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ORIGINAL PAPER

Increased risk of fracture in patients with bipolar disorder: a nationwide cohort study

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Abstract
Objectives Bipolar disorder (BD) is a systemic inflammatory disease, and disrupted bone metabolism due to the inflammatory process can cause fracture. Despite evidence of an association between lower bone mineral density and an increased risk of fracture among patients with depression, schizophrenia, and anorexia nervosa, whether BD is a risk factor for subsequent fracture is unknown. To determine the association between BD and fracture and to examine the risk factors for fracture among patients with BD.
Methods In this study, we enrolled patients diagnosed with BD from the Taiwan National Health Insurance Research Database. Patients newly diagnosed with BD (ICD-9-CM 296) from 2001 to 2008 were included in the BD cohort, and the date of the initial diagnosis of BD was used as the index date. The comparison cohort, comprising participants without BD, was frequency matched to the BD cohort by age, sex, and index year, and the occurrence of fracture was evaluated in both cohorts.
Results The BD and comparison cohorts were comprised of 47,271 patients with BD and 1,89,084 frequency-matched participants without BD, respectively. The incidence of fracture was higher among patients with BD than among the controls. Cox models showed that BD was an independent risk factor for fracture irrespective of comorbidities [hazard ratio (HR) = 1.79, 95 % confidence interval (CI) = 1.73–1.84, $p < .001$].
Conclusion Our study showed that patients with BD have a higher risk of subsequent fracture. Additional prospective clinical studies investigating the relationship between BD and fracture are warranted.

Keywords Bipolar disorder · Fracture · Taiwan National Health Insurance Research Database

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Introduction

Bipolar disorder (BD), a group of affective disorders in psychiatry, manifests as multiple depressive or manic episodes [1]. These symptoms render BD a burden to the patients, caregivers, and society [2]. Currently, treatment for BD mainly comprises a combination

therapy of mood stabilizers and antipsychotics for the prevention of relapse [3]. Although treatment for BD has been extensively investigated, the characteristics of the high relapse and recurrence rates can impair the function and cognition of these patients after each episode [4]. Moreover, patients with BD have been reported to exhibit such medical conditions as cardiovascular disease, diabetes, thyroid disease, and arthritis, which not only burdens the patients but also affect the outcome and course of BD [5–7]. Medical conditions such as rheumatoid arthritis (RA) have been associated with BD because of the common pathogenesis of chronic inflammation [8]. Chronic inflammation in BD is associated with immune dysregulation, which involves proinflammatory cytokine secretion and inflammation in the central nervous system (CNS) [9, 10]. Although proinflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukins (ILs), are mostly secreted in the periphery [11, 12], studies have implied that the linkage of immune dysregulation between the body and the brain may be through the disruption of the blood–brain barrier, which protects the CNS [13]. Consequently, BD can be considered a systemic inflammatory disease [14].

Fractures can result from various bone diseases, including osteoporosis [15]. In normal bone metabolism, osteoblasts and osteoclasts play a vital role in bone remodeling through interaction with external mechanical signals and the process of mechanotransduction [16]. Osteoclasts, derived from monocytes in the periphery, are responsible for bone resorption, in which many cytokines are involved [17]. Although proinflammatory cytokines, such as IL-1, IL-6, and TNF-α, are critical in bone metabolism, these cytokines have also been attributed to the pathogenesis of osteoporosis and an increased risk of fracture [18]. Studies have shown that chronic inflammation can mediate bone loss through the disturbance of the receptor activator of nuclear factor κ-B ligand (RANKL)–RANK–osteoprotegerin (OPG) axis, an essential regulator in bone metabolism [19, 20]. Except for inflammatory autoimmune diseases, such as RA and systemic lupus erythematosus [21], an increased risk of fracture has been reported for such medical conditions as diabetes mellitus and chronic kidney disease [22, 23]. Moreover, psychiatric illnesses, such as depression, schizophrenia, and anorexia nervosa, have been associated with lower bone mineral density and an increased risk of fracture [24–28]. Hence, we hypothesized that BD may be a risk factor for subsequent fracture.

To test our hypothesis, we conducted a nationwide population-based study to investigate the fracture risk in BD patients.

Methods

Data source

The data of this study were collected from the National Health Insurance Research Database (NHIRD). The NHIRD contains reimbursement claims data, including registry of beneficiaries, clinic and hospital care data, and medical services, from the Taiwan NHI program, a nationwide, single-payer health insurance program established in 1995. The Taiwan NHI program covered nearly 99.9 % of the 23 million Taiwanese citizens as of 2007. The Taiwanese government appointed the National Health Research Institutes (NHRI) to establish and manage the NHIRD, which is updated annually. To protect patient privacy, the NHRI encrypts the original identification numbers and assigns anonymous identification numbers before releasing the database for research purposes. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

Data on the history of comorbidities were collected from the inpatient and outpatient files, and the record of BD was collected from the registry for catastrophic illness patients. Disease diagnosis in the NHIRD is based on the criteria of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

Study population

To determine the association between BD and fracture, we used a retrospective population-based cohort study design. This study included two study cohorts: a BD cohort and a comparison cohort. The BD cohort comprised patients newly diagnosed with BD (ICD-9-CM 296) from 2001 to 2008, and the initial diagnosis date was used as the index date. The comparison cohort comprised individuals without a history of BD in the NHIRD and was frequency matched to the BD cohort in a 4:1 ratio by age (per 5 years), and sex. Individuals in the comparison cohort were randomly assigned an index date within the same year of the matched cases. We excluded individuals with a history of fracture who were diagnosed before the index date. The occurrence of fracture was evaluated in both cohorts (ICD-9-CM 800–829). Each participant was followed until withdrawal from the insurance program, the occurrence of fracture, or December 31, 2011.

Age, sex, and fracture-associated comorbidities were the confounding factors. Comorbidities were defined as diseases diagnosed before the index date and included DM (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), hypertension (HTN)

(ICD-9-CM 401–405), coronary artery disease (CAD) (ICD-9-CM 410–414), osteoporosis (ICD-9-CM 733.0 and 733.1), alcohol-related illness (ICD-9-CM 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, and V11.3), stroke (ICD-9-CM 430–438), and epilepsy (ICD-9-CM 345).

Statistical analyses

The descriptive statistics of study cohorts are presented as mean and standard deviation (SD) for age and as number and percentage for sex and comorbidity. The difference in the distribution of these statistics between the study cohorts was assessed using the *t* test for age and the Chi-square test for sex and comorbidity. We calculated the incidence of fracture in the study cohort by dividing the number of fracture events by the total follow-up time (per 1000 person years). The cumulative incidence curves of fracture occurrence were generated using the Kaplan–Meier method. The difference in the curves was assessed using the log rank test. Poisson regression analysis was used to estimate the incidence rate ratio (IRR) in the BD and comparison cohorts. The main effect of BD was estimated using uni- and multivariate Cox proportional hazard models; the results are presented as hazard ratios (HRs) and 95 % confidence intervals (CIs). Moreover, we estimated the risk of fracture in the BD and comparison cohorts by assessing differences in demographic characteristics and comorbidities through stratified analyses using the Cox models. The influence of the frequency of hospital care for BD was considered. We calculated the average frequency of hospital care for BD and categorized it into five levels: non-BD, ≤6, 6–12, 13–18, and >18 times. We used Cox models to estimate the fracture risk for each level of hospital care. In addition, we evaluated the effects of multiplicative interaction between BD and the various comorbidities for fracture risk by using Cox models. To present the multiplicative interaction, we determined the risk of fracture for those participants both BD and comorbidity, patients with BD only, those with comorbidity only, and those with both BD and comorbidity. We further analyze the risk of fracture localization and fracture cause were separated by ICD-9-CM code. The fracture localization were divided into 4 sub-groups, including skull (ICD-9-CM: 800–804), trunk (ICD-9-CM: 805–809), upper limbs (ICD-9-CM: 810–819), and lower limbs (ICD-9-CM: 820–829). Fracture patients were further divided into the trauma patient, who with external causes of injury code (E code), and non-trauma subgroups. Data management and statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA), and the cumulative curve was generated using R software. The significance level was set as two-sided $p < .05$.

Results

Table 1 presents the demographic characteristics and comorbidities of the BD and comparison cohorts. In total, we enrolled 47,271 patients with BD and 1,89,084 controls

Table 1 Demographics factors and comorbidity between bipolar and non-bipolar cohorts

	Bipolar				*p* value
	No ($N = 189,084$)		Yes ($N = 47,271$)		
	n	%	*n*	%	
Age, year					.99
<35	58,640	31.0	14,660	31.0	
35–64	110,812	58.6	27,703	58.6	
≥65	19,632	10.4	4908	10.4	
Mean (SD)[a]	43.7 (15.5)		43.8 (15.5)		.65
Sex					.99
Women	118,048	62.4	29,512	62.4	
Men	71,036	37.6	17,759	37.6	
Comorbidity					
Diabetes	15,632	8.27	6445	13.6	<.0001
Hypertension	34,580	18.3	12,762	27.0	<.0001
Hyperlipidemia	23,799	12.6	9255	19.6	<.0001
CAD	15,848	8.38	7525	15.9	<.0001
Osteoporosis	7354	3.89	3350	7.09	<.0001
Stroke	9242	4.89	5530	11.7	<.0001
Epilepsy	966	.51	1605	3.40	<.0001
Alcohol-related illness	1445	.76	3558	7.53	<.0001

Chi-square test

[a] Student's *t* test

Table 2 Incidence and adjusted hazard ratios of fracture in bipolar and non-bipolar cohorts stratified by sex, age, comorbidity and follow-up time

Variables	Bipolar						Compared to non-bipolar	
	No			Yes				
	Event	PY	Rate	Event	PY	Rate	IRR (95 % CI)	Adjusted HR[a] (95 % CI)
Overall	13,600	1,257,533	10.8	6288	294,032	21.4	1.98 (1.93–2.02)***	1.79 (1.73–1.84)***
Sex								
Women	8422	783,152	10.8	4001	184,196	21.7	2.02 (1.96–2.08)***	1.91 (1.84–1.99)***
Men	5178	474,381	10.9	2287	109,836	20.8	1.91 (1.84–1.98)***	1.63 (1.55–1.72)***
Age, year								
<35	2521	403,485	6.3	1415	97,087	14.6	2.33 (2.24–2.43)***	2.10 (1.96–2.25)***
35–64	7792	738,068	10.6	3750	171,598	21.9	2.07 (2.01–2.13)***	1.76 (1.69–1.83)***
≥65	3287	115,981	28.3	1123	25,347	44.3	1.56 (1.46–1.67)***	1.42 (1.33–1.53)***
Comorbidity								
No	7427	915,520	8.1	2338	160,442	14.6	1.80 (1.74–1.85)***	1.92 (1.83–2.01)***
Yes	6173	342,014	18.1	3950	133,590	29.6	1.64 (1.58–1.70)***	1.88 (1.81–1.96)***
Follow time (year)								
<1	1894	187,304	10.1	1261	46,064	27.4	2.71 (2.64–2.78)***	2.40 (2.22–2.58)***
1–3	3906	363,668	10.7	1938	86,220	22.5	2.09 (2.04–2.15)***	1.84 (1.74–1.95)***
3–5	3412	315,582	10.8	1465	72,922	20.1	1.86 (1.81–1.91)***	1.69 (1.58–1.80)***
5–7	2498	230,019	10.9	981	51,975	18.9	1.74 (1.68–1.80)***	1.62 (1.50–1.75)***
≥7	1890	160,960	11.7	643	36,851	17.5	1.49 (1.43–1.55)***	1.42 (1.29–1.56)***

PY person-year, *Rate* incidence rate (per 1000 person-years), *IRR* incidence rate ratio

* $p < .05$, ** $p < .01$, *** $p < .001$

[a] Multiple analysis including age, sex, and comorbidities history by Cox proportional hazard regression model

with a similar average age (43 years) and the same sex ratio (men: 37.6 %). We observed that the percentage of listed comorbidities in the BD cohort was higher than that in the comparison cohort ($p < .0001$ for all).

The incidence of fracture was 21.4 per 1000 person-years in the BD cohort and only 10.8 per 1000 person-years in the comparison cohort (Table 2). In addition, Fig. 1 reveals that the incidence of fracture in patients with BD is significantly higher than that in participants without BD (log rank test $p < .0001$). After adjustment for age, sex, and comorbidities, patients with BD had a 1.79-fold higher risk of subsequent fracture than the controls (HR = 1.79, 95 % CI = 1.73–1.84).

Furthermore, Table 2 summarizes the analysis stratified by age, sex, comorbidities, and follow-up time. Female patients with BD had a 1.91-fold higher risk of fracture than the controls (HR = 1.91, 95 % CI = 1.84–1.99); the risk of fracture was 1.63-fold higher in male patients with BD than in the controls (HR = 1.63, 95 % CI = 1.55–1.72). Relative to participants without BD, the risk of fracture was 2.10-, 1.76-, and 1.42-fold in patients with BD who were aged <35 years (HR = 2.10, 95 % CI = 1.96–2.25), 35–64 years (HR = 1.76, 95 % CI = 1.69–1.83), and ≥65 years (HR = 1.42, 95 % CI = 1.33–1.53). Regardless of comorbidities, patients with BD showed an increased risk of fracture. In the different follow-up times, relative to the comparison cohort,

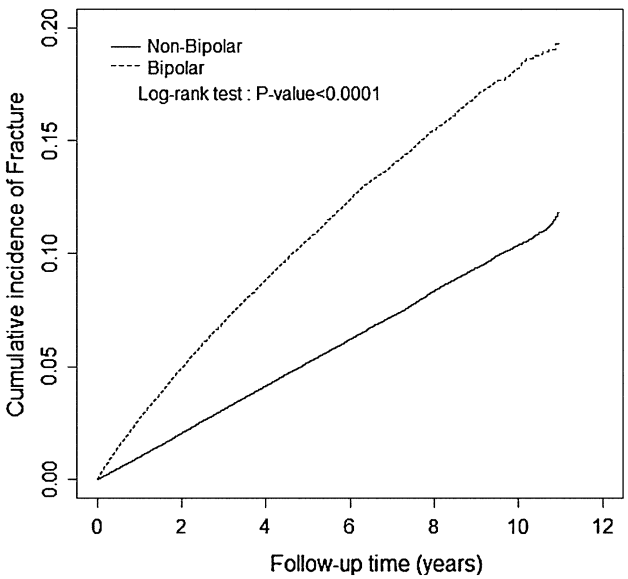

Fig. 1 The cumulative incidence of fracture among non-Bipolar (*solid line*) and Bipolar (*dashed line*) cohorts

Table 3 The adjusted hazard ratios of fracture associated bipolar interaction of comorbidity

Variable		*N*	Event	Adjusted HR (95 % CI)	*p* value[#]
Bipolar	Diabetes				<.0001
No	No	197708	35762	Ref	
No	Yes	18759	5221	1.80 (1.75–1.86)***	
Yes	No	16570	5064	5.45 (5.29–5.62)***	
Yes	Yes	3318	1224	7.18 (6.77–7.61)***	
Bipolar	Hypertension				<.0001
No	No	175751	30569	Ref	
No	Yes	40716	10414	1.81 (1.76–1.86)***	
Yes	No	13262	3940	5.62 (5.43–5.81)***	
Yes	Yes	6626	2348	7.88 (7.53–8.24)***	
Bipolar	Hyperlipidemia				<.0001
No	No	187654	33374	Ref	
No	Yes	28813	7609	1.69 (1.64–1.73)***	
Yes	No	15647	4642	5.39 (5.22–5.56)***	
Yes	Yes	4241	1646	7.88 (7.48–8.29)***	
Bipolar	CAD				<.0001
No	No	196649	34895	Ref	
No	Yes	19818	6088	2.07 (2.01–2.13)***	
Yes	No	16333	4851	5.44 (5.28–5.61)***	
Yes	Yes	3555	1437	8.60 (8.14–9.09)***	
Bipolar	Osteoporosis				.0002
No	No	207829	38446	Ref	
No	Yes	8638	2537	1.62 (1.56–1.69)***	
Yes	No	17822	5475	5.25 (5.10–5.41)***	
Yes	Yes	2066	813	7.26 (6.76–7.80)**	
Bipolar	Stroke				<.0001
No	No	204152	36539	Ref	
No	Yes	12315	4444	2.48 (2.40–2.57)***	
Yes	No	17431	5202	5.39 (5.23–5.55)***	
Yes	Yes	2457	1086	9.58 (9.00–10.2)***	
Bipolar	Epilepsy				<.0001
No	No	214284	39655	Ref	
No	Yes	2183	1328	3.44 (3.26–3.63)***	
Yes	No	19500	6011	5.21 (5.06–5.36)***	
Yes	Yes	388	277	13.4 (11.9–15.1)***	
Bipolar	Alcohol-related illness				<.0001
No	No	212313	38130	Ref	
No	Yes	4154	2853	5.96 (5.74–6.20)***	
Yes	No	19039	5583	5.11 (4.97–5.26)***	
Yes	Yes	849	705	24.4 (22.6–26.3)***	

Model adjusted for age and sex

ref reference group

* $p < .05$, ** $p < .01$, *** $p < .001$

[#] *p* value for interaction

the risk of fracture in the BD cohort was highest for follow-up time ≤1 year (HR = 2.40, $p < .001$), and the risk decreased with increasing follow-up time.

Table 4 Adjusted hazard ratios of fracture associated with number of used hospital care service per year due to bipolar during the study period

Variables	*N*	Event	Adjusted HR[a] (95 % CI)
Non-Bipolar	189084	13600	Ref
Number of used hospital care service per year			
≤6	16655	1539	1.21 (1.15–1.28)***
6–12	13454	1575	1.51 (1.43–1.59)***
12–18	10464	1673	2.22 (2.11–2.34)***
>18	6698	1501	3.78 (3.57–3.99)***
p value for trend			<.0001

* $p < .05$, ** $p < .01$, *** $p < .001$

[a] Multivariable analysis including for age, sex, and comorbidities history by Cox proportional hazard regression model; Hospital care service including outpatient and hospitalized services

Table 3 shows the interaction of BD with the comorbidities; the results reveal significantly increased risks of fracture ($p < .001$). Patients with both BD and comorbidities had increased risks of fracture compared with participants without BD, and patients with comorbidities or participants with neither BD nor comorbidities.

Table 4 clarifies the association between the risk of fracture and the frequency of hospital care for BD (per year). Relative to participants without BD, patients with BD having an average frequency of ≤6 times for hospital care had a 1.21-fold higher risk of fracture (HR = 1.21, 95 % CI = 1.15–1.28), and the risk of fracture increased with the increased frequency of hospital care services: 6–12 times (HR = 1.51, $p < .001$), 12–18 times (HR = 2.22, $p < .001$), and >18 times per year (HR = 3.78, $p < .001$) (*P* for trend <.001).

Table 5 showed the bipolar cohort had statistically significant higher risk than non-bipolar cohort regardless of fracture localization, such as skull (HR = 1.99, 95 % CI = 1.74–2.27), trunk (HR = 2.01, 95 % CI = 1.89–2.15), upper limbs (HR = 1.65, 95 % CI = 1.56–1.74), and lower limbs (HR = 1.79, 95 % CI = 1.70–1.89). The fracture of trauma was presented 2.01-fold risk in bipolar patient, compared to non-bipolar cohort (95 % CI = 1.92–2.10; Table 5).

Discussion

Our study is the first retrospective population-based study to investigate BD as a risk factor for fracture by using a matched cohort and a long-term (10 years) follow-up. The major finding of our study is the higher incidence of subsequent fracture among patients with BD. We found that BD is an independent risk factor for subsequent fracture regardless of age, sex, and comorbidities.

Table 5 Incidence and adjusted hazard ratios of fracture in different localization and causes between bipolar and non-bipolar cohorts

Variables	Bipolar				Compared to non-bipolar	
	Event	Rate	Event	Rate	IRR (95 % CI)	Adjusted HR[a] (95 % CI)
Fracture localization						
Skull	715	.57	398	1.35	2.38 (2.31–2.45)***	1.99 (1.74–2.27)***
Trunk	2750	2.19	1463	4.98	2.28 (2.22–2.34)***	2.01 (1.89–2.15)***
Upper limbs	5280	4.20	2210	7.52	1.79 (1.74–1.84)***	1.65 (1.56–1.74)***
Lower limbs	4855	3.86	2217	7.54	1.95 (1.90–2.00)***	1.79 (1.70–1.89)***
Fracture cause						
Trauma	5640	4.48	2978	10.1	2.26 (2.20–2.31)***	2.01 (1.92–2.10)***
Non-trauma	7960	6.33	3310	11.3	1.03 (.99–1.07)	1.05 (1.01–1.10)*

Rate, incidence rate (per 1000 person-years)

IRR incidence rate ratio

* $p < .05$, ** $p < .01$, *** $p < .001$

[a] Multiple analysis including age, sex, and comorbidities history by Cox proportional hazard regression model

The possible mechanism underlying the increased risk of fracture in patients with BD involves the interaction between inflammatory cytokines and osteoclasts. Evidence has shown that the pathogenesis of BD is related to immune dysregulation in both the periphery and CNS [29]. TNF-α is a crucial cytokine that not only is involved in the pathogenesis of BD but also influences bone resorption [12, 30]. In addition, the differentiation of osteoclasts, originating from monocyte-macrophage lineage cells, is vital for bone resorption [31]. Moreover, the expression of RANKL may accelerate bone resorption [32]. Furthermore, evidence has shown that TNF-α can induce the production of RANKL and promote osteoclastogenesis [33, 34]. Consequently, we hypothesize that inflammation-induced osteoclastogenesis, enhanced by TNF-α, may be more active in patients with BD, thus increasing the risk of fracture in these patients. On the other hand, our study also revealed that BD is an independent risk factor for fracture, regardless of comorbidities.

In addition to inflammatory process, disturbed hypothalamic-pituitary-adrenocortical (HPA) axis may be another hypothesis for the association between BD and subsequent fracture. Dysfunction of HPA axis activity was reported having association with BD [35] and stress played a important role [36]. Also, HPA axis was influenced under chronic psychological stress and increased risk of osteoporosis was noted [37]. Therefore, the risk of subsequent fracture was increased in patients with BD.

Our data showed that the risk of fracture increased with the increased frequency of hospital care for BD (Table 4). An association between the disease activity of BD and the development of fracture has been implicated. Patients with BD have been reported to have a high recurrence rate [38]. Behavioral manifestations of BD, including impulsivity, risk-taking behaviors and even violence, particularly observed during manic episodes [39–41], may expose these patients to the danger of physical injury, thereby increasing the risk of fracture. Low levels of physical activity increase the risk of osteoporosis and bone loss.

In our study, we used a population-based cohort of patients with BD and adequate controls for comorbidity, thus further strengthening our study. However, this study had some limitations inherent in the use of a claims database. First, the diagnosis of BD in the NHIRD is based on ICD-9-CM codes. Hence, the severity of BD as a risk factor for fracture was not extensively explored. Second, the causal relationship was evaluated mainly in the chronological order when these two conditions were diagnosed. Even though we indeed included patients with BD diagnosed before the occurrence of the fracture, we could not exclude the possibility that the occult or undiagnosed fracture caused subsequent diagnosis of BD. Third, the current study did not record details of medication (psychotropic and non-psychotropic medication) in the BD cohort, there was no information provided about treatments. Fourth, information on many demographic variables and lifestyle factors, including socioeconomic status, family history, physical activities, and diet intake, are unavailable in the database; these variables may have provided useful information on factors responsible for the association of BD with fracture. For instance, adequate physical activities, enough calcium and vitamin D are vital for bone mineral density and has been implicated in preventing osteoporosis and further fracture [42.] Finally, although other psychiatric diagnoses are associated with an increased risk of fracture, which may in part be attributed to antipsychotic medication, we did not exclude other psychiatric diagnoses (such as depression or schizophrenia) from the control group in the present study.

Consequently, the findings of our study suggest that BD increases the risk of subsequent fracture. Additional prospective clinical studies investigating the relationship between BD and fracture are warranted.

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Compliance with ethical standards

Conflict of interest All authors report no conflicts of interest.

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