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Predictive nomogram for postoperative delirium in elderly patients with a hip fracture

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ABSTRACT

To evaluate the risk factors for the development of postoperative delirium and design a predictive nomogram for the prevention of delirium in elderly patients with a hip fracture, we retrospectively studied 825 patients who sustained a femoral neck fracture from January 2005 to December 2015. Independent risk factors for developing delirium within 6 months of surgery were identified using multivariable logistic regression analyses. A predictive nomogram model was built based on the results, and the discrimination and calibration were determined by C-index and calibration plot. Of the 825 patients who met inclusion criteria, 118 (14.3%) developed postoperative delirium. According to the results, preoperative cognitive impairment (OR, 4.132, 95% CI, 1.831 to 9.324, P<0.001), multiple medical comorbidities (OR, 1.452, 95% CI, 0.958–2.202, P = 0.079), ASA classification (OR, 1.655, 95% CI, 1.073–2.553, P = 0.023), transfusion exceeding 2 units of red blood cell (OR, 1.599, 95% CI, 1.043–2.451, P = 0.035), and intensive care (OR, 1.817, 95% CI, 1.127–2.930, P = 0.014) were identified to be the independent predictors of the development of postoperative delirium. The risk of postoperative delirium increased with the increasing risk score of predictive nomogram, and the C-index was 0.67 (0.62 - 0.72). The calibration showed that the predicted probabilities of delirium in the predictive nomogram were close to the observed frequency of delirium, and the decision curve analysis confirmed the clinical utility of the nomogram when the threshold probabilities were between 8% and 35% due to the net benefit.

Introduction

Hip fracture has become a major public health concern due to the increasing life expectancy of the global population and subsequent aging of the demographic structure [1]. It has been estimated that there would be approximately 2.6 million people sustaining a hip fracture worldwide by the year 2025, and this number could range between 7 and 21 million by 2050 depending on secular trends [2–4]. Delirium associated with hip fracture is often seen as one of the complications of complex hip fracture surgery, with a prevalence ranging between 5% and 61% [5–7]. As a serious medical condition consisted of a disturbance of consciousness, delirium is often misdiagnosed and undertreated. Multiple studies have shown that patients with postoperative delirium are less likely to return to their pre-injury level of function, and are more likely to have a higher risk of morbidity and mortality [8–10]. However, little is known regarding the occurrence of delirium following hip fracture surgery. The purpose of this study is to determine the incidence, risk factors, and a predictive nomogram of postoperative delirium after femoral neck fractures in elderly people.

Patients and methods

Patient population

In this study, we collected data on 1156 patients who sustained a femoral neck fracture and treated by surgical management between January 2005 and December 2015 from a single institution. To meet the inclusion criteria for this study, first, patients were required to be given a postoperative diagnosis of unilateral femoral neck fracture. Second, patients were required to have undergone a total hip arthroplasty, or a hemiarthroplasty, or a percutaneous fixation, or a plate/screw fixation. The exclusion criteria included: pathological fractures, age < 65 years, or multiple fractures. 331 of the 1156 patients, of which 304 were under 65 years old, 17 were diagnosed with a pathological fracture, and 10 were diagnosed as having multiple injuries, were excluded from

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this study. In the end, there were 825 patients included in this study. A detailed flow chart was built for the inclusion process in the Supplementary Fig. 1 in the Appendix.

Patients were characterized at baseline according to sex, age, body mass index (BMI), comorbidities, current smoking status, current drug use, cause of injury, history of surgery, pre-injury walk ability, fracture pattern, classification of risk of anesthesia according to American Association of Anesthesiologists (ASA), type of anesthesia, operation type, operation time, blood loss, transfusion, hemoglobin, serum albumin concentration, intensive care, interval between surgery and first walk, length of hospital stay, and death (Table 1). Age was stratified into 65–74, and ≥ 75 years. The number of comorbidities was stratified into <2, and ≥ 2. Transfusion was stratified into > 2 units of RBC or not. Hemoglobin was stratified into <120 g/L in male and <110 g/L in female (anemia) versus ≥120 g/L in male and ≥110 g/L in female (normal). Serum albumin was stratified into < 35 g/L (hypoalbuminemia) versus ≥ 35 g/L (normal). The procedure was stratified as described above. Current drug use primarily referred to medically prescribed drugs used for treating common comorbidities and traumatic pain, such as cardiovascular drugs (aspirin, atorvastatin), antihypertensive drugs, pulmonary drugs, NSAIDs, anti-osteoporosis drugs (salmon calcitonion).

Patients were characterized according to whether or not they developed delirium postoperatively. The diagnostic criteria for delirium referred to Diagnostic and Statistical Manual of Mental Disorders: 5th Ed (DSM-5.) established by the American Psychiatric Association [11]. Delirium consists of a disturbance of cognitive features with a reduced ability to focus, sustain, or shift attention. Patients had to meet the criteria for signs and symptoms according to DSM-5 in order to be identified as having developed delirium. According to the definition of delirium, acute confusional states are the synonymous symptoms while common distinguishing characteristics of the different diagnosis of dementia, depression and psychosis were listed in Table 4 [10]. Patients' symptoms and signs of delirium were observed and recorded by nursing staff and attending doctors twice a day when making usual rounds in the ward. In addition, the doctor and nurse on duty would also momentarily report to the attending doctor when abnormal cognitive and behavioral changes appeared in patients. A neurologic consultation might be suggested based on the assessment of the attending doctor. The patients' abnormal states and suggestions of consultation would be recorded. Two experienced doctors (the co-first authors of this study) independently diagnosis the postoperative delirium for all patients based on their medical record data according to DSM-V. Any controversies in diagnosis between the two doctors were settled by discussion, and a final diagnosis for postoperative delirium on each patient was generated. The two doctors were both acquainted with the DSM-V.

Statistical analysis

The primary end point of interest in this study was the development of delirium. Multivariable regression analysis was conducted using a logistic regression model, and this model formed the basis of the delirium prediction model. The potential predictors of delirium analyzed in this study included age, sex, body mass index, history of depression, smoking status, number of medical comorbidities, current drug use, cause of injury, history of surgery, walking ability, fracture pattern, ASA, LVEF, LV systolic dysfunction, LV diastolic dysfunction, serum albumin, hemoglobin, time to surgery, operation type, operation time, blood loss, transfusion, and intensive care. An initial univariate logistic regression model was fitted to evaluate the association between the clinical factors and postoperative delirium. To identify independent risk factors, variables achieving a significance of $p < 0.05$ were selected for multivariable analyses. The independent statistically significant predictors in the final model were determined using the backward method based on the AIC criteria. Discrimination was evaluated using the concordance index (c-index), which measured the probability that, given a pair of randomly selected patients, the model correctly predicted which patient will experience an event first. The c-index of the model can range between 0.5, which represents random chance, and 1.0, which represents a perfectly discriminating model (Harrell et al, 1982). The relatively correctional C-index of the nomogram was calculated using bootstraps with 1000 resamples. The calibration abilities of the prognostic model were measured by the Hosmer-Lemeshow test and calibration plot respectively (Hanley and McNeil, 1982; Hosmer and Lemeshow, 2000). In addition, the decision curve analysis was carried out using the code found at https://www.mskcc.org/departments/epidemiology biostatistics/health-outcomes/decision-curve-analysis-01 according to its tutorials. All statistical analyses were conducted using R software version 3.5.0 (http://www.r-project.org/), with rms package (Harrell, 2012).

Results

Patient baseline

There were 825 patients who met the inclusion criteria for this study. The clinical and pathologic characteristics of patients are listed in Table 1. There were 231 (28.0%) male and 594 (72.0%) female patients in total with a median age of 79 (IQR, 65–93 years) at the time of diagnosis. Eventually, 118 (14.3%) patients developed delirium postoperatively, of which 33 (28.0%) were male and 85 (72.0%) were female. Hypertension, diabetes, preoperative cognitive impairment and arrhythmia were the most common comorbidities and 263 (31.9%) patients had multiple comorbidities.

The comparison of the clinicopathological features between patients with and without postoperative delirium

Compared to patients without postoperative delirium, those with delirium showed a higher rate of preoperative cognitive impairment (9.3% vs. 38.6%, $p = 0.001$), multiple medical comorbidities (41.5% vs. 29.6%, $p = 0.013$), transfusion with 2 or more units of RBC (34.7% vs. 24.2%, $p = 0.021$), and ICU stay (28.0% vs. 15.3%, $p = 0.001$). There was no statistical difference in age, sex, and fracture pattern between these two groups (Table 1).

Development of a nomogram

To provide the physicians with a quantitative method for predicting the risk of postoperative delirium, we constructed a nomogram based on the multivariable logistic regression results (Table 2). The results of the univariate regression analysis are shown in supplementary Table 1. In the univariate analysis, number of medical comorbidities, ASA classification, intraoperative transfusion, and intensive care were significant predictors of postoperative delirium. Five variables, including preoperative cognitive impairment, multiple medical comorbidities, ASA classification, transfusion > 2 units of red blood cell, and intensive care, showed relative frequencies > 50% using the bootstrapping method. When applied to the multivariable model, these five covariates were found to be significant. A nomogram for predicting postoperative delirium was constructed with these five parameters based on the multivariable model (Fig. 1).

The predictive model showed a C-index of 0.67 (95% CI 0.62–0.72). The calibration curve showed good concordance between

Table 1
Baseline characteristics.

Variable	Total (n = 825)	Without delirium (n = 707)	With delirium (n = 118)	P value
Sex				1
female	594 (72.0%)	509 (72.0%)	85 (72.0%)	
male	231 (28.0%)	198 (28.0%)	33 (28.0%)	
Age, years	79.0 (74.0-84.0)	79.0 (74.0-84.0)	79.0 (74.0-84.0)	0.459
Body mass index, Kg/m^2	22.2 (20.0-24.3)	22.3 (20.0-24.4)	22.2 (19.9-23.5)	0.317
Atrial fibrillation(AF)				1
no	804 (97.5%)	689 (97.5%)	115 (97.5%)	
yes	21 (2.55%)	18 (2.55%)	3 (2.54%)	
Diabetes				0.667
no	706 (85.6%)	603 (85.3%)	103 (87.3%)	
yes	119 (14.4%)	104 (14.7%)	15 (12.7%)	
Hypertension				
no	471 (57.1%)	410 (58.0%)	61 (51.7%)	0.238
yes	354 (42.9%)	297 (42.0%)	57 (48.3%)	
Preoperative cognitive impairment				0.001
no	797 (96.6%)	690 (97.6%)	107 (90.7%)	
yes	28 (3.4%)	17 (2.4%)	11 (9.3%)	
Smoking				0.219
never smoked	711 (87.1%)	607 (86.6%)	104 (90.4%)	
current smoked	36 (4.41%)	30 (4.28%)	6 (5.22%)	
former smoked	69 (8.46%)	64 (9.13%)	5 (4.35%)	
Number of medical comorbidities				0.013
1	567 (68.7%)	498 (70.4%)	69 (58.5%)	
>=2	258 (31.3%)	209 (29.6%)	49 (41.5%)	
Current drug use				0.148
none	347 (42.1%)	306 (43.3%)	41 (34.7%)	
NSAIDS	6 (0.73%)	4 (0.57%)	2 (1.69%)	
general cardiac	35 (4.24%)	31 (4.38%)	4 (3.39%)	
pulmonary drugs	3 (0.36%)	2 (0.28%)	1 (0.85%)	
anti-hypertension drugs	355 (43.0%)	295 (41.7%)	60 (50.8%)	
osteoporosis drugs	5 (0.61%)	4 (0.57%)	1 (0.85%)	
not included above	71 (8.61%)	63 (8.91%)	8 (6.78%)	
Missing	3 (0.36%)	2 (0.28%)	1 (0.85%)	
Cause of injury				0.72
fall	780 (94.5%)	666 (94.2%)	114 (96.6%)	
spontaneous	13 (1.58%)	12 (1.70%)	1 (0.85%)	
other low energy trauma	32 (3.88%)	29 (4.10%)	3 (2.54%)	
History of surgery				0.658
no	666 (80.7%)	573 (81.0%)	93 (78.8%)	
yes	159 (19.3%)	134 (19.0%)	25 (21.2%)	
Pre-injury walk ability				0.336
no walking disability	622 (75.4%)	538 (76.1%)	84 (71.2%)	
moderate walking disability	173 (21.0%)	145 (20.5%)	28 (23.7%)	
does not walk	25 (3.03%)	19 (2.69%)	6 (5.08%)	
unknown	5 (0.61%)	5 (0.71%)	0 (0.00%)	
Fracture pattern				0.787
Garden I	19 (2.3%)	18 (2.5%)	1 (0.9%)	
Garden II	55 (6.7%)	48 (6.8%)	7 (5.9%)	
Garden III	273 (33.1%)	232 (32.8%)	41 (34.7%)	
Garden IV	478 (57.9%)	409 (57.9%)	69 (58.5%)	
Preoperative traction				0.678
none	559 (67.8%)	477 (67.5%)	82 (69.5%)	
skin traction	239 (29.0%)	205 (29.0%)	34 (28.8%)	
skeletal traction	27 (3.27%)	25 (3.54%)	2 (1.69%)	
ASA				0.163
1	21 (2.55%)	19 (2.69%)	2 (1.69%)	
2	565 (68.5%)	494 (69.9%)	71 (60.2%)	
3	189 (22.9%)	153 (21.6%)	36 (30.5%)	
4	9 (1.09%)	7 (0.99%)	2 (1.69%)	
Missing	41 (4.97%)	34 (4.81%)	7 (5.93%)	
LVEF	62.0 (60.0-65.0)	62.0 (60.0-65.0)	62.0 (60.0-64.0)	0.764
ALB	36.0 (33.0-39.0)	36.0 (33.0-39.0)	36.0 (33.0-38.0)	0.809
>35				0.951
<35	519 (62.9%)	444 (62.8%)	75 (63.6%)	
Missing	259 (31.4%)	222 (31.4%)	37 (31.4%)	
SCR	67.0 (56.0-81.0)	66.0 (56.0-80.0)	68.0 (57.5-85.0)	0.249
BG	6.20 (5.40-7.20)	6.20 (5.40-7.20)	6.20 (5.40-7.20)	0.897
HB				0.737
>120	393 (47.6%)	337 (47.7%)	56 (47.5%)	
<120	377 (45.7%)	321 (45.4%)	56 (47.5%)	
Missing	55 (6.67%)	49 (6.93%)	6 (5.08%)	
RBC				0.750
>4	380 (46.1%)	324 (45.8%)	56 (47.5%)	
<4	390 (47.3%)	334 (47.2%)	56 (47.5%)	
Missing	55 (6.67%)	49 (6.93%)	6 (5.08%)	

Table 1 (*Continued*)

Variable	Total (n = 825)	Without delirium (n = 707)	With delirium (n = 118)	P value
WBC				0.731
<10	616 (74.7%)	528 (74.7%)	88 (74.6%)	
>10	155 (18.8%)	131 (18.5%)	24 (20.3%)	
Missing	54 (6.55%)	48 (6.79%)	6 (5.08%)	
Time to surgery, days	4.00 (3.00-6.00)	4.00 (3.00-5.00)	4.00 (3.00-6.00)	0.791
Type of anaesthesia				0.522
general	218 (26.4%)	182 (25.7%)	36 (30.5%)	
spinal	554 (67.2%)	480 (67.9%)	74 (62.7%)	
nerve block	53 (6.4%)	45 (6.4%)	8 (6.8%)	
Operation type				0.301
internal fixation	85 (10.3%)	74 (10.5%)	11 (9.32%)	
hemiarthroplasty	338 (41.0%)	282 (39.9%)	56 (47.5%)	
total hip arthroplasty	402 (48.7%)	351 (49.6%)	51 (43.2%)	
Operation time, minutes	80.0 (60.0-105)	80.0 (60.0-105)	80.0 (60.0-100)	0.895
Blood loss, mL	250 (150-400)	230 (150-400)	300 (150-400)	0.942
Transfusion >2 units of RBC				0.021
no	613 (74.3%)	536 (75.8%)	77 (65.3%)	
yes	212 (25.7%)	171 (24.2%)	41 (34.7%)	
ICU				0.001
no	684 (82.9%)	599 (84.7%)	85 (72.0%)	
yes	141 (17.1%)	108 (15.3%)	33 (28.0%)	
Re-surgery				0.396
no	780 (94.5%)	666 (94.2%)	114 (96.6%)	
yes	45 (5.45%)	41 (5.80%)	4 (3.39%)	
Interval to first walk	50.0 (45.0-60.0)	50.0 (45.0-60.0)	60.0 (45.0-60.0)	0.295
First walk duration	5.00 (4.00-7.00)	5.00 (4.00-7.00)	5.00 (5.00-8.00)	0.244
Dead during follow-up				0.923
no	665 (80.6%)	569 (80.5%)	96 (81.4%)	
yes	160 (19.4%)	138 (19.5%)	22 (18.6%)	
Length of hospital stay, days	10.0 (7.00-12.0)	10.0 (7.00-12.0)	9.50 (8.00-12.0)	0.768

predicted probability and actual probability (Fig. 2A).The Hosmer-eLemeshow test also showed the predictive efficiency of the nomogram in the patients cohort (P = 0.620).

Clinical utility of the nomogram for predicting postoperative delirium

The risk of postoperative delirium increased with the increasing risk score (Table 3). To use the nomogram, a vertical line is drawn up to the top point row to assign points for each variable. Then, the total number of points is calculated, and a vertical line is drawn downwards from the total point row to obtain the probability of postoperative delirium. After the prediction of postoperative delirium, we postulated that the predicted probability above a defined threshold would determine the decision on treatment for a patient, while the predicted probability below the threshold would generate a decision otherwise. Hence, we built a decision analysis curve for the assessment of the net benefit of the nomogram to decision-making. Based on the threshold probability, the decision analysis curve was leveraged to evaluate the clinical application of a prediction model. In the decision analysis curve, the nomogram is compared with the null model for its added value, which turned out that the nomogram is applicable when thresholds are in the range of 0.08 to 0.35 due to the net benefit (Fig. 2B).

Table 2
Multivariable logistic regression of predictors for postoperative delirium.

Variable	OR	95%CI	P value
Preoperative cognitive impairment			<0.001
no	Ref.		
yes	4.132	1.831-9.324	
Number of medical comorbidities			0.079
1	Ref.		
>=2	1.452	0.958-2.202	
ASA class			0.023
1-2	Ref.		
3-4	1.655	1.073-2.553	
Transfusion >2 units of RBC			0.035
no	Ref.		
yes	1.599	1.043-2.451	
ICU			0.014
no	Ref.		
yes	1.817	1.127-2.930	

C-index: 0.6728838 [0.6222535 - 0.723514].

Discussion

Delirium is characterized by an acute disturbance of attention and awareness, with cognitive disorders fluctuating over time [11]. The pathogenesis of delirium is not fully understood, and a generalized, nonspecific dysfunction of higher cortical processes was considered. It was reported that delirium occurred in more than one out of five patients in acute and rehabilitation hospital wards [12]. Postoperative delirium is common among elderly people with hip fracture, and the reported incidence rates varied from 5% ~ 61%. [13–15].

Compared to deep vein thrombosis, which has been regarded as the most threatening fatal complication, postoperative delirium received little attention in the orthopedic literature. However, the fact is, morbidity and mortality associated with postoperative delirium are far greater than those associated with deep vein thrombosis. It has been found that patients with delirium had a significant increase in the length of the overall hospital stay and increased one-year mortality associated with poor functional outcome, high costs, nursing home placement [16,17]. Prolonged delirium is also a risk factor for the development or worsening of dementia and is upsetting for the patient and their loved ones [7].

Clinical research on delirium in hip fracture patients was rarely seen because delirium is often transient and has multiple underlying causes [18]. Also, delirium was often undetected and was more likely to be misdiagnosed, as similar symptoms of other mental disorders such as dementia, depression, and psychosis

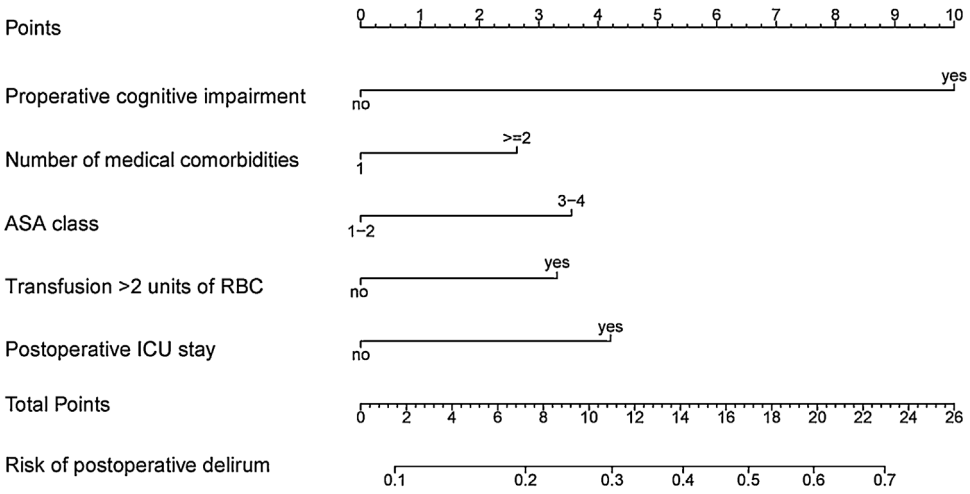

Fig. 1. Predictive nomogram for postoperative delirium.
This predictive nomogram was constructed based on the multivariable model. To use the nomogram, a vertical line is drawn up to the top point row to assign points for each variable. Then, the total number of points is calculated, and a vertical line is drawn downwards from the total point row to obtain the probability of postoperative delirium.

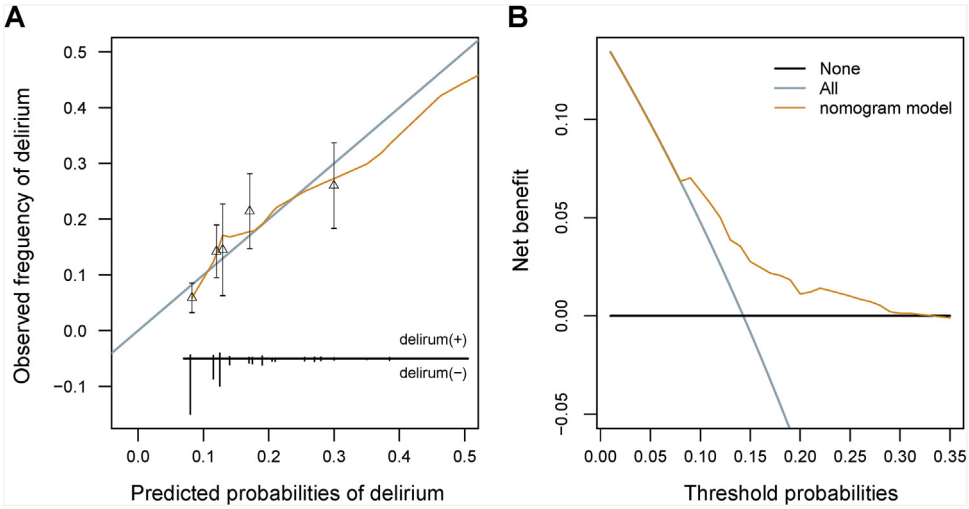

Fig. 2. Calibration and decision plot.
The calibration curve showed good concordance between predicted probability and actual probability (Fig. 2A).
In the decision analysis curve, the nomogram is compared with the null model for its added value, which turned out that the nomogram is applicable when thresholds are in the range between 0.08 and 0.35, due to the net benefit (Fig. 2B).

were confusable. In delirious patients, hypoactive and hyperactive states could both be found, as well as the fluctuating states between the two. In our study, the preliminary diagnosis was based on the documented clinical symptoms and cognitive testing both in the medical record and the collected data during follow-up after discharge. The final diagnosis was identified carefully according to the criteria referred to Diagnostic and Statistical Manual of Mental Disorders: 5th Ed (DSM-5.) [11], while the differential diagnosis of the distinguishing characteristics refers to the summaries in Table 4 [10]. In the previous DSM versions, alterations in the content and/or level of consciousness were central to the diagnosis of delirium, whereas in DSM-5, delirium is more restrictively defined in terms of its cognitive features, due to the recognition that it is difficult to assess construct 'consciousness' objectively [19], thus the term 'consciousness' is not used anymore.

In the elderly patients with a hip fracture, delirium can develop with the impaction from multiple factors such as traumatic fractures, anesthesia, surgical procedure, loss of blood, intensive care unit, and so on. However, the specific risk factors remain controversial. This study attempted to determine the incidence, risk factors, and a predictive nomogram for postoperative delirium. The prevalence of delirium during the hospital stay was 14.3%. This incidence was slightly lower than that in the majority of recent literature [20]. We considered that the larger number of samples might have the primary influence on the result, according to a recently published review [21]. In addition, ethnological difference, and the expert opinion about the observation of the clinical symptoms of delirium might also play a role in the discrepancy of the result. In our study, preoperative cognitive impairment, number of medical comorbidities, ASA classification, transfusion exceeding 2 units of red blood cell, and intensive care were identified to be the independent risk factors for the development of postoperative delirium.

The main limitations of this study are that it was a retrospective study, and the observation of the clinical symptoms of delirium

Table 3
Risk score table.

Variable	Score
Preoperative cognitive impairment	
no	0
yes	10
Number of medical comorbidities	
<2	0
>=2	3
ASA class	
1-2	0
3-4	4
Transfusion >2 units of RBC	
no	0
yes	3
ICU	
no	0
yes	4

Total Points	Risk of postoperative delirium
1	0.1
7	0.2
11	0.3
14	0.4
17	0.5
20	0.6
23	0.7

was assessed only by nursing staff and the attending doctors, combined with expert opinion, while no objective testing method was applied.

In conclusion, preoperative cognitive impairment, number of medical comorbidities, ASA classification, transfusion exceeding 2 units of red blood cell, and intensive care were independent predictors of the development of postoperative delirium. The risk of postoperative delirium increased with the increasing risk score of predictive nomogram. This predictive nomogram was designed to be used for the assessment of the risk of postoperative delirium preoperatively by calculating the risk score. Further work and expanded studies are to be carried out to find out more evidential outcomes for the prevention and treatment of postoperative delirium in elderly patients with a hip fracture.

Conflict of interest statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled “Predictive nomogram for postoperative delirium in the elderly patients with a hip fracture”.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.injury.2018.10.034.

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Table 4
Distinguishing Characteristics of Delirium, Dementia, Psychotic Disorders, and Depression*.

Disorder	Distinguishing Feature	Associated Symptoms	Course
Delirium	Fluctuating levels of cognitive with decreased attention	Disorientation, visual hallucinations, agitation, apathy, withdrawal, impairment in memory and attention	Acute onset; most cases remit with correction of underlying medical condition
Dementia	Memory impairment	Disorientation, agitation	Chronic, slow onset, progressive
Psychotic disorders	Deficits in reality testing	Social withdrawal, apathy	Usually slow onset with prodromal syndrome; chronic with exacerbations
Depression	Sadness, loss of interest and pleasure in usual activities	Disturbances of sleep, appetite, concentration, and energy; feelings of hopelessness and worthlessness; thoughts of suicide	Single episode or recurrent episodes; may be chronic

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