Association between preoperative neutrophil-lymphocyte ratio, uric acid, and postoperative delirium in elderly patients undergoing degenerative spine surgery

（脊椎変性疾患術後の高齢者の術後せん妄と、好中球-リンパ球比および尿酸との関連性について）

申 請 者　弘前大学大学院医学研究科

脳神経科学領域　麻酔・疼痛制御医学教育研究分野

氏　　名　加藤　広大

指導教授　廣田　和美

ABSTRACT

Purpose: There are few reports regarding the association between the neutrophil–lymphocyte ratio (NLR), uric acid, and the development of postoperative delirium (POD) in patients who are undergoing spine surgeries. We investigated the associations between the NLR, uric acid as a natural antioxidant, and POD in elderly patients undergoing degenerative spine surgery.

Patients and Methods: This was a single-center, observational and retrospective study conducted in Japan. We enrolled 410 patients who underwent degenerative spine surgeries. POD was diagnosed after the surgeries by psychiatrists, based on the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). We performed a multivariable logistic regression analysis to clarify whether the NLR and uric acid values were associated with the development of POD in the patients.

Results: 129 of the 410 patients were excluded from the analysis. Of the 281 patients (137 females, 144 males), 32 patients (11.4%) were diagnosed with POD. The multivariable logistic regression analysis revealed that the preoperative uric acid level (adjusted odds ratio [aOR]: 0.67, 95% confidence interval [CI]: 0.49–0.90, p=0.008) and age (aOR: 1.09, 95%CI: 1.02–1.16, p=0.008) were significantly associated with POD. The preoperative NLR (aOR: 0.82, 95%CI: 0.60–1.13, p=0.227) and antihyperuricemic medication (aOR: 0.97, 95%CI: 0.24–3.82, p=0.959) were not significantly associated with POD.

Conclusion: Our results demonstrated that in elderly patients undergoing degenerative spine

surgery, the preoperative NLR was not significantly associated with POD, but a lower preoperative uric acid value was an independent risk factor for developing POD. Uric acid could have a neuroprotective impact on POD in patients with degenerative spine diseases.

Introduction

Postoperative delirium (POD) is a major potential complication of surgery and is associated with postoperative cognitive decline, and POD is a burden for patients, their families, medical and nursing staff, and healthcare systems [1, 2]. POD can cause or contribute to adverse outcomes such as longer hospital stays and higher mortality [3]. Being able to predict POD's occurrence at an early time point before surgery and preventing POD are thus very desirable for achieving better prognoses in surgical patients.

The reported incidence of POD after spine surgery has ranged from 8.0% to 40.5% and is higher than the incidences after other major orthopedic surgeries [4]. As the presence of POD after spine surgery can make it difficult for a patient to undergo a complete neurological examination and impede the patient's postoperative rehabilitation, POD may also be associated with adverse outcomes after spine surgery.

A possible pathophysiological mechanism underlying the development of POD is neuroinflammation that is induced by surgery [5]. As a marker reflecting systemic inflammation, the neutrophil–lymphocyte ratio (NLR), which is derived by dividing the neutrophil count by the lymphocyte count, is an easily obtained and inexpensive inflammatory marker [6]. The NLR was reported to be positively correlated with interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) values. The NLR may thus become a substitute for IL-6 and TNF-α as a marker associated with neuroinflammation [7]. Several studies have also shown that the NLR is a more useful marker for predicting POD compared to other inflammatory markers such as the platelet–lymphocyte ratio and the C-reactive protein (CRP) level [8, 9]. One of our earlier investigations demonstrated that the preoperative NLR was associated with the development of POD in individuals who underwent a free-flap reconstruction of the head and neck after surgery for cancer [10] and patients with a radical subtotal esophagectomy [11] that was performed under total intravenous anesthesia. There are few reports regarding the association between POD and the NLR in spine surgery patients [12].

The neuroprotective effects of uric acid have been attracting attention in recent years. Although uric acid is associated with higher-than-normal risks of stroke, myocardial infarction, and cardiovascular mortality [13, 14], uric acid is a natural antioxidant that has exerted a neuroprotective impact on neurogenerative diseases such as Alzheimer's and Parkinson's disease [15, 16]. An association between lower uric acid values and POD was documented in knee replacement patients and hip fracture patients [17, 18], but the preoperative uric acid level in patients undergoing spine surgeries has not been established. We conducted the present study to determine whether the preoperative NLR and the uric acid level may be associated with POD in patients who undergoing spine surgeries.

Patients and Methods

Patients and study approval

We enrolled 410 patients who underwent a degenerative spine surgery at Hirosaki University Hospital (Hirosaki, Japan) between January 1, 2015 and December 31, 2022. We excluded patients who were under hemodialysis or aged <60 years. This retrospective, observational single-center study was performed in accord with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and was approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine (no. 2023-013). The requirement of patients' written informed consent was waived by the Ethics Committee since the study design was retrospective and no additional intervention was administered to the patients.

Data collection

We reviewed our hospital's electronic medical and anesthesia records to obtain the characteristics and perioperative data of the patients including sex, age, body mass index (BMI), diagnosis, preoperative comorbidities, tobacco-smoking habit, and medication presenting a risk for POD. The severity of comorbidities on admission was calculated using the Charlson Comorbidity Index (CCI) [19]. The CCI is validated and enables the prediction of post-treatment adverse events. The CCI is derived by adding the score based on each of the following comorbidities: acquired immunodeficiency syndrome, any solid tumor, cerebral vascular disease, chronic obstructive pulmonary disease, congestive heart failure, connective tissue disease, dementia, diabetes, diabetes with end-organ damage, hemiplegia, leukemia, lymphoma, metastatic solid tumor, mild liver disease, moderate/severe liver damage, moderate/severe renal disease, myocardial infarction, peptic ulcer disease, and peripheral vascular disease. The preoperative laboratory data included the NLR and the levels of albumin and CRP as inflammatory markers. The NLR was derived by dividing the absolute neutrophil count by the absolute lymphocyte count. All preoperative blood tests of the patients enrolled in this study were done within 14 days before their surgeries.

The perioperative data included the anesthetic methods used, the number of operated vertebrae, the intraoperative fluid volume, the intraoperative blood loss, the use of allogeneic blood transfusion, the duration of anesthesia, the duration of the prone position, the duration of surgery, the instrumentation, the postoperative use and dose of fentanyl, intensive care unit admission, and the length of stay in the hospital. The perioperative complications included the postoperative incidences of dural tear, surgical site infection, cerebrospinal leakage, urinary tract infection, hematoma, stroke, and complications of respiration, cardiovascular disease, and the gastrointestinal tract. We assigned the patients to a POD group and a non-POD group as described below.

Anesthesia and perioperative management

The preoperative management for the patients was performed as described [20]. Patients who described having a tobacco-smoking habit were instructed to stop the habit for ≥4 weeks before their surgery. The patients who had diabetes and a hemoglobin A1c level >7% undertook efforts to improve their glycemic control before their surgery.

All of the patients were placed under general anesthesia for their spine surgery. The following variables were continuously monitored during the anesthesia: electrocardiography, pulse oximetry, the end-tidal carbon dioxide concentration, body temperature, urinary output, direct arterial blood pressure, train-of-four monitoring, and electroencephalography. The anesthesia in each surgery was induced with propofol and remifentanil, ketamine, and rocuronium and was maintained with propofol and/or desflurane, ketamine, remifentanil and/or fentanyl, morphine, and rocuronium. The depth of each patient's general anesthesia was adjusted in order to prevent bursts and suppression in the electroencephalogram. The target bispectral index (BIS) range was 40–60.

After the surgery, each of the patients was given acetaminophen and/or fentanyl for pain control when necessary and benzodiazepine for insomnia when necessary. Vascular and urinary catheters were removed within 3–7 days. The patients' continuous negative-pressure suction drainage was removed 48 hr after surgery.

Delirium assessment

The confused assessment method (CAM) [21] was used to screen the presence of POD every 8 hr by a nurse and/or orthopedist. If POD was suspected based on a CAM observation, the orthopedist asked one of the hospital's psychiatrists to confirm the presence of POD based on the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Patients diagnosed as having POD at least one time during their stay were assigned to the POD group.

Statistical analyses

The patients' data are presented as a median (25th–75th percentiles) or a number (percentage of each group). We used Fisher's exact test to examine the significance of between-group differences for categorical variables and the Mann-Whitney U-test for continuous variables. A receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values of the preoperative NLR and uric acid for predicting POD. We calculated the area under the curve (AUC) to evaluate the differentiation power for POD.

We conducted a multivariable logistic regression analysis to determine whether the preoperative NLR and uric acid values were associated with the development of POD, after adjusting for possible confounders. The number of events per predictor variable in a multivariate logistic regression should generally be at least 10 in order to provide an adequate predictive model, but Vittinghoff et al. proposed that 5–9 events per predictor variable is sufficient [22]. In the present study, as 32 patients developed POD, a maximum of six variables could be included. First, the NLR and uric acid were forced into the logistic regression model. The CCI was also included in the model to adjust for the patient background. Additionally, as older age is reported to be associated with POD after spine surgery [4], patient age was included in the model. Since antihyperuricemic medication affect the level of uric acid, antihyperuricemic medication was included in the model. We evaluated the presence of multicollinearity between two predictors by applying the variance inflation factor (VIF). When we observed a VIF >2.0, one of the two factors was deleted from the final model because of multicollinearity. The results of the analysis are presented as the adjusted odds ratios (aORs) with 95% confidence intervals (CIs).

EZR software was used for all of the statistical analyses (Saitama Medical Center, Jichi Medical University, Saitama, Japan), and p-values <0.05 were accepted as significant.

Results

We excluded 129 of the original series of 410 patients from the analysis based on the two exclusion criteria (age <60 yrs, n=111; hemodialysis, n=18). The cases of the remaining 281 patients were the subject of the analyses (Fig. 1). Of the 281 enrolled patients, 32 (11.4%) were diagnosed with POD.

Table 1 provides a summary of the patient characteristics and perioperative data. We identified significant differences in the patients' age, history of stroke, and preoperative uric acid level between the POD and non-POD groups. There were no significant differences in any of the other background characteristics or perioperative factors. The length of hospital stay did not differ significantly between the POD and non-POD groups: 24.5 (19.0–35.0) vs. 24.0 (20.0–32.0) days, respectively; p=0.986. Figure 2 presents a diagram of the relationship between the preoperative uric acid distribution and POD. As depicted in Figure 3, the AUC of the ROC analysis of uric acid for POD was 0.634 (95%CI: 0.54–0.73, cut-off value: 5.90, sensitivity 0.94, specificity 0.34). The AUC of the ROC analysis of the preoperative NLR for POD was 0.537 (95%CI: 0.43–0.64, cut-off value: 1.94, sensitivity 0.58, specificity 0.53).

The results of the multivariable logistic regression analysis demonstrated that the preoperative uric acid level and patient age were significantly associated with the development of POD (Table 2). However, there was no significant differences in the preoperative NLR and antihyperuricemic medication between two groups. The reason why we did not include stroke, the incidence of which was significantly greater in the POD patients versus the non-POD patients, in the model is that stroke was used to calculate the CCI.

As shown in Table 3's summary of the patients' postoperative complications, the incidence of dural tear was significantly higher in the POD patients compared to the non-POD group.

Discussion

These results of our retrospective analyses revealed no significant association between the preoperative NLR and POD in elderly patients with degenerative spine diseases, whereas a lower preoperative uric acid value was an independent risk factor for POD in this patient series. Our findings also demonstrated that antihyperuricemic medication was not significantly associated with POD.

In this investigation, 11.4% of the patients were diagnosed with POD, which is comparable to previous studies' findings [4, 23, 24]. Bak and colleagues performed a meta-analysis and reported that the risk factors for POD in elderly patients who are undergoing spine surgery are the presence of pulmonary disease, spine fusion, hypertension, or cerebrovascular disease, cervical spine surgery, the preoperative use of opioid medication, the duration of surgery, and the infused intravenous fluid volume [25]. Aging, preoperative cognitive dysfunction, and postoperative pain are also common risk factors for POD [26]. Consistently, our present univariable analysis detected significant differences in the patient age and stroke history between the POD and non-POD patients, but no other significant between-group differences were identified in other background characteristics or perioperative factors.

Moreover, in postoperative analgesia, the use of multimodal opioid-sparing analgesia is likely to be the optimal management option for minimizing the risk of the development of POD. Our present findings showed no significant differences in the use or dose of fentanyl for postoperative analgesia between the POD and non-POD groups. It is thus quite possible that our analgesic protocol using the combination of acetaminophen and a small amount of fentanyl was effective for all of the patients in this study.

A possible pathophysiological mechanism underlying POD involves neuroinflammation and oxide stress [27]. The NLR is a marker of inflammation and oxidative stress. Severe illness can increase the production of neutrophils from bone marrow and may lead to lymphopenia via several possible mechanisms [28, 29]. The eventual result can be relative neutrophilia and lymphopenia, leading to an abnormally high NLR. We have shown that systemic inflammation observed before malignant surgery can be associated with neuroinflammation and heightened brain vulnerability [30]. Although the results of a retrospective analysis indicated that the preoperative NLR was significantly associated with POD development in patients undergoing lumbar spinal-fusion surgery, the accuracy of the NLR for predicting POD was low [12]. Our present study also demonstrated no significant association between the preoperative NLR and POD in elderly patients with degenerative spine diseases. These results suggest that the mechanism of developing POD in elderly patients with degenerative spine surgery could differ from the reported mechanism in patients undergoing malignancy surgery. However, as this result may have been due to small sample size (our post hoc power calculation for NLR to observe a significant difference between two groups showed that estimated power was 0.121), further large prospective studies are needed to confirm this result. On the other hand, even among patients with the same orthopedic disorder, the preoperative NLR in fracture patients was described as likely to be useful in predicting POD [31, 32].

Epidemiological studies have identified hyperuricemia as an independent cardiovascular risk factor but uric acid can have beneficial functions based on its antioxidant properties, and this may be particularly relevant in the treatment of neurodegenerative diseases [15, 16]. It was also reported that uric acid helps eliminate superoxide anions and hydroxyl radicals from both the brain and blood [33] and that it inhibits the lipid peroxidation and damage to DNA that is induced by free radicals [34]. The neuroinflammation associated with microglial activation is very relevant to the development of POD [35], and it was reported that uric acid suppressed the activation of microglia and prevented neuronal death in vitro and in vivo [36]. Lower uric acid levels could thus be associated with reduced protection against the oxidative stress induced by surgery and could increase the POD risk. Our present findings suggest that the preoperative uric acid level could be an important marker for the differentiation of patients who are likely to develop POD.

We also observed that the prevalence of dural tear was markedly greater in the POD patients compared to the non-POD patients. An association between dural tear and POD in patients with spinal disease has been described [37, 38]. The mechanisms that underlie POD development following a dural tear are unknown, but one of the possible mechanisms is drainage of cerebrospinal fluid that can lead to a drop in intracranial pressure and traction on the meninges. As a similar mechanism, Partownavid et al. reported the case of a patient with a post-dural puncture headache with delirium that developed after a lumbar spinal drain [39]. Further research in this area is necessary.

Several potential study limitations should be considered. The study had a single-center, observational, retrospective design, and there may have been undetected cofounders. Our patients' preoperative cognitive function was not examined. A recent prospective study showed that a lower Mini-Cog score was significantly related to POD development [40]. Our patient series may also have included a number of patients with undiagnosed preoperative cognitive dysfunction. Moreover, a postoperative pain assessment was not performed. Postoperative pain and pain management have been reported to be associated with POD development [41]. We may also have overlooked cases of hypoactive delirium, because the nurses performed the screening test for POD. Nevertheless, this study is apparently the first to assess the relationship between preoperative uric acid and POD in elderly individuals with degenerative spine diseases. In the development of POD in elderly individuals with degenerative spine diseases, preoperative inflammation may be less closely associated, but the maintenance of an adequate level of uric acid may have a neuroprotective effect against the intraoperative invasion.

In conclusion, there have no significant association between the preoperative NLR and POD in elderly patients with degenerative spine diseases, but a preoperative lower level of uric acid was significantly associated with POD. Uric acid might have a neuroprotective impact on POD in patients with degenerative spine diseases. Further investigations of the mechanisms underlying the association between uric acid and POD are warranted.

References

1. Gou RY, Hshieh TT, Marcantonio ER, Cooper Z, Jones RN, Travison TG, Fong TG, Abdeen A, Lange J, Earp B, Schmitt EM, Leslie DL, Inouye SK. One-Year Medicare Costs Associated With Delirium in Older Patients Undergoing Major Elective Surgery. JAMA Surg. 2021;156:430-42. doi: 10.1001/jamasurg.2020.7260.
2. Hsieh SJ, Otusanya O, Gershengorn HB, Hope AA, Dayton C, Levi D, Garcia M, Prince D, Mills M, Fein D, Colman S, Gong MN. Staged Implementation of Awakening and Breathing, Coordination, Delirium Monitoring and Management, and Early Mobilization Bundle Improves Patient Outcomes and Reduces Hospital Costs. Crit Care Med. 2019;47:885-93. doi: 10.1097/ccm.0000000000003765.
3. Hernandez BA, Lindroth H, Rowley P, Boncyk C, Raz A, Gaskell A, García PS, Sleigh J, Sanders RD. Post-anaesthesia care unit delirium: incidence, risk factors and associated adverse outcomes. Br J Anaesth. 2017;119:288-90. doi: 10.1093/bja/aex197.
4. Wu X, Sun W, Tan M. Incidence and Risk Factors for Postoperative Delirium in Patients Undergoing Spine Surgery: A Systematic Review and Meta-Analysis. Biomed Res Int. 2019;2019:2139834. doi: 10.1155/2019/2139834.
5. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013;21:1190-222. doi: 10.1016/j.jagp.2013.09.005.
6. Kulaksizoglu B, Kulaksizoglu S. Relationship between neutrophil/lymphocyte ratio with oxidative stress and psychopathology in patients with schizophrenia. Neuropsychiatr Dis Treat. 2016;12:1999-2005. doi: 10.2147/ndt.S110484.
7. Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, Demirtas L, Turk S, Tonbul HZ. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int. 2013;17:391-6. doi: 10.1111/hdi.12040.
8. Sarejloo S, Shojaei N, Lucke-Wold B, Zelmanovich R, Khanzadeh S. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as prognostic predictors for delirium in critically ill patients: a systematic review and meta-analysis. BMC Anesthesiol. 2023;23:58. doi: 10.1186/s12871-023-01997-2.
9. Seo CL, Park JY, Park J, Kim HE, Cho J, Seok JH, Kim JJ, Shin CS, Oh J. Neutrophil-Lymphocyte Ratio as a Potential Biomarker for Delirium in the Intensive Care Unit. Front Psychiatry. 2021;12:729421. doi: 10.3389/fpsyt.2021.729421.
10. Kinoshita H, Saito J, Takekawa D, Ohyama T, Kushikata T, Hirota K. Availability of preoperative neutrophil-lymphocyte ratio to predict postoperative delirium after head and neck free-flap reconstruction: A retrospective study. PLoS One. 2021;16:e0254654. doi:

10.1371/journal.pone.0254654.
11. Oyama T, Kinoshita H, Takekawa D, Saito J, Kushikata T, Hirota K. Higher neutrophil-to-lymphocyte ratio, mean platelet volume, and platelet distribution width are associated with postoperative delirium in patients undergoing esophagectomy: a retrospective observational study. J Anesth. 2022;36:58-67. doi: 10.1007/s00540-021-03007-6.
12. Yang JS, Lee JJ, Kwon YS, Kim JH, Sohn JH. Preoperative Inflammatory Markers and the Risk of Postoperative Delirium in Patients Undergoing Lumbar Spinal Fusion Surgery. J Clin Med. 2022;11. doi: 10.3390/jcm11144085.
13. Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. Stroke. 2006;37:1503-7. doi: 10.1161/01.STR.0000221716.55088.d4.
14. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. Jama. 2000;283:2404-10. doi: 10.1001/jama.283.18.2404.
15. Scheepers L, Jacobsson LTH, Kern S, Johansson L, Dehlin M, Skoog I. Urate and risk of Alzheimer's disease and vascular dementia: A population-based study. Alzheimers Dement. 2019;15:754-63. doi: 10.1016/j.jalz.2019.01.014.
16. Shi X, Zheng J, Ma J, Wang Z, Sun W, Li M, Huang S, Hu S. Low serum uric acid levels are associated with the nonmotor symptoms and brain gray matter volume in Parkinson's disease. Neurol Sci. 2022;43:1747-54. doi: 10.1007/s10072-021-05558-8.
17. Wang F, Tang X, Wang J, Liu S, Wu X, Dong R, Lin X, Wang B, Bi Y. Potential Value of Serum Uric Acid in the Identification of Postoperative Delirium in Geriatric Patients Undergoing Knee Replacement. Front Aging Neurosci. 2022;14:909738. doi: 10.3389/fnagi.2022.909738.
18. Xu L, Lyu W, Wei P, Zheng Q, Li C, Zhang Z, Li J. Lower preoperative serum uric acid level may be a risk factor for postoperative delirium in older patients undergoing hip fracture surgery: a matched retrospective case-control study. BMC Anesthesiol. 2022;22:282. doi: 10.1186/s12871-022-01824-0.
19. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. Psychother Psychosom. 2022;91:8-35. doi: 10.1159/000521288.
20. Kumagai G, Wada K, Tanaka S, Asari T, Nitobe Y, Ishibashi Y. Association between intraoperative computed tomography navigation system and incidence of surgical site infection in patients with spinal surgeries: a retrospective analysis. J Orthop Surg Res. 2022;17:52. doi: 10.1186/s13018-022-02936-6.
21. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying

confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113:941-8. doi: 10.7326/0003-4819-113-12-941.
22. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165:710-8. doi: 10.1093/aje/kwk052.
23. Kang SY, Seo SW, Kim JY. Comprehensive risk factor evaluation of postoperative delirium following major surgery: clinical data warehouse analysis. Neurol Sci. 2019;40:793-800. doi: 10.1007/s10072-019-3730-1.
24. Urban MK, Sasaki M, Schmucker AM, Magid SK. Postoperative delirium after major orthopedic surgery. World J Orthop. 2020;11:90-106. doi: 10.5312/wjo.v11.i2.90.
25. Baek W, Kim YM, Lee H. Risk Factors of Postoperative Delirium in Older Adult Spine Surgery Patients: A Meta-Analysis. Aorn j. 2020;112:650-61. doi: 10.1002/aorn.13252.
26. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth. 2020;125:492-504. doi: 10.1016/j.bja.2020.06.063.
27. Subramaniyan S, Terrando N. Neuroinflammation and Perioperative Neurocognitive Disorders. Anesth Analg. 2019;128:781-8. doi: 10.1213/ane.0000000000004053.
28. Guo Z, Zhang Z, Prajapati M, Li Y. Lymphopenia Caused by Virus Infections and the Mechanisms Beyond. Viruses. 2021;13. doi: 10.3390/v13091876.
29. Suwa T, Hogg JC, English D, Van Eeden SF. Interleukin-6 induces demargination of intravascular neutrophils and shortens their transit in marrow. Am J Physiol Heart Circ Physiol. 2000;279:H2954-60. doi: 10.1152/ajpheart.2000.279.6.H2954.
30. Kinoshita H, Saito J, Kushikata T, Oyama T, Takekawa D, Hashiba E, Sawa T, Hirota K. The Perioperative Frontal Relative Ratio of the Alpha Power of Electroencephalography for Predicting Postoperative Delirium After Highly Invasive Surgery: A Prospective Observational Study. Anesth Analg. 2023. doi: 10.1213/ane.0000000000006424.
31. He R, Wang F, Shen H, Zeng Y, LijuanZhang. Association between increased neutrophil-to-lymphocyte ratio and postoperative delirium in elderly patients with total hip arthroplasty for hip fracture. BMC Psychiatry. 2020;20:496. doi: 10.1186/s12888-020-02908-2.
32. Ji S, Li Z, Li M, Lu Y, Ma T, Qi H, Cui Y, Du B, Huang Q, Zhang K, Lin H, Yang Y. Relationship between neutrophil/lymphocyte ratio and postoperative delirium in elderly patients with proximal femoral nail anti-rotation for intertrochanteric fractures. Am J Transl Res. 2023;15:1367-73.
33. Stinefelt B, Leonard SS, Blemings KP, Shi X, Klandorf H. Free radical scavenging, DNA protection, and inhibition of lipid peroxidation mediated by uric acid. Ann Clin Lab Sci. 2005;35:37-45.
34. Regoli F, Winston GW. Quantification of total oxidant scavenging capacity of antioxidants for peroxynitrite, peroxyl radicals, and hydroxyl radicals. Toxicol Appl

Pharmacol. 1999;156(2):96-105. doi: 10.1006/taap.1999.8637.
35. Kawano T, Eguchi S, Iwata H, Tamura T, Kumagai N, Yokoyama M. Impact of Preoperative Environmental Enrichment on Prevention of Development of Cognitive Impairment following Abdominal Surgery in a Rat Model. Anesthesiology. 2015;123:160-70. doi: 10.1097/aln.0000000000000697.
36. Bao LH, Zhang YN, Zhang JN, Gu L, Yang HM, Huang YY, Xia N, Zhang H. Urate inhibits microglia activation to protect neurons in an LPS-induced model of Parkinson's disease. J Neuroinflammation. 2018;15:131. doi: 10.1186/s12974-018-1175-8.
37. Kelly AM, Batke JN, Dea N, Hartig DP, Fisher CG, Street JT. Prospective analysis of adverse events in surgical treatment of degenerative spondylolisthesis. Spine J. 2014;14:2905-10. doi: 10.1016/j.spinee.2014.04.016.
38. Takenaka S, Makino T, Sakai Y, Kashii M, Iwasaki M, Yoshikawa H, Kaito T. Dural tear is associated with an increased rate of other perioperative complications in primary lumbar spine surgery for degenerative diseases. Medicine (Baltimore). 2019;98:e13970. doi: 10.1097/md.0000000000013970.
39. Partownavid P, Wang L, Alaei S, Rahman S. Post-dural puncture headache following lumbar spinal drain: an atypical presentation with cognitive symptoms. Anaesth Rep. 2021;9:e12127. doi: 10.1002/anr3.12127.
40. Kimura A, Shiraishi Y, Sawamura H, Sugawara R, Inoue H, Takeshita K. Predictors of Postoperative Delirium in Older Patients Undergoing Elective Spine Surgery. Spine Surg Relat Res. 2023;7:13-8. doi: 10.22603/ssrr.2022-0118.
41. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. Anesth Analg. 2006;102:1267-73. doi: 10.1213/01.ane.0000199156.59226.af.

Financial Disclosures: This study was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (no. 21K16556). The funding source had no involvement in the study design, collection, analysis, or interpretation of data; the writing of the report; or the decision to submit the article for publication.

Conflicts of Interest: None.

Author contributions:
K.K. collected data. H.K. designed the study, drafted the manuscript, collected data, and performed statistical analyses. G.K. designed the study, collected data, and revised the manuscript. D.T. performed statistical analyses and revised the manuscript. Y.N. collected data. T.A. collected data. K.W. collected data and revised the manuscript. T.K. designed the study and revised the manuscript. Y.I. and K.H. extensively revised the manuscript. All authors evaluated the study data and reviewed the manuscript.

Acknowledgement: Not applicable.

Table 1. Characteristics and perioperative data of the patients with and without postoperative delirium (POD)

		POD n=32	**Non-POD n=249**	**p-value**
Female/male, n (%)		13 (40.6)/19 (59.4)	124 (49.8)/125 (50.2)	0.353
Age, yrs		77.0 [73.0, 79.0]	71.0 [66.0, 76.0]	0.001
BMI, kg/m^2		25.40 [22.69, 27.69]	25.01 [22.28, 27.48]	0.773
Diagnosis	Cervical degenerative disease	15 (46.8)	118 (47.4)	0.390
	Thoracic degenerative disease	2 (6.3)	15 (6.0)	
	Lumbar degenerative disease	14 (43.8)	115 (46.2)	
	Spinal deformity	1 (3.1)	1 (0.4)	
CCI		2.00 [1.00, 3.00]	2.00 [0.00, 3.00]	0.142
Preoperative comorbidities, n (%)	Coronary artery disease	6 (18.8)	26 (10.4)	0.230
	Congestive heart failure	3 (9.4)	11 (4.4)	0.201
	Atrial fibrillation	2 (6.3)	22 (8.8)	1.000
	Chronic kidney disease	13 (40.6)	93 (37.3)	0.704
	Diabetes mellitus	8 (25.0)	78 (31.3)	0.545
	COPD	0 (0.0)	2 (0.8)	1.000
	Stroke	6 (18.8)	14 (5.6)	0.016

	Dyslipidemia	3 (9.4)	19 (7.6)	0.725
	Dementia	1 (3.1)	1 (0.4)	0.210
	Cancer	9 (28.1)	42 (16.4)	0.144
Current smoker, n (%)		3 (9.4)	16 (6.4)	0.463
Former smoker, n (%)		1 (3.1)	14 (5.6)	1.000
	Benzodiazepine	8 (25.0)	38 (15.3)	0.201
Medication, n (%)	Steroid	0 (0.0)	14 (5.6)	0.620
	Antihyperuricemic medication	3 (9.4)	20 (8.0)	0.734
	NLR	1.92 [1.46, 2.68]	2.11 [1.59, 2.86]	0.492
Preoperative laboratory data	Uric acid, mg/dL	4.65 [3.80, 5.65]	5.30 [4.40, 6.30]	0.014
	Alb, g/dL	4.30 [4.07, 4.50]	4.20 [4.00, 4.40]	0.350
	CRP, mg/dL	0.05 [0.02, 0.14]	0.06 [0.03, 0.16]	0.542
	TIVA, n (%)	31 (96.9)	248 (99.6)	0.215
	Duration of anesthesia, min	248.0 [209.0, 350.8]	254.5 [213.0, 307.0]	0.643
	Duration of prone position, min	195.50 [170.0, 289.0]	211.0 [175.0, 260.0]	0.883
Intraoperative factors	Duration of surgery, min	190.0 [133.3, 253.5]	180.0 [137.0, 236.0]	0.730
	No. of operated vertebrae	3.50 [1.75, 5.00]	2.00 [1.00, 4.00]	0.364
	Instrumentation	9 (28.1)	80 (32.1)	0.693
	Estimated blood loss, g	100.0 [42.5, 265.0]	100 [50.0, 210.0]	0.726
	Blood transfusion, n (%)	1 (3.1)	5 (2.0)	0.519

	Infusion volume, mL/hr	424.6 [328.5, 481.4]	398.9 [326.3, 460.4]	0.457
ICU admission, n (%)		30 (93.8)	227 (91.2)	1.000
Postoperative analgesia	Fentanyl use, n (%)	30 (93.8)	233 (93.6)	1.000
	Fentanyl dose for postoperative analgesia, μg/hr	12.5 [12.5, 16.7]	12.5 [12.5, 16.7]	0.635
Length of hospital stay, days		24.5 [19.0, 35.0]	24.0 [20.0, 32.0]	0.986

Continuous variables were analyzed by the Mann-Whitney U-test if not normally distributed. Categorial variables were analyzed by Fisher's exact test. The continuous data are presented as median [25th to 75th percentiles]. The categorial data are presented as number (%). Alb: albumin, BMI: body mass index, CCI: Charlson Comorbidity Index, CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, TIVA: total intravenous anesthesia.

Table 2. Multivariable logistic regression analysis with five variables to identify the predictable factors of development of postoperative delirium

	aOR	95%CI	p-value
Age, per 1-yr increase	1.09	1.02–1.16	0.008**
CCI, per 1-point increase	1.23	0.95–1.60	0.124
Uric acid, per 1-mg/dL increase	0.67	0.49–0.90	0.008**
Antihyperuricemic medication	0.97	0.24-3.82	0.959
Preoperative NLR, per 1-point increase	0.82	0.60–1.13	0.227

The AUC value was 0.755 (95%CI: 0.677–0.832). All VIFs were <2. **p<0.01. aOR: adjusted odds ratio, CCI: Charlson Comorbidity Index, NLR: neutrophil-lymphocyte ratio.

Table 3. Perioperative complications

	POD n=32	Non-POD n=249	p-value
Dural tear	5 (15.6)	5 (2.0)	0.002**
Surgical site infection	3 (9.4)	8 (3.2)	0.117
Cerebrospinal fluid leakage	0 (0.0)	0 (0.0)	NA
Urinary tract infection	2 (6.2)	12 (4.8)	0.665
Hematoma	0 (0.0)	3 (1.2)	1.000
Respiratory complication	0 (0.0)	3 (1.2)	1.000
Cardiac complication	0 (0.0)	5 (2.0)	1.000
Gastrointestinal complication	1 (3.1)	5 (2.0)	0.520
Stroke	0 (0.0)	1 (0.4)	1.000

Categorial variables were analyzed by Fisher's exact test. The categorial data are presented as number (%). **$p<0.01$.

Figure legends

Fig. 1. The study cohort flowchart. POD: postoperative delirium.

Fig. 2. Diagram of the relationship between the uric acid distribution and POD. POD: postoperative delirium.

Fig. 3. The receiver operating characteristic (ROC) curve used to determine the optimal cut-off value of uric acid for predicting POD. POD: postoperative delirium.

Fig. 1

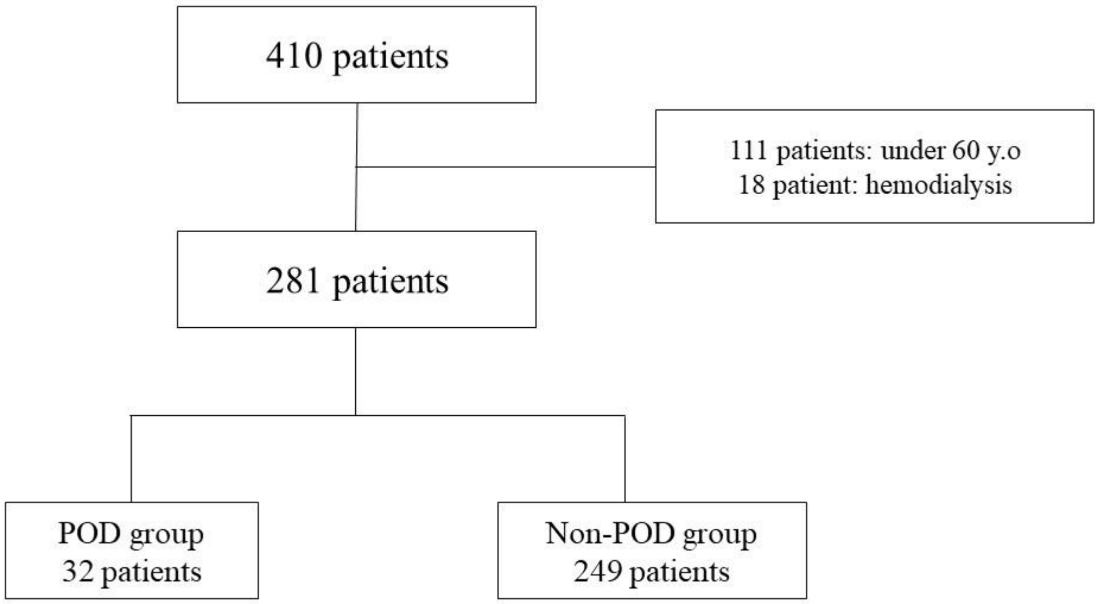

410 patients
111 patients: under 60 y.o
18 patient: hemodialysis
281 patients
POD group
32 patients
Non-POD group
249 patients

Fig. 2

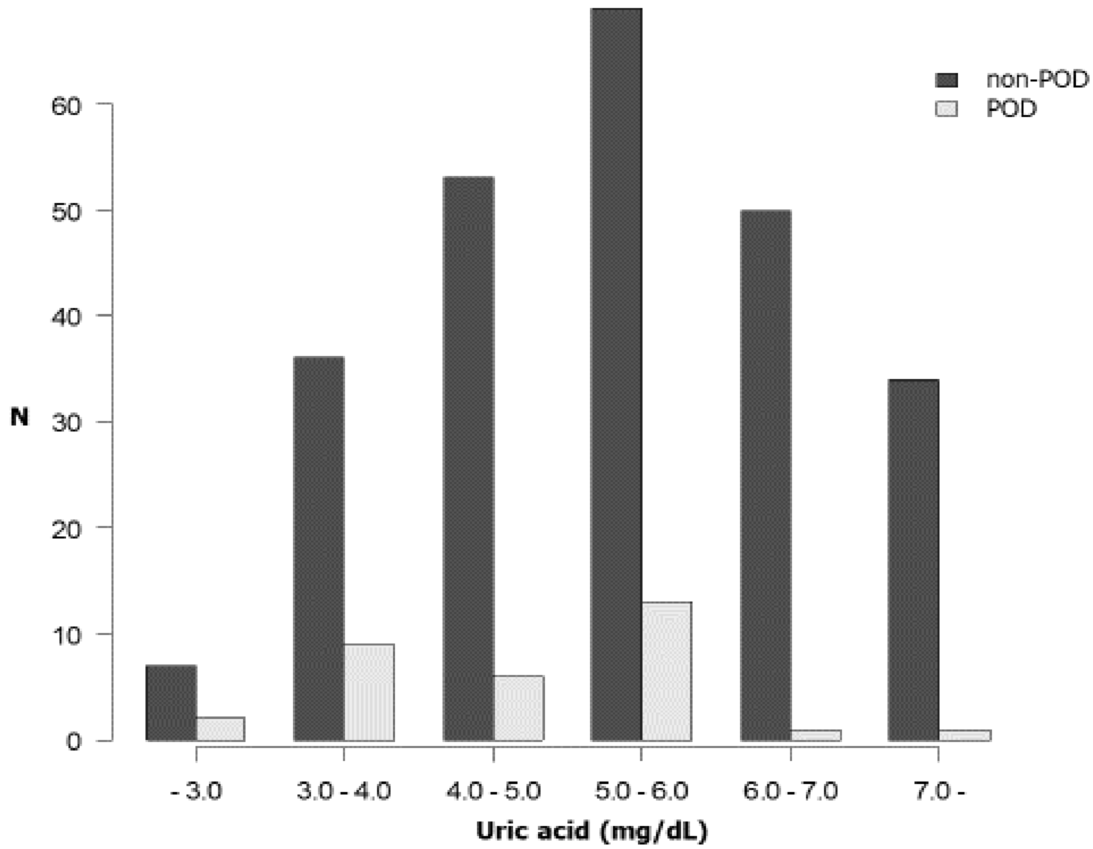
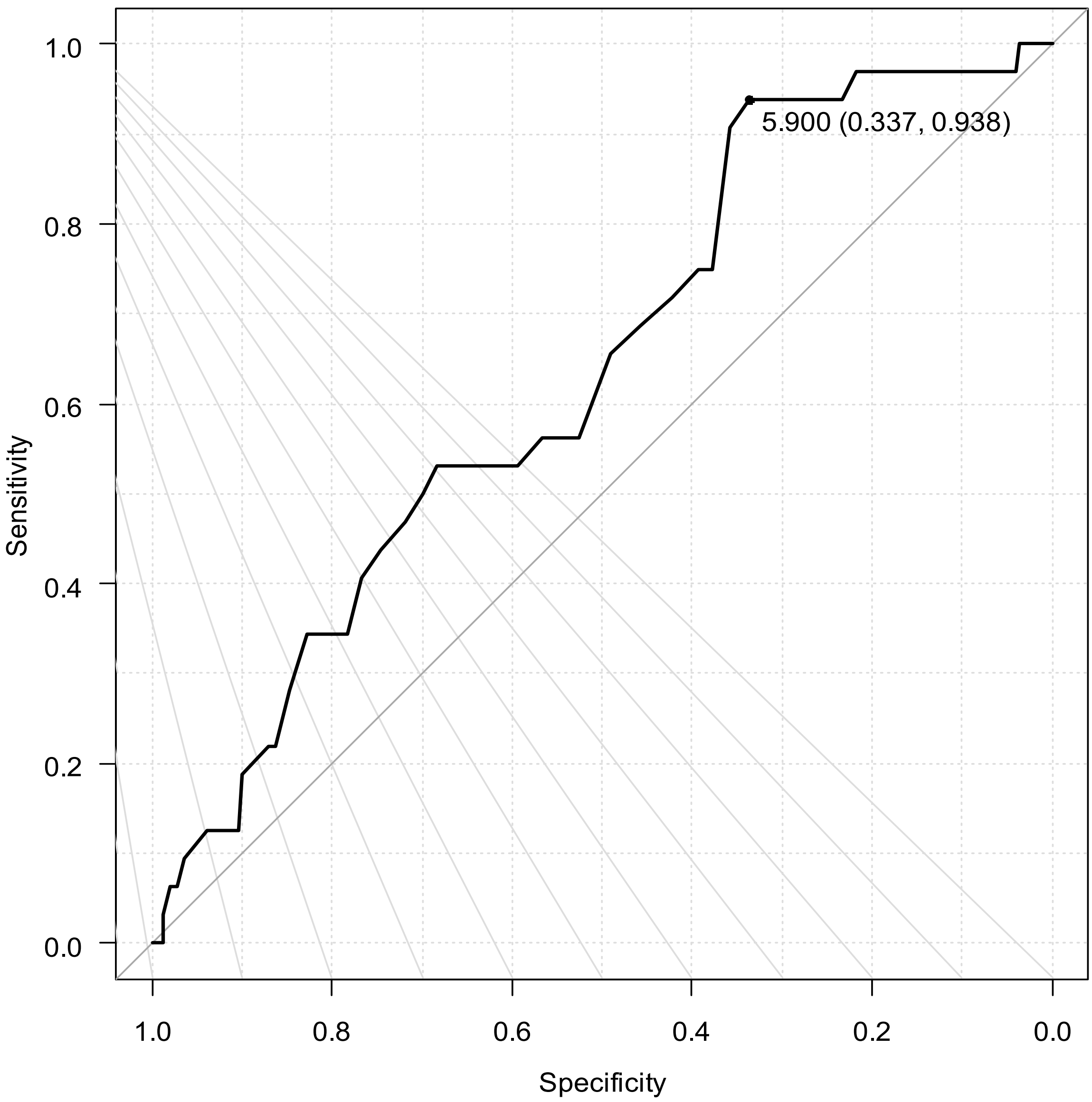

non-POD
POD
60
50
40
30
20
10
0
N
- 3.0
3.0 - 4.0
4.0 - 5.0
5.0 - 6.0
6.0 - 7.0
7.0 -
Uric acid (mg/dL)

Fig. 3


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
5.900 (0.337, 0.938)
1.0
0.8
0.6
0.4
0.2
0.0
Specificity