

The Relationship between Delirium and Statin Use According to Disease Severity in Patients in the Intensive Care Unit

Jun Yong An^{1,2}, Jin Young Park^{2,3}, Jaehwa Cho⁴, Hesun Erin Kim², Jaesub Park^{2,5}, Jooyoung Oh^{1,2}

¹Department of Psychiatry, Gangnam Severance Hospital, Yonsei University College of Medicine, ²Institute of Behavioral Sciences in Medicine, Yonsei University College of Medicine, Seoul, ³Department of Psychiatry, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, ⁴Department of Pulmonary and Critical Care Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, ⁵Department of Psychiatry, National Health Insurance Service Ilsan Hospital, Goyang, Korea

Objective: 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.

Methods: We obtained clinical and demographical information from 3,604 patients admitted to the ICU 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 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.

Conclusion: 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.

KEY WORDS: Delirium; Intensive care unit; Neuroinflammation; Statin; Disease severity; APACHE II score.

INTRODUCTION

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 in-

terventions 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 re-

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Address for correspondence: Jooyoung Oh

Department of Psychiatry, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea

E-mail: ojjuoju@yuhs.ac

ORCID: <https://orcid.org/0000-0001-6721-399X>

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duce 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. 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]. The inconsistency of previous studies on the relationship between statin and delirium may be explained by the lack of analyses on the types of statins used in previous studies. It is known that lipophilic statins can cross the blood brain barrier [25], and lower the level of cholesterol in the brain, below the level required for normal cognitive functioning [26]. 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 [27,28], was considered as a confounding variable in previous studies and adjusted. These study designs had the advantage of being able to investigate the overall association between the use of statin and the occurrence of delirium [21-23]. However, the pleiotropic effects of statins such as anti-inflammation, immunomodulation, and endothelial enhancing effects are inevitably more prominent in inflammatory conditions [17,29] and may vary depending on the disease severity. We hypothesized that by analyzing the association between the use of statins and delirium in each group by classifying the patients according to disease severity, the controversial results of previous studies could be relatively clear. In other words, we expected to know whether the delirium-inducing or preventive effect of statins at

each disease severity is prominent. In addition, it was expected that if statins act more prominently, it may be possible to reveal which effect of statins (delirium-inducing versus delirium-preventing) is superior.

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]. During every rotation, three times a day, trained nurses assessed the condition of ICU patients including whether each patient was in a delirious state or not. In addition, each day around 10 AM, trained psychiatrists made the final decision on each patient's state based on the evaluation records of nurses and the current state of patients.

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”. Patients designated in the “delirious” group were additionally classified as hyperactive, hypoactive, or mixed type of delirium according to the Delirium Motor Subtype Scale (DMSS) [33], which consists of a total 11 pure motor symptoms (four hyperactive and seven hypoactive features). If definite evidence of at least two of the four hyperactive features appeared within 24 hours, the patients were assigned to the “hyperactive type”. If two of more of the seven hypoactive features were met, the patients were assigned to the “hypoactive type”. Finally, patients who met both criteria (“hyperactive type” and “hypoactive type”) were classified as “mixed type”.

Initially, 9,151 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 = 2,868). Of the remaining 6,283 patients, those who were missing admission data (e.g., APACHE II score was not assessed or recorded) were additionally excluded (n = 2,027). Finally, patients who were in a comatose state during their ICU stay were also excluded (n = 652). The final study population consisted of 3,604 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 pa-

tients was estimated based on the APACHE II score, the most widely used evaluation test in such scenarios [34,35]. 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 [36] that was based on propensity scores to control the influence of confounding variables while preserving as many subjects as possible in the population. Using this method, we constructed sub-groups of patients who differed with respect to statin use but were similar with re-

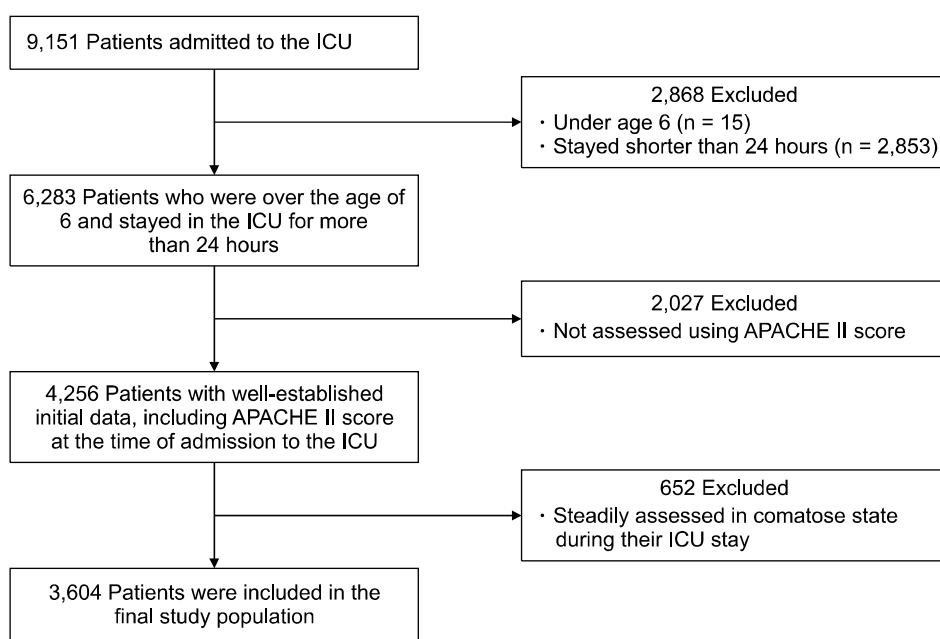


Fig. 1. The flowchart of study. ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation-II.

Table 1. Demographics and clinical patient characteristics (n = 3,604)

Variable	Total	Group 1 (n = 678)	Group 2 (n = 1,708)	Group 3 (n = 934)	Group 4 (n = 284)
Age (yr)	69.1 ± 15.9	58.6 ± 16.3	70.9 ± 15.3	71.6 ± 14.1	75.7 ± 12.8
Male sex	2,142 (59.4)	460 (67.9)	987 (57.8)	537 (57.5)	158 (55.6)
Admission for medical problem	1,179 (32.7)	247 (36.4)	585 (34.3)	297 (31.8)	50 (17.6)
Length of hospital stay (d)	21 (1–1,848)/ 41.3 ± 70.2	16 (2–571)/ 31.9 ± 51.9	21 (1–1,848)/ 41.0 ± 77.9	24 (2–738)/ 45.8 ± 70.4	32 (3–479)/ 50.8 ± 54.8
Length of ICU stay (d)	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	461 (12.8)	38 (5.6)	207 (12.1)	152 (16.3)	64 (22.5)
Emergent admission	2,299 (63.8)	430 (63.4)	1,043 (61.1)	594 (63.6)	232 (81.7)
Surgery prior to ICU admission	2,181 (60.5)	350 (51.6)	1,001 (58.6)	603 (64.6)	227 (79.9)
Emergent surgery prior to ICU admission	1,018 (28.2)	115 (17.0)	413 (24.2)	314 (33.6)	176 (62.0)

Values are presented as mean ± standard deviation (SD), number (%), or median (range).

Group 1: APACHE 1–10, Group 2: APACHE 11–20, Group 3: APACHE 21–30, Group 4: APACHE > 30.

ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation-II.

spect to age and sex [37]. Patients who had not used statin were assigned a weight of $1 - \text{propensity score} / \text{propensity score}$ and those who had used statin were assigned a weight of 1 [38]. 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.

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, 2,142 patients (59.4%) were male patients, and 1,184 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, 2,299 (63.8%) were admitted via the emergency department, 2,181 (60.5%) underwent surgery prior to ICU admission, and 1,018 (28.2%) underwent emergency surgery prior to ICU admission. Additional data on the subdivisions regarding hospitalization is available in Supplementary Table 1 (available online).

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 1,219 patients (33.8%) were diagnosed with delirium during the ICU stay, of which 314

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				Cohort after			
		Inverse probability of treatment weighting				Inverse probability of treatment weighting			
		All	Non-statin	Statin	<i>p</i> value	All	Non-statin	Statin	<i>p</i> value
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)	1,708	1,509	199		398.7	199.7	199.0	
	Age	70.9 ± 15.3	70.1 ± 15.6	76.6 ± 11.4	< 0.001 ^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	< 0.001 ^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
	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

Cohort before: Values are presented as mean ± standard deviation or number (%). Cohort after: Values are presented as weighted mean ± standard error or weighted number (%).

ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation-II.

^a*p* < 0.05.

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 (available online).

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. In group 2, the proportion of delirium occurrence was significantly higher (*p* = 0.004, with the odds ratio [OR] of 1.58) in the statin use group

(Table 2).

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).

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 group (*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

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

Group	Lipophilic			Hydrophilic		Intermediate
	Atorvastatin	Pitavastatin	Simvastatin	Pravastatin	Rosuvastatin	Fluvastatin
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 > 30)	35	0	1	0	9	0

APACHE II, Acute Physiology and Chronic Health Evaluation-II.

Table 4. The ratio of delirium occurrence in lipophilic and hydrophilic statin groups 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	Lipophilic	Hydrophilic	<i>p</i> value	All	Lipophilic	Hydrophilic	<i>p</i> value
		1	Patients (n)	59	41	18		36.0	18.0
	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)	> 0.999	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

Cohort before: Values are presented as mean ± standard deviation or number (%). Cohort after: Values are presented as weighted mean ± standard error or weighted number (%).

APACHE II, Acute Physiology and Chronic Health Evaluation-II.

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 3,604 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 [39-41]. 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, large amounts of NO are produced [42]. Overproduction of NO leads to changes in the vascular tone in systemic circulation, and causes migration of leukocytes and oxidative stress, which results in widespread tissue damage and cognitive decline [42-44]. Statin has been shown to modulate the production of NO and restore systemic circulation. Consequently, statin may help in attenuating inflammation and even delirium severity [18,45]. However, some researchers suggested that during inflammation, the modulation of NO by statins may impact cerebral autoregulation resulting in cerebral ischemia [46,47]. 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 [24,48]. Hypoperfusion and inadequate cerebral oxygenation play an important role in the pathophysiology of delirium [10,49]. 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, uses 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. 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 sig-

nificantly 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 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, we tried to control for confounding variables such as disease severity, age, and sex, but due to the multifactorial nature of delirium, not all variables that could affect the outcomes were controlled. For example, control for confounding variables such as presence of underlying disease including dementia or cerebrovascular diseases, whether major surgery had been performed, and whether other medications such as hypnotics or sedatives had been used were not sufficiently controlled. Insufficient control of confounding variables may have confused the interpretation of association between the use of statins and the occurrence of delirium. Further studies, in which more various confounding variables are controlled, need to be conducted. 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.

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. Our results may have clinical implications that patients taking statins with mild to moderate disease severity should be more closely monitored for the development of delirium. Future multi-center studies using larger cohorts could verify our results and more clearly identify the relationship between statin treatment and delirium.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Jun Yong An, Jooyoung Oh. Data collection: Jun Yong An, Jin Young Park, Jaehwa Cho, Hesun Erin Kim, Jaesub Park, Jooyoung Oh. Data analysis, supervision: Jun Yong An, Jooyoung Oh. Data interpretation: Jun Yong An, Jooyoung Oh. Writing—original draft & editing: Jun Yong An, Jooyoung Oh.

■ ORCID

Jun Yong An	https://orcid.org/0000-0002-7222-5861
Jin Young Park	https://orcid.org/0000-0002-5351-9549
Jaehwa Cho	https://orcid.org/0000-0002-3432-3997
Hesun Erin Kim	https://orcid.org/0000-0001-9855-9475
Jaesub Park	https://orcid.org/0000-0003-2597-2204
Jooyoung Oh	https://orcid.org/0000-0001-6721-399X

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