

Predictors of Postoperative Delirium in Older Patients Undergoing Elective Spine Surgery

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Abstract:

Introduction: This prospective study was conducted to investigate the prevalence and predictors of postoperative delirium (POD) in a cohort of patients aged ≥ 65 years who were scheduled to undergo elective spine surgery.

Methods: Patients aged ≥ 65 years who were scheduled to undergo elective spine surgery from February 2018 to May 2019 were prospectively recruited for this study. Delirium was diagnosed according to the Confusion Assessment Method algorithm. Candidate predictors included patient characteristics, comorbidities, surgical time, blood loss, preoperative laboratory parameters, and preoperative cognitive function, as assessed by the Mini-Cog test. These variables were compared between patients with and without POD. Multivariate logistic regression was performed to identify the independent predictors of POD. For the continuous variables, a receiver operating characteristic curve was used to determine the optimal cutoff value for predicting POD.

Results: Of the 106 patients included in the study, 12 (11.3%) patients developed POD, with a median time to onset of 3 d and median duration of 2 d. After adjusting for confounders, the occurrence of POD was independently associated with older age, a higher blood urea nitrogen (BUN) concentration, and a lower Mini-Cog score. The optimal cutoff point of the Mini-Cog score for predicting the occurrence of POD was ≤ 3 .

Conclusions: POD was a common complication after spine surgery, showing an incidence of 11.3% in this study. Older age, a higher BUN concentration, and impaired cognition, as defined by the Mini-Cog, were independent predictors of POD. The current results may be useful for early identification of patients at risk of POD and facilitation of targeted interventions for preventing POD or mitigating its severity.

Keywords:

spine surgery, delirium, cognitive impairment, renal dysfunction

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Introduction

Many developing countries are currently facing the problem of an aging population because of the declining birth rate and rising life expectancy. According to the World Population Prospects 2019 published by the United Nations, one in six people worldwide will be older than 65 years by 2050, which has increased, from one in 11 people in 2019. This increase in the older population is associated with increases in the incidence of musculoskeletal degenerative conditions such as osteoarthritis, osteoporosis, spinal canal stenosis, and spinal deformity. Because musculoskeletal disorders have a markedly deleterious effect on health-related quality of life¹⁾, the number of older patients who seek mus-

culoskeletal surgery, including spine surgery, is dramatically increasing.

Postoperative delirium (POD) is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as an acute onset fluctuating change in the mental status, which is characterized by reduced awareness of the environment and a disturbance in attention^{2,3)}. POD is one of the most common complications in older patients, particularly after hip fracture and vascular surgery⁴⁾. POD is associated with adverse outcomes, including impaired physical function, cognitive decline, a longer hospital stay, increased mortality, and increased healthcare costs^{5,6)}. Early identification of patients at risk for POD is important because timely interventions could prevent the occurrence of POD and its

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detrimental outcomes⁷). Furthermore, identification of the risk factors for POD may ultimately lead to a better understanding of the pathophysiology of POD.

Several studies have identified the risk factors for POD following spine surgery, such as older age, comorbidities, preexisting cognitive impairment, malnutrition, and greater blood loss⁸). However, the incidence of POD after spine surgery differs greatly, and the risk factors for POD are inconsistent. Thus, this study was performed to investigate the prevalence and predictors of POD in a prospective cohort of older patients undergoing elective spine surgery.

Materials and Methods

This study prospectively evaluated the risk factors for POD in patients undergoing elective spine surgery from February 2018 to May 2019. Patients aged ≥ 65 years who were scheduled to undergo spine surgery were eligible for inclusion. An institutional review board approval was obtained before study commencement. The protocol for this study followed the guidelines outlined in the Declaration of Helsinki and all of its later amendments. All participants provided a written informed consent at the time of enrollment.

The patients' symptoms and signs of delirium were observed and recorded by the nursing staff and attending doctors twice a day during their usual rounds in the ward. If POD was suspected based on the presence of symptoms, the diagnosis of POD was confirmed using the Confusion Assessment Method (CAM), which comprises four criteria: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness⁹). The CAM algorithm for the diagnosis of delirium requires the presence of both the first and second criteria and either the third or fourth criteria. We also recorded the time of onset and duration of POD.

The patients were characterized at baseline according to sex, age, body mass index, comorbidities, number of medications, use of psychoactive medication, classification of anesthetic risk according to the American Association of Anesthesiologists (ASA) scoring system, lesion treated by spine surgery, operation time, amount of bleeding, and length of hospital stay. The severity of comorbidities was evaluated using the 14-system version of the Cumulative Illness Rating Scale (CIRS)¹⁰). Baseline cognitive function was assessed using the Mini-Cog test^{11,12}), which combines two simple cognitive tasks (three-item word memory and clock drawing) with an empirical algorithm for scoring. It takes about 3 min to complete; tests visuospatial representation, recall, and executive function; and detects cognitive impairment or dementia with reasonable sensitivity and specificity¹²). The Mini-Cog score ranges from 0 (severe cognitive impairment) to 5 (normal cognition). A cutoff of ≤ 2 points on the Mini-Cog has been validated for dementia screening, and impaired cognition has been defined as a Mini-Cog score of ≤ 3 ¹²).

We also collected data on the preoperative routine laboratory blood tests. These included the white blood cell count, red blood cell count, hemoglobin concentration, hematocrit, platelet count, total protein concentration, albumin concentration, aspartate transaminase concentration, alanine aminotransferase concentration, blood urea nitrogen (BUN) concentration, creatinine concentration, estimated glomerular filtration rate, sodium concentration, potassium concentration, chloride concentration, and C-reactive protein concentration.

Statistical analysis

The patients were divided into two groups according to the presence or absence of POD. Between-group comparisons were performed using the unpaired t-test for mean values, Pearson's chi-square test or Fisher's exact test for proportions, and the Wilcoxon rank-sum test for median values. To reveal the risk factors for POD, candidate risk factors, including patient characteristics, baseline functions, and laboratory blood test results, were compared between patients with and without POD. Variables that were found to be statistically significant in the univariate analyses were applied to multiple logistic regression models (forward stepwise selection, $P < 0.05$) to adjust for confounders. Receiver operating characteristic (ROC) curves, which depict the relationship between true-positive (sensitivity) and false-positive ($1 - \text{specificity}$) cases, were constructed for the variables in the final model. The area under the ROC curve (AUC), which depicts the accuracy of the test, was calculated for each variable. In general, the AUC is interpreted as follows: 0.5-0.7 (low accuracy), 0.7-0.9 (moderate accuracy), and 0.9-1.0 (high accuracy)¹³). The optimum cutoff point that maximized the sensitivity and specificity of predicting POD was determined based on the ROC curve. All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

Results

In total, 106 patients were included in the study. Of the 106 patients, 12 (11.3%) patients developed POD, with a median time to onset of 3 d and median duration of 2 d. Table 1 compares the clinical characteristics, baseline functions, and surgical parameters between patients with and without POD. Patients with POD were significantly older, had a higher CIRS comorbidity score, were taking a larger number of medications, and showed a lower Mini-Cog score than those without POD. The length of hospital stay was also significantly longer in patients with than without POD. Comparisons of preoperative laboratory parameters between patients with and without POD are shown in Table 2. Patients with POD had a significantly lower hemoglobin concentration, lower albumin concentration, higher BUN concentration, higher creatinine concentration, and higher CRP concentration than patients without POD.

Multivariate logistic regression analysis identified older

Table 1. Comparisons of Patient Characteristics, Baseline Functions, and Surgical Parameters between Patients with and without Postoperative Delirium.

Variable	Total (n=106)	With delirium (n=12)	Without delirium (n=94)	P value
Age (year)	71.6±5.9	77.3±5.0	71.0±5.7	<0.001
Sex (male)	65 (61)	8 (67)	57 (60)	0.763
BMI	24.3±4.0	24.5±3.8	24.3±4.1	0.933
CIRS Comorbidity Score	8.2±4.0	10.5±4.8	8.0±4.0	0.048
Number of medications	6 (4–10)	10 (6–12)	6 (4–9)	0.027
Psychoactive medication use	30 (28)	6 (50)	24 (26)	0.076
ASA PS classification				
ASA I	4 (4)	0 (0)	4 (4)	0.291
ASA II	76 (72)	7 (58)	69 (73)	
ASA III	26 (24)	5 (42)	21 (22)	
Mini-Cog score	3.8±1.1	2.9±0.9	3.9±1.1	0.006
EQ-5D-3L	0.56±0.18	0.58±0.05	0.56±0.19	0.804
Surgical lesion				
Cervical spine	35 (33)	5 (42)	30 (32)	0.771
Thoracic spine	8 (8)	1 (8)	7 (7)	
Lumbar spine	63 (59)	6 (50)	57 (61)	
Operative time (min)	188.5±124.1	195.5±117.5	187.7±125.5	0.845
Bleeding volume (mL)	458.7±676.2	275.9±284.3	481.3±707.5	0.345
Length of hospital stay (day)	27.0±12.5	35.2±13.1	26.0±12.1	0.019

Data are shown as mean±standard deviation, number (%), or median (interquartile range). *P values were calculated using unpaired t-test for means, Fischer's exact test for proportions, or Wilcoxon signed-rank test for medians. BMI, body mass index; CIRS, Cumulative Illness Rating Scale; ASA PS, American Society of Anesthesiologists Physical Status; EQ-5D-3L, EuroQol 5 Dimensions 3-level version

Table 2. Comparisons of Patient Preoperative Laboratory Parameters between Patients with and without Postoperative Delirium.

Laboratory parameter	Total (n=106)	With delirium (n=12)	Without delirium (n=94)	P value
White blood cell ($10^3/L$)	5.8±1.8	6.2±1.8	5.8±1.8	0.498
Red blood cell ($10^3/L$)	407.2±62.4	377.0±63.4	411.1±61.6	0.075
Hemoglobin (g/dL)	12.9±1.9	11.7±1.9	13.0±1.9	0.025
Platelet ($\times 10^4/mm^3$)	20.9±8.5	18.1±4.9	21.3±8.8	0.228
Total protein (g/dL)	7.0±0.5	7.0±0.8	7.0±0.5	0.759
Albumin (g/dL)	4.3±0.5	4.0±0.7	4.3±0.5	0.023
AST (U/L)	23.8±11.4	19.0±6.8	23.9±11.3	0.086
ALT (U/L)	21.1±12.7	16.3±6.4	21.3±12.9	0.121
Blood urea nitrogen (mg/dL)	21.4±10.3	30.0±17.4	20.4±8.5	0.002
Creatine (mg/dL)	1.6±1.9	2.7±3.0	1.4±1.7	0.032
eGFR	58.6±28.6	46.4±38.3	60.1±27.0	0.118
Sodium	141.2±2.6	140.8±2.1	141.3±2.7	0.561
Potassium	4.3±0.5	4.1±0.8	4.3±0.5	0.321
Chlorine	104.8±3.1	104.8±4.0	104.8±3.0	0.999
C-reactive protein (mg/dL)	0.4±1.3	1.4±3.5	0.3±0.7	0.010

Data are shown as mean±standard deviation, number (%), or median (interquartile range). *P values were calculated using unpaired t-test for means, Fischer's exact test for proportions, or Wilcoxon signed-rank test for medians. AST, aspartate transaminase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate

age (odds ratio [OR], 1.26; 95% confidence interval [CI], 1.08-1.47), a lower Mini-Cog score (OR, 0.492; 95% CI, 0.25-0.97), and a higher BUN concentration (OR, 1.11; 95% CI, 1.03-1.21) as independent predictors of the occurrence of POD (Table 3). The adjusted R^2 of the predictive model

was 0.462.

The ROC curves for age, the Mini-Cog score, and the BUN concentration are shown in Fig. 1. The optimal cutoff value for predicting the occurrence of POD was ≥ 75 years for age, with a sensitivity of 0.75 and specificity of 0.79; ≤ 3

points for the Mini-Cog score, with a sensitivity of 1.00 and specificity of 0.40; and ≥ 24 mg/dL for the BUN concentration, with a sensitivity of 0.67 and specificity of 0.69. The diagnostic accuracies defined by the AUCs were 0.81 for age, 0.75 for the Mini-Cog score, and 0.65 for the BUN concentration.

Discussion

In the present study, we investigated the predictors of POD in a prospective cohort of patients undergoing elective spine surgery. The three key findings of this study are as follows. First, 12 of the 106 patients (11.3%) developed POD, with a median time to onset of 3 d and median duration of 2 d. Second, after adjusting for numerous confounders, the occurrence of POD was independently associated with older age, a higher BUN concentration, and a lower Mini-Cog score. Third, the optimal cutoff value of the Mini-Cog score for identifying patients with an increased risk of POD was ≤ 3 points.

The incidence of POD following spine surgery ranges widely from 0.49% to 21.00% because of the heterogeneity across studies, such as the heterogeneity caused by differences in patients' age, comorbidities, surgical lesions, degree of surgical stress, and diagnostic criteria for POD¹⁴. A recent meta-analysis of 40 studies on spine surgery showed that the pooled incidence of POD was estimated at 8.0%, which was lower than that after knee and hip arthroplasty (17.6%)¹⁵ and hip fracture surgery (28.0%)¹⁶. The lower incidence could be partly explained by the missed diagnosis of POD

in the retrospective studies included. Of the 40 studies included in the meta-analysis, 31 studies were conducted retrospectively, and the retrospective studies showed a lower incidence of POD than that in the prospective studies⁸. The slightly higher incidence of POD (11.3%) in the present study may also reflect the prospective identification of POD in this study. These findings highlight the importance of a prospective study design in assessing the incidence of POD.

Consistent with our results, older age has been shown to be a strong risk factor for POD regardless of the type of surgery^{7,17,18}. POD occurs through the complex inter-relationship between multiple predisposing factors in a vulnerable patient and exposure to noxious insults or precipitating factors⁷. Older age is inherently associated with the accumulation of medical comorbidities and the decline of functional reserve^{18,19}. Therefore, a relatively mild surgical insult may be enough to induce POD in older patients with multiple comorbidities and limited physiological reserve, whereas a younger patient in better health will be able to handle the stress of surgery.

In this study, coexistence of reduced renal function, as measured by the BUN concentration, was an independent predictor of POD. In line with our findings, several studies have demonstrated that patients with coexisting renal dysfunction have an increased risk of POD²⁰⁻²². In a study of 293 patients undergoing lumbar decompression and fusion, Adogwa et al.²¹ showed that patients with chronic kidney disease (CKD) had a three-fold higher rate of delirium than those without CKD (27.8% vs. 8.4%, respectively). In a prospective cohort of 627 patients undergoing elective major abdominal surgery, Janssen et al.²⁰ demonstrated that risk factors for POD included renal impairment, cognitive impairment, and an ASA score of ≥ 3 after adjusting for confounding factors. Similarly, Sasajima et al.²² showed that POD was independently associated with an age of ≥ 72 years, end-stage renal failure, and cognitive impairment in patients who underwent bypass surgery for lower limb ischemia. One proposed mechanism underlying the development of POD in patients with CKD is the vascular hypothe-

Table 3. Multivariate Logistic Regression Analysis.

Variable	Odds ratio (95% CI)	P value
Age	1.25 (1.08–1.47)	0.004
Mini-Cog	0.49 (0.25–0.97)	0.039
BUN	1.11 (1.03–1.21)	0.011

CI, confidence interval; BUN, blood urea nitrogen. Nagelkerke's generalized $R^2=0.462$.

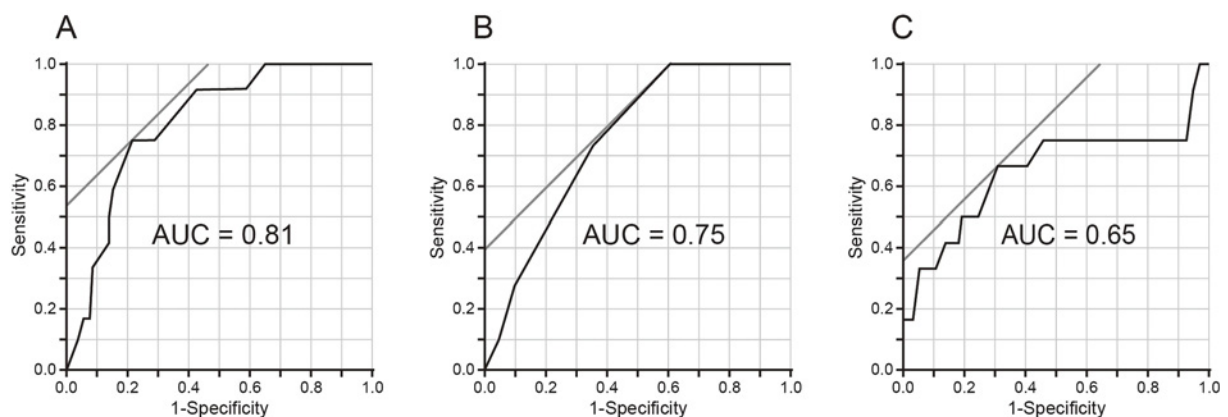


Figure 1. Receiver operating characteristic (ROC) analysis. ROC curves were constructed to determine the optimal cutoff values of (A) age, (B) the Mini-Cog score, and (C) the blood urea nitrogen (BUN) concentration for predicting the occurrence of postoperative delirium (POD).

sis²³). CKD-induced metabolic derangement causes a generalized, chronic proinflammatory state, leading to vascular remodeling processes and subsequent systemic atherosclerosis²⁴. Cerebrovascular disease is an important risk factor for POD in patients undergoing cardiac surgery²⁵. Furthermore, multiple uremic toxins have been shown to induce toxic metabolic encephalopathy, which is clinically diagnosed as “delirium” or an “acute confusion state²⁶.”

Mild cognitive impairment or dementia is a risk factor for POD and is associated with increased morbidity and mortality in geriatric patients undergoing major elective surgeries². In this study, we used the Mini-Cog, a brief screening tool designed to detect cognitive impairment or dementia. It takes only 3 min to complete; tests visuospatial representation, recall, and executive function; and detects dementia with reasonable sensitivity and specificity¹¹. We found that 41 of 106 patients (39%) in the present study had cognitive impairment, as defined by a Mini-Cog score of ≤ 3 , and the diagnosis of cognitive impairment was independently associated with the occurrence of POD. Consistent with our findings, Robinson et al.¹² showed that the incidence of cognitive impairment, defined as a Mini-Cog score of ≤ 3 , was 42% in older patients undergoing elective major surgery and that cognitive impairment was associated with an increased incidence of POD, longer hospital stay, higher rate of discharge institutionalization, and higher 6-month mortality. These results suggest that a relatively high rate of older patients undergoing elective surgery have previously undiagnosed cognitive impairment at baseline and that preoperative cognitive screening can help identify those at risk of postoperative cognitive and medical complications.

The current results may be useful for early identification of patients at risk of POD and facilitation of targeted interventions for preventing POD. Among the risk factors identified in this study, older age and cognitive dysfunction are non-modifiable risk factors, whereas an increased BUN concentration can be partly modifiable²⁷. Treatment of a high BUN concentration by renal replacement therapy is associated with a significantly decreased risk of delirium and coma in patients with acute kidney injury²⁸. An increased BUN concentration may also be associated with dehydration, which is a typical modifiable risk factor for delirium²⁷. Therefore, preoperative control of uremia and appropriate hydration may decrease the risk of POD in patients with a high BUN concentration. Furthermore, it is important to minimize other modifiable risk factors such as opioid use, benzodiazepine use, uncontrolled pain, hypoxia, anemia, postoperative infection, and respiratory complications²⁷.

This study has several limitations. First, because of the small sample size, we may have missed significant relationships between baseline variables and the occurrence of POD. Second, although our analysis was limited to spine surgeries, the degree of surgical stress as indicated by the blood loss volume and operation time varied widely. The heterogeneity in surgical stress may have affected the results of our analysis. Third, we did not assess the patients' his-

tory of alcohol abuse, which is an established risk factor for POD. Adding the history of alcohol abuse and the amount of alcohol consumption into the investigation may improve the accuracy of our predictive model. Finally, surgical postoperative outcomes were not analyzed in this study. POD can lead to poorer surgical outcomes such as increased postoperative complications, impaired physical function, and poorer long-term cognitive function. A further large-scale study is warranted to reveal the impact of POD on surgical outcomes.

In conclusion, POD was a common complication after elective spine surgery, showing an incidence of 11.3% in this study. Older age, a higher BUN concentration, and impaired cognition, as defined by the Mini-Cog, were independent predictors of POD. Adding a brief cognitive screening test such as the Mini-Cog into routine preoperative assessments may provide important information on the risk of POD in older patients undergoing spine surgery.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

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Author Contributions: Atsushi Kimura designed the study; Atsushi Kimura, Yasuyuki Shiraishi, Hideaki Sawamura, Ryo Sugawara, and Hirokazu Inoue collected and analyzed the data; Katsushi Takeshita supervised the study; Atsushi Kimura wrote the manuscript.

Ethical Approval: This study was approved by the Institutional Review Board of Jichi Medical University (Approval code: A17-092).

Informed Consent: Informed consent for publication was obtained by all participants in this study.

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