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

（好中球-リンパ球比、平均血小板容積、血小板分布幅の上昇は食道癌切除術後患者における術後せん妄に関連する：後方観察研究）

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ABSTRACT

Purpose: We investigated whether preoperative inflammatory markers, i.e., the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV), and platelet distribution width (PDW) can predict the development of postoperative delirium (POD) after esophagectomy.

Patients and Methods: This single-center, retrospective, observational study included 110 patients who underwent an esophagectomy. We assigned the patients with the Intensive Care Delirium Screening Checklist score ≥4 to the POD group. We performed multivariable logistic regression analyses to determine whether the NLR, PLR, MPV, and PDW can be used to predict the development of POD.

Results: The POD group was 20 patients; the non-POD group was the other 90 patients. Although only the preoperative NLR in the POD group was significantly higher than in the non-POD group (3.20 [2.52–4.30] vs. 2.05 [1.45–3.02], p=0.001), multivariable logistic regression analyses showed that the following three parameters were independent predictors of POD: preoperative NLR ≥2.45 (adjusted odds ratio [aOR]: 8.68, 95%CI 2.33–32.4, p=0.001), MPV ≥10.4 (aOR: 3.93, 95%CI: 1.37–11.2, p=0.011), and PDW ≥11.8 (aOR: 3.58, 95%CI: 1.22–10.5, p=0.020).

Conclusion: Our analysis results demonstrated that preoperative NLR ≥2.45, MPV ≥10.4, and PDW≥11.8 were significantly associated with a higher risk of POD after adjustment for possible confounding factors. However, as the AUCs of the preoperative MPV and PDW for the prediction of the development of POD in univariable ROC analyses were low, large prospective studies are needed to confirm this result.

Background

Esophagectomy is a standard treatment option for patients with esophageal cancer, but it is a highly invasive procedure with a 64% postoperative complication rate and a 3.3% morbidity rate [1]. The postoperative complications include pneumonia, acute kidney injury (AKI), anastomotic leak, atrial fibrillation (Af), and delirium [2]. Of these postoperative complications, delirium is reported to be associated with a prolonged hospital and intensive care unit (ICU) stay, an increased incidence of pulmonary complications, and increased hospital costs [3]. The early prediction and prevention of postoperative delirium (POD) is thus crucially important to improve the prognosis of patients with esophageal cancer.

Although the mechanism underlying the development of POD is not yet clear, neuroinflammation caused by surgery-induced systematic inflammation has been reported to be involved [4]. An increased level of interleukin-6 (IL-6) was also reported to be associated with the development of POD [5, 6], but a cohort study indicated that there was no relationship between the plasma IL-6 level and delirium in elderly medical inpatients [7]. The relationship between plasma inflammatory marker and POD thus remains controversial.

The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), which are calculated as the neutrophil and platelet count, respectively, divided by the lymphocyte count, are easily obtained and inexpensive inflammatory markers. Indeed, a few retrospective observational studies showed that an increased NLR and an increased PLR were associated with the development of POD after total hip arthroplasty and delirium in critically ill patients, respectively [8, 9]. However, there are no published studies that investigated whether the preoperative NLR and PLR are associated with the development of POD after esophagectomy.

The mean platelet volume (MPV) and the platelet distribution width (PDW),

which are platelet parameters that are measured easily and inexpensively, have been reported to reflect the severity of inflammation in patients with inflammatory diseases such as rheumatoid arthritis and systemic sclerosis [10, 11]. We thus investigated whether the preoperative MPV and PDW values could be used to predict the development of POD. The aim of the present study was to determine whether the preoperative inflammatory markers of NLR, PLR, MPV, and PDW can predict the development of POD after esophagectomy.

Patients and Methods

Study procedure and patients

This single-center retrospective observational study was approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine, Hirosaki, Japan and publicized on our department homepage using an opt out approach that participants are included in the research unless they give their express decision to be excluded (2021-062). Written informed consent from each patient was waived due to the study's retrospective manner, and the Ethics Committee approved the waiver.

We analyzed the cases of the patients with esophageal cancer who underwent esophagectomy at Hirosaki University Hospital from July 1, 2015 to March 31, 2021. We excluded patients who had cirrhosis, used an opioid for chronic pain, or underwent an esophagectomy without esophageal reconstruction. Each patient's characteristics and peri-operative data were collected from anesthetic and medical records. The Intensive Care Delirium Screening Checklist (ICDSC) was used to screen for POD [12]; the maximum score is 8 points, and higher scores are associated with severe POD. In this study, we defined POD as an ICDSC score $\geq$4. The ICDSC scoring was performed every 8 h by ICU nurses, anesthesiologists, and intensivists during ICU admission. We assigned the patients with an ICDSC score $\geq$4 at one or more time point to the POD

group. The patients whose ICDSC scores were all ≤3 were assigned to the non-POD group.

Data collection

The following patient characteristics were collected: sex, age, body mass index (BMI), medical history, American Society of Anesthesiologists Physical Status (ASA-PS), preoperative anticancer therapy, and TNM classification of malignant tumors. The following perioperative data were collected: preoperative laboratory data including the white blood cell count, neutrophil count, lymphocyte count, hemoglobin concentration (Hb), hematocrit (Hct), platelet count, mean platelet volume (MPV), platelet distribution width (PDW), blood urea nitrogen (BUN), creatinine (Cre), aspartate transferase (AST), alanine transferase (ALT), postoperative laboratory data (postoperative day 1) including neutrophil count, lymphocyte count, MPV, PDW, use of a thoracoscope, use of epidural anesthesia, the durations of the surgery and the anesthesia; the use of anesthetics and opioids, intra-operative crystalloid, colloid fluid administration, and blood transfusion; intraoperative blood loss and urine output, postoperative use of an inotrope, the durations of ICU stay, hospital stay, and mechanical ventilation; and postoperative-complications until discharge from the ICU including pneumonia, AKI, anastomotic leak, Af, postoperative bleeding which required hemostasis, and ICU death. In our institution, the preoperative blood test is done within 2 weeks before surgery. Indeed, all preoperative blood tests of the patients included in this study were done within 9 days before surgery. There were no patients who received cancer treatment after performing a preoperative blood test. As the blood test on postoperative day 1 before May 25, 2017 did not include differential count of leukocytes, 29 patients who underwent esophagectomy before that day were excluded from the analyses related to postoperative NLR and PLR.

Inflammatory markers

The relationships between the inflammatory markers NLR, PLR, MPV, and PDW and the development of POD were investigated. The NLR was determined as the absolute neutrophil count divided by the absolute lymphocyte count. The PLR was determined as the absolute platelet count divided by the absolute lymphocyte count.

Anesthesia and postoperative intensive care

All surgeries were conducted under general anesthesia with/without epidural anesthesia and standard monitoring. General anesthesia was induced and maintained with propofol, ketamine, remifentanil and/or fentanyl, morphine and rocuronium. The depth of general anesthesia was adjusted using the bispectral index, and the value was maintained between 40 and 60. After the surgery, patients were transferred to the ICU with tracheal intubation. Continuous intravenous infusions of propofol, dexmedetomidine, and/or fentanyl were given to maintain a Richmond Agitation Sedation Scale (RASS) score between −2 and 0 overnight.

The following morning, a spontaneous breathing trial (SBT) was conducted. If the patient passed the SBT, the patient was extubated after confirming awaking upon discontinuation of the anesthetics. After the extubation, the postoperative course of the patient was observed in order to maintain a RASS score of −1 to 1 in the ICU. Patients were discharged from the ICU when hemodynamic and respiratory stability was confirmed.

Statistical analyses

The data of the patient characteristics are presented as the median (25th to 75th percentile) and the number (a percentage of each group). Statistical differences between

the POD and non-POD groups were assessed using Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables. We performed multivariable logistic regression analyses to determine whether the four inflammatory markers can predict the development of POD after adjusting for possible confounders (Model 1–4). To estimate the optimal cutoff values of the inflammatory markers for predicting the development of POD in the multivariable logistic regression analyses, we conducted a receiver operating characteristic (ROC) curve analysis for each score. We calculated the sample size needed to conduct ROC curve analyses in order to estimate the optimal cutoff values of each inflammatory marker. The reported incidence of POD after esophagectomy ranges from 32% to 50% [13, 14]. We performed the power analysis based on its incidence of 32% (type I error rate: 5%, power: 80%, null hypothesis value: 0.5, AUC: 0.7), and determined that a sample size of 57 patients was needed. The sample size in the present study was 110 patients, which means that our sample size was appropriate for ROC analyses. Each inflammatory marker was forced into each model as an explanatory variable in the multivariable logistic regression analyses. The variables with p-values <0.05 in univariable logistic analyses to identify the predictive factors of the development of POD were included in the multivariable logistic regression analyses. The Age-adjusted Charlson Comorbidity Index (ACCI) was also included to adjust for the patients' age and comorbidities. Generally, the number of events per predictor variable in a multivariable logistic regression analysis should be at least 10 in order to provide an adequate predictive model. However, a recent simulation study suggested that 5–9 events per predictor variable is sufficient [15]. In the present study, considering the number of events (20 patients were in POD group), we included the 3 variables in each model (one variable was included in the model for 6 events).

We used the variance inflation factor (VIF) to check for multicollinearity among the variables. Discrimination was measured using the area under the curve (AUC). The

results are expressed as crude and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All data analyses were performed with EZR software ver. 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). P-values <0.05 were considered significant in all tests.

Results

Of the 117 patients, a final total of 110 patients were analyzed (Fig. 1). Of the 110 patients, 20 patients comprised the POD group, and 90 patients comprised the non-POD group. The patients' characteristics are summarized in Table 1; there were no significant differences in these characteristics between two groups. The patients' perioperative data are shown in Table 2. The amount of intraoperative red blood cell transfusion was significantly higher in the POD group than compared to the non-POD group. The ICDSC score was significantly higher in the POD group compared to the non-POD group. There were no significant differences in other data.

The results of the comparisons of inflammatory markers between the POD and non-POD groups are provided in Table 3. The preoperative NLR in the POD group was significantly higher than that in the non-POD group. There were no significant differences in other preoperative inflammatory markers. A diagram of the relationship between preoperative NLR distribution and POD is shown in Fig. 2. Additionally, there were no significant differences in postoperative inflammatory markers (Table 3). On the other hand, change in PDW [(postoperative PDW) − (preoperative PDW)] in the POD group was significantly lower than that in the non-POD group and was negative value (Table 3).

The ROC curves revealed the following cut-off values for the preoperative markers of inflammation to predict POD: NLR, 2.45; PLR, 136.2; MPV, 10.4; and PDW,

11.8 (Table 4). The AUCs were: NLR, 0.743; PLR, 0.543; MPV, 0.576; and PDW, 0.568, showing moderate accuracy for the NLR and low accuracy for the PLR, MPV, and PDW.

The results of the univariable logistic regression analyses to identify the predictive factors of the development of POD are presented in Table 5. The univariable logistic regression analyses showed that the following preoperative values were significant predictors for the development of POD: NLR ≥2.45, MPV ≥10.4, PDW ≥11.8, and the use of intraoperative RBC transfusion.

Table 6 provides the results of the multivariable logistic regression analyses to identify whether inflammatory markers can predict the development of POD after the adjustment for possible confounders, in Models 1–4. Preoperative NLR ≥2.45, MPV ≥10.4, and PDW ≥11.8 were significant predictors for the development of POD. The use of an intraoperative RBC transfusion was a significant predictor for the development of POD in Models 2, 3, and 4.

The postoperative complications are summarized in Table 7. There were no significant differences in the postoperative complications between the POD and non-POD groups.

Discussion

We retrospectively evaluated the associations between the development of POD and the preoperative inflammatory markers NLR, PLR, MPV, and PDW. The results of our analyses demonstrated that a preoperative NLR ≥2.45, MPV ≥10.4, and PDW ≥11.8 were each associated with a higher risk of POD after the adjustment for possible confounding factors. The administration of an intraoperative RBC transfusion was also associated with a higher risk of POD. There were no significant differences in the postoperative complications between the POD and non-POD group.

Accumulating evidence indicates that neuroinflammation may contribute to POD

[4]. Neuroinflammation is reported to be caused by excessive levels of inflammatory cytokines secreted by activated microglia when the homeostasis of the central nervous system is disturbed [16]. Although increased inflammatory cytokine levels are reported to associated with the development of POD, the measurement of inflammatory cytokines is expensive and cannot be done in all hospitals. On the other hand, as the inflammatory markers in the present study can be obtained from the results of a complete blood count test, they are easy-to-use and inexpensive markers. The NLR in particular is reported to serve as a marker of not only systemic inflammation but also neuroinflammation in patients with Parkinson's disease [17]. Indeed, our present findings demonstrated that the preoperative NLR could be used to predict the development of POD, as have previous studies [8, 18]. The present study showed that cutoff value of the preoperative NLR for predicting the development of POD after esophagectomy was 2.45. On the other hand, previous studies showed that cutoff values of the preoperative NLR for predicting the development of POD after total hip arthroplasty and head and neck free-flap reconstruction were 3.5 and 3.0, respectively [8, 16].

Platelets are reported to play an important role in the pathology of neuroinflammation as well as systemic inflammation [19]. The MPV and PDW are platelet parameters that reflect the size of platelets and the variability in the size of platelets, respectively. An increased MPV and an increased PDW may suggest the increased production of larger reticulated platelets caused by inflammation [20]. Indeed, increased MPV and PDW are reported to be associated with some inflammatory diseases [10, 11, 21, 22]. However, there was no significant difference in the preoperative MPV and PDW between the two groups. In addition, AUCs of the preoperative MPV and PDW for the prediction of the development of POD were 0.576 and 0.568, respectively, which was quite low compared to that of NLR and means that

these cutoff values have low accuracy for prediction of POD. On the other hand, the results of the multivariable logistic analyses indicated that a preoperative MPV ≥10.4 and a preoperative PDW ≥11.8 were associated with a higher risk of the development of POD after adjustment for possible confounding factors. Furthermore, AUCs of the multivariable logistic regression model including MPV ≥10.4 and PDW ≥11.8 were 0.726 and 0.712, respectively, which means that the abilities of discrimination of these models were evaluated as “Fair”. Thus, as this study was a single-center, retrospective observational study with a small sample size, there might be possible confounding factors to be adjusted in the patient’s background such as ACCI. These factors might affect the result of the univariable analyses. Additionally, the incidence of POD in the present study was 18.2%, and it was lower than the incidence that previous studies reported. This difference might be due to the differences in institutions and evaluation methods for POD. Indeed, a systematic review and meta-analysis indicated that the incidence of POD after the major surgical procedures was 17–61% [23]. This low incidence in the present study also might affect the result of our analyses. Thus, our results should be interpreted with caution. Large prospective studies are needed to confirm the evidence.

The present study demonstrated that change in PDW [(postoperative PDW) − (preoperative PDW)] in the POD group was significantly lower than that in the non-POD group and was negative value, which means that PDW of patients with POD decreased significantly after surgery [preoperative PDW vs. postoperative PDW: 11.3 (9.47, 12.1) vs. 10.1 (9.40, 11.1), p=0.011]. A recent prospective study showed that PDW was significantly lower in the patients with sepsis than in the patients without sepsis after colorectal surgery [24]. However, multivariable logistic analysis indicated that increased preoperative PDW was associated with a higher risk of the development

of POD in the present study. This conflicting result may be due to the small sample size, cofounding factors, and difference in the amount of platelets loss because of postoperative bleeding that we have not evaluated.

The use of intraoperative RBC transfusion was reported to be an independent predictor for POD in patients undergoing non-cardiac surgery [25]. Our present findings also showed that intraoperative RBC transfusion administration was associated with a higher risk of POD. Indeed, in another investigation the patients whose surgeries included an intraoperative RBC transfusion had higher levels of inflammatory markers, including IL-6, than patients without intraoperative RBC transfusion [26]. On the other hand, postoperative anemia is also an independent predictor for POD in patients undergoing elective surgery [27], and lower cerebral oxygen saturation caused by anemia is associated with the development of POD after abdominal surgery [28]. Optimal perioperative blood management is therefore important for the prevention of POD.

This study has some limitations to address. As a single-center, retrospective observational study with a small sample size, there may have been selection bias and undetected confounding factors that affected the results. Indeed, only one variable (RBC transfusion) with a p-value <0.05 in univariable logistic analyses was included in the multivariable logistic regression analyses due to the small sample size. In addition, we did not evaluate the patients' preoperative cognitive function, the amounts of anesthetics and opioids, postoperative Hb, or postoperative pain; these might affect the results. Second, almost all of the patients are extubated the day after esophagectomy in our institution, but they are extubated immediately after esophagectomy in some institutions. Sedatives on the day of surgery might have a potential to affect the development of POD, but there was no significant difference in sedatives between the POD and non-POD groups, and the incidence of POD was similar to those in the previous studies. We

therefore speculate that the timing of extubation had little impact on the development of POD. Third, the patients were not followed after discharge from the ICU, and we thus could not evaluate POD and postoperative complications after discharge from the ICU, and the long-term outcomes of the patients with POD.

In conclusion, this retrospective study showed that a preoperative NLR ≥2.45, MPV ≥10.4, and PDW ≥11.8 were each associated with a higher risk of POD after esophagectomy, and our results also suggested that preoperative inflammation could have a significant impact on the development of POD after esophagectomy. However, as the AUCs of the preoperative MPV and PDW for the prediction of the development of POD in univariable ROC analyses were low, large prospective studies are needed to confirm this result.

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Contributions: TO, HK, and DT collected the data. TO, DT, and JS analyzed the data and drafted the manuscript. TK and KH extensively revised the manuscript. All authors read and approved the final manuscript for submission.

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Figure legend

Fig.1. Flow chart of this study cohort.
POD: postoperative delirium

Fig.2. Diagram of the relationship between NLR distribution and POD
NLR: neutrophil-to-lymphocyte ratio, POD: postoperative delirium

Fig. 1.

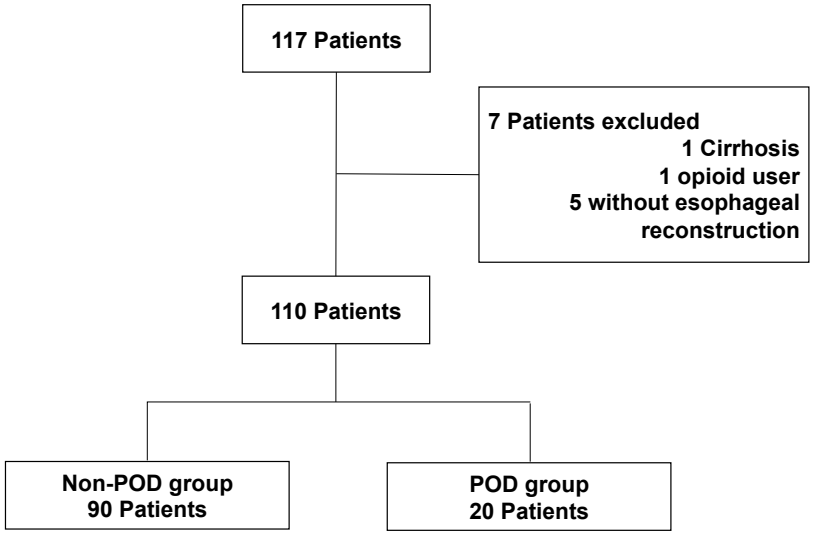
117 Patients
7 Patients excluded
1 Cirrhosis
1 opioid user
5 without esophageal reconstruction
110 Patients
Non-POD group
90 Patients
POD group
20 Patients

Fig. 2.

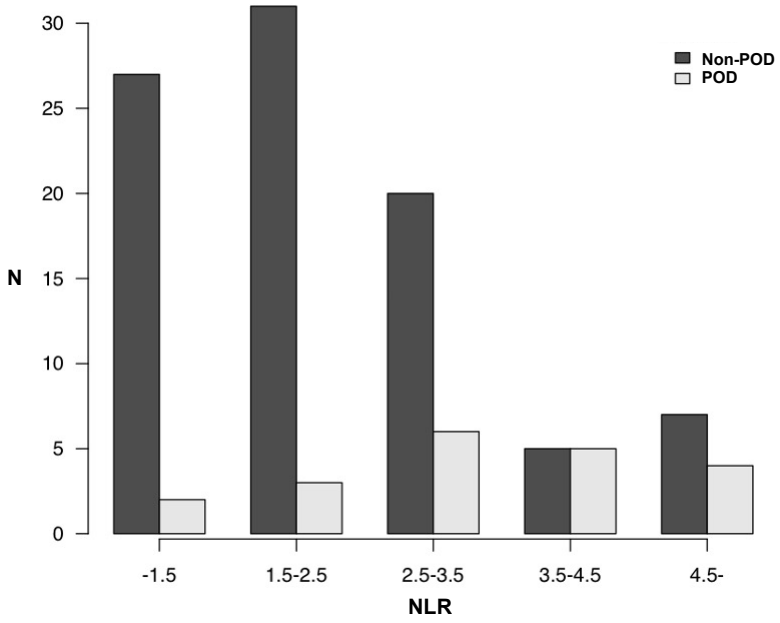

Table 1. Patient characteristics

	POD	Non-POD	p-value
n	20	90	
Male, n	18 (90.0%)	75 (83.3%)	0.733
Age, yrs			0.660
–50, n	1 (5.0%)	4 (4.4%)	
51–60, n	4 (20.0%)	18 (20.0%)	
61–70, n	9 (45.0%)	51 (56.7%)	
71–, n	6 (30.0%)	17 (18.9%)	
BMI (kg/m^2)			0.682
–18.5 (N)	4 (20.0%)	15 (16.7%)	
18.5–25, n	15 (75.0%)	63 (70.0%)	
25–, n	1 (5.0%)	12 (13.3%)	
ASA-PS			0.385
1 or 2, n	17 (75.0%)	83 (91.2%)	
3, n	3 (15.0%)	7 (7.8%)	
Medical history			
Hypertension, n	8 (40.0%)	44 (48.9%)	0.621
DM, n	3 (15.0%)	9 (10.0%)	0.454
Dyslipidemia, n	2 (10.0%)	12 (13.3%)	1.000
COPD, n	4 (20.0%)	10 (11.1%)	0.280
Stroke, n	1 (5.0%)	3 (3.3%)	0.557
IHD, n	0 (0%)	2 (2.2%)	1.000
Smoker, n	13 (65.0%)	73 (81.1%)	0.137
Af, n	1 (5.0%)	5 (5.6%)	1.000
Preoperative anticancer therapy			
NAC, n	15 (75.0%)	63 (70.0%)	0.789
PRT, n	0 (0%)	1 (1.1%)	1.000
T stage			1.000
I or II, n	9 (45.0%)	39 (43.3%)	
III or IV, n	11 (55.0%)	51 (56.7%)	
N stage			0.685
0, I, or II, n	19 (95.0%)	80 (88.9%)	
III or IV, n	1 (5.0%)	10 (11.1%)	
M stage			1.000
0, n	20 (100%)	90 (100%)	
I, n	0 (0%)	0 (0%)	
ACCI	5.0 (4.75, 6.00)	5.0 (4.25, 6.00)	0.801

*Significant difference. Differences between the POD and non-POD groups were estimated using Fisher's exact test for categorical variables and Mann-Whitney U-test for continuous variables. Data are number (percentage of each group) or median (25th to 75th percentile). ACCI: Age-adjusted Charlson Comorbidity Index, Af: atrial fibrillation, ASA-PS: American Society of Anesthesiologists Physical Status, BMI: body mass index, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, IHD: ischemic heart disease, NAC: neoadjuvant chemotherapy, POD: postoperative delirium, PRT: preoperative radiotherapy.

Table 2. Perioperative data of the patients

	POD group	Non-POD group	p-value
Pre. Labo data			
Hb, g/dL	11.7 (11.0, 12.4)	12.4 (11.2, 13.7)	0.106
Hct, %	34.2 (31.1, 38.4)	36.4 (33.4, 40.1)	0.083
Plt, $\times 10^4/\mu L$	23.5 (17.8, 30.0)	24.5 (19.8, 29.9)	0.436
AST, U/L	21.0 (19.5, 23.0)	20.0 (17.0, 25.0)	0.573
ALT, U/L	13.5 (11.0, 17.0)	14.0 (11.3, 20.0)	0.558
BUN, mg/dL	17.0 (11.5, 18.5)	16.5 (13.0, 19.8)	0.935
Cre, mg/dL	0.76 (0.64, 0.87)	0.82 (0.71, 0.99)	0.094
Thoracoscopic surgery, n	2 (10.0%)	23 (25.8%)	0.153
TIVA+Epi, n	18 (90.0%)	80 (88.9%)	1.000
Duration of			
Surgery, h	8.39 (7.29, 10.2)	8.31 (7.41, 9.52)	0.383
Anesthesia, h	9.67 (8.29, 11.3)	9.43 (8.48, 10.5)	0.234
Intra. use of sedative			
Propofol, n	20 (100%)	90 (100%)	1.000
Remifentanil, n	15 (75.0%)	71 (78.9%)	0.766
Fentanyl, n	19 (95.0%)	76 (84.4%)	0.297
Ketamine, n	8 (40.0%)	57 (63.3%)	0.078
Morphine, n	17 (85.0%)	83 (92.2%)	0.385
Post. use of sedative			
Propofol, n	20 (100%)	90 (100%)	1.000
Fentanyl, n	16 (80.0%)	55 (61.1%)	0.128
Dexmedetomidine, n	11 (55.0%)	59 (65.6%)	0.444
Intra. BO, g	500 (338, 798)	500 (350, 737)	0.988
Intra. UO, mL	565 (360, 746)	605 (454, 1068)	0.530
Intra. infusion			
Crystalloid, mL	3800 (3238, 4125)	3900 (3225, 4538)	0.530
Colloid, mL	650 (500, 1500)	1000 (500, 1000)	0.849
Intra. ABT			
RBC, g	0 (0, 280)	0 (0, 0)	0.040*
FFP, mL	0 (0, 0)	0 (0, 0)	0.637
PC, mL	0 (0, 0)	0 (0, 0)	1.000
Post. use of inotropes			
Naradrenaline, n	3 (15%)	4 (4.4%)	0.111
Landiolol, n	15 (75%)	51 (57.3%)	0.206
ICDSC score	4 (4, 4)	1 (0, 1)	<0.001*
Duration of			
ICU stay, days	4 (4, 6)	4 (4, 5)	0.087
Hospital stay, days	25 (21, 39)	26 (21, 38)	0.675

*Significant difference. Differences between the POD and non-POD groups were estimated using Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables. Data are number (percentage of each group) or median (25th to 75th percentile). ABT: allogeneic blood transfusion, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BO: blood output, BUN: blood urea nitrogen, Cre: creatinine, Epi: epidural anesthesia, FFP: fresh-frozen plasma, Hb: hemoglobin, Hct: Hematocrit, ICDSC: Intensive Care Delirium Screening Checklist, ICU: intensive care unit, Intra: intraoperative, Labo: laboratory, PC: platelet concentrate, Plt: platelet count, POD: postoperative delirium, Post: postoperative, Pre: preoperative, RBC: red blood cell, TIVA: total intravenous anesthesia, UO: urine output.

Table 3. Comparison of inflammatory markers between the POD and non-POD groups

	POD group	Non-POD group	p-value
Preoperative			
NLR	3.20 (2.52, 4.30)	2.05 (1.45, 3.02)	0.001*
PLR	165 (136, 214)	157 (123, 204)	0.546
MPV	10.4 (9.35, 10.5)	9.80 (9.30, 10.4)	0.289
PDW	11.3 (9.47, 12.1)	10.6 (9.50, 11.6)	0.346
Postoperative			
NLR	16.2 (9.55, 23.3)	8.84 (6.53, 13.7)	0.064
PLR	194 (141, 248)	177 (143, 215)	0.607
MPV	9.90 (9.47, 10.4)	10.1 (9.53, 10.5)	0.606
PDW	10.1 (9.40, 11.1)	10.7 (9.83, 11.8)	0.105
Amount of change [(postoperative value) − (preoperative value)]			
NLR	12.4 (6.17, 17.0)	6.56 (4.37, 11.3)	0.146
PLR	-1.34 (-25.4, 19.8)	22.0 (-11.7, 58.6)	0.173
MPV	0.10 (-0.33, 0.30)	0.10 (-0.17, 0.40)	0.537
PDW	-0.45 (-1.25, 0.10)	0.10 (-0.40, 0.70)	0.003*

*Significant difference. Differences between the POD and non-POD groups were estimated using the Mann-Whitney U-test. Data are median (25th to 75th percentile). MPV: mean platelet volume, NLR: neutrophil-lymphocyte ratio, PDW: platelet distribution width, PLR: platelet-lymphocyte ratio, POD: postoperative delirium.

Table 4. Optimal cutoff values of inflammatory markers for predicting the development of POD

	Cutoff value	AUC (95%CI)	Sensitivity	Specificity
NLR	2.45	0.74 (0.62–0.87)	0.85	0.63
PLR	136.2	0.54 (0.40–0.69)	0.80	0.34
MPV	10.4	0.58 (0.43–0.72)	0.56	0.74
PDW	11.8	0.57 (0.42–0.72)	0.45	0.79

Receiver operating characteristic curve analyses were conducted to estimate optimal cutoff values of each inflammatory marker for predicting the development of postoperative delirium. AUC: area under the curve, MPV: mean platelet volume, NLR: neutrophil-lymphocyte ratio, PDW: platelet distribution width, PLR: platelet-lymphocyte ratio, POD: postoperative delirium.

Table 5. Univariable logistic regression analyses to identify the predictive factors of the development of POD

	cOR	95%CI	p-value
NLR ≥2.45	9.79	2.67–35.9	0.0006*
PLR ≥136.2	2.21	0.68–7.16	0.188
MPV ≥10.4	3.56	1.31–9.68	0.013*
PDW ≥11.8	3.06	1.11–8.45	0.031*
Male	1.80	0.38–8.59	0.461
Age, yrs			
–50	ref.		
51–60	0.89	0.07–10.2	0.925
61–70	0.71	0.07–7.06	0.767
71–	14.1	0.13–15.3	0.776
BMI (kg/m^2)			
–18.4	ref.		
18.5–24.9	0.89	0.26–3.08	0.858
25–	0.31	0.03–3.18	0.326
ASA-PS			
1 or 2	ref.		
3	2.09	0.49–8.92	0.318
Medical history			
Hypertension	0.70	0.26–1.87	0.473
DM	1.59	0.39–6.49	0.519
Dyslipidemia	0.72	0.15–3.51	0.687
COPD	2.00	0.56–7.18	0.288
Stroke	1.53	0.15–15.5	0.721
IHD	n.a.		
Af	0.90	0.09–8.10	0.921
Smoker	0.43	0.15–1.25	0.121
Preoperative anticancer therapy			
NAC	1.29	0.43–3.89	0.657
PRT	n.a.		
T stage			
I or II	ref.		
III or IV	0.94	0.35–2.5	0.892
N stage			
0, I, or II	ref.		
III or IV	0.42	0.05–3.49	0.423
ACCI, per 1 increase	1.04	0.65–1.67	0.860
Pre. Labo data			
Hb, per 1 g/dL increase	0.76	0.57–1.01	0.062

Hct, per 1% increase	0.91	0.82–1.00	0.053
Plt, per 1×10^4/ μL increase	0.10	0.99–1.00	0.298
AST, per 1 U/L increase	1.01	0.94–1.08	0.774
ALT, per 1 U/L increase	0.97	0.91–1.04	0.416
BUN, per 1 mg/dL increase	1.00	0.93–1.08	0.962
Cre, per 1 mg/dL increase	0.12	0.01–1.56	0.105
Thoracoscopic surgery	0.32	0.08–1.48	0.145
TIVA+Epi	1.13	0.23–5.58	0.885
Duration of			
Surgery, per 1 h increase	1.22	0.88–1.69	0.235
Anesthesia, per 1 h increase	1.24	0.91–1.71	0.198
Intra. use of sedative			
Propofol	n.a.		
Remifentanil	0.80	0.26–2.49	0.704
Fentanyl	3.50	0.43–28.3	0.240
Ketamine	0.39	0.14–1.04	0.060
Morphine	0.48	0.11–2.04	0.318
Post. use of sedative			
Propofol	n.a.		
Fentanyl	2.55	0.79–8.24	0.119
Dexmedetomidine	0.64	0.24–1.72	0.377
Intra. BO, g, per 100-mL increase	0.99	0.87–1.12	0.856
Intra. UO, mL, per 100-mL increase	0.95	0.86–1.06	0.360
Intra. infusion			
Crystalloid, mL, per 100-mL increase	0.99	0.94–1.04	0.600
Colloid, mL, per 100-mL increase	1.03	0.95–1.11	0.546
Intra. ABT			
RBC, g, per 280 g increase	2.04	1.05–3.96	0.036*
FFP, mL	n.a.		
PC, mL	n.a.		
Post. use of inotropes			
Naradrenaline	0.26	0.05–1.29	0.099
Landiolol	2.24	0.75–6.69	0.150

*Significant difference. Univariable logistic analyses were performed in order to identify the predictive factors of the development of POD. ABT: allogeneic blood transfusion, ACCI: Age-adjusted Charlson Comorbidity Index, Af: atrial fibrillation, ALT: alanine aminotransferase, ASA-PS: American Society of Anesthesiologists Physical Status, AST: aspartate aminotransferase, BMI: body mass index, BO: blood output, BUN: blood urea nitrogen, COPD: chronic obstructive pulmonary disease, cOR: crude odds ratio, Cre: creatinine, DM: diabetes mellitus, Epi: epidural anesthesia, FFP: fresh-frozen plasma, Hb: hemoglobin, Hct: Hematocrit, IHD: ischemic heart disease, Intra: intraoperative, MPV: mean platelet volume,

NAC: neoadjuvant chemotherapy, NLR: neutrophil-lymphocyte ratio, PC: platelet concentrate, PDW: platelet distribution width, PLR: platelet-lymphocyte ratio, Plt: platelet count, POD: postoperative delirium, Post: postoperative, Pre: preoperative, PRT: preoperative radiotherapy, RBC: red blood cell, TIVA: total intravenous anesthesia, UO: urine output.

Table 6. Multivariable logistic regression analyses to identify whether inflammatory markers can predict the development of POD after adjusting possible confounders

Model 1

	aOR	95%CI	p-value
NLR ≥2.45	8.68	2.33–32.4	0.001*
ACCI, per 1 increase	1.01	0.62–1.65	0.952
Intra. RBC transfusion, per 280-g increase	1.59	0.77–3.27	0.204
AUC: 0.751 (0.62–0.88)			

Model 2

	aOR	95%CI	p-value
PLR ≥136.2	2.41	0.72–8.05	0.154
ACCI, per 1 increase	1.13	0.69–1.84	0.637
Intra. RBC transfusion, per 280-g increase	2.11	1.06–4.18	0.032*
AUC: 0.611 (0.47–0.75)			

Model 3

	aOR	95%CI	p-value
MPV ≥10.4	3.93	1.37–11.2	0.011*
ACCI, per 1 increase	0.99	0.61–1.61	0.960
Intra. RBC transfusion, per 280-g increase	2.20	1.10–4.41	0.026*
AUC: 0.726 (0.60–0.85)			

Model 4

	aOR	95%CI	p-value
PDW ≥11.8	3.58	1.22–10.5	0.020*
ACCI, per 1 increase	1.00	0.62–1.61	0.983
Intra. RBC transfusion, per 280-g increase	2.27	1.13–4.54	0.021*
AUC: 0.712 (0.58–0.85)			

*Significant difference. Multivariable logistic regression analyses were performed to identify whether inflammatory markers can predict the development of POD after adjusting possible confounders. (Models 1–4). Models 1, 2, 3, and 4 included NLR, PLR, MPV, and PDW, respectively. No variance inflation factor value was up to 10, indicating that there was no collinearity in the model. ACCI: Age-adjusted Charlson Comorbidity Index, aOR: adjusted odds ratio, AUC: area under the curve, Intra: intraoperative, MPV: mean platelet volume, NLR: neutrophil-lymphocyte ratio, PDW: platelet distribution width, PLR: platelet-lymphocyte ratio, POD: postoperative delirium, RBC: red blood cell.

Table 7. Postoperative complications

	POD	Non-POD	p-value
Overall, n	4 (20.0%)	32 (35.6%)	0.291
Pneumonia, n	1 (5.0%)	12 (13.3%)	0.456
Anastomotic leak, n	0 (0.0%)	5 (5.6%)	0.582
Af, n	1 (5.0%)	8 (8.9%)	1.000
AKI, n	0 (0.0%)	8 (8.9%)	0.347
Bleeding, n	2 (10.0%)	12 (13.3%)	0.456
ICU death, n	0 (0.0%)	1 (1.1%)	1.000

*Significant difference. Differences between the POD and non-POD groups were estimated using Fisher's exact test. Data are number (percentage of each group). Af: atrial fibrillation, AKI: acute kidney injury, ICU: intensive care unit, POD: postoperative delirium.