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Clinical treatment and medication in decreasing the development of major depression caused by spinal fracture

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Abstract

Background: Chronic pain and limited activities of daily living after spinal fracture may induce the occurrence of major depression (MD); however, risk factors regarding medications, surgical intervention, and severity of fracture are unclear. We aimed to analyze risk factors of MD development after spinal fracture.

Methods: This was a retrospective database study, using the health care database of the Taiwan government. We included 11,225 patients with new spinal fracture (study group), and 33,675 matched patients without fracture (comparison group). We respectively reviewed data of each participant for 3 years to assess the development of MD. The Cox proportional hazards model was used to determine the prevalence of MD, after adjusting for patient demographics, medications, surgical interventions, spinal cord involvement, and postfracture comorbidities.

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Results: In total, 187 fracture patients (1.7%) and 281 nonfracture patients (0.8%) developed new-onset MD (hazard ratio [HR]:1.96, (95% confidence interval [CI]: 1.63–2.36)). Spinal cord involvement (HR: 2.96, 95% CI: 2.54–3.42) and postfracture comorbidities (HR: 3.51, 95% CI: 2.86–3.97) obviously increased the risk of MD.
Conclusions: Patients with spinal fracture (spinal cord involvement and postfracture comorbidities) were more likely to develop MD. Early surgical interventions (vertebroplasty) and medications (narcotics) may decrease the risk of MD.

Keywords
Spinal fracture, depression, surgical intervention, narcotics, chronic pain, activities of daily living

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Introduction

Spinal cord injuries with chronic pain are often seen in older people and the incidence of spinal fracture is increased in the age group over 50 years (the age-standardized incidence is 10.7/1000 in women and 5.7/1000 in men).[1] A previous study has reported that most traumatic spinal cord injuries exhibit a bimodal age distribution. The first peak incidence occurs in young adults between the ages of 15 and 29 years; the second peak can be seen in adults older than age 65 years.[2] Among patients with blunt trauma injuries, 5% to 10% have cervical spinal injuries and 8% to 15% have thoracolumbar spinal injuries.[3,4] The incidence of nontraumatic spinal cord injuries increases with advancing age.[2] In addition, patients with geriatric spinal cord injury have fewer neurological deficits but higher proportions of chronic pain and mortality than their younger counterparts.[5]

Life expectancy is significantly decreased after spinal fracture, and this reduction is greater in men than in women.[6,7] Spinal fracture has been demonstrated to result in several adverse medical outcomes, including reduced pulmonary function, lower cardiac output, immune disorders, muscular deconditioning, chronic back pain, and impaired functional capacity.[8,9] In psychosocial terms, spinal fracture not only decreases quality of life but also has considerable impacts on society.

A depressive event interferes with several important areas of life at emotional, psychomotor, cognitive, and consciousness levels. In addition, a higher prevalence of depression is found among female individuals, as well as social helplessness, a low social and economic level, comorbid underlying disease, pain, and functional disability.[10] Consequently, we hypothesized that patients with spinal fracture might have higher odds of experiencing a major depressive (MD) episode owing to the presence of several items that lead to MD during the postfracture period, in comparison with individuals who do not have a spinal fracture. This relationship has not been thoroughly investigated. Furthermore, clinical treatment (medications, surgical interventions), the severity of spinal fracture (cord involvement), and postfracture comorbidities have not been considered together as impact factors. In this study, we aimed to analyze the risk factors of MD after spinal fracture with respect to medications, surgical interventions, and severity of fracture.

Methods

Database

We used the Taiwanese government database of the National Health Insurance

Program in this study. This database includes patient demographics and medical records, covering nearly 100% of the population in Taiwan. This study was performed with the permission of the Taiwan Ministry of Health and Welfare. In addition, the study was approved by the Institutional Review Board of Changhua Christian Hospital on 15 January 2019 (Changhua, Taiwan). All information in this database was deidentified secondary data, released for research purposes only in this retrospective database study. Therefore, a waiver of the requirement for documentation of informed consent was granted (IRB No. 181110).

Setting and population

This was a retrospective database study. During the study period (January 2003 to December 2007), data on the following two groups were randomly obtained from the database: a study group (spinal fracture patients) and a comparison group (patients without spinal fractures). For the study group, the index hospitalization was defined as the first hospital visit for spinal fracture treatment. For the comparison group, the selected index hospitalization was in the same month as that of patients in the study group. Data for each patient were respectively reviewed for the past 3 years. The odds of developing new-onset MD were analyzed between the two groups.

Selection process

Spinal fracture and severe spinal cord injury. Patients admitted to the hospital with a main diagnosis code 805.0 to 806.9, according to International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) were defined as having spinal fracture. Among these patients, those who had severe neurologic complications (neurogenic shock, bradyarrhythmia, low blood pressure, abnormal temperature, sweating, severe vasodilatation, and dysreflexia) were classified as having severe spinal cord injury.[11]

MD. MD was defined as a main diagnosis code 296.2 or 296.3 (ICD-9-CM). The diagnosis of MD adhered to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV). In this database, the code for MD was recorded by psychiatrists.[12]

Exclusion criteria.

1. All pediatric patients (age <18 years, n = 467)
2. Any history of spinal fracture or MD
3. Presenting with other types of depression (e.g., bipolar disease, depression caused by substance abuse or medication, dysthymic disorder, and postpartum depression)
4. Presenting with a depressive episode but not meeting the criteria of MD (e.g., affective disorder, anxiety, panic attack)

Data verification

For patient safety and to prevent potential overuse of medical resources, treatments and disease processes are routinely reviewed by government-appointed experts. Inappropriate or overtreatment (or overcoding) will incur a fine.

Study protocol

The study group included patients with spinal fracture. The comparison group was chosen from among the remaining individuals in the database, matching three comparison patients with one study patient based on sex and age, number of hospital visits, and number of years of data available in the database.

Data analysis

SAS 9.2 statistical software (SAS Institute Inc., Cary, NC, USA) was used to analyze the data in this study. The data of each

patient were retrospectively reviewed for 3 years to identify the occurrence of new-onset MD. Information regarding patient characteristics, demographics, baseline comorbidities, and time from spinal fracture to MD onset were reported using descriptive statistics as percentage or mean ± standard deviation (SD). Moreover, we used the χ^2 test to analyze demographic differences between the study and comparison groups. Demographic variables included sex, age, economic status, urbanization degree of residence, location of residence, baseline comorbidities, and mortality. The degree of urbanization of a community was defined according to the population size and degree of urban development. The classifications of these demographic variables were made according to a previous national database study.[13] Rates of new-onset MD were compared between the two groups using crude hazard ratios (HRs) calculated with the Cox proportional hazards model. Furthermore, adjusted HRs were calculated, after adjusting for demographic variables (mode 1), baseline comorbidities (mode 2), surgical treatments (mode 3), medications used in patients with spinal fracture (mode 4), severe spinal cord injury (mode 5), and postfracture comorbidities (mode 6).

Survival analysis (MD-free survival curves) was conducted using the Kaplan–Meier method and log-rank test between the study and comparison groups. For the study group, the time since spinal fracture to the onset of MD was recorded and divided into 11 periods (<100, 101–200, 201–300, 301–400, 401–500, 501–600, 601–700, 701–800, 801–900, 901–1000, and >1000 days). Relationships between the characteristics of study participants and the occurrence of MD were analyzed with the χ^2 test. These characteristics included demographics and surgical interventions performed to treat a spinal fracture (including vertebroplasty, open reduction, and spinal fusion). Surgical interventions that were not performed during the follow-up period were not included. In this study, vertebroplasty included bone cement injection (for one or more vertebral bodies). Spinal fusion included vertebral immobilization.

The relationship between the initial medications administered in the treatment of spinal fracture and the development of MD was also analyzed. The initial medications used (including any oral or injected medications used within the first 30 days of treatment after the fracture) were divided into the following four major pharmacological groups: narcotics (including morphine, meperidine, codeine, and tramadol); muscle relaxants (including chlorzoxazone, baclofen, and methocarbamol); nonsteroidal anti-inflammatory drugs (NSAIDs, including salicylates and COX-1 and COX-2 inhibitors); and acetaminophen.

Results

Demographics of patients with spinal fracture

This study included 44,900 patients. The characteristics and baseline comorbidities of study patients (with spinal fracture; n = 11,225) and comparison patients (without spinal fracture; n = 33,675) are shown in Table 1. In the study group, patients aged 70 to 79 years formed the largest age group (24.9%), followed by patients <40 years of age (18.4%). The residence cities of study patients had a lower average level of urbanization than those of comparison patients. Moreover, study patients had significantly higher prevalence rates of the following baseline comorbidities: diabetes mellitus, hypertension, chronic kidney disease, liver disease, stroke, and osteoporosis (all $p<0.001$). Among study patients, 164 (1.5%) had severe spinal cord injury. In addition, 1394 (12.4%) patients received surgical treatments. Peptic ulcer (n = 1312), pneumonia (n = 1043), urinary tract infection (n = 957), cellulitis or soft tissue infection

Table 1. Characteristics and baseline comorbidities of study and comparison patients.

	Study group (with spinal fracture) (n = 11,225)		Comparison group (n = 33,675)		
	No.	%	No.	%	*p*-value
Sex					1.000
Male	3912	34.9	11,736	34.9	
Female	7313	65.1	21,939	65.1	
Mean age, years (mean ± SD)	59.7 ± 19.0		59.3 ± 18.9		1.000
Age group (years)					1.000
<40	2071	18.4	6213	18.4	
40–49	1309	11.7	3927	11.7	
50–59	1510	13.5	4530	13.5	
60–69	1959	17.5	5877	17.5	
70–79	2791	24.9	8373	24.9	
>79	1585	14.1	4755	14.1	
Monthly income[a,b]					<0.001
Level 1	5472	48.7	17,533	52.1	
Level 2	5030	44.8	13,029	38.7	
Level 3	723	6.4	3113	9.2	
Urbanization degree of residence[a]					<0.001
1 (highest level)	2271	20.2	8540	25.4	
2	808	7.2	2656	7.9	
3	2620	23.3	7891	23.4	
4	5526	49.2	14,588	43.3	
Location of residence[a,c]					<0.001
Northern	4589	40.9	16,326	48.5	
Central	2263	20.2	6066	18.0	
Southern	4066	36.2	10,404	30.9	
Eastern	307	2.7	879	2.6	
Baseline comorbidities					
DM[a]	2171	19.3	5488	16.3	<0.001
HTN[a]	3153	28.1	8673	25.8	<0.001
CKD[a]	1099	9.8	2453	7.3	<0.001
Liver disease[a]	402	3.6	787	2.3	<0.001
Stroke[a]	1353	12.1	3024	9.0	<0.001
Osteoporosis[a]	4242	37.8	3862	11.5	<0.001

[a]Significantly different.
[b]Level 1: <600 USD; Level 2: 601–1000 USD; Level 3: 1000 USD.
[c]Locations in Taiwan.
DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; SD, standard deviation.

(n = 970), and heart failure (n = 554) were the five most common comorbidities after spinal fracture. In general, the mortality rate throughout the study period in the study group (4.9%, n = 554) was higher than that in the comparison group (4.5%, n = 1509; $p = 0.047$).

Likelihood of major depression (MD)

In the 3-year study period, the study group had a significantly higher incidence of new-onset MD than the comparison group. Specifically, 1.7% of study patients (n = 187) developed new-onset MD following spinal

fracture whereas only 0.8% of comparison patients (n = 281) experienced new-onset MD during the same time period. Stratified Cox proportional hazards analysis showed that the study group had a crude HR of 1.96 (95% confidence interval [CI]: 1.63–2.36, $p < 0.001$), as compared with the comparison group (Table 2).

MD-free survival curves

The MD-free survival curves for study patients and comparison patients during the study period are presented in Figure 1. The results indicated that the study group (patients with spinal fracture) had a lower incidence of 3-year MD-free survival than the comparison group ($p < 0.001$).

Time between fracture and onset of MD

The times between spinal fracture and occurrence of new-onset MD are shown in Figure 2. The largest proportion (15.5%) of MD occurred within the first 100 days after spinal injury.

Table 2. Crude and covariate-adjusted hazard ratios for the prevalence of MD in study and comparison groups.

Presence of MD during the study period	Total sample (n = 44,900)		Study group (n = 11,225)		Comparison group (n = 33,675)	
	No.	%	No.	%	No.	%
Yes	468	1.0	187	1.7	281	0.8
No	44,432	99.0	11,038	98.3	33,394	99.2
Crude hazard ratio (95% confidence interval)	–		1.96 (1.63–2.36) [a]		–	

[a] $p < 0.001$.
MD, major depression.

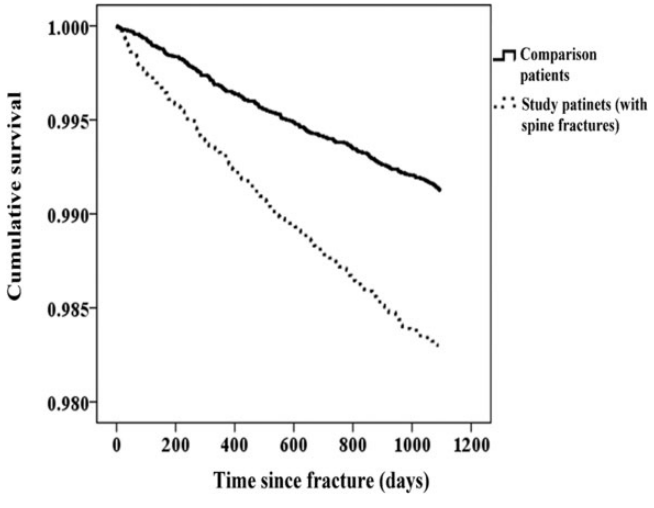

Figure 1. Major depression-free survival curves for the study and comparison groups ($p < 0.001$).

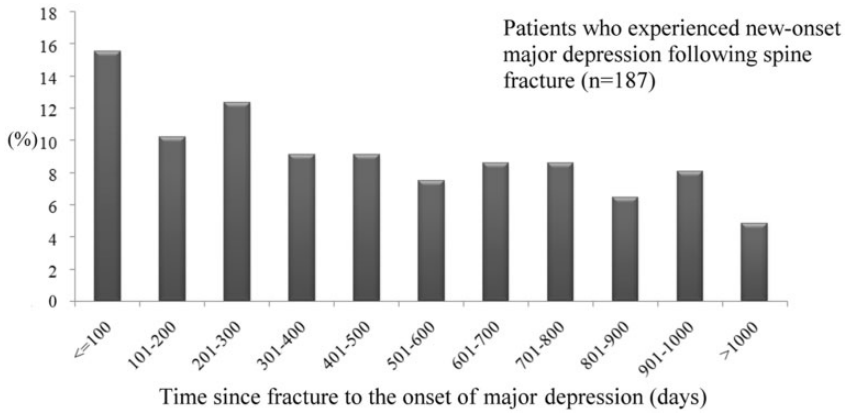

Figure 2. Time to new-onset depression after spinal fracture.

Adjusted effect estimates for MD

The adjusted HRs are shown in Figure 3. After separately adjusting for demographics (mode 1), baseline comorbidities (mode 2), surgical treatments (mode 3), medications (mode 4), severe spinal cord injury (mode 5), and postfracture comorbidities (mode 6), study patients remained more likely to develop new-onset MD than comparison patients (all $p < 0.05$). Moreover, we found that patients who received surgical treatment (HR = 1.56, 95% CI: 1.24–2.05) and medications (HR = 1.43, 95% CI: 1.05–1.86) had significantly lower HRs for MD. Among the three surgical treatments, patients who received vertebroplasty (n = 319) had the lowest HR (1.54, 95% CI: 1.15–1.92). Narcotics (n = 691) were the most effective medication for decreasing the risk of MD (HR = 1.24, 95% CI: 1.06–1.54). Unfortunately, patients who had severe spinal cord injury (HR = 2.96; 95% CI: 2.54–3.42) and postfracture comorbidities (HR = 3.51; 95% CI: 2.86–3.97) had a markedly higher risk of MD.

Characteristics associated with new-onset MD in patients with spinal fracture

Among the study patients, we found that female sex, low socioeconomic level, and baseline comorbidity with stroke were significantly associated with MD (Table 3, all $p < 0.05$).

Discussion

Life stressors, including a poor quality of life, restricted activity, chronic pain, and comorbidities, are common in patients with spinal fracture.[8,14] Because elevated life stress levels have previously been demonstrated to cause depressive episodes[10,11] we hypothesized that patients with spinal fracture would have an elevated risk of MD subsequent to the injury. However, no previous studies have elucidated the association between spinal fracture and MD. In this large population-based study, we found that spinal fracture was significantly associated with subsequent MD (HR = 1.96, 95% CI: 1.63–2.36). Furthermore, some confounding factors that might have an effect on the incidence of MD, including demographics, baseline comorbidities, surgical treatments, severity of spinal fracture, and postfracture comorbidities, were separately considered in the adjusted effect model. Compared with patients who did not have spinal injury, the adjusted HRs for MD remained significantly elevated following spinal fracture for each mode (modes 1 to 6).

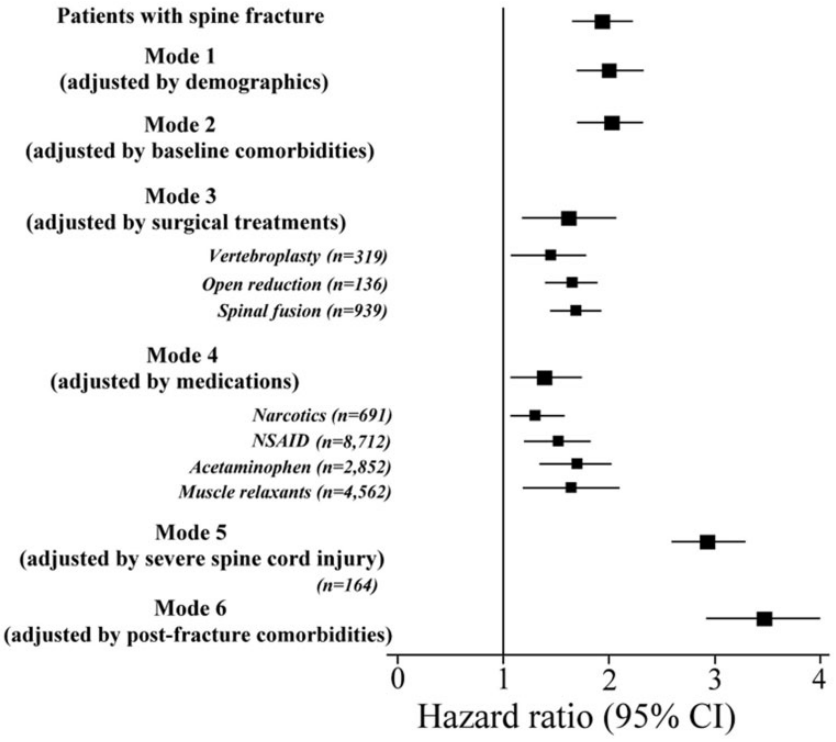

Figure 3. Adjusted risk of occurrence of major depression.
Mode 1: Adjusted by demographics.
Mode 2: Adjusted by baseline comorbidities.
Mode 3: Adjusted by surgical treatments.
Mode 4: Adjusted by medications used in patients with spinal fracture.
Mode 5: Adjusted by severe spinal cord injury.
Mode 6: Adjusted by postfracture comorbidities (peptic ulcer, pneumonia, urinary tract infection, cellulitis or soft tissue infection, and heart failure).

Several previous studies have reported that surgical interventions for spinal fracture can reduce acute or chronic pain and facilitate the recovery of activity (height restoration and greater kyphotic angle reduction).[14–17] Moreover, for patients with painful spinal fracture refractory to analgesic treatment, surgical intervention results in a better life quality and reduced levels of pain and activity limitation.[15] However, the relationship between patients' psychological condition and surgical treatments is unclear. New and accumulated stressors (for example, surgical wound pain and medical bills) might affect patients after (or before) receiving surgical treatment.[16–18] In this study, after adjusting for surgical treatments (mode 3), we found that the three surgical treatments all decreased the risk of MD. Among them, vertebroplasty (n = 319) had the lowest HR (1.54). Therefore, to decrease the risk of MD, early surgical treatment should be considered for early recovery of activity and pain relief, if patients fit the surgical indications.

Patients with spinal fracture who receive conservative treatment have been reported

Table 3. Characteristics related to the occurrence of MD in the study group.

	Study group (with spinal fracture; n=11,225)		
	Occurrence of MD		
	Yes (n=187) No. (%)	No (n=11,038) No. (%)	*p*-value
Sex[a]			0.046
Male	52 (27.8)	3860 (35.0)	
Female	135 (72.2)	7178 (65.0)	
Age group (years)			0.329
<40	36 (19.3)	2035 (18.4)	
40–49	26 (13.9)	1283 (11.6)	
50–59	30 (16.0)	1480 (13.4)	
60–69	37 (19.8)	1922 (17.4)	
70–79	39 (20.9)	2752 (24.9)	
>79	19 (10.2)	1566 (14.2)	
Monthly income[a,b]			0.025
Level 1	109 (58.3)	5363 (48.6)	
Level 2	66 (35.3)	4964 (45.0)	
Level 3	12 (6.4)	711 (6.4)	
Urbanization degree of residence			0.090
1 (highest level)	48 (25.7)	2223 (20.1)	
2	18 (9.6)	790 (7.2)	
3	35 (18.7)	2585 (23.4)	
4	86 (46.0)	5440 (49.3)	
Location of residence[c]			0.365
Northern	85 (45.5)	4504 (40.8)	
Central	29 (15.5)	2234 (20.2)	
Southern	67 (35.8)	3999 (36.2)	
Eastern	6 (3.2)	301 (2.7)	
Baseline comorbidities			
DM	46 (24.6)	2125 (19.3)	0.073
HTN	49 (26.2)	3104 (28.1)	0.619
CKD	22 (11.8)	1077 (9.8)	0.387
Liver disease	5 (2.7)	397 (3.6)	0.690
Stroke[a]	40 (21.4)	1313 (11.9)	<0.001
Osteoporosis	79 (42.2)	4163 (37.7)	0.223
Surgical treatments			
Vertebroplasty	4 (2.1)	315 (2.8)	0.614
Open reduction	5 (2.7)	131 (1.2)	0.077
Spinal fusion	22 (11.8)	917 (8.3)	0.108
Spinal cord injury	6 (3.2)	158 (1.4)	0.056

[a]Characteristics significantly associated with major depression.
[b]Level 1: <600 USD; Level 2: 601–1000 USD; Level 3: 1000 USD.
[c]Locations in Taiwan.
MD, major depression; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease.

to exhibit a decrease in pain of 50% or more by 6 months.[15] In this study, after adjusting for medications (mode 4), we found that painkillers and muscle relaxants were both effective in decreasing the risk of MD. More powerful painkillers decreased this risk to a greater extent. Among the three types of painkillers assessed (narcotics, NSAIDs, and acetaminophen), narcotics (n = 691) were the most effective in decreasing the risk of MD (HR = 1.24, 95% CI: 1.06–1.54), followed by NSAIDs and acetaminophen. Therefore, emotional support and adequate pain control (in the absence of contraindications) are important during the early period of recovery from spinal fracture, and early consultation with a psychologist may be necessary.

In this study, we found that spinal cord injury and postfracture comorbidities might be very strong risk factors for postfracture MD. In addition to impairment of activity and neurological symptoms, spinal cord injury following spinal fracture results in increased pain, poor daily functioning, and the development of comorbidities (including thromboembolism, pressure ulcer, and respiratory and cardiovascular complications).[11,19,20] Some recent studies have also reported an association between stress-related anxiety and spinal cord injury;[21,22] therefore, it is reasonable to believe that psychological stress increases after patients experience a spinal bone injury. However, we suspect that more severe psychiatric problems (e.g., MD) might arise with cord involvement and postfracture comorbidities. For example, cord injury-related limb paralysis and incontinence could further limit the activities of patients and contribute to family stress. Postfracture peptic ulcer, pneumonia, and urinary tract infection (the most common comorbidities observed in this study) increase physical stress and might further influence spinal recovery and impede rehabilitation. Treatment as early as possible of neurological defects (from spinal cord injury) and comorbidities might be effective for decreasing the likelihood of developing MD.

Several previous studies have highlighted the importance of enhancing postfracture quality of life. One study, including 107 patients with spinal fracture, reported an improvement in this parameter between 3 weeks and 3 months after fracture.[23–25] However, the onset of psychological problems in patients was not well described or followed in these studies. In the present study, we increased the observational time and found that the largest proportion of MD episodes (15.5%) occurred within the initial 100 days after spinal fracture; this result was most likely owing to acute stress caused by the fracture. In addition, we noted that the number of depressive episodes gradually increased until reaching a second peak (12.3%) at approximately 201 to 300 days after the fracture. Overall, the rate of patients with MD steadily declined as the observational period proceeded. Finally, we suspect that emotional assistance and measures to prevent MD should be considered by primary medical practitioners during the early stages after spinal fracture.

Study limitations

The first limitation was the accuracy of ICD-9 coding, which was made by primary physicians and could have potentially resulted in overcoding or miscoding. The second limitation is that the government database (longitudinal health insurance database) included patient information from 1995 (medical records prior to 1995 were not included in this database). This is a natural limitation for researchers who analyze data from this database.[26,27] To clarify the associations between spinal fracture and MD, we excluded patients with a history of affective or psychiatric disorders.

Patients with a history of MD or other types of depression, or those with a depressive episode but who did not meet the criteria of MD, were also not included. Our database covers nearly 100% of the population of Taiwan; however, it is possible that the database includes a few patients with psychiatric disorders but who did not go to a hospital or who were not correctly diagnosed. The HR for MD was generally higher in patients who underwent surgery compared with those who received medications. We suspect that the main reason for this finding is that patients who required surgery might have had more severe conditions. Finally, a higher incidence of MD occurred in the study group (187 of 11,225, 1.7%) than in the comparison group (281 of 33,675, 0.8%). The sample size between the two groups was very heterogeneous; therefore, the results should be interpreted with caution and other potential confounding factors should be considered in further investigation.

Conclusions

Our study results indicated that patients with spinal fracture are more likely to develop MD, and this risk is markedly increased in those with spinal cord involvement and postfracture comorbidities. Early surgical interventions and medications may be effective in decreasing the risk of developing MD, particularly treatment with vertebroplasty and narcotics. Importantly, most MD events occurred within the first 100 days after spinal fracture.

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Author contributions

Authors Ho, Chen, and Lin conceived the study. Authors CY Chang and Lin supervised the data collection. Authors Lin and Law managed the data and performed quality control. Authors Lin, Chen, Chou, and CF Chang provided statistical advice on the study design and analyzed the data. Authors Lin and Chen chaired the data oversight committee. Author Chang wrote the manuscript, Hsieh revised the data, and Lin takes responsibility for the paper as a whole.

Declaration of conflicting interest

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