Increased Risk of New-Onset Depression in Patients With Traumatic Brain Injury and Hyperlipidemia:

The Important Role of Statin Medications

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ABSTRACT

Objective: Depression is a common complication after traumatic brain injury (TBI). This study aimed to evaluate the risk of hyperlipidemia for new-onset depression after TBI and the role of statin medications using a longitudinal population database.

Method: A matched longitudinal cohort study of 3,792 subjects (1,264 TBI patients [*ICD-9-CM* code: 801–804 and 850–854] with preexisting hyperlipidemia [*ICD-9-CM* code: 272.0, 272.1, 272.2, 272.4] and 2,528 age- and sex-matched TBI patients without hyperlipidemia) was conducted using the Taiwan Longitudinal Health Insurance Database from January 2001 to December 2008. The incidence and hazard ratios (HRs) for the development of new-onset depression (*ICD-9-CM* code: 296.2X–296.3X, 300.4, and 311.X) after TBI were compared between the 2 groups.

Results: The incidence rate of depression in TBI with preexisting hyperlipidemia was 136.61 per 10,000 person-years. TBI patients with preexisting hyperlipidemia had a 1.72-fold increased incidence rate ratio compared with those without hyperlipidemia ($P = .0056$). A Cox model showed hyperlipidemia to be an independent predictor of depression (HR = 1.61; 95% CI, 1.03–2.53). TBI patients with hyperlipidemia who were not treated with statins experienced a 1.95-fold incidence risk ratio ($P = .0017$) and higher risk of new-onset depression (HR = 1.61; 95% CI, 1.03–2.53) compared to TBI patients without hyperlipidemia.

Conclusions: Preexisting hyperlipidemia could be an independent predictor of new-onset depression in TBI patients, and TBI patients with preexisting hyperlipidemia who were not treated with statins presented a higher risk of new-onset depression than TBI patients without hyperlipidemia. Our findings may provide some insight into the important role of statin medications in the development of new-onset depression in patients with traumatic brain injury.

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Traumatic brain injury (TBI) is a leading cause of neurologic deficits, cognitive impairment, and psychiatric disorders in survivors.[1] It has become a major public issue for an estimated 3.17 million individuals in the United States[2] and was associated with 3.39 times the medical costs in TBI patients with psychiatric disorders compared to those without psychiatric disorders.[3]

Among these psychiatric disorders, depression is the most common psychiatric complication of TBI and ranges from 6% to 77%, with variations according to the studied population and the diagnostic criteria or rating instruments used.[4–7] Depression is associated with a 3-fold increase of medical regimens in patients with chronic illness or comorbidities.[8] Age,[9] sex,[10] socioeconomic status,[11] cardiovascular disease,[12] hypertension,[13] diabetes mellitus,[14] hyperlipidemia,[15,16] and TBI[17] are risk factors associated with depressive disorder.

Hyperlipidemia is a common symptom in the general population. From the different population surveys,[18,19] the range of hyperlipidemia prevalence was from 19.9% to 33.5% among adults aged ≥ 20 years. Hyperlipidemia was also related to the risk of cardiovascular disease,[20] diabetes mellitus,[21] and hypertension,[22] which are all risk factors for depression. Furthermore, some evidence indicate that statin medications, an antihyperlipidemic agent, has neuroprotective effects on the hippocampus, which may be associated with the depression developed in TBI animal models.[23,24] Therefore, hyperlipidemia may play a role in the development of new-onset depression after TBI. Neurosurgeons can expect to see more TBI patients who have preexisting hyperlipidemia in daily practice. We suggest that paying more attention to these factors associated with depression would help clinicians have a deeper understanding of the sequelae in TBI patients.

No studies have evaluated the association between preexisting hyperlipidemia and the risk of new-onset depression in TBI patients when considering the associated risk factors simultaneously. Therefore, the aim of this study was to evaluate the incidence and risk ratio of preexisting hyperlipidemia, including statin-treated and non–statin-treated, for the development of new-onset depression in TBI patients using data from the nationwide database of the National Health Insurance (NHI) Program in Taiwan (1997–2011). We propose that awareness of the incidence and risk factors for new-onset depression in TBI patients can improve one's understanding of the sequelae of brain injury and patient treatment, the rehabilitation protocol, and preventive medicine strategies.

METHOD

Data Source

Taiwan's National Health Insurance Research Database (NHIRD) is an inpatient and outpatient medical benefit claims database that includes diagnostic codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), and prescription details. Of Taiwan's 23 million residents, 99% were covered by the NHI Program. For the purpose of medical research, the National Health Research Institute has released a database of medical claims of 1,000,000 random subjects based on the 2000 reimbursement data (Longitudinal Health Insurance Database 2000). Each individual's unique personal identification number in NHIRD has been interlinked. The study obtained ethics approval from institutional review board of Chi-Mei Medical Center, Tainan, Taiwan.

Patient Selection and Definition

Traumatic brain injury (*ICD-9-CM* code: 801–804 and 850–854) inpatients from January 2001 to December 2008 were enrolled, and those with preexisting hyperlipidemia were defined as cases. Controls were TBI patients without hyperlipidemia before and after their TBI diagnosis. The presence of hyperlipidemia (*ICD-9-CM* code: 272.0, 272.1, 272.2, 272.4) was defined as at least 3 outpatient visits within 1 year or 1 inpatient admission for the disorder. For examining the incidence of related depressive disorders between cases and controls, all of the patients were followed for at least 3 years until December 31, 2011. The diagnosis of depression was based on the criteria of the *ICD-9-CM* codes such as major depressive disorder, single episode (*ICD-9-CM* code: 296.2X); major depressive disorder, recurrent episode (*ICD-9-CM* code: 296.3X); dysthymic disorder (*ICD-9-CM* code: 300.4); and depressive disorder, not elsewhere classified (*ICD-9-CM* code: 311.X). The event of depressive disorders was defined as at least 3 outpatient visits within 1 year or 1 inpatient admission with a depressive disorders diagnosis. To minimize potential confounding in estimating the incidence of depressive disorders, patients with existing depressive disorders before their TBI diagnosis or those who died within 1 month after their TBI diagnosis were excluded. For each case, 2 controls matched by age and sex were selected.

The baseline covariates included age, sex, income, Charlson Comorbidity Index (CCI)[25] score, hyperlipidemia-related comorbidities, and use of a statin medication. Age was grouped into 5 categories: less than 35, 35–50, 50–65, 65–80, and older than 80 years. The patients' income, based on the insurance amount, was classified into 3 categories: less than $640 (NT$20,000), $640–$1,280 (NT$20,000–NT$39,999), and $1,281 (NT$40,000) or more. The CCI was used to summarize important concomitant diseases based on the *ICD-9-CM* codes.[26] Hyperlipidemia-related comorbidities were hypertension (*ICD-9-CM* code: 401–405, 437.2, and 362.11), cardiovascular disease (*ICD-9-CM* code: 410–414), and diabetes mellitus (*ICD-9-CM* code: 250, 357.2, 362.0, and 366.41). The comorbidities of the CCI and hyperlipidemia-related comorbidities were defined as at least 3 outpatient visits or 1 inpatient admission before 1 year of first TBI diagnosis for a given illness. The medical records for these patients screened for having used statins at least 3 times or longer than 6 months were identified by treatment of hyperlipidemia.

Clinical Points

- The association between preexisting hyperlipidemia and the risk of new-onset depression in patients with traumatic brain injury (TBI) is not established.
- Preexisting hyperlipidemia could be an independent predictor of new-onset depression in TBI patients.
- Statin-treated hyperlipidemia patients presented a lower risk of new-onset depression than did those who received no statins or had no hyperlipidemia in TBI patients.

Statistical Analysis

The differences in baseline characteristics between the TBI patients with preexisting hyperlipidemia and those without were evaluated using Student *t* tests and Pearson χ^2 tests for continuous and categorical variables, respectively. The incidence rate of depressive disorders was calculated by dividing the number of the TBI patients with depressive disorders by the total person-years and was reported as events per 10,000 person-years of follow-up. The incidence rate ratios (IRRs) of depression with 95% confidence intervals (CIs) between the TBI patients with preexisting hyperlipidemia and those without were estimated by a Poisson regression. The Kaplan-Meier plot was presented to describe the proportion of patients who had depressive disorders, and the log-rank test was used to compare the risk difference between the 2 groups. A Cox proportional hazard regression was applied to estimate the relative risks of depressive disorders adjusted for potential confounders. A P value of $< .05$ was considered significant. SAS 9.3 for Windows (SAS Institute, Inc; Cary, North Carolina) was used for all statistical analyses. Kaplan-Meier curves were plotted using STATA (version 12; StataCorp; College Station, Texas).

RESULTS

A total of 3,792 patients were enrolled in this study. Table 1 presents the distribution of the baseline characteristics between the TBI patients with and without hyperlipidemia. After matching by age and sex, the distribution of income, CCI, and comorbidities showed significant differences between the TBI patients with and without hyperlipidemia. In addition, 3.96% and 2.33% of the TBI patients with and without hyperlipidemia, respectively, developed new-onset depression during the follow-up period. The overall follow-up median time was 0.84 years (interquartile range [IQR] = 0.33–1.71). The TBI patients with hyperlipidemia developed new-onset depression (median = 0.83 years, IQR = 0.32–1.54) earlier than those without (median = 0.87 years, IQR = 0.35–1.92).

Table 1. Demographics and Clinical Characteristics of Patients With Traumatic Brain Injury (TBI) With and Without Preexisting Hyperlipidemia

Variable	TBI With Hyperlipidemia (n = 1,264)	TBI Without Hyperlipidemia (n = 2,528)	*P* Value[a]
Age, mean ± SD, y	59.88 ± 14.99	59.88 ± 14.99	.9989
Age group, n (%), y			
<35	68 (5.38)	136 (5.38)	.9985
35–50	263 (20.81)	528 (20.89)	
50–65	431 (34.10)	856 (33.86)	
65–80	389 (30.78)	788 (31.17)	
>80	113 (8.94)	220 (8.70)	
Sex, n (%)			
Male	802 (63.45)	1,604 (63.45)	1.0000
Female	462 (36.55)	924 (36.55)	
Income (Taiwanese new dollar), n (%)			
<NT$20,000	750 (59.34)	1,402 (55.46)	.0420
NT$20,000–NT$39,999	437 (34.57)	980 (38.77)	
≥NT$40,000	77 (6.09)	146 (5.78)	
CCI score, mean ± SD	1.53 ± 2.13	0.73 ± 1.84	<.0001
CCI score, n (%)			
0	499 (39.48)	1,815 (71.80)	<.0001
1	342 (27.06)	380 (15.03)	
≥2	423 (33.47)	333 (13.17)	
Hypertension			
Yes	603 (47.71)	537 (21.24)	<.0001
No	661 (52.29)	1,991 (78.76)	
Diabetes mellitus			
Yes	477 (37.74)	199 (7.87)	<.0001
No	787 (62.26)	2,329 (92.13)	
Cardiovascular disease			
Yes	232 (18.35)	133 (5.26)	<.0001
No	1,032 (81.65)	2,395 (94.74)	
Statin treatment			
Yes	483 (38.21)		
No	781 (61.79)		
Depression			
Yes	50 (3.96)	59 (2.33)	.0048
No	1,214 (96.04)	2,469 (97.67)	
Time to depression,[b] median (IQR), y	0.83 (0.32–1.54)	0.87 (0.35–1.92)	.5212

[a]The *P* value was applied by Student *t* test or Wilcoxon test for continuous variables and Pearson χ^2 for categorical variables.
[b]Overall time to depressive disorders (median [IQR]) is 0.84 (0.33–1.71).
Abbreviations: CCI = Charlson Comorbidity Index, IQR = interquartile range.

The incidence of depression in TBI patients with hyperlipidemia was 1.72 times higher than in TBI patients without hyperlipidemia (*P* = .0056) (Table 2). Of the TBI patients aged 35–50 and 65–80 years, those with hyperlipidemia had a risk of depression 2.41 and 2.31 times higher, respectively, than those without hyperlipidemia. The female TBI patients with hyperlipidemia were more likely to develop depression than those without hyperlipidemia. Of the TBI patients with low income, those with hyperlipidemia had a significantly higher incidence of new-onset depression than those without hyperlipidemia (IRR = 1.78, 95% CI, 1.10–2.88). Moreover, of the TBI patients without comorbidities before their surgery, those with hyperlipidemia showed 1.74 times the incidence risk of new-onset depression compared with those without hyperlipidemia.

After we controlled for potential confounders, hyperlipidemia and cardiovascular disease significantly increased the risk of depression, with hazard ratios (HRs) of 1.61 (95% CI, 1.03–2.53) and 1.78 (95% CI, 1.03–3.08), respectively (Table 3). The Kaplan-Meier plots show that TBI patients with hyperlipidemia had a significantly higher risk of depression than did those without (log rank: *P* = .0047) (Figure 1A). Table 4 presents the risk of new-onset depression stratified by the treatment of statin in TBI patients. TBI patients with preexisting hyperlipidemia not treated with statins had a 1.61-fold (95% CI, 1.03–2.53) increased hazard of depression compared with TBI patients without hyperlipidemia (*P* = .0378). Figure 1B reveals that TBI patients with preexisting hyperlipidemia not treated with statins had a significantly higher risk of depression during the follow-up period than did TBI patients without hyperlipidemia.

DISCUSSION

To our knowledge, this is the first study to present that preexisting hyperlipidemia is an independent risk factor of developing new-onset depression after TBI, especially in patients who were never treated with statins before TBI. This information will hopefully serve as a foundation for future studies on antidepressant therapy for TBI.

In the general population, hyperlipidemia,[15,16] age,[9] sex,[10] socioeconomic status,[11] cardiovascular disease,[12] hypertension,[13] and diabetes mellitus[14] are risk factors of developing depression. In our study, we further elucidated these relationships and provided novel findings that preexisting hyperlipidemia is an independent risk factor of new-onset depression after TBI when adjusting for all potential confounders. Furthermore, hyperlipidemia patients who received statins exhibited a significantly lower risk for depression than did those who did not receive statins. Therefore, we want to emphasize that hyperlipidemia's neuropathological effects on the development of depression after TBI are worth investigating.

Former studies have shown that women are at a higher risk for depressive disorder than men. Kessler et al[27] indicated that women are approximately 1.7 times as likely as men to report a lifetime history of depression. The possible explanations of the greater susceptibility of women to depression may be multifactorial, such as coping styles, responses to stress, and endocrine influences.[28–30] Consistent with previous reports, our study further found that the effect of hyperlipidemia on women was larger than that on men (IRR [women] = 1.86; 95% CI, 1.03–3.35; vs IRR [men] = 1.63; 95% CI, 1.00–2.65). However, the definite mechanisms in our cases of new-onset depression are unclear; nevertheless, we propose that hyperlipidemia could have a more important role as a predisposing factor in depression pathology after TBI for women than for men . This information can provide strategic reference for depression prevention after TBI.

As shown in Table 1, the percentages of TBI patients with hyperlipidemia were higher in low-income (<NT$20,000, 59.34%) and high-income (≥NT$40,000, 6.09%) patients than in those of TBI patients without hyperlipidemia. These variations support the previous findings[31] that household income levels are associated with health insurance

Table 2. Incidence of Depression in Patients With Traumatic Brain Injury (TBI) With and Without Preexisting Hyperlipidemia

	TBI With Hyperlipidemia (n = 1,264)				TBI Without Hyperlipidemia (n = 2,528)					
Variable	n	Depression, n	Person-Years	Rate[a]	n	Depression, n	Person-Years	Rate[a]	IRR (95% CI)	*P* Value
Total	1,264	50	3,659.98	136.61	2,528	59	7,410.64	79.62	1.72 (1.18–2.50)	.0056
Statin treatment										
Yes	483	15	1,409.01	106.46					1.34 (0.76–2.36)	.3150
No	781	35	2,250.97	155.49					1.95 (1.29–2.97)	.0017
Age, y										
< 35	68	3	197.33	152.03	136	4	399.87	100.03	1.52 (0.34–6.79)	.5837
35–50	263	14	754.98	185.44	528	12	1,559.87	76.93	2.41 (1.11–5.21)	.0253
50–65	431	13	1,255.61	103.54	856	19	2,520.79	75.37	1.37 (0.68–2.78)	.3778
65–80	389	18	1,121.02	160.57	788	16	2,301.90	69.51	2.31 (1.18–4.53)	.0148
> 80	113	2	331.04	60.42	220	8	628.22	127.34	0.47 (0.10–2.23)	.3456
Sex										
Male	802	29	2,328.01	124.57	1,604	36	4,704.35	76.53	1.63 (1.00–2.65)	.0508
Female	462	21	1,331.96	157.66	924	23	2,706.29	84.99	1.86 (1.03–3.35)	.0406
Income (Taiwanese new dollar)										
< NT$20,000	750	32	2,164.50	147.84	1,402	34	4,094.17	83.05	1.78 (1.10–2.88)	.0192
NT$20,000–NT$39,999	437	15	1,277.25	117.44	980	22	2,885.92	76.23	1.54 (0.80–2.97)	.1969
≥ NT$40,000	77	3	218.23	137.47	146	3	430.55	69.68	1.97 (0.40–9.78)	.4053
CCI score										
0	499	17	1,451.11	117.15	1,815	36	5,353.96	67.24	1.74 (0.98–3.10)	.0592
1	342	13	996.84	130.41	380	13	1,097.26	118.48	1.10 (0.51–2.37)	.8067
≥ 2	423	20	1,212.03	165.01	333	10	959.42	104.23	1.58 (0.74–3.38)	.2355
Hypertension	603	21	1,745.19	120.33	537	17	1,547.01	109.89	1.10 (0.58–2.08)	.7809
Diabetes mellitus	477	20	1,378.43	145.09	199	7	563.14	124.30	1.17 (0.49–2.76)	.7247
Cardiovascular disease	232	10	670.68	149.10	133	9	369.66	243.47	0.61 (0.25–1.51)	.2859

[a]Per 10,000 years per person. Overall incidence rate of depression is 98.46 per 10,000 years per person.
Abbreviations: CCI = Charlson Comorbidity Index, IRR = incidence rate ratio.

Table 3. Cox Model for Risk of Depression in Patients With Traumatic Brain Injury

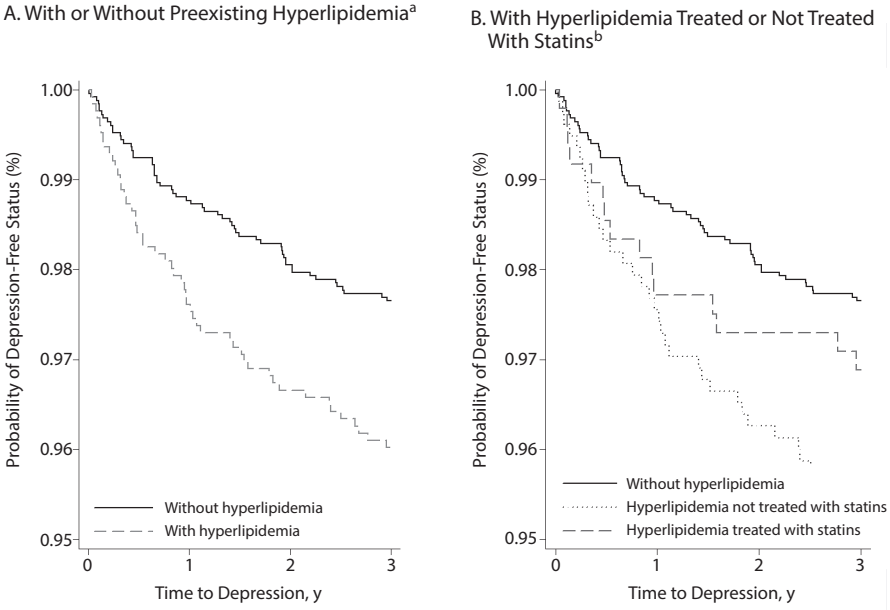
Variable	Crude HR (95% CI)	*P* Value	Adjusted[a] HR (95% CI)	*P* Value
Hyperlipidemia				
Without	1.00 (reference)		1.00 (reference)	
With	1.71 (1.17–2.50)	.0052	1.61 (1.03–2.53)	.0378
Stain treatment				
No	1.00 (reference)		1.00 (reference)	
Yes	1.09 (0.64–1.89)	.7456	0.63 (0.34–1.17)	.1433
Age, y				
< 35	1.00 (reference)		1.00 (reference)	
35–50	0.96 (0.42–2.21)	.9242	0.92 (0.40–2.13)	.8394
50–65	0.73 (0.32–1.64)	.4412	0.63 (0.27–1.45)	.2730
65–80	0.85 (0.38–1.91)	.6925	0.66 (0.28–1.55)	.3382
> 80	0.89 (0.34–2.34)	.8136	0.62 (0.22–1.73)	.3600
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	1.18 (0.80–1.73)	.3997	1.26 (0.85–1.86)	.2428
Income (Taiwanese new dollar)				
< NT$20,000	1.00 (reference)		1.00 (reference)	
NT$20,000–NT$39,999	0.84 (0.56–1.26)	.4095	0.89 (0.59–1.34)	.5734
≥ NT$40,000	0.88 (0.38–2.03)	.7604	0.88 (0.37–2.08)	.7694
CCI score				
0	1.00 (reference)		1.00 (reference)	
1	1.59 (0.99–2.54)	.0532	1.48 (0.87–2.52)	.1469
≥ 2	1.77 (1.13–2.77)	.0124	1.60 (0.89–2.88)	.1132
Hypertension				
No	1.00 (reference)		1.00 (reference)	
Yes	1.26 (0.85–1.87)	.2464	0.94 (0.59–1.49)	.7992
Diabetes mellitus				
No	1.00 (reference)		1.00 (reference)	
Yes	1.54 (1.00–2.39)	.0501	0.99 (0.57–1.74)	.9789
Cardiovascular disease				
No	1.00 (reference)		1.00 (reference)	
Yes	2.03 (1.24–3.33)	.0051	1.78 (1.03–3.08)	.0401

[a]The adjusted hazard ratios were derived from the final multiple regression model.
Abbreviations: CCI = Charlson Comorbidity Index, HR = hazard ratio.

status, medical care use, health, life style, and employment. For example, people with a relatively high income may have the opportunity to search for relatively better health care and, thus, have an artificially increased awareness rate of hyperlipidemia in our study. People with a relatively low income level may be linked to food insecurity, which is the inability to afford nutritionally adequate and safe foods, and, thus, are associated with hyperlipidemia.[32] Several studies have shown that low income is associated with increased depression in type 2 diabetes and other chronic illnesses[33] among patients with chronic obstructive pulmonary disease.[34] Pabayo et al[35] additionally indicated that living in a higher income inequality region could increase the risk of the depression. As shown in Table 2, low income TBI patients with preexisting hyperlipidemia showed a significantly higher incidence of depression compared to those without hyperlipidemia (IRR = 1.78; 95% CI, 1.10–2.88; *P* = .0406).

We further examined if the treatment of hyperlipidemia prior to a TBI episode would affect the risk of posttraumatic new-onset depression. Statins are used mainly for the treatment of hyperlipidemia, but the relationship between depression and statins is not consistent. Simvastatin was found to be associated with decreases in positive affect in elderly people.[36] However, another study[37]

Figure 1. Kaplan-Meier Probability for Depression-Free Status in Patients With Traumatic Brain Injury (A) With or Without Preexisting Hyperlipidemia and (B) With Hyperlipidemia Treated or Not Treated With Statins



[a]Log rank test: $P = .0047$.
[b]Log rank test: $P = .0065$.

Table 4. Risk of Depression for Patients With Traumatic Brain Injury (TBI) With Hyperlipidemia Treated With Statin Compared With Those Without Hyperlipidemia

TBI	Depression, n (%)	No Depression, n (%)	Adjusted HR[a] (95% CI)	*P* Value
Without hyperlipidemia	59 (54.13)	2,469 (67.04)	1.00 (reference)	
With nontreated hyperlipidemia	35 (32.11)	746 (20.26)	1.61 (1.03–2.53)	.0378
With treated hyperlipidemia	15 (13.76)	468 (12.71)	1.02 (0.55–1.89)	.9611

[a]The adjusted hazard ratios were derived from the multiple regression model with the interested variables in Table 3.

showed that hyperlipidemia is associated with increased risk of depression and that the use of statins decreases the risk of depression in patients with hyperlipidemia. This discrepancy maybe due to the final serum cholesterol level since low cholesterol concentration is associated with depression.[38,39] In our study, we found that preexisting hyperlipidemia is a risk factor of new-onset depression and that using statins could decrease the probability of developing posttraumatic new-onset depression. From the trend of development of new-onset depression (Figure 1B), we also found that, in the early stage, there is no difference in the probability of new-onset depression-free status between statin-treated and non–statin-treated groups for TBI patients with preexisting hyperlipidemia. However, around 1-year later, the group not treated with statins presented a significantly higher risk of new-onset depression compared to the statin-treated group. In addition, the finding of no difference in the risk of new-onset depression between TBI patients without hyperlipidemia and statin-treated TBI patients implies that statins may play a critical role in the development of new-onset depression. Thus, the findings could provide some insights into the important role of preexisting hyperlipidemia in the development of new-onset depression in TBI patients. We also suggest that evaluating the lipid profile in the acute stage to prevent depression developing later may be a promising strategy in the neurotrauma field.

Our study has several strengths. It is a population-matched cohort study that investigated the effect of prehyperlipidemia on new-onset depression among TBI patients. Based on the population database, the large sample size and long duration of follow-up made it possible to examine the incidence and risk factors associated with depression. The prospective association between hyperlipidemia and depression in our study design allowed the direction of the effect to be explored. The finding that hyperlipidemia was an independent risk factor of new-onset depression after TBI may indicate an important role in preventive medicine.

However, several limitations in our study should be considered. First, the diagnoses relied on the claims data and the *ICD-9-CM* diagnosis, and, thus, some disease misclassifications may exist. Second, the true outcome (new-onset depression) could be underestimated because of the underdiagnosis and undertreatment of depression in the claims data. Third, we did not evaluate smoking, obesity, or alcohol, which may

influence the development of depression after TBI. Thus, other potential contributors to our results may be undetected. Fourth, information on the severity of TBI (such as Glasgow coma scale) and hyperlipidemia, which may be associated with the occurrence of depression, was unavailable. Although some studies have indicated that the severity of TBI may relate to the length of intensive care unit stay[40–42] or TBI classification into 2 categories based on the *ICD-9-CM*: mild brain injury (*ICD-9-CM* 850) and severe brain injury (*ICD-9-CM* 851–854),[43] the potential limitations of TBI severity definition were still existing. However, some studies[44,45] have indicated that the severity of TBI was not associated with emotional dysfunction in early postsurgery periods. Thus, this evidence supports the view that hyperlipidemia may be an important risk factor of depression in TBI patients. In the future research, it would be of interest to investigate whether the severity of TBI may affect the association between hyperlipidemia and the long-term effect of the new-onset depression. Finally, we expect this study underestimated the numbers of TBI patients without hyperlipidemia because the amount of undiagnosed disease in those without any access to health care is impossible to report.

CONCLUSIONS

Preexisting hyperlipidemia is an independent predictor of new-onset depression in TBI patients, even when controlling for other demographic and clinical covariates. TBI patients with hyperlipidemia, especially for those untreated with statin medications, had a significantly higher risk than did those without hyperlipidemia. Future studies should investigate the role of statins in TBI-induced depression syndromes to determine the effect and safety of long-term statin use.

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