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A reduced risk of stroke with lithium exposure in bipolar disorder: a population-based retrospective cohort study

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Running head: Lithium reduces risk of stroke in bipolar disorder

Abstract

Objectives: The risk of stroke is increased in patients with bipolar disorder. Lithium exhibits neuroprotective effects but the association of lithium use and the risk of stroke are unknown.

Methods: A population-based retrospective cohort study was conducted by utilizing the National Health Insurance Research Database in Taiwan. Subjects firstly diagnosed with bipolar disorder from 2001 to 2006 were identified. A propensity score (PS) for receiving lithium was calculated with variables of age, gender, and comorbidities. The patients with bipolar disorder receiving lithium within the period from diagnosis through December 2011 were designated as the lithium group (n = 635). A 1:2 ratio was used to select PS-matched subjects with bipolar disorder without lithium use (n = 1,250). Multivariate Cox proportional-hazards regression models were used to explore the association, rather than causal inference, of lithium exposure and the risk of stroke.

Results: Of the 1,885 subjects, 86 (4.6%) experienced stroke, including 2.8% of the lithium group and 5.4% of the non-lithium group. Lithium use was associated with a significant reduced risk of stroke [hazard ratio (HR) = 0.39, 95% confidence interval (CI): 0.22–0.68]. Reduced risks of stroke were also associated with the highest cumulative lithium dose [≥ 720

defined daily dose (DDD), HR = 0.25, 95% CI: 0.10–0.59], the longest cumulative exposure period (≥ 720 days, HR = 0.20, 95% CI: 0.06–0.64), and the highest exposure rate (≥ 2 DDD/day, HR = 0.39, 95% CI: 0.21–0.70).

Conclusions: Lithium use was significantly related to a reduced risk of stroke in patients with bipolar disorder.

Keywords: bipolar disorder – lithium – neuroprotection – risk –stroke

Stroke is one of the most severe medical conditions and it accounted for 5.5 million deaths and 44 million disability-adjusted life-years lost worldwide annually (1). Previous studies have demonstrated increased risk of stroke of up to two-fold among patients with bipolar disorder (2-4). However, the possible effects of medication on the risk of stroke were not further analyzed in these studies. Lithium was first suggested as a treatment for psychotic excitement in 1949 (5) and established of its efficacy in the management of bipolar disorder in the 1970s (6). In addition, lithium has been shown to increase neuronal density and gray matter volume in patients with bipolar disorder (7, 8).

In vitro and *in vivo* animal studies have demonstrated multiple neurotrophic and neuroprotective effects of lithium (9). The principle mechanisms underlying lithium's neuroprotection are: 1. Inhibition of glycogen synthase kinase-3 (GSK-3), an enzyme linked to apoptosis induced by various neural insults (10). In animal stroke models, GSK-3 beta was up-regulated, and its inhibition by lithium was implicated as an important neuroprotective mechanism (11). 2. Induction of brain-derived neurotrophic factor (BDNF), which plays a key role in neuronal development, plasticity and survival (12). 3. Increased expression of vascular endothelial growth factor (VEGF), which induces neuronal proliferation and neurovascular remodeling (13). 4. Inhibition of N-methyl–D-aspartate (NMDA) receptor-mediated calcium influx and downstream apoptotic pathways, resulting in decreased glutamate excitotoxicity (14). 5. Inhibition of phosphoinositol phosphatase and regulation of autophagy (15), a critical process for neuronal survival and functioning.

Animal studies also showed that lithium reduced neuronal injury after various insults including ischemia (16-18), hemorrhage (19), and trauma (20). However, only one human study

investigated the neuroprotective effects of lithium after stroke, and the results were inconclusive that only the subgroup of patients with cortical ischemic stroke showed enhanced motor recovery with lithium treatment (21).

It is still unclear whether lithium has any effect on the susceptibility to cerebrovascular disease. The progression from atherosclerotic plaque formation, plaque rupture to ischemic stroke is driven by inflammation, extracellular matrix degradation, and neovascularization (22). Macrophages played an important role in the inflammatory process of atherosclerosis. In an animal study, lithium chloride induced macrophage apoptosis via inhibition of inositol monophosphatase (23). Lithium also reduced the expression of vascular cell adhesion molecule (VCAM)-1 and infiltration of macrophages into the atherosclerotic plaque (24). This in turn decreased the macrophage load within the atherosclerotic plaques and implicated a plaque-stabilizing effect exhibited by lithium. Metalloproteinases participated in the initiation, progression, and rupture of atherosclerotic plaque and the formation of thrombus (25). Matrix metalloproteinase (MMP)-9 was associated with abnormal degradation of the extracellular matrix when its production by macrophages was deregulated. Lithium treatment was found to suppress MMP-9 gene expression and reduce the level of this metalloproteinase (26), thereby reducing plaque instability. Vascular smooth muscle cell (VSMC) proliferation and migration in the intima of the arterial wall also play an important role in atheroma progression (27). VSMCs are also important mediators of abnormal neovascularization in the atherosclerotic plaque which expedites the process toward plaque rupture (28). Lithium inhibited VSMC proliferation and migration in an animal study (29). Lithium also reduced blood glucose and cholesterol levels in mice fed with high fat diet (24) and this may alleviate the detrimental effects of diabetes or hyperlipidemia on stroke events. The above mechanisms contribute to the beneficial effect of lithium on atherosclerosis and cerebral ischemia.

Lithium treatment has been demonstrated to dramatically reduce atherosclerotic plaque formation in mice (24). Another animal study discovered that the combination of low-dose lithium with captopril prevented stroke and improved survival in salt-loaded, stroke-prone spontaneously hypertensive rats, an animal model for cerebrovascular disease (30). However, no study has focused on the effect of lithium on the risk of stroke in human populations. If lithium were to consistently demonstrate neurotrophic and neuroprotective effects that could be translated into clinical benefits for central nervous system disorders such as stroke, it would have significant implications for patients at risk for stroke and other cerebral insults.

We conducted a retrospective cohort study by analyzing a population-based dataset from the National Health Insurance Research Database in Taiwan. The aim was to determine whether lithium is related to the susceptibility to stroke and its occurrence in patients with bipolar disorder.

Methods

Database

The National Health Research Institutes (NHRI), Taiwan, maintain the National Health Insurance Research Database (NHIRD) for research purposes. We obtained a subset of the NHIRD with 1,000,000 random subjects, which accounted for about 5% of all enrollees in the National Health Insurance program. The random sampling process from the NHIRD to yield the one-million subject database were performed by the NHRI and including the following main steps: (i) A serial number was assigned to each of the 23,251,700 subjects in the original population; (ii) A random number generator was used to generate one million random numbers; (iii) The subjects with their serial number matching the generated random numbers were selected to form the database subset (31). There were no statistically significant differences in age, gender, or costs between the sample group and all other enrollees. The database contains information of medical claims for ambulatory care, inpatient care, dental services, and prescription drugs as well as registration files of the enrollees, insured from January 1996 to December 2011. The International Classification of Diseases, Ninth Revision (ICD-9) diagnostic system was incorporated into the data since the year 2000.

Study design

This is an 11-year retrospective cohort study from January 1, 2001 to December 31, 2011. Subjects newly diagnosed with bipolar disorder (i.e., ICD-9 codes: 296.0, 296.1, 296.4~296.9 in three or more outpatient visits or any inpatient hospitalization records) within the interval of January 1, 2001 through December 31, 2006 were first identified. The subjects were excluded if they had any diagnosis of stroke before the diagnosis of bipolar disorder. The patients with bipolar disorder were further divided into the lithium group and the non-lithium group

depending on lithium exposure from the prescription record. This comprised the unmatched cohort in our study.

Since the patients with bipolar disorder in the study were not randomly assigned to lithium treatment, we further utilized propensity score (PS) to reduce potential confounding and selection biases. A multivariate logistic regression model was generated to predict the probability of receiving lithium, given the following set of covariates: age, gender, and comorbidities including diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, and chronic kidney disease. A PS was calculated for each subject and subsequently utilized to match the lithium group with the non-lithium group at a ratio of 1:2. Both the unmatched cohort and the PS-matched cohort were analyzed. The endpoints of the follow-up were the occurrences of the first stroke event (after lithium exposure in the lithium group), death, or end of study on December 31, 2011.

To further clarify the association of lithium exposure and the risk of stroke in patients with bipolar disorder, we utilized three indexes, the cumulative lithium dose, the cumulative lithium exposure period, and the lithium exposure rate, to describe these specific characteristics in the PS-matched cohort. The cumulative lithium dose of each subject was represented by the number of cumulative defined daily dose (DDD) of lithium. This number of cumulative DDD was acquired from dividing the total lithium dosage during the study period by the DDD of lithium (one DDD equals 24 mmol of lithium). The cumulative lithium dose was stratified into 5 subgroups: no use, < 60 DDD, 60–359 DDD, 360–719 DDD, and ≥ 720 DDD. The cumulative lithium exposure period was the sum of the number of days each subject was prescribed with lithium; it was stratified into five subgroups: no use, < 60 days, 60–359 days, 360–719 days, and ≥ 720 days. And the lithium exposure rate was the ratio of the cumulative lithium dose divided by the cumulative lithium exposure period; it was stratified into four subgroups: 0 DDD/day, < 1 DDD/day, 1–2 DDD/day, ≥ 2 DDD/day.

Definition of stroke and comorbidities

The stroke diagnosis was defined by ICD-9 codes 430 to 438 (ischemic: 433–437, hemorrhagic: 430–432) in any inpatient or three or more outpatient treatments during the study period. Patients who had a diagnosis of transient ischemic attack (ICD-9 code: 435) were excluded. Comorbidities in the 12-month period prior to the diagnosis of bipolar disorder including

diabetes mellitus (ICD-9 code: 250), hypertension (code: 401–405), hyperlipidemia (code: 272), chronic kidney disease (code: 585), coronary artery disease (code: 410–413), and congestive heart failure (code: 428) were confirmed by any inpatient or two or more outpatient treatments for the diagnoses in the NHI records.

Statistical analysis

Distributions of lithium users and non-users in age, gender, clinical comorbidities, use of typical antipsychotics, use of atypical antipsychotics, use of mood stabilizers including valproate and carbamazepine, and stroke were examined using Student *t*-tests for continuous variables and chi-square tests for categorical variables. Multivariate Cox proportional hazards regression models were used in both the unmatched cohort and the PS-matched cohort to explore the relationship between lithium exposure and occurrence of stroke, adjusted for age, gender, comorbidities, use of antipsychotics, and use of mood stabilizers. Three additional Cox proportional hazards regression models were implemented in the PS-matched cohort. *Model 1* was adjusted for age, gender, comorbidities, use of antipsychotics, use of mood stabilizers, and the cumulative lithium dose. *Model 2* was adjusted for age, gender, comorbidities, use of antipsychotics, use of mood stabilizers, and the cumulative lithium exposure period. *Model 3* was adjusted for age, gender, comorbidities, use of antipsychotics, use of mood stabilizers, and the lithium exposure rate. The proportional hazard assumptions were satisfied by testing graphically and by including the interaction of time with each covariate in the Cox regression models. The stroke-free survival curves of the lithium group and non-lithium group of both the unmatched cohort and the PS-matched cohort were plotted with the product-limit survival estimators for stroke. All statistical tests were two-sided, conducted at a significance level of 0.05, and reported using p values and 95% confidence intervals. All analyses were performed using the SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

Data for a total of 3,681 subjects in the unmatched cohort and 1,885 subjects in the PS-matched cohort during the observation period from 2001 to 2011 were analyzed. The lithium group of the unmatched cohort was younger in age, consists of more male subjects, and had significantly lower rates of diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease compared to the non-lithium group and had zero case of chronic kidney disease

(Table 1). In the contrary, the propensity score matching process successfully removed these differences in the PS-matched cohort. The lithium group in the PS-matched cohort was not significantly different in terms of age, gender, and comorbidities compared to the non-lithium group (Table 1). Of note, none of the subjects in the PS-matched cohort had chronic kidney disease. The rates of the use of typical antipsychotics, atypical antipsychotics and mood stabilizers were all significantly lower in the non-lithium group compared to the lithium group in both the unmatched and the PS-matched cohort.

Among the total sample of 3,681 subjects in the unmatched cohort, 325 (8.8%) had stroke, including 18 (2.8%) among the lithium group and 307 (10.1%) among non-users. Among the 1,885 subjects in the PS-matched cohort, 86 (4.6%) had stroke, including 18 (2.8%) among the lithium group and 68 (5.4%) among non-users.

As shown in Table 2, after adjusting for possible confounders by using the multivariate Cox proportional hazards regression model, lithium users in the unmatched cohort were associated with a significantly lower risk of stroke compared to non-users [hazard ratio (HR) = 0.43, $p = 0.0010$]. The age-related risk on stroke was 1.06 times per decade older (HR = 1.06, $p < 0.0001$). An increased risk of stroke was also associated with male gender (HR = 1.32, $p = 0.0130$), diabetes mellitus (HR = 1.87, $p < 0.0001$), hypertension (HR = 1.45, $p = 0.0055$), and mood-stabilizer use (HR = 1.54, $p = 0.008$). Typical antipsychotic use (HR = 0.95, $p = 0.6784$) or atypical antipsychotics use (HR = 1.05, $p = 0.6992$) were not significantly associated with the risk of stroke.

In the PS-matched cohort, the lithium group also associated with a significant reduced risk of stroke compared to non-users (HR = 0.39, $p = 0.001$). The age-related risk on stroke was 1.07 times per decade older (HR = 1.07, $p < 0.0001$). No comorbidities were shown to be associated with the risk of stroke in the PS-matched cohort. Typical antipsychotic use (HR = 0.81, $p = 0.4392$) or atypical antipsychotics use (HR = 1.32, $p = 0.2792$) were not significantly associated with the risk of stroke. The use of mood stabilizers was associated with an increased risk of stroke (HR = 2.23, $p = 0.0017$).

The risk of stroke associated with different levels of lithium exposure among the PS-matched cohort was listed in Table 3. Significant reduced risks of stroke was demonstrated in the subgroups with the cumulative lithium dose $\geq$ 720 DDD (HR = 0.25, $p < 0.01$), the subgroup

with the cumulative exposure lithium period of 60–359 days (HR = 0.35, $p < 0.05$), ≥ 720 days (HR = 0.20, $p < 0.01$), and the subgroup with the lithium exposure rate of ≥ 2 DDD/day (HR = 0.39, $p < 0.05$).

The stroke-free survival curves of the lithium group and the non-lithium group of the unmatched cohort and the PS-matched cohort were shown in Figure 1 and Figure 2, respectively. The stroke-free survival probabilities were significantly lower in the non-lithium group in both the unmatched cohort and the PS-matched cohort ($p < 0.0001$ and $p = 0.0080$, respectively). The HRs within each subsequent year during the study period were also marked in the figure. The HRs for stroke associated with lithium use reached statistical significance in the seventh and eighth year of follow-up in the unmatched cohort and the PS matched cohort, respectively.

Discussion

Our study showed that lithium treatment was significantly related to reduced risk of stroke in patients with bipolar disorder. The association appeared to be most prominent with greater amount or longer duration of lithium treatment. Significant reduced risks of stroke were observed in the subgroups with the highest cumulative lithium dose, the longest cumulative lithium exposure period, and the highest lithium exposure rate. This indicated that the dose, duration, and rate of lithium exposure might be related to the risk of stroke in patients with bipolar disorder.

Around 93% of the stroke cases in the PS-matched cohort were of ischemic origin. Additional analysis revealed that the HR of ischemic stroke associated with lithium use in the PS-matched cohort was 0.40, [95% confidence interval (CI): 0.22–0.71, $p = 0.0019$] after adjusted for age, sex, and related confounders. Lithium might alter the process of atherosclerosis via its effect on inflammation, extracellular matrix degradation, and neovascularization.

Our findings that age, male gender, diabetes mellitus, and hypertension associating with an increased risk of stroke in patients with bipolar disorder were compatible with two previous studies similarly focusing on patients with bipolar disorder (2, 3). Of note, our finding that female gender was associated with a reduced risk of stroke was consistent with these two studies but the underlying mechanism is not well understood. Lin et al. (3) also pointed out that

renal disease was a risk factor. However, lithium treatment is generally avoided in patients with severe renal disease due to heightened risk of toxicity (32). None of the 635 patients with bipolar disorder in the lithium group in our study had chronic kidney disease. This reflected the extreme precaution doctors took when prescribing lithium to patients with bipolar disorder with renal dysfunction.

By implementing propensity score matching, we successfully removed the differences of comorbidities between the original groups of patients with bipolar disorder. In the unmatched cohort, the subjects in the non-lithium group were significantly older in age and more prevalent of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease and chronic kidney disease, which were all by themselves risk factors of stroke (33, 34). This may potentially cause overestimation of the association between lithium exposure and the reduced risk of stroke, as the lithium group possessed significant fewer risk factors at baseline. The finding that the risk of stroke remained significantly reduced in association with the lithium group in the PS-matched cohort strengthened our findings.

Psychiatric disorders such as depression (35) and schizophrenia (36) also possessed higher risks for stroke. Lithium may be used as adjunctive treatment for subjects with mood swings or those at risk of suicide in these psychiatric patient groups. There is possibility that lithium alters the risk of stroke in such patients but our results could not be extrapolated to subjects beyond the bipolar disorder group.

Various psychotropic agents may as well alter the risk of stroke. Unfortunately, there is no previous study focusing on the association of medication use and the risk of stroke in patients with bipolar disorder. In our analyses of the unmatched cohort and the PS-matched cohort, we adjusted for both the use of typical antipsychotics and atypical antipsychotics, which were not associated with the risk of stroke in patients with bipolar disorder. From studies targeting other disease populations, such as schizophrenia and dementia, the risk of stroke associated with antipsychotics use were equivocal. Some studies reporting no difference in the association between the risk of stroke and both typical and atypical antipsychotics use (37), others reported increased risk of stroke associated with typical antipsychotics (38-40), and still others reported increased risk of stroke associated with atypical antipsychotics (41). This finding of no significant association may also be related to the distinctive effects on the risk of stroke among different individual antipsychotics. In addition, we found that the use of mood stabilizers was

associated with and increased risk of stroke. No previous study has evaluated the association of the risk of stroke and mood stabilizers use. However, in previous epilepsy studies, in which the mood stabilizers in our study were used as anticonvulsants, a similar increased risk of stroke associated with anticonvulsants use was demonstrated (42, 43). Further studies with a broader range of subjects and a detailed differentiation of prescribed medication, are needed to fully delineate the effect of lithium treatment on the risk of stroke.

Strengths and limitations

One of the strengths of the current study was the use of the National Health Insurance Research Database of Taiwan, which included diagnostic coding and records of prescribed medication in detail. Lithium is a medication with clear clinical indications; records of lithium prescriptions are therefore considered valid and reliable. The database also provided a sample with a large number of subjects, allowing for analysis with strong statistical power. We focused on the lithium use among people with bipolar disorder, and this can avoid the bias of use by indication. Propensity score matching and Cox proportional hazards regression models minimized possible confounding effects. In addition, this is the first study to take into consideration of psychotropic medications when analyzing the risk of stroke in patients with bipolar disorder.

There were several limitations in our study. One of the most important limitations was that our study design precludes causal inference and the associations of lithium use and reduced risk of stroke should be interpreted with caution. In addition, because of the lack of information in NHIRD records of other possible risk factors of stroke, such as body-mass index, cigarette smoking, and alcohol consumption, our study could not control these confounders. Due to the fact that lithium was rarely prescribed for patients with severe renal dysfunction and the lithium group in our cohorts contained no patients with chronic kidney disease, the results could not be extrapolated to patients with bipolar disorder with chronic kidney disease. Finally, the results should not be generalized to patients receiving lithium treatment for conditions other than bipolar disorder.

Conclusions

Lithium use may be associated with reduced risk of stroke in patients with bipolar disorder. This association may be most prominent among the patients with bipolar disorder with higher dose, longer duration, and higher rate of lithium exposure. In clinical practice, prevention of stroke by monitoring and early intervention for relevant cerebrovascular risk factors is of paramount importance for patients with bipolar disorder, since bipolar disorder itself is a risk factor for stroke. Lithium treatment in patients with bipolar disorder may be a reasonable choice if the patient does not have chronic kidney disease. The lithium treatment duration or timing of discontinuation may influence the association with the risk of stroke. As our study design precludes causal inference, future studies are indicated to clarify whether lithium exerts protective effect on stroke and the possible underlying mechanisms if such a protective effect exists.

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Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

Figure legends

Fig. 1. The product-limit survival estimates for stroke of the unmatched cohort. [a]Hazard ratio. *p < 0.50, **p < 0.01.

Fig. 2. The product-limit survival estimates for stroke of the propensity score matched cohort. [a]Hazard ratio. *p < 0.50.

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Table 1. Characteristics of study participants

Variables	Unmatched cohort			PS-matched cohort		
	Without lithium (n = 3,046)	With lithium (n = 635)	p-value	Without lithium (n = 1,250)	With lithium (n = 635)	p-value
Age, years, mean ± SD	44.5 ± 17.2	36.0 ± 13.7	< 0.0001	37.0 ± 14.3	36.0 ± 13.7	0.1610
Sex, n (%)						
Female	1800 (59.1)	335 (52.8)	0.0030	692 (55.4)	335 (52.8)	0.2830
Male	1246 (40.9)	300 (47.2)		558 (44.6)	300 (47.2)	
Diabetes mellitus, n (%)						
No	2849 (93.5)	624 (98.3)	< 0.0001	1232 (98.6)	624 (98.3)	0.6260
Yes	197 (6.5)	11 (1.7)		18 (1.4)	11 (1.7)	
Hypertension, n (%)						
No	2561 (84.1)	602 (94.8)	< 0.0001	1185 (94.8)	602 (94.8)	0.9980
Yes	485 (15.9)	33 (5.2)		65 (5.2)	33 (5.2)	
Hyperlipidemia, n (%)						
No	2886 (94.7)	621 (97.8)	0.0010	1221 (97.7)	621 (97.8)	0.8740
Yes	160 (5.3)	14 (2.2)		29 (2.3)	14 (2.2)	
Chronic kidney disease, n (%)						
No	3017 (99.1)	635 (100)	0.0140	–	–	–
Yes	29 (0.9)	0 (0)		–	–	–
Coronary artery disease, n (%)						
No	2882 (94.6)	625 (98.4)	< 0.0001	1233 (98.6)	625 (98.4)	0.7110
Yes	164 (5.4)	10 (1.6)		17 (1.4)	10 (1.6)	
Congestive heart failure, n (%)						
No	3004 (98.6)	630 (99.2)	0.2270	1243 (99.4)	630 (99.2)	0.5520
Yes	42 (1.4)	5 (0.8)		7 (0.6)	5 (0.8)	
Typical antipsychotics, n (%)						
No	882 (29.0)	76 (12.0)	< 0.0001	338 (27.0)	72 (11.3)	< 0.0001
Yes	2164 (71.0)	559 (88.0)		912 (73.0)	563 (88.7)	
Atypical antipsychotics, n (%)						

No	1855 (60.9)	154 (24.3)	< 0.0001	727 (58.2)	150 (23.6)	< 0.0001

Variables	Unmatched cohort		PS-matched cohort	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Lithium	0.43 (0.26–0.71)	0.0010	0.39 (0.22–0.68)	0.0010
Age (10 years)	1.06 (1.05–1.07)	< 0.0001	1.07 (1.06–1.09)	< 0.0001
Sex (male/female)	1.32 (1.06–1.65)	0.0130	1.50 (0.98–2.32)	0.0639
Diabetes mellitus	1.87 (1.37–2.54)	< 0.0001	2.60 (0.87–7.78)	0.0872

Yes	1191 (39.1)	481 (75.7)		523 (41.8)	485 (76.4)	
Mood stabilizers, n (%)						
No	1949 (64.0)	185 (29.1)	< 0.0001	742 (59.4)	180 (28.3)	< 0.0001
Yes	1097 (36.0)	450 (70.9)		508 (40.6)	455 (74.7)	
Incident stroke events, n (%)						
No	2739 (89.9)	617 (97.2)	0.0030	1182 (94.6)	617 (97.2)	0.0100
Yes	307 (10.1)	18 (2.8)		68 (5.4)	18 (2.8)	

PS = propensity score; SD = standard deviation.

Table 2. Multivariate Cox proportional analyses for hazard ratio of stroke

Hypertension	1.45 (1.12–1.89)	0.0055	1.56 (0.86–2.84)	0.1458
Hyperlipidemia	0.85 (0.57–1.26)	0.4139	0.70 (0.20–2.41)	0.5659
Chronic kidney disease	0.96 (0.42–2.19)	0.9125	–	–
Coronary artery disease	1.15 (0.82–1.61)	0.4114	1.29 (0.49–3.39)	0.6002
Congestive heart failure	0.62 (0.27–1.42)	0.2599	0.59 (0.08–4.40)	0.6082
Typical antipsychotics	0.95 (0.74–1.22)	0.6784	0.81 (0.48–1.37)	0.4392
Atypical antipsychotics	1.05 (0.82–1.34)	0.6992	1.32 (0.80–2.19)	0.2792
Mood stabilizers	1.54 (1.19–1.97)	0.0008	2.23 (1.35–3.67)	0.0017

CI = confidence interval.

Table 3. Adjusted hazard ratios (HR) of lithium dosage or duration for stroke in PS-matched cohort

Variables		Model 1		Model 2		Model 3	
	n	Adjusted HR	95% CI	Adjusted HR	95% CI	Adjusted HR	95% CI
Age (10 years)		1.07	(1.06–1.09)[a]	1.07	(1.06–1.09)[a]	1.07	(1.06–1.09)[a]
Sex		1.51	(0.98–2.33)	1.52	(0.99–2.35)	1.48	(0.96–2.27)
Male	858						
Female	1,027						
Cumulative lithium dose							
No use	1,250	1.00	Reference				
< 60 DDD	86	0.61	(0.19–1.98)				
60–359 DDD	151	0.49	(0.19–1.24)				
360–719 DDD	75	0.58	(0.20–1.63)				
≥ 720 DDD	323	0.25	(0.10–0.59)[b]				
Cumulative lithium exposure period							
No use	1,250			1.00	Reference		
< 60 days	179			0.70	(0.33–1.48)		
60–359 days	181			0.35	(0.14–0.88)[c]		
360–719 days	79			0.36	(0.09–1.51)		
≥ 720 days	196			0.20	(0.06–0.64)[b]		
Lithium exposure rate							
0 DDD/day	1,250					1.00	Reference
< 1 DDD/day	24					1.05	(0.24–4.58)
1–2 DDD/day	67					0.19	(0.03–1.41)
≥ 2 DDD/day	544					0.39	(0.21–0.70)[c]

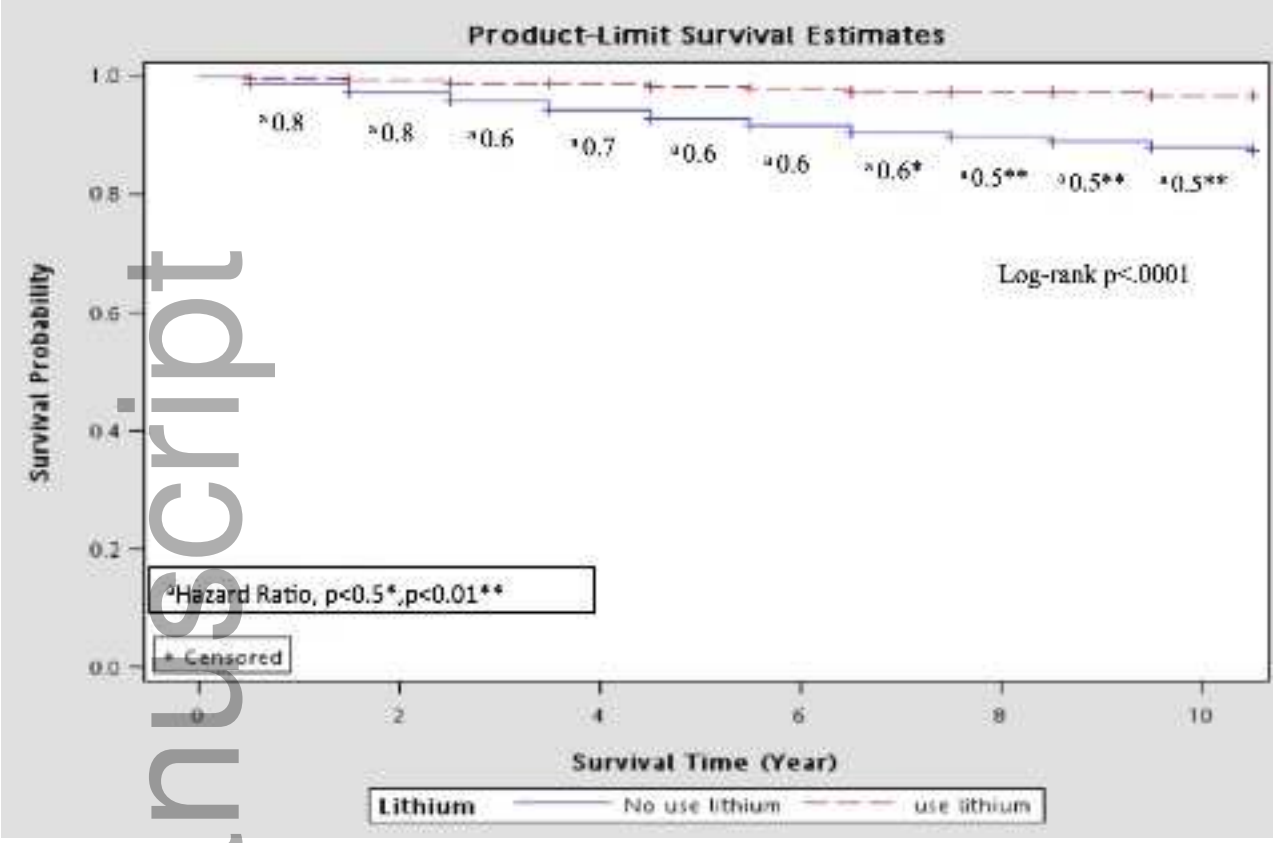
Diabetes mellitus		2.65	(0.88–7.98)	2.62	(0.87–7.87)	2.70	(0.89–8.13)
Yes	29						
No	1,856						
Hypertension		1.54	(0.85–2.81)	1.54	(0.85–2.82)	1.53	(0.84–2.80)
Yes	98						
No	1,787						
Hyperlipidemia		0.66	(0.19–2.28)	0.67	(0.19–2.29)	0.68	(0.19–2.39)
Yes	43						
No	1,842						
Coronary artery disease		1.32	(0.50–3.48)	1.28	(0.49–3.38)	1.26	(0.48–3.33)
Yes	27						
No	1,858						
Congestive heart failure		0.54	(0.07–4.09)	0.52	(0.07–4.03)	0.52	(0.07–3.98)
Yes	12						
No	1,873						
Typical antipsychotic		0.82	(0.49–1.38)	0.81	(0.48–1.37)	0.81	(0.48–1.37)
Yes	1,475						
No	410						
Atypical antipsychotic		1.31	(0.79–2.18)	1.34	(0.81–2.21)	1.32	(0.79–2.19)
Yes	1,008						
No	877						
Mood stabilizers		2.27	(1.38–3.72)[b]	2.28	(1.39–3.74)[b]	2.23	(1.35–3.67)[b]
Yes	963						
No	922						

PS = propensity score; CI = confidence interval; DDD = defined daily dose.

[a] $p < 0.001$.

[b] $p < 0.01$.

[c] $p < 0.05$.



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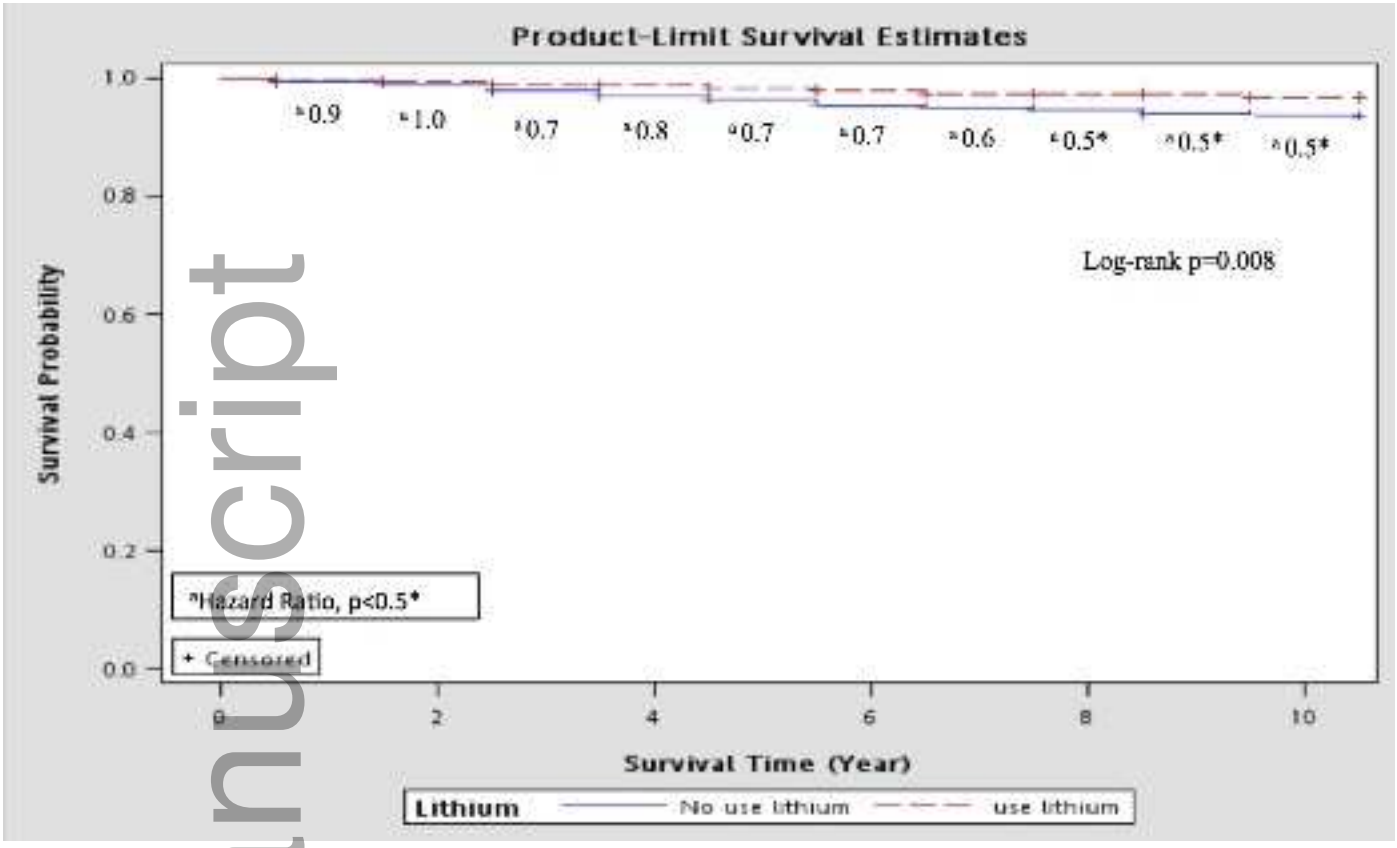

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