Original Article

The risk factors associated with delirium after lumbar spine surgery in elderly patients

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Background: To prospectively explore the incidence and risk factors for postoperative delirium in elderly patients following lumbar spine surgery.

Methods: This prospective study enrolled 148 consecutive patients over the age of 65 who were scheduled to undergo spine surgery. Patients were screened for delirium using the short Confusion Assessment Method (CAM) postoperatively. Patient demographics and relevant medical information were collected. Logistic regression analysis was used to identify the risk factors associated with postoperative delirium.

Results: Eighty-three patients (56.1%) who underwent lumbar spine surgery (not coexisting with cervical or thoracic spine surgery) were enrolled in our study. Post-operative delirium was noted in 14.5% of patients over 65 years old. The presence of preoperative Parkinsonism was significantly higher in the delirium group (41.7% *vs.* 8.5%, P=0.002), as was a higher preoperative C-reactive protein (CRP) (7.0±15.2 *vs.* 1.3±2.3 mg/L, P=0.017) when compared with the non-delirium group. Of the risk factors, male sex [odds ratio (OR) =0.10, 95% confidence interval (CI): 0.01–0.66, P=0.017], Parkinsonism (OR =5.83, 95% CI: 1.03–32.89, P=0.046), and lower baseline MMSE score (OR =0.71, 95% CI: 0.52–0.97, P=0.032) were independently associated with postoperative delirium in elderly patients undergoing lumbar spine surgery.

Conclusions: Post-operative delirium occurred in 14.5% of elderly patients who underwent lumbar spine surgery. Male sex, Parkinsonism, and lower baseline MMSE score were identified as independent risk factors for postoperative delirium in elderly patients following lumbar surgery.

Keywords: Delirium; elderly patients; lumbar surgery; risk factors

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Introduction

Delirium is a well-defined complication in hospitalized patients characterized by an acute change in cognition with fluctuating levels of consciousness. Although delirium is often reversible, it has also been identified as a risk factor for numerous hospital complications including preventable neuropsychiatric syndrome and permanent cognitive impairment (1-8). In addition to the numerous adverse effects on an individual's quality of life, delirium places a large burden to the healthcare system due to the prolonged hospital stay related to the extensive work-up patients undergo, and treatment once the causes have been recognized. In the postoperative setting, delirium is often not recognized despite a prevalence ranging from 11% to 51% in adult patients (4). Furthermore, a meta-analysis of more than 3,000 patients identified delirium as an independent risk factor for death, institutionalization, and dementia (9).

In concurrence with the aging population and increased life span trends, an increasing number of elderly patients are undergoing spine surgery. In particular, lumbar surgery and revision surgery are performed frequently, and the associated surgical trauma and complications have been drawing increasing attention. Delirium, for instance, a common postoperative complication, indicates adverse outcomes in patients more than 65 years old (3,4,10-13). Several studies have identified old age as a significant risk factor for postoperative delirium (1,13,14). Cognitive impairments, including delirium, are in turn correlated with complications in elderly patients (4,15). In addition, the hypoactive form of delirium is more common in elderly people and often goes unrecognized (16). Postoperative delirium following spine surgery has been reported to occur in 24.3% (17/70) of elderly patients (17). A retrospective analysis identified postoperative delirium in 13.6% (11/81) of patients following lumbar spine surgeries (18). Despite the increasing volume of spine surgeries amongst elderly patients and a high incidence of postoperative delirium, risk factors for developing delirium have not yet been systematically evaluated (19).

The origin of delirium is known to be multifactorial and may be preventable in 30–40% of all cases (4,20-22). Identifying the risk factors for developing delirium could allow for earlier intervention to prevent delirium following spine surgery, significantly reducing the associated morbidity and mortality (1,4,23,24). Currently, our understanding of the prominent risk factors is limited and further research is needed to identify preventable risk factors for postoperative delirium (4,25,26). To our knowledge, there is no prospective study that has investigated the risk factors for delirium after lumbar spine surgery. Consequently, we initiated a prospective study which aimed to explore the incidence and risk factors for postoperative delirium in elderly patients who underwent lumbar spine surgery.

Methods

Study overview

Our study enrolled 148 consecutive patients over the age of 65 years who were scheduled to undergo spine surgeries at one institution (*Figure 1*). Of these, 42 patients did not meet the inclusion criteria while 2 cases had to be postponed immediately prior to surgery. The remaining 104 participants (70.3%) underwent spine surgery between October 2015 and July 2016. The inclusion criteria were the following: (I) patients of age ≥65 years old, who were scheduled to undergo spinal surgery mainly consisting of discectomy, laminectomy and fusion (*Figure 2*); (II) hospital stay of more than 3 days; (III) indication for surgery including herniated nucleus pulposus, degenerative disc disease, spondylolisthesis, and spinal stenosis. Exclusion criteria were the following: (I) a history of delirium before surgery; (II) presence of a distinct intracranial disease such as tumor and infection; (III) patients with critical organ failure or multiple organ comorbidities known prior to surgery; (IV) patients who underwent a concurrent cervical or thoracic surgery were excluded to decrease data bias and clinical heterogeneity.

Individual characteristics and clinical data were obtained from patient interviews, caregiver statements and medical records (*Table 1*). Patients with postoperative delirium were assigned to a delirium group, while patients without delirium were enrolled in the control group. The

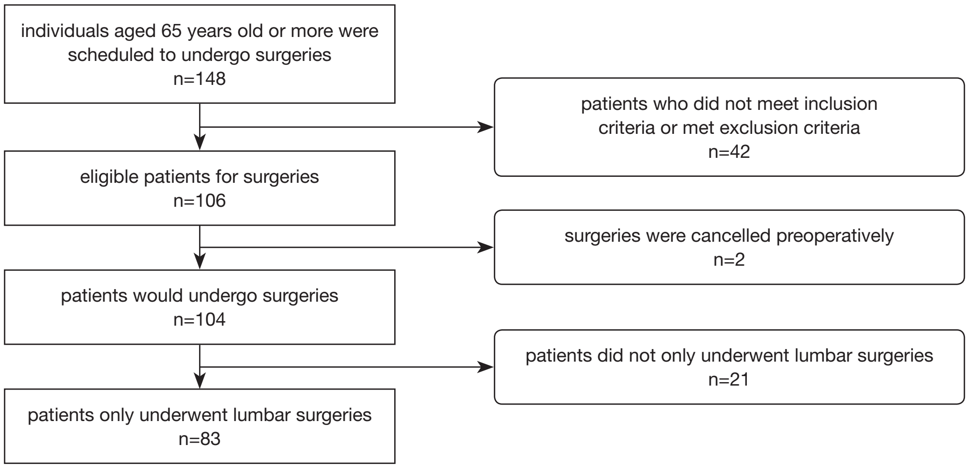

Figure 1 Participant enrollment. Enrollment in the study excluded the following: (I) patients did not meet inclusion criteria (n=42); (II) surgeries were temporarily cancelled before operations (n=2); (III) patients underwent the lumbar surgery combining cervical or thoracic surgery (n=21).

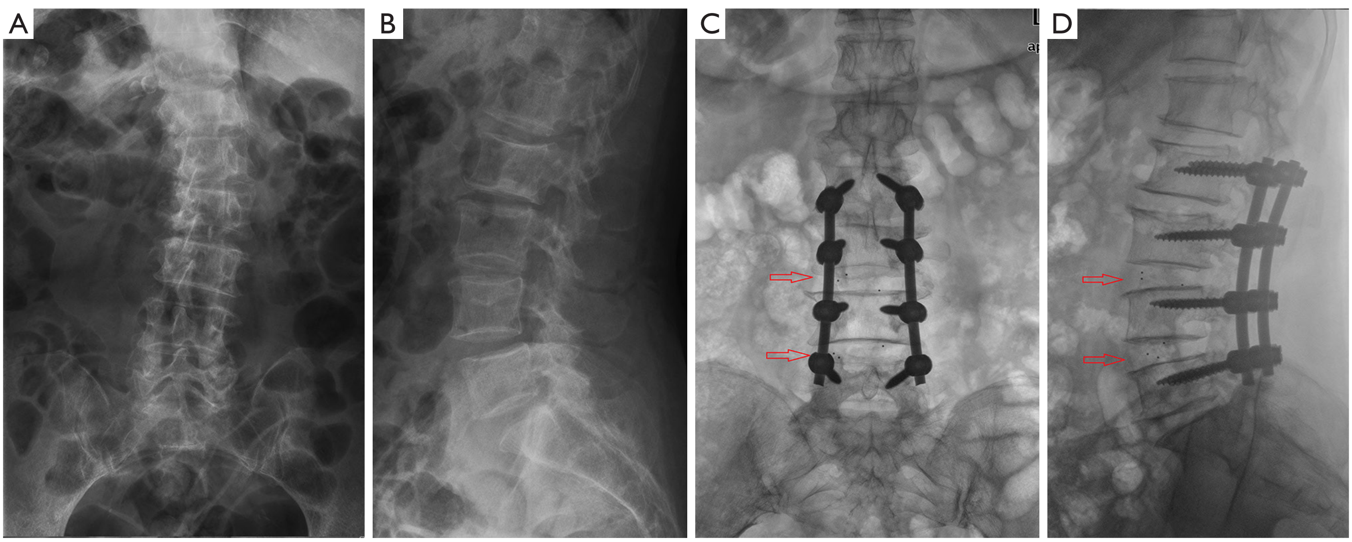

Figure 2 Spinal fusion and non-fusion surgery were partial inclusion criteria for this study. (A,B) An 80-year-old female patient who underwent laminectomies at L3/4 and L4/5 did not suffer postoperative delirium; (C,D) another elderly woman who received a spinal fusion at L3/4 and L4/5 (red arrows) suffered delirium postoperatively.

investigative protocol was approved by our hospital's Institutional Review Board (NCT 02550626), and informed consent was obtained for experimentation with human subjects. This study was designed in conformity with the Declaration of Helsinki.

Assessment of delirium

Diagnosis of delirium was regularly conducted between 9 am and 12 pm on postoperative days 1–3 on the basis of the participant's cognitive status or records from the nurse and caretaker, and observation was continued until discharge (25). Delirium was diagnosed by the previously accepted short Confusion Assessment Method (CAM) (11,27), which is a scoring system for delirium severity and has been demonstrated to have predictive validity for clinical outcomes of delirium. Participant's cognitive status was evaluated by the Korean version of the Mini-Mental

Table 1 Factors in the delirium group and the non-delirium group

Variable	Total, n=83	Postoperative delirium		P value
		Yes, n=12 (14.5%)	No, n=71 (85.5%)	
Age (yrs)	71.4±4.6	73.4±4.9	71.0±4.6	0.102
Sex				
Male	27	8	19	0.060
Female	56	4	52	
BMI (kg/m^2)	24.4±2.9	24.9±2.3	24.4±3.0	0.517
MMSE score [0–30]	26	25 [23–27]	26 [24–29]	0.076
Comorbidities				
Hypertension	56	9	47	0.547
Diabetes mellitus	18	3	15	0.763
History of CVA or TIA	8	3	5	0.051
Cardiovascular comorbidity	21	5	16	0.159
Parkinsonism	11	5	6	0.002
Previous dementia or MCI	8	3	5	0.051
Psychiatric disorder	12	2	10	0.814
Depression	28	5	23	0.434
Medications (quantity)	5.2	5.5±2.3	5.2±3.3	0.737
Statin	40	7	33	0.447
ARB	31	4	27	0.756
Psychoactive drugs[†]	25	5	20	0.346
Lab findings				
Albumine (g/dL)[§]	4.1±0.32	4.2±0.28	4.1±0.33	0.851
BUN (mg/dL)[§]	17.1±4.6	16.8±4.7	17.2±4.6	0.618
Creatinine (mg/dL)[§]	0.77±0.19	0.83±0.20	0.76±0.19	0.248
Hemoglobin (g/dL)[§]	13.6±1.4	13.8±1.2	13.6±1.4	0.716
Hematocrit (%)[§]	40.5±0.42	40.6±3.4	40.5±3.9	0.980
WBC (10^3/μL)[§]	6.7±1.8	6.4±0.80	7.1±1.9	0.210
Platelet (10^3/μL)[§]	235±56.8	217±43.6	238±58.5	0.242
CRP (mg/L)[§]	2.2±6.3	7.0±15.2	1.3±2.3	0.017
Postoperative CRP (mg/L)	62.7±38.0	76.7±36.2	60.2±38.1	0.186
Surgical method				
Spinal fusion	65	10	55	0.632
Decompression	18	2	16	
Intraoperative blood loss (cc)	656±609	491±465	684±628	0.314
Operation time (min)	199.7±83.4	173±67.5	204±85.4	0.229
Admission to ICU	10	3	7	0.136
Postoperative fever (>37.8 ℃)	12	8	4	0.503

Data are expressed as mean ± standard deviation (SD), median [interquartile range], or number (%). [†]Psychoactive drugs included prescribed anti-psychotics, sedative hypnotics, benzodiazepines, opioids, anti-histamine, anticholinergics, and dopaminergic medications; [§]preoperative lab finding. BMI, body mass index; MMSE, mini-mental state examination; CVA, cerebrovascular accident; TIA, transient ischemic attack; MCI, mild cognitive impairment; ARB, angiotensin II receptor blocker; BUN, blood urea nitrogen; WBC, white blood cell; CRP, C-reactive protein; ICU, intensive care unit.

State Examination (K-MMSE) (28). The MMSE is a disease-specific tool and contains 11 items that test 5 areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30, with higher scores indicating better cognition. Baseline examinations were performed preoperatively in order to assess the postoperative delirium accordingly; these were performed by two independent, trained research assistants who did not participate in the surgical care of the participants in order to reduce potential subjective bias. The short CAM consists of scoring derived from the following 4 clinical assessment protocols (12,16): (I) determine the presence of an acute mental change from baseline behavior and if present, the nature of this behavior's fluctuation course (mental status changes from hours to days); (II) determine if the patient is inattentive, easily distracted, or unable to participate in an interview; (III) evaluate the presence of disorganized thought, pressured speech or tangential speech; (IV) assess the patient's level of consciousness (12,16). A diagnosis of postoperative delirium requires the presence of features 1 and 2 accompanied by either feature 3 or 4.

Patients were not evaluated on the day of surgery because of potential confounding due to intraoperative anesthetic medications. Patient's characteristics, MMSE score, comorbidities, medications, preoperative laboratory findings, surgical methods, intraoperative blood loss, operation time, admission to intensive care unit (ICU), and presence of postoperative fever were examined for the purpose of identifying potential associations with postoperative delirium (*Table 1*).

Intraoperative and perioperative administrations

All patients underwent consistent general anesthetic regimens. Sedatives included propofol (intravenous anesthetic) and a combination of desflurane and nitrous oxide (inhaled anesthetics). Analgesic agents included remifentanil, and muscle relaxants consisted of pancuronium and vecuronium. To decrease outcome bias and clinical heterogeneity, surgical procedures and instrumentations were performed consistently for patients with the same lumbar etiology. After surgery, quantitative analgesics including fentanyl (2 μg/mL) and ropivacaine (0.15%) dosed by weight, were administered for 3 days in each patient. Antibiotics were used for 2 days in patients who underwent instrumentation. Two mg of haloperidol per 4 hours was intravenously administered for patients with postoperative delirium, and another 2 mg per hour was administered as needed for agitation.

Statistical analysis

Statistical analysis was performed with SAS version 9.4 and SPSS version 22 (IBM; Chicago, IL, USA). Numerical variables and ordinal variables were presented as mean value ± standard deviation (SD), while absolute numbers were used for categorical variables. A P value less than 0.05 was considered statistically significant. t-test was used for analyzing the data between the delirium and non-delirium (control). Chi-square test was used for the comparison of categorical data. Logistic regression analysis identified independent risk factors correlated with postoperative delirium.

Results

Eighty-three patients only underwent lumbar surgeries were finally enrolled in this study, postoperative delirium occurred in 12 patients (14.5%). Of the 12 delirium patients, 10 were diagnosed within three days after surgery, 1 was diagnosed postoperatively at day 4, and 1 was diagnosed postoperatively at day 6. The mean duration of postoperative delirium was 2.6 days (ranged from 1 to 5 days). The delirium group was composed of 8 males and 4 females with an average age of 73.4±4.9 years (ranging from 66 to 81 years). Meanwhile, the non-delirium group consisted of 19 males and 52 females with an average age of 71.0±4.6 years (P=0.102). The mean operation time was 173±67.5 minutes in the delirium group as compared to 204±85.4 minutes in the non-delirium group (P=0.229). The mean blood loss was 491±465 mL in the delirium group as compared to 684±628 mL in the non-delirium group (P=0.314). Patient information and surgical data are summarized in *Table 1*.

Significant differences between the delirium group and the control group

As compared to the control group, there was a higher prevalence of Parkinsonism amongst patients who developed postoperative delirium (41.7% *vs.* 8.5%, P=0.002). Furthermore, pre-operative C-reactive protein (CRP) was significantly higher in the delirium group as compared to the non-delirium group (7.0±15.2 *vs.* 1.3±2.3 mg/L, P=0.017). In addition, previous dementia, mild cognitive

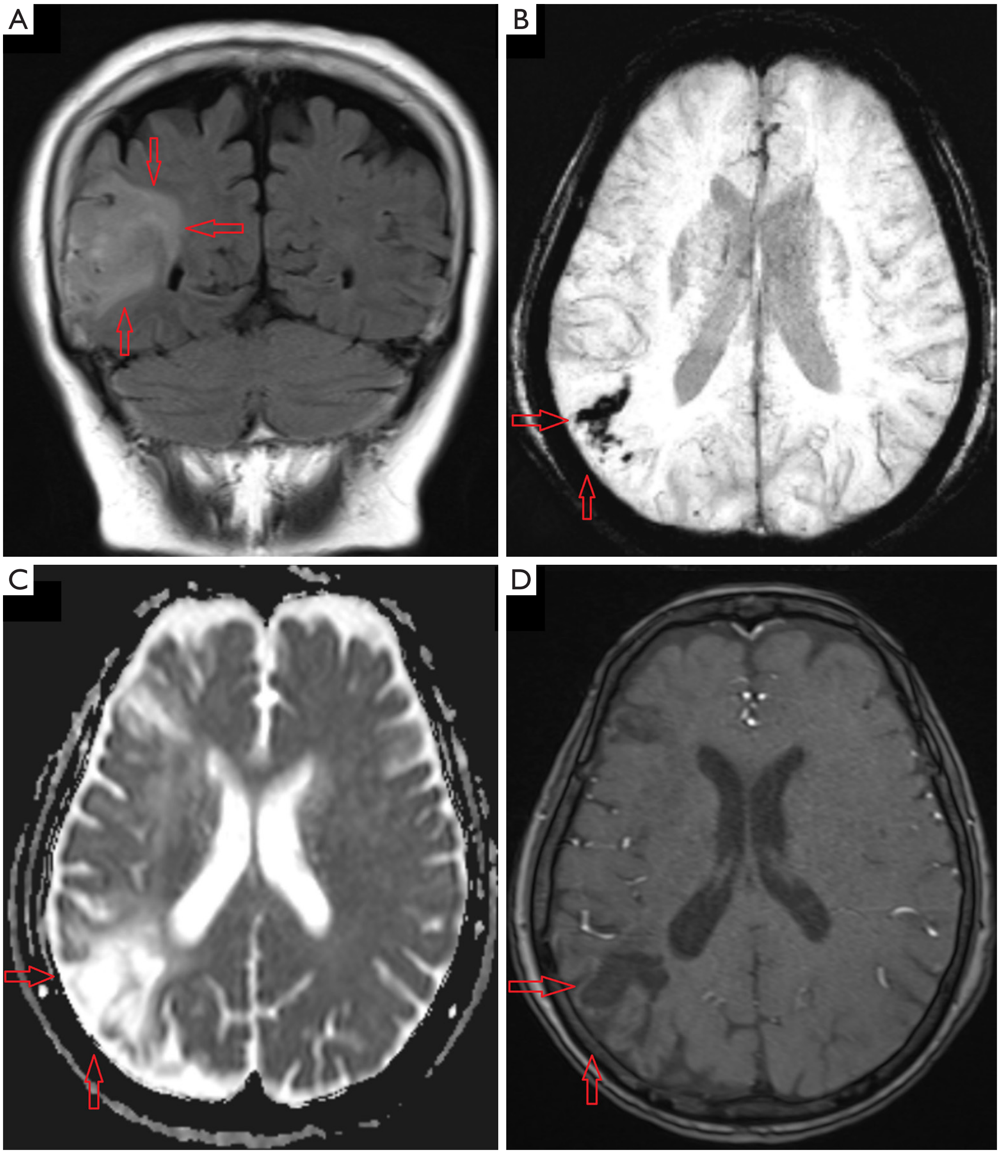

Figure 3 MRI scans showed cerebrovascular accident in some patients with/without delirium. (A) The elderly patient with postoperative delirium had cerebral infarction in the right occipitotemporal lobe (red arrows); (B) susceptibility-weighted imaging revealed the old infarction; (C) diffusion-weighted imaging showed cerebral infarction with hemorrhage during the patient's first admission; (D) magnetic resonance angiography (3dTOF) showed the old infarction lesion and intracranial blood vessels.

impairment (MCI), and prior cerebrovascular accident (CVA) or transient ischemic attack (TIA) appeared to be more common in the delirium group (both P=0.051), although these factors did not reach statistical significance (*Table 1*, *Figure 3*). Other factors including patient characteristics, MMSE score, medications, surgical methods, intraoperative blood loss, operation time, admission to ICU, and postoperative fever had no significant differences between the delirium and non-delirium groups (*Table 1*).

Risk factors for postoperative delirium

The results of the logistic regression analysis for identifying the risk factors for postoperative delirium are summarized in *Table 2*. In the univariate analysis, we found that male sex [odds ratio (OR) =0.18, 95% confidence interval (CI):

Table 2 Associations between risk factors and postoperative delirium assessed by logistic regression analyses

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.11 (0.98–1.27)	0.108	1.10 (0.09–1.32)	0.276
Sex	0.18 (0.05–0.67)	0.011	0.10 (0.01–0.66)	0.017
Hypertension	1.53 (0.38–6.19)	0.549		
Diabetes mellitus	1.24 (0.30–5.18)	0.764		
Cardiovascular comorbidity	0.41 (0.11–1.46)	0.168		
Previous dementia or MCI	0.23 (0.46–1.12)	0.068		
Previous old CVA or TIA	0.23 (0.46–1.12)	0.068		
Parkinsonism	7.74 (1.87–32.0)	0.005	5.83 (1.03–32.89)	0.046
MMSE score	0.83 (0.67–1.03)	0.084	0.71 (0.52–0.97)	0.032
Admission to ICU	3.05 (0.67–14.0)	0.151	11.18 (0.92–135)	0.058
Blood loss during operation (cc)	0.999 (0.998–1.0)	0.311	0.99 (0.99–1.00)	0.262
Operation time (min)	0.995 (0.987–1.0)	0.229		

OR, odds ratio; CI, confidence interval; MCI, mild cognitive impairment; CVA, cerebrovascular accident; TIA, transient ischemic attack; MMSE, mini-mental state examination; ICU, intensive care unit.

0.05–0.67, P=0.011) and Parkinsonism (OR =7.74, 95% CI: 1.87–32.0, P=0.005) were associated with delirium after lumbar surgeries. In the multivariate analysis, male sex (OR =0.10, 95% CI: 0.01–0.66, P=0.017), Parkinsonism (OR =5.83, 95% CI: 1.03–32.89, P=0.046), and lower baseline MMSE score (OR =0.71, 95% CI: 0.52–0.97, P=0.032) were independently related to postoperative delirium in the elderly patients following lumbar surgery. Additionally, admission to the ICU was observed as a factor for delirium after geriatric lumbar surgery (OR =11.18, 95% CI: 0.92–135, P=0.058), although this was not statistically significant.

Discussion

Delirium has long been acknowledged as a significant complication in postoperative patients, with a higher prevalence amongst elderly patients; however, delirium is still frequently not recognized, evaluated, or managed appropriately (4,13). Due to the morbidity and mortality that arise from its complications, delirium needs to be identified and treated, or prevented in the perioperative setting of major surgeries including cardiothoracic surgery, organ transplantation, and spine surgery. As the frequency of spine surgery is increasing in parallel with the aging population and spinal degenerative diseases, a more comprehensive understanding of the risk factors for postoperative delirium is vital to reduce the incidence of delirium and complications following spine surgery (25). In this prospective study, 14.5% of patients over the age of 65 developed post-operative delirium. We discovered that preoperative Parkinsonism and elevated CRP levels were present more often in elderly patients who developed post-operative delirium, as compared to the control group. Additionally, male sex, Parkinsonism and lower baseline MMSE score were each independently associated with postoperative delirium in elderly patients following lumbar surgery.

Significant differences between two groups

Several statistically significant differences were identified between the delirium and non-delirium group. Patients with preoperative Parkinsonism had a higher risk for post-operative delirium (P=0.002). This finding is consistent with a retrospective study which compared 5,637 participants with Parkinsonism to 8,143 control subjects, and concluded that patients with Parkinson's disease were treated for delirium approximately 5 times more than the control group (10.3% *vs.* 1.8%) (29). These differences may derive from the neurodegenerative nature of preoperative parkinsonism, thus correlating it as a risk factor for post-operative delirium (30,31). Secondly, compared with the control group, preoperative CRP was significantly higher in the delirium group (P=0.017). CRP is an acute phase protein whose level rises in response to inflammation. This inflammatory response may lead to a cascade of local neuroinflammation (32). Specifically, CRP has been considered a potential factor in neuropsychological dysfunction and may also contribute to the development of delirium by compromising the blood-brain barrier and damaging brain function (32,33). Finally, our findings noted that patients with a history of CVA/TIA and previous dementia/MCI were more common in the delirium group (*Table 1*). Disorders of the blood vessels may endanger oxygenation to the brain and facilitate postoperative cerebral hypoxia, which in turn contributes to the development of delirium (34).

Incidence and risk factors for postoperative delirium

Our study used short CAM and MMSE scores to diagnose delirium and measure cognitive function, respectively. This method has been validated in over 1,000 patients with a sensitivity of 94%, a specificity of 89%, and high inter-rater reliability. In this study, postoperative delirium was noted in 14.5% of patients which is a similar figure to the 19.82% of patients in Avidan *et al.*'s study (27). In addition to this, they found that 17.65% of patients in the 0.5 mg/kg ketamine group, and 21.30% of patients in the 1.0 mg/kg ketamine group were diagnosed with delirium after cardiac and non-cardiac surgery. Furthermore, the incidence of delirium after lumbar surgery in this study was consistent with a meta-analysis which reported post-operative delirium in 0.84% to 21.3% of patients (19).

In the present study, logistic regression analysis revealed that Parkinsonism was independently related to postoperative delirium. This finding is consistent with the Lubomski *et al.*'s study (29), which demonstrated that patients with Parkinsonism were more likely to suffer delirium, adverse drug reactions, and syncope as compared to their controls. A matched-pair cohort study found that Parkinsonism was a significant predictor of major postoperative complications, and delirium was the most frequently observed complication (35). The logistic regression models, including univariate and multivariate analysis, revealed that postoperative delirium occurred more frequently in male patients as compared to females. This finding is inconsistent with a meta-analysis which concluded that delirium was more common in female patients (19). Notably, MMSE score emerged as a risk factor only in multivariate regression but not in univariate regression (*Table 2*): a potential correlation may exist among the independent variables (risk factors such as MMSE score, age, gender, etc.) which might have led to data bias in the univariate regression model but which was eliminated in the multivariate regression model. Hence, MMSE score was an independent risk factor associated with postoperative delirium in the multivariate regression analysis of this study. In the current study, factors such as operative time and blood loss were not found to be significant intraoperative risk factors for postoperative delirium. However, a meta-analysis did note both longer operative time and severe bleeding as risk factors for postoperative delirium (19). Other intraoperative factors such as invasive or emergency procedures were also considered as risk factors for delirium following spine surgery (36). Nevertheless, there was no significant difference between surgical procedures (spinal fusion *vs.* compression) in the present study. Similarly, there is no consistent conclusion for the association between age and surgical outcomes of degenerative cervical myelopathy (37), although a retrospective database analysis with logistic regression demonstrated that independent predictors of delirium included age ≥65 years, depression, and psychotic disorders (38). The aforementioned inconsistencies may be related to the homogeneity of patients in this prospective study. Additionally, intraoperative procedures may decrease or increase the risk of delirium; for example, the decompression of the spinal cord carries more chance of producing confounding factors (neck immobilization, airways manipulation, failure of respiratory drive, etc.) for postsurgical delirium than decompression of the thecal sac or nerve roots (39).

Quantitative imaging was demonstrated as a predictor for cognitive decline (40,41), which may be used in predicting postoperative delirium. Wei *et al.* compared the regions of interest (ROIs) defined on MRI templates to reveal patients' cognitive states between participants with early mild cognitive impairment (EMCI) and late mild cognitive impairment (LMCI) (40). They found that, between the EMCI group and the LMCI group, there were significant differences in ROIs on structural MRIs, which included imaging of the bilateral entorhinal, bilateral hippocampus, bilateral amygdala, etc. They further found that the average thickness of the left entorhinal, left middle temporal, left superior temporal, or right isthmus cingulate was the main contributor to a decreased global cognition level. Inspired by these findings, we would like to conduct another study involving the potential association between relevant ROIs on MRI templates and patient's delirium after spine surgery.

Outlook and future investigation

Prevention or early recognition of delirium has an important role in reducing postoperative complications, and a better understanding of risk factors is necessary to effectively implement new management strategies including more precise diagnostic criteria and targeted treatments. Specifically, a clinical scoring system covering electrophysiology and neuroimaging biomarkers could be used to screen patients with varying severities of delirium and enable targeted treatments for the patients (42). These targeted treatments may include use of sedation, neuroinflammation, or neurotransmitters according to the patient's delirium severity. To an extent, minimally invasive spine surgery may decrease post-operative delirium, as which has less invasion to normal tissues and less surgical complications (43-47). In addition, the etiology of delirium is multifactorial and will likely require a multimodal approach to be effective for its prevention and treatment (4). Defining and stratifying risk factors requires further investigation. Of note, biomarkers may have a significant role in the evaluation, diagnosis, and monitoring of delirium severity.

Limitations

There are multiple limitations to our study. Factors including pre-operative medication, anesthetics, operation segments, various laboratory findings, and postoperative fever were not stratified. The associations between stratifying risk factors and postoperative delirium may yield valuable data to guide treatment and improve outcomes. Also, only 56.1% of patients were ultimately enrolled into the study, which may have resulted in the exclusion of some risk factors that were identified by other studies. For example, preoperative depression and movement disorders were not investigated as possible risk factors for postoperative delirium although a recent study reported that these may be independent risk factors following spinal deformity surgery (48). A complete list of all factors that contribute to delirium is beyond the scope of this study as the fundamental pathophysiology of delirium has yet to be elucidated. Thus, relevant basic research needs to be conducted in order to continue pioneering the field. A multicenter randomized controlled trial with a large sample size may also help further identify and stratify the risk factors associated with postoperative delirium following lumbar surgery.

Conclusions

Post-operative delirium occurred in 14.5% of elderly patients who underwent lumbar spine surgery. Male sex, Parkinsonism, and a lower baseline MMSE score were identified as independent risk factors. These clinical findings may contribute to identifying patients at high risk for delirium to allow for prevention or earlier intervention in the post-operative course.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The investigative protocol was approved by our hospital's Institutional Review Board (NCT 02550626), and informed consent was obtained for experimentation with human subjects.

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