilic statins, with 41, 143, 125, and 36 patients taking lipophilic statins in each disease severity sub-group (1 to 4), respectively. In both the statin type groups, atorvastatin and rosuvastatin accounted for the largest proportion of statins (Table 3).

Table 4
The ratio of delirium occurrence in lipophilic and hydrophilic statin groups before and after inverse probability of treatment weighting

APA CHE Group	Variable	Cohort before Inverse probability of Treatment Weighting				Cohort after Inverse probability of Treatment Weighting			
		All	Lipophilic	Hydrophilic	P-value	All	Lipophilic	Hydrophilic	P-value
		Mean ± Standard deviation or Number (%)				Weighted mean (Standard Error) or Weighted Number (%)			
1	Patients (n)	59	41	18		36.0	18.0	18	
	Age	64.3 ± 14.9	62.0 ± 15.4	69.5 ± 12.8	0.074	69.4 (1.8)	69.4 (2.0)	69.5 (3.0)	0.972
	Male (%)	43 (72.88)	30 (73.17)	13 (72.22)	>.999	26.12 (72.55)	13.12 (72.88)	13.00 (72.22)	0.960
	Delirium (%)	13 (22.0)	10 (24.4)	3 (16.7)	0.735	7.4 (20.5)	4.4 (24.3)	3.0 (16.7)	0.526
2	Patients (n)	196	143	53		106.0	53.0	53	
	Age	76. 5 ± 11.3	76.3 ± 12.0	76.9 ± 9.3	0.728	76.9 (0.8)	76.9 (0.9)	76.9 (1.3)	0.978
	Male (%)	120 (61.2)	83 (58.0)	37 (69.8)	0.133	73.9 (69.7)	36.9 (69.6)	37.0 (69.8)	0.980
	Delirium (%)	80 (40.8)	56 (39.2)	24 (45.3)	0.439	44.3 (41.8)	20.3 (38.3)	24.0 (45.3)	0.378
3	Patients (n)	154	125	29		58.0	29.0	29	
	Age	76.3 ± 12.1	76.7 ± 11.8	74.4 ± 13.4	0.349	74.5 (1.4)	74.6 (1.3)	74.4 (2.5)	0.936
	Male (%)	90 (58.4)	69 (55.2)	21 (72.4)	0.090	41.9 (72.3)	20.9 (72.2)	21.0 (72.4)	0.980
	Delirium (%)	84 (54.6)	69 (55.2)	15 (51.7)	0.735	29.7 (51.2)	14.7 (50.6)	15.0 (51.7)	0.916
4	Patients (n)	45	36	9		18.0	9.0	9	
	Age	77.3 ± 10.5	76.7 ± 10.7	79.7 ± 9.8	0.450	79.7 (1.8)	79.8 (1.7)	79.7 (3.3)	0.967

Male (%)	26 (57.8)	20 (55.6)	6 (66.7)	0.712	12.1 (66.8)	6.1 (67.0)	6.0 (66.7)	0.985
Delirium (%)	34 (75.6)	28 (77.8)	6 (66.7)	0.666	13.4 (74.1)	7.4 (81.5)	6.0 (66.7)	0.329

When comparing non-statin and lipophilic statin groups, no significant relationship was found between the occurrence of delirium and the use of statin in groups 1, 3, and 4. Similar to the previous result, in group 2, a significant difference was found between non-statin and statin groups (p=0.036, OR = 1.47). Likewise, only in group 2, the hydrophilic statin group showed a significant association with the occurrence of delirium (p=0.032, OR =1.84). The proportion of delirium occurrence was significantly higher in both the hydrophilic and lipophilic statin groups than in the non-statin group. Table 4 shows the ratios of delirium occurrence in the lipophilic and hydrophilic statin groups before and after the propensity-score weighting. As can be seen in Table 4, after correcting for age and sex covariates using propensity score weighting, there was no significant association between the occurrence of delirium and the type of statin in all disease severity sub-groups including group 2.

Discussion

In this observational cohort study of 3604 patients who were admitted to the ICU, the current findings indicate that there was an association between the use of statins and the occurrence of delirium but only in patients with mild to moderate disease severity. Specifically, the delirium occurrence was higher in the statin group with an APACHE-II score of 10-20. These findings were obtained regardless of the type of statin administered (lipophilic or hydrophilic), both before and after propensity score weighting.

To our knowledge, this is the first study to analyze how the association between the use of statins and the occurrence of delirium varied according to the disease severity. The results of these analyses suggest that the use of statins may increase the risk of delirium occurrence in patients with mild to moderate severity. This contradicts, to a degree, the existing hypothesis that the pleiotropic effects of statins, which include anti-inflammation and immunomodulation, may prevent delirium.

It can be argued that the specific underlying condition for which statins are prescribed may increase the risk of delirium in patients with mild to moderate disease severity, and not the statins themselves. However, some meta-analysis and cohort studies demonstrated that some of the diseases for which statins are recommended according to the guidelines, such as atherosclerotic cardiovascular disease and dyslipidemia [14], did not seem to be associated with delirium, or that delirium and such diseases are mutually exclusive [38–40]. Nonetheless, the effect of disease severity on the association between the specific underlying disease and delirium is still unknown. Thus, the hypothesis that the underlying conditions requiring statin treatment may have influenced our results is not supported by previous evidence. In this study, we discuss the effect of statin and disease severity on biological mechanisms, which are more specific than underlying disease conditions, such as the role of nitric oxide (NO) in the systemic inflammation state and hypoperfusion of the brain.

In the inflammatory state, cytokines trigger over-production of inducible nitric oxide synthase (iNOS), which is inactive under normal physiological conditions. This is known as one of the crucial mechanisms of sepsis, by which large amounts of NO are produced [41]. Overproduction of NO leads to changes in the vascular tone by affecting the endothelium and small blood vessels involved in systemic circulation, and causes hypotension and migration of leukocytes, which results in widespread tissue damage and multiple organ failure [41, 42]. Statin has been shown to

lead to concomitant up-regulation of endothelial nitric oxide synthase (eNOS), which is an isoform of iNOS, and down-regulation of iNOS. As such, statin modulates the production of NO and restores systemic circulation. Consequently, statin may help in attenuating inflammation and even delirium severity [18, 43].

However, some researchers suggested that during inflammation, the modulation of NO by statins may impact cerebral autoregulation resulting in cerebral ischemia [44, 45]. When the microvascular tone is recovered by the modulation of NO, the blood flow is distributed to peripheral small blood vessels, which reduces the blood flow to the brain [24, 25]. Hypoperfusion and inadequate cerebral oxygenation play an important role in the pathophysiology of delirium [10, 46, 47]. If this hypothesis applies to our results, it can be inferred that patients with mild to moderate disease severity under statin treatment may be more susceptible to the delirium-inducing effect of statins through hypoperfusion than the delirium-preventing effect through anti-inflammation.

As for the statin type, use of both lipophilic and hydrophilic statins in patients with mild to moderate severity was associated with delirium, but there were no significant differences between the two. Hydrophilic statins have been reported to up-regulate eNOS expression to levels comparable to those seen with lipophilic statins [43, 48], but there is still some uncertainty about how much the overall expression of NO differs depending on the statin types. Our results suggest that the NO synthesis may not significantly vary according to the statin types.

In contrast, except for group 2, the use of statins in the remaining groups was not significantly associated with the occurrence of delirium, regardless of the statin types. Since patients in group 1 were in a relatively less inflammatory state than those in group 2, we assume that the amount of iNOS was much lower in group 1. Thus, the balancing effect of statins on NO synthases in peripheral blood vessels and the accompanying hypoperfusion effect on the brain may have also been insignificant. Meanwhile, in groups 3 and 4, the higher disease severity may have played the primary role in the occurrence of delirium [10]; however, the function of statins in these groups remaining unclear.

This study has several limitations. First, due to the multifactorial nature of delirium, the potential risk factors which may have affected the outcomes were not sufficiently controlled, except for age and disease severity. Second, the differential roles of pitavastatin and pravastatin were difficult to examine in either statin group, because both of them were under-represented; the lipophilic statin group consisted mostly of atorvastatin treatment while the other group was mainly represented by rosuvastatin. Lastly, it is difficult to generalize our results because this study included data from a single hospital.

Conclusions

In conclusion, the present study showed that, in ICU patients with mild to moderate disease severity, the use of statins may be associated with increases in the risk of delirium, irrespective of the statin type. Future multi-center studies using larger cohorts could verify our results and more clearly identify the relationship between statin treatment and delirium.

List Of Abbreviations

ICU: intensive care unit; APACHE-II: Acute Physiology and Chronic Health Evaluation-II; CAM-ICU: Confusion Assessment Method for intensive care unit; RASS: Richmond Agitation-Sedation Scale; SD:standard deviation; NO: nitric oxide; iNOS: inducible nitric oxide synthase; eNOS: endothelial nitric oxide synthase

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. We obtained ethical approval to conduct our study and for the waiver of informed consent from the institutional review board at Gangnam Severance Hospital (IRB No. 3-2014-0041).

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

JYA and JO designed and conceptualized the study. JYA, JYP, JC, HK, JP and JO collected the data. JYA performed data analysis under supervision of JO. JYA and JO interpreted the data. JYA and JO drafted and revised the manuscript. All authors approved the final version of the draft.

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Figures

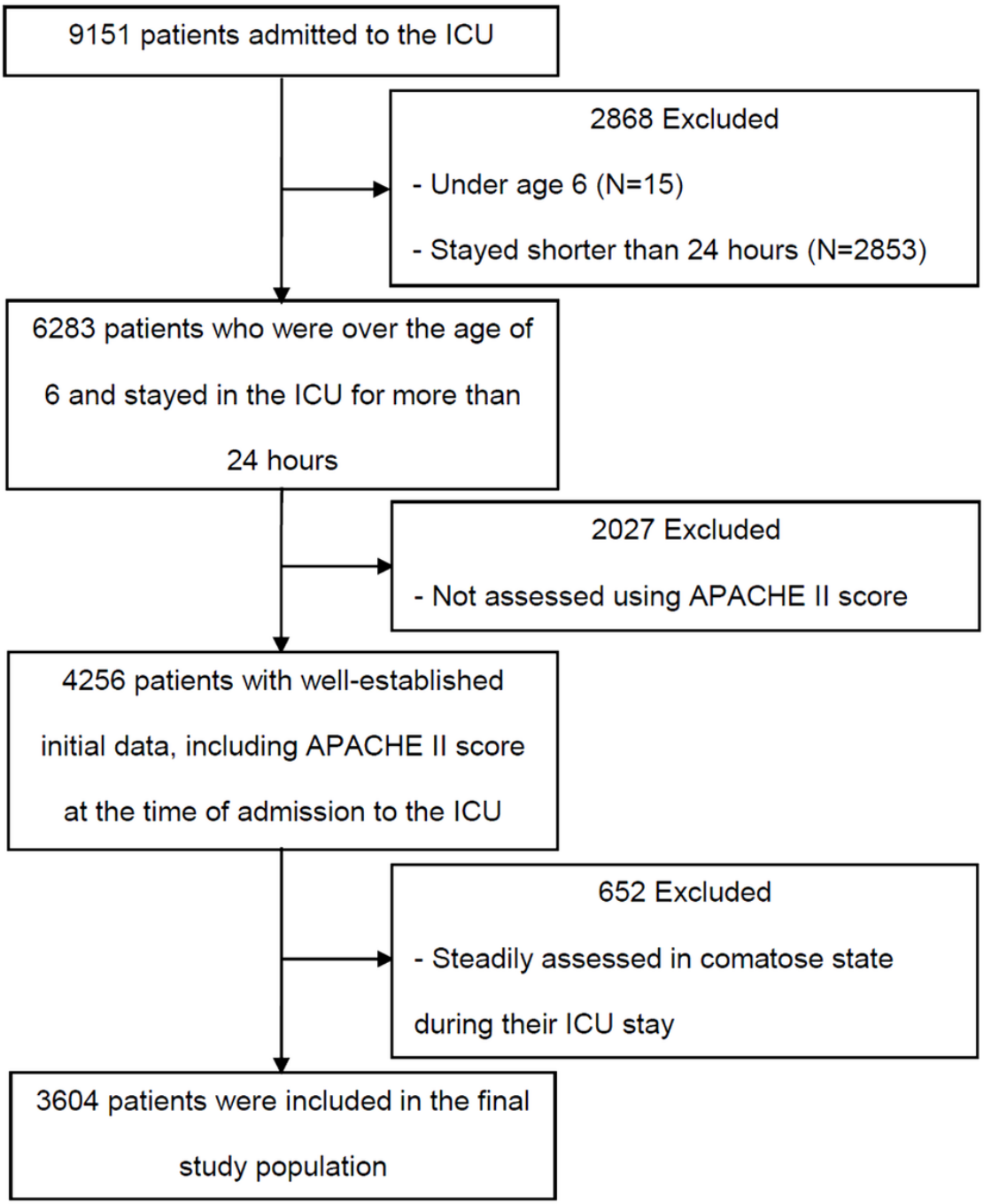

Figure 1

The flowchart of study

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