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Original Article

Impact of prognostic nutritional index on the occurrence of post-operative delirium after total knee arthroplasty

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ABSTRACT

Purpose: Delirium has been reported to cause delayed functional recovery, prolonged hospitalization, future institutionalization, increased mortality, and increased healthcare costs. However, there are no reports on how prognostic nutritional index (PNI), Controlling Nutritional Status (CONUT) score, and geriatric nutritional risk index (GNRI) are related to delirium after total knee arthroplasty (TKA). This study aimed to identify risk factors for post-operative delirium after TKA using various pre-operative nutritional assessments (PNI, CONUT score, and GNRI).

Methods: In total, 289 patients who underwent primary TKA between September 2011 and April 2022 in our institute (Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan) were enrolled. Patients were divided into two groups: those who developed post-operative delirium (Group D), and those who did not (Group ND). Pre-operative risk factors, including nutritional indices, for post-operative delirium were evaluated.

Results: Group D comprised 16 participants, while Group ND comprised 273 participants. Comparisons between the two groups revealed significant differences in age, PNI, CONUT score, GNRI, and history of cerebrovascular disease. Multiple logistic regression analysis revealed that significant risk factors for delirium after TKA were age, PNI, and history of cerebrovascular disease. A receiver operating characteristic curve indicated that the cutoff values for delirium were 47.4 for PNI (sensitivity, 0.810; specificity, 0.875) and 78.5 years for age (sensitivity, 0.813; specificity, 0.722).

Conclusions: Risk factors for post-operative delirium after TKA were PNI <47.4, age >78.5 years, and history of cerebrovascular disease. Patients exceeding these pre-operative cutoff values or with a history of cerebrovascular disease should receive counseling about delirium before surgery.

1. Introduction

Delirium is a common complication in elderly patients undergoing surgical procedures and receiving anesthesia, usually occurring 1–3 days after surgery [1]. Delirium has been reported to cause delayed functional recovery, prolonged hospitalization, future institutionalization, increased mortality, and increased healthcare costs [2–5]. Oxidative stress is involved in the development of delirium, and surgery and infection produce inflammatory substances, such as cytokines and oxygen free radicals, that cause oxidative stress in neural tissue [6,7]. The incidence of delirium after total knee arthroplasty (TKA) has been reported to be 0.59–16% [8–10]. Previous reports have noted that higher mean age, male sex, lower body mass index (BMI), chronic opioid use, higher C-reactive protein to albumin ratio (CRP/Alb), and polypharmacy (defined as concurrent use of six or more medications) may be associated with a high risk of post-operative delirium [8,11,12]. In addition to these pre-operative factors, intra-operative factors such as blood loss and decreased albumin levels as well as post-operative factors such as the extensive use of opioids and high blood urea nitrogen level on the third post-operative day have been reported as risk factors for post-operative delirium [9,13–15]. Furthermore, Losina *et al.* [16] noted that the number of TKA procedures is increasing each year, and with the aging of the global population care must be taken in managing older patients.

Several reports have shown that malnutrition and delirium are closely associated [17,18]. In recent years, the prognostic nutritional index (PNI), Controlling Nutritional Status (CONUT) score, and geriatric nutritional risk index (GNRI) have been used to assess the nutritional status of patients with heart failure and those undergoing surgical

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procedures [19–22]. Using a PNI cutoff value of 45.5, Tokunaga *et al.* [23] reported that the 5-year overall survival probability in patients with colorectal cancer was 90.5% for patients with a PNI of ≥45.5 and 57.8% for patients with a PNI <45.5. In a study of hypertensive patients aged ≥80 years, Sun *et al.* [24] reported a CONUT score cutoff value of 3.0 as a predictor of all-cause mortality at 90 days after admission. Ruan *et al.* [25] reported that the total mortality rate of elderly patients with cancer cachexia was 34.3% at 12 months, with a GNRI cutoff value of 91.959. However, there are no reports on how PNI, CONUT score, and GNRI are related to delirium after undergoing TKA.

The purpose of this study was to identify risk factors for post-operative delirium after TKA, including nutritional assessment, and to determine the cutoff values for these factors. Our hypothesis is that nutritional indicators, particularly PNI, are associated with an increased risk of post-operative delirium.

2. Materials and methods

2.1. Patients

Consecutive patients with knee osteoarthritis who underwent primary TKA at our hospital (Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan) between May 2010 and April 2022 were included in this study. Informed consent was obtained from all individual participants involved in the study. The Ethics Committee of the authors' affiliated institutions approved the study protocol (approval no. 23–014) on March 29, 2023, which was consistent with the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2013. Patients with rheumatoid arthritis or previous history of joint infection and those who underwent revision surgery were excluded from this study. The study population included 234 patients (289 knees) with more than 1 year of follow-up. Intra-operative anesthesia was general anesthesia in all cases. The addition of a femoral nerve block and intravenous patient-controlled analgesia (IV-PCA), which included opioids, was determined at the discretion of the anesthesiologist. Although posterior stabilized-type implants were used in all TKA procedures, patellar replacement was not performed in most cases. Post-operative measures were taken to prevent delirium, which included preventing dehydration, adequately managing pain, and promoting early ambulation. Patients were typically scheduled for discharge to their homes approximately 2 weeks post-surgery. However, if a patient experienced significant pain, walking difficulties, or if there were challenging family circumstances, an alternative arrangement for transfer to a suitable facility was made. The background data of each patient, such as age at surgery, sex, BMI, operative duration, intra-operative blood loss, pre-operative nutritional status, and comorbidities, were collected.

2.2. Measured data

The incidence of delirium, serum albumin (g/dL), hemoglobin (g/dL), total cholesterol (mg/dL), white blood cell count (/μL), total lymphocyte count (/μL), CRP/Alb ratio, pre-operative opioid use, pre-operative polypharmacy, post-operative use of IV-PCA, length of hospital stay (days), and rate of home discharge were investigated. Blood sampling data were evaluated within 3 months before surgery.

Post-operative delirium was assessed within 14 days following surgery based on the criteria set by the Confusion Assessment Method [26], as documented in the medical records. Routine assessments were carried out daily by orthopedic surgeons. If delirium was suspected at any time outside these routine checks, additional evaluations were promptly conducted to ensure timely diagnosis and intervention.

The PNI was calculated using the following equation [23]: PNI = 10 × albumin (g/dL) + 0.005 × lymphocyte count (/mm^3). The CONUT score [24] was calculated based on the serum albumin concentration, total lymphocyte count, and total cholesterol level. Albumin concentrations of ≥3.50, 3.00–3.49, 2.50–2.99, and <2.50 g/dL were scored as 0, 2, 4, and 6 points, respectively. Total lymphocyte counts of ≥1600, 1200–1599, 800–1199, and <800 cells/mm^3 were scored as 0, 1, 2, and 3 points, respectively. Total cholesterol levels of ≥180, 140–179, 100–139, and <100 mg/dL were scored as 0, 1, 2, and 3 points, respectively. The CONUT score was calculated based on the sum of the albumin, total lymphocyte, and total cholesterol points at the time of diagnosis. GNRI [21] was calculated using the following formula: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × [present body weight (kg)/ideal body weight (kg)]. Ideal weight was defined as [height (m)]^2 × 22.

2.3. Statistical analysis

Based on the results of the intermediate analysis of the rate of post-operative delirium for 50 cases, a power analysis was performed. Nine knees in each group (total of 18 knees) were needed to detect a minimal clinically important difference in each group as a primary outcome, with >80% statistical power and an α cutoff of 5% (0.05) as the probability of a type I error. Thus, nine or more knees (total >18 knees) were enrolled in each group.

Patients were divided into two groups according to whether they became delirious post-operatively, and statistical comparisons were performed between the groups regarding age, sex, BMI, serum albumin level, hemoglobin level, total lymphocyte count, total cholesterol level, CRP/Alb ratio, PNI, CONUT score, GNRI, operative duration, intra-operative blood loss, hospital stay, rate of polypharmacy, opioid use, femoral nerve block, and comorbidities. Then, to calculate the odds ratio (OR) for post-operative delirium, multivariate regression analysis was performed. The receiver

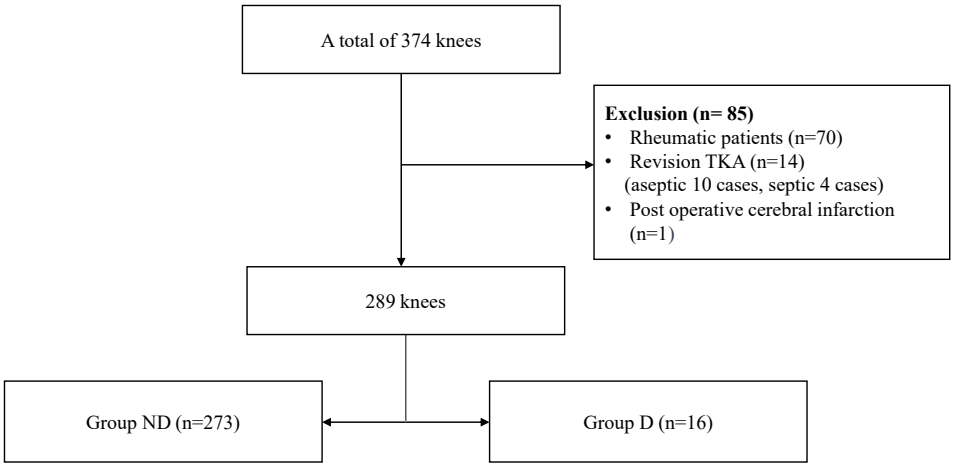


Fig. 1. Flowchart depicting the categorization of 289 total knee arthroplasty (TKA) cases into those with post-operative delirium (Group D) and those without post-operative delirium (Group ND).

Table 1
Demographic characteristics of the patients included in the study.

Characteristic	234 patients (289 knees)
Age (y)	74.1 ± 7.5
Sex (men/women)	49 (61 knees)/185 (228 knees)
Body height (cm)	151.8 ± 8.0
Body weight (kg)	59.8 ± 11.0
BMI (kg/m^2)	25.9 ± 4.2
Operative duration (min)	164.0 ± 33.2
Intra-operative blood loss (mL)	186.7 ± 148.3
Pre-operative serum albumin (g/dL)	4.2 ± 0.3
Pre-operative CRP/Alb	0.073 ± 0.18
Pre-operative lymphocyte count (/μL)	1806.0 ± 659.7
Pre-operative total cholesterol (mg/dL)	195.0 ± 33.3
Pre-operative PNI	50.6 ± 4.8
Pre-operative CONUT score	0.98 ± 1.1
Pre-operative GNRI	111.1 ± 9.5
Home discharge	269/289 (93.1)
Hospital stay (d)	20.3 ± 8.0

Data are presented as number, mean ± standard deviation, or *n/N* (%).
BMI = body mass index; CONUT = Controlling Nutritional Status; CRP/Alb = C-reactive protein/albumin ratio; GNRI = geriatric nutritional risk index; PNI = prognostic nutritional index.

operating characteristic (ROC) curve was used to determine the optimal cutoff value, and the area under the ROC curve (AUC) was evaluated using the predictive value. The ratio closest to the point with the maximum sensitivity and specificity was defined as the optimal cutoff value.

Comparisons of patients' backgrounds and surgical data were performed using a *t*-test. Categorical variables, such as sex and comorbidities, were compared using the χ^2 test. All statistical analyses were performed using IBM SPSS Statistics Version 27 (IBM Corp., Armonk, NY, USA). A *p*-value of <0.05 was considered statistically significant.

3. Results

As shown in Fig. 1, of the 374 knees recruited for this study, 85 were excluded due to rheumatoid arthritis (70 knees), revision TKA (14 knees), and post-operative cerebral infarction (1 knee). There were 49 men (61 knees) and 185 women (228 knees) with a mean age of 74.1 years. The incidence of delirium was 5.5% (16 of 289 knees). Patients were divided into a delirium group (Group D, 16 patients) and a non-delirium group (Group ND, 273 knees). Table 1 shows the patient characteristics. Due to a lack of data, total cholesterol and CONUT scores were only evaluated for 257 knees (15 knees in Group D and 242 knees in Group ND).

Comparisons between the two groups revealed significant differences in age (Group D, 80.6 years *vs.* group ND, 73.7 years; $p < 0.001$), serum albumin and hemoglobin levels, PNI (Group D, 43.8 *vs.* Group ND, 51.0; $p < 0.001$), CONUT score (Group D, 2.1 *vs.* group ND, 0.9; $p < 0.001$), GNRI (Group D, 101.8 *vs.* Group ND, 111.7; $p < 0.001$), and history of cerebrovascular disease (Group D, 5/16 *vs.* Group ND, 13/273; $p = 0.043$) (Tables 2 and 3). Multiple logistic regression analysis revealed that significant risk factors for delirium after TKA were age [OR = 1.25, 95% confidence interval (CI) 1.11–1.40; $p < 0.001$], PNI (OR = 0.69, 95% CI 0.50–0.97; $p = 0.032$), and history of cerebrovascular disease (OR = 33.61, 95% CI 4.56–247.81; $p = 0.002$) (Table 4).

The cutoff PNI value for the incidence of post-operative delirium was 47.4. The AUC was 0.912 (95% CI 0.859–0.965). Sensitivity and specificity were 0.810 and 0.875, respectively (Fig. 2). The cutoff value of age for the incidence of post-operative delirium according to the Youden index was 78.5 years. The AUC was 0.793 (95% CI 0.653–0.932). Sensitivity and specificity were 0.813 and 0.722, respectively (Fig. 3).

4. Discussion

The most important finding of this study was that post-operative delirium was significantly associated with age, pre-operative PNI, and history of cerebrovascular disease. Moreover, of several nutritional indicators, PNI was found to be a greater risk factor for post-operative delirium compared with CONUT score or GNRI.

Several studies have reported that advanced age is associated with post-operative delirium after TKA [8–10,27], which is consistent with the results in the present study. The observed 5.5% incidence of delirium

Table 2
Comparison of characteristics of patients with (Group D) and without (Group ND) post-operative delirium.

Characteristic	Group D (16 patients, 16 knees)	Group ND (218 patients, 273 knees)	*p*-value
Age (y)	80.6 ± 7.7	73.7 ± 7.3	<0.001 ***
Male sex	6 (37.5)	55 (20.0)	0.192
Height (cm)	151.8 ± 8.6	151.8 ± 8.0	0.998
Weight (kg)	56.9 ± 9.2	59.9 ± 11.1	0.290
BMI	24.7 ± 4.0	26.0 ± 4.2	0.247
Operative time (min)	164.1 ± 26.3	164.4 ± 33.6	0.976
Intra-operative blood loss (mL)	231.9 ± 161.0	184.0 ± 147.4	0.225
Pre-operative hemoglobin (g/dL)	12.3 ± 1.7	12.9 ± 1.5	0.115
Post-operative hemoglobin (g/dL)	10.6 ± 1.4	10.6 ± 1.4	0.926
Peri-operative hemoglobin change (g/dL)	1.7 ± 0.8	2.3 ± 1.1	0.043 *
Pre-operative serum albumin (g/dL)	3.69 ± 0.35	4.19 ± 0.29	<0.001 ***
Post-operative serum albumin (g/dL)	3.11 ± 0.30	3.32 ± 0.28	0.005 **
Peri-operative serum albumin change (g/dL)	0.58 ± 0.24	0.88 ± 0.29	<0.001 ***
Pre-operative CRP/Alb	0.11 ± 0.14	0.07 ± 0.18	0.35
Lymphocyte count (/μL)	1475.0 ± 378.4	1824.3 ± 667.4	0.046 *
Total cholesterol (mg/dL)[a]	171.1 ± 30.7	196.4 ± 32.9	0.004 **
PNI	43.8 ± 3.2	51.0 ± 4.5	<0.001 ***
CONUT score[a]	2.1 ± 1.4	0.9 ± 1.0	<0.001 ***
GNRI	101.8 ± 8.2	111.7 ± 9.3	<0.001 ***
Post-operative opioid use	12 (75.0)	228 (83.5)	0.379
Femoral nerve block	9 (56.3)	118 (43.2)	0.433
Home discharge	12 (75.0)	257 (94.1)	0.109
Hospital stay (d)	26.0 ± 15.5	20.0 ± 7.3	0.141

Data are presented as mean ± standard deviation or *n* (%).
BMI = body mass index; CONUT, Controlling Nutritional Status; CRP/Alb = C-reactive protein/albumin ratio; GNRI = geriatric nutritional risk index; PNI = prognostic nutritional index.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
[a] Due to lack of data, total cholesterol and CONUT scores were only evaluated for 257 knees (15 knees in Group D and 242 knees in Group ND).

Table 3
Comorbidities of patients with (Group D) and without (Group ND) post-operative delirium.

Comorbidity	Group D (16 patients, 16 knees)	Group ND (218 patients, 273 knees)	*p*-value
Hypertension	6 (37.5)	128 (46.9)	0.476
Hyperlipidemia	3 (18.8)	66 (24.2)	0.622
Diabetes mellitus	4 (25.0)	71 (26.0)	0.929
Chronic renal failure	2 (12.5)	11 (4.0)	0.341
Liver cirrhosis	1 (6.3)	6 (2.2)	0.530
Cardiovascular disease	2 (12.5)	22 (8.1)	0.533
Chronic heart failure	1 (6.3)	5 (1.8)	0.494
Thyroid disease	1 (6.3)	18 (6.6)	0.367
Parkinson's disease	0 (0)	4 (1.5)	0.627
Cerebrovascular disease	5 (31.3)	13 (4.8)	0.043 *
Malignant tumor	5 (31.3)	25 (9.2)	0.087
Osteoporosis	4 (25.0)	23 (8.4)	0.162
Polypharmacy (≥6 oral medications)	9 (56.3)	118 (43.2)	0.556
Chronic opioid use	1 (6.3)	12 (4.4)	0.729

Data are presented as *n* (%).
*$p < 0.05$.

Table 4
Multivariate logistic regression analysis of risk factors for post-operative delirium.

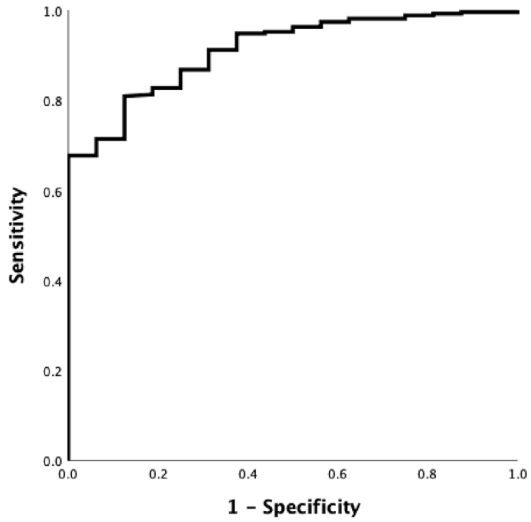
Risk factor	OR (95% CI)	*p*-value
Age	1.248 (1.111–1.404)	<0.001
PNI	0.693 (0.496–0.969)	0.032
Cerebrovascular disease	33.606 (4.557–247.812)	0.002

CI = confidence interval; OR = odds ratio; PNI = prognostic nutritional index.

following TKA surgery in the current study is in agreement with the previously reported range of 0.59–16% [8–10]. We posit that the implementation of delirium countermeasures was instrumental in maintaining this incidence rate, despite the patient population being older compared with previous studies. Furthermore, the cutoff age for post-operative delirium after TKA was 78.5 years. Wang *et al.* [10] reported that a medical history of dementia and cerebrovascular disease are risk factors for post-operative delirium after TKA. Although the current study did not have data on dementia, a history of cerebrovascular disease was found to be a risk factor for post-operative delirium.

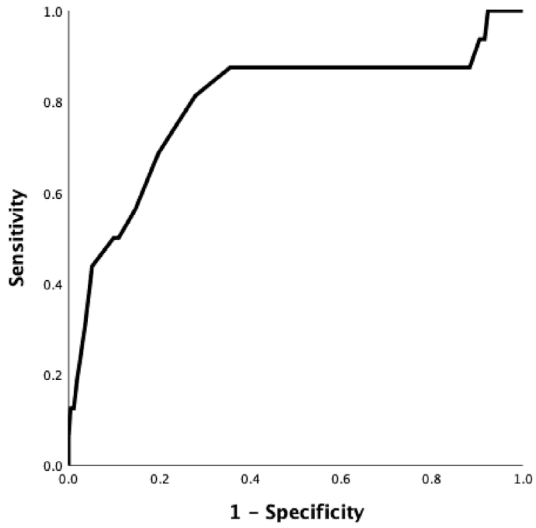
In examining the relationship between medication use and post-operative delirium, this study found no significant difference in pre-operative opioid use or polypharmacy between the delirium and non-delirium groups. This lack of difference could be attributed to the low incidence of opioid use in the patient population as well as the restriction to small doses of tramadol, a relatively weak opioid. While some studies have reported no link between post-operative opioid use and delirium [28], our findings similarly suggest an absence of association. However, caution should be exercised in interpreting these findings as the scope of opioid use in this study was limited and may not be generalizable to settings with broader ranges of opioid administration. Several other risk factors have been reported, such as differences in blood hemoglobin and albumin levels during surgery [10]. In the current study, the observed changes in hemoglobin and albumin levels did not emerge as risk factors for post-operative delirium. This finding contrasts with previous research where such changes were significant predictors. A contributing factor to this discrepancy may be that in the current cohort both hemoglobin and albumin levels were significantly lower in the Group D pre-operatively. This suggests that the baseline nutritional and anemic status could have a more pronounced effect on the risk of delirium than the intra-operative or immediate post-operative changes.

Although several studies have reported that pre-operative PNI is a risk factor for post-operative aseptic wound complications and infection after TKA [29,30], this is the first study to investigate the relationship between pre-operative nutritional status, as measured by PNI, and post-operative delirium after TKA. Albumin is a commonly used indicator to evaluate the nutritional status of surgical patients. Several studies have shown that hypoalbuminemia is significantly associated with an increased risk of post-operative complications including delirium [11,31]. Tei *et al.* [32]



PNI	
AUC	0.912
95% CI	0.859-0.965
cut-off	47.4

Fig. 2. Receiver operating characteristic (ROC) curve of prognostic nutritional index (PNI) in identifying subjects with post-operative delirium. Estimates of area under the ROC curve (AUC) with its 95% confidence interval (CI), and the cutoff value are also shown.



Age	
AUC	0.793
95% CI	0.653-0.932
cut-off	78.5

Fig. 3. Receiver operating characteristic (ROC) curve of age in identifying subjects with post-operative delirium. Estimates of area under the ROC curve (AUC) with its 95% confidence interval (CI), and the cutoff value are also shown.

reported that a low PNI is a significant risk factor for post-operative delirium in laparoscopic surgery. Furthermore, Oe *et al.* [33] reported an incidence of post-operative delirium in 30 (9.4%) of 319 patients who underwent adult spinal deformity surgery, identifying a PNI of <49.7 as a risk factor. Similarly, Chen *et al.* [34] observed post-operative delirium in 67 (6.7%) of 994 patients who underwent total joint replacement [either total hip arthroplasty (THA) or TKA] and identified a PNI of <47.05 as a risk factor. However, THA and TKA differ in their surgical invasiveness and the backgrounds of the patients they are recommended for. Notably, there have been no specific reports that exclusively investigated the relationship between pre-operative PNI and post-operative delirium in TKA. In our research, focusing solely on TKA, we determined that PNI is a more significant risk factor for post-operative delirium compared with other nutritional indices (such as albumin, CONUT score, and GNRI), with a cutoff value of 47.4. Since TKA is a less invasive procedure and patients undergoing TKA are older than those undergoing adult spinal deformity surgeries, the PNI cutoff value for post-operative delirium may have been lower than the values reported in previous studies.

Sze *et al.* [35] reported that PNI was considered more appropriate than CONUT score as a nutritional assessment method because many older adults were using statins (54% of the cohort were using statins). According to Yan *et al.* [36], while univariate analysis showed that albumin level and lymphocyte count had no prognostic impact on malignant lymphoma, multivariate analysis showed that PNI based on these two indices was a more independent prognostic factor than GNRI.

This study had several limitations. First, this was a retrospective study and the degree of delirium was not considered. We believe that prospective studies with large databases are needed in the future; however, our data may be beneficial for researchers to better understand the association between pre-operative nutritional status and post-operative delirium. Second, we evaluated only pre-operative laboratory data in assessing nutritional status but did not examine immediate post-operative laboratory data. Post-operative nutritional status may be more relevant to post-operative delirium. However, in this study, our focus was on identifying pre-operative risk factors for post-operative delirium. Third, total cholesterol data were not evaluated in 32 patients. Therefore, the CONUT score could only be evaluated using data from 257 patients.

In conclusion, the risk factors for post-operative delirium in patients undergoing TKA were a PNI of <47.4, age >78.5 years, and history of cerebrovascular disease. When performing TKA on patients exceeding these pre-operative cutoff values or with a history of cerebrovascular disease, the risk of post-operative delirium should be carefully considered. Further studies are warranted with a larger sample size and post-operative nutritional assessment.

Author contributions

K.H. was the chief investigator and responsible for the data analysis. M.H. developed the trial design. All authors contributed to the writing of the final manuscript.

Data statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declarations of competing interest

The authors declare no competing interests.

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