

Neutrophil-to-lymphocyte ratio as a predictor of postoperative morbidity in patients with distal cholangiocarcinoma

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Abstract. Systemic inflammatory-, immunological- and nutritional-based indices, such as the neutrophil-to-lymphocyte ratio (NLR), the prognostic nutritional index (PNI) and the Glasgow prognostic score (GPS), are drawing considerable research attention to predict the long-term prognosis of many types of cancer. Recently, these parameters have also been reported to be useful in predicting postoperative morbidity in several fields, including colorectal and otolaryngological cancer. However, while distal cholangiocarcinoma exhibits a high morbidity rate, its risk factors of morbidity have not yet been established. This is because previous studies have analyzed distal cholangiocarcinoma as periampullary tumors combined with pancreatic head cancer. Therefore, the aim of the present study was to investigate the application of the NLR, the PNI and the GPS in evaluating risk factors for postoperative morbidity in patients with distal cholangiocellular or ampullary carcinoma. Eighty-four patients who underwent pancreaticoduodenectomy (PD) for distal cholangiocellular or ampullary carcinoma at the Department of Surgery in Kitasato University Hospital between 2008 and 2016 were enrolled. Associations between perioperative characteristics (NLR, PNI and GPS) and postoperative complications

(Clavien-Dindo classification grade III or higher) were retrospectively analyzed. In the univariate analysis, neutrophil and lymphocyte counts, body mass index (BMI) and the NLR were associated with postoperative complications ($P < 0.05$). In the multivariate analysis, BMI [$> 23.0 \text{ kg/m}^2$; odds ratio (OR): 3.80, 95.0% confidence interval (CI): 1.35-11.83; $P = 0.011$] and the NLR (> 2.0 ; OR: 6.77, 95.0% CI: 2.44-21.13; $P < 0.001$) were independent risk factors for postoperative complications. BMI and the NLR are valuable predictors of postoperative morbidity following PD in patients with distal cholangiocarcinoma. It would be beneficial to determine treatment strategies for distal cholangiocarcinoma based on the NLR to reduce postoperative complications.

Introduction

It is increasingly recognized that the prognosis of patients with cancer is influenced by not only the oncological characteristics of the tumor, but also the conditions of the host. The relationship between the inflammatory and immunonutritional status and the prognosis of patients with cancer has been reported in several studies (1-4) in recent years. A number of indicators, including the neutrophil-to-lymphocyte ratio (NLR), the prognostic nutritional index (PNI), and the Glasgow prognostic score (GPS), have been reported to be useful predictors of overall or disease-free survival in numerous types of cancers (1-6). The NLR was first shown to correlate with short-term outcome in patients in an intensive care unit by Zahorec (7) in 2001. Recently, other studies (8-11) have also shown that these parameters are good predictors of postoperative complications in patients with colorectal or otolaryngological cancer. Therefore, these indicators may be effective markers of short-term outcome in various fields.

Distal cholangiocarcinoma is associated with a high morbidity rate. The majority of patients with these tumors already show signs of liver dysfunction, jaundice, and malnutrition (e.g., hypoalbuminemia due to obstruction of the biliary duct) at the first visit to the hospital (12,13). Moreover, some patients exhibit an inflammatory reaction, such as cholangitis, and require biliary drainage during the preoperative period. Therefore, the biochemical data of patients with distal cholangiocarcinoma are likely to show abnormal values to some extent before surgery.

The only curative treatment for distal cholangiocarcinoma is surgical resection, such as pancreaticoduodenectomy (PD),

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Abbreviations: AUC, area under the curve; BMI, body mass index; CD, Clavien-Dindo; CI, confidence interval; CRP, C-reactive protein; GPS, Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PD, pancreaticoduodenectomy; PNI, prognostic nutritional index; PP, pylorus-preserving; PPPD, pylorus-preserving pancreaticoduodenectomy; ROC, receiver operating characteristic; SSP, subtotal stomach-preserving; SSPPD, substomach-preserving pancreaticoduodenectomy; TNM, tumor-node-metastasis; UICC, International Union Against Cancer

Key words: body mass index, complication, distal cholangiocarcinoma, neutrophil-to-lymphocyte ratio, pancreaticoduodenectomy, postoperative morbidity

which is a highly invasive and complicated procedure. Although the mortality rate of PD has decreased satisfactorily to 5.0% in high volume centers, due to improvements in surgical techniques and perioperative management, the postoperative morbidity rate remains high, with values ranging from 30.0-65.0% (14,15). Several studies (16-18) have reported risk factors for postoperative complications after PD. However, the patients recruited to these studies included those with distal cholangiocarcinoma, as well as, pancreatic head cancer. A recent study of a large cohort of patients with resected periampullary cancer (13) showed that patients with cholangiocarcinoma had a higher morbidity rate than those with pancreatic head cancer and that apparent biological differences existed between the 2 groups. Few studies have evaluated the risk of morbidity associated with only distal cholangiocarcinoma (19) and risk factors for postoperative complications after PD in patients with distal cholangiocarcinoma have not yet been established.

We hypothesized that systemic inflammatory, immunological, and nutritional status would influence the morbidity rate of patients with distal cholangiocarcinoma. The aim of this study was to determine the effectiveness of the NLR, the PNI, and the GPS in evaluating risk factors for postoperative complications after PD in patients with distal cholangiocarcinoma.

Materials and methods

Patients. We conducted a retrospective analysis of 84 patients who underwent PD for pathologically confirmed distal cholangiocarcinoma, including distal cholangiocellular and ampullary carcinoma, at Kitasato University Hospital (Kitasato, Japan) between January 2008 and December 2016. Patients who had undergone simultaneous hepatic resection were excluded. Clinical, surgical, and tumor characteristics, including age, sex, body mass index (BMI), biliary drainage, bile culture, laboratory data, operating times, blood loss and transfusion, International Union Against Cancer (UICC) tumor-node-metastasis (TNM) stage, and postoperative hospital stay, were collected and analyzed from the clinical database.

All patients underwent pylorus-preserving (PP), subtotal stomach-preserving (SSP), or conventional PD with regional lymph node dissection. Portal vein resection was performed when the tumor had invaded to achieve resection-free margins. Reconstruction was a modified Child's reconstruction. Pancreaticojejunostomy was performed according to the Kakita *et al* (20) method, as described previously (i.e., duct-to-mucosa anastomosis with a lost pancreatic stent and end-to-side anastomosis with 4 stitches of transpancreatic suture in all patients). Two closed drains were routinely inserted at the Winslow's space in front of the pancreaticojejunostomy. Drain management was as follows, the drains were removed on day 4 under condition that the amylase level of drain fluid were less than 4,000 U/ml or the volume of drain fluid were less than 30 ml. If this condition was not satisfied or drain fluid were infected, the drains were continued to drainage.

Postoperative complications. Postoperative complications, such as anastomotic leakage, postpancreatectomy hemorrhage,

liver abscess, intraperitoneal abscess, allergic reaction, and pneumonia, were classified according to the Clavien-Dindo (CD) classification (21). Patients with CD classification grade III or higher postoperative complications were assigned to the major complications group, and the remainder assigned to the non-major complications group.

NLR, PNI, and GPS evaluation. Blood test results from the day immediately prior to surgery were used. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The PNI was calculated as $10 \times \text{albumin} + 0.05 \times \text{the lymphocyte count}$. The GPS was determined based on C-reactive protein (CRP) and albumin. Patients with elevated CRP (>0.3 mg/dl) and hypoalbuminemia (<3.5 mg/dl) were assigned a score of 2. Patients with either one of these 2 biochemical outliers were assigned a score of 1. Patients with neither of these biochemical outliers were assigned a score of 0 (22).

Statistical analyses. Categorical variables were compared using the Chi-square test or Fisher's exact test. Continuous variables were compared using the Student's t-test or Mann-Whitney U test. Continuous variables were presented as the mean and standard deviation. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values for several variables to predict postoperative complications. Variables associated with postoperative complications in the univariate analysis were included in the multivariate logistic regression analysis. Odds ratio (OR) and 95.0% confidence intervals (CIs) were used to quantify the strength of the association between predictors and morbidity. All statistical analyses were conducted using JMP[®] software (version 11.2.0; SAS Institute Inc., Cary, NC, USA). A $P < 0.05$ was considered statistically significant.

Results

In total, 84 patients were enrolled in the study. The characteristics of the patients are summarized in Table I. The mean age was 68.1 ± 8.7 years. Sixty-three patients were male and 21 patients were female. Fifty-seven patients had distal cholangiocellular carcinoma and 27 patients had ampullary carcinoma. Seventy-four patients underwent PPPD, 7 patients underwent SSPPD, and 3 patients underwent conventional PD. Thirty-nine patients (46.4%) experienced postoperative complications of CD classification grade III or higher. The most common postoperative complication was anastomotic leakage ($n=31$; 36.9%) [pancreaticojejunostomy leakage ($n=27$), choledochojejunostomy leakage ($n=2$), and duodenojejunostomy leakage ($n=2$)]. Other complications included bleeding ($n=2$), intraperitoneal abscess ($n=2$), pneumonia ($n=2$), liver abscess ($n=1$), and anaphylactic shock ($n=1$).

First of all, we compared patients with ampullary carcinoma and those with distal cholangiocellular carcinoma. The clinical characteristics of each group are summarized in Table II. Biliary drainage rate was over 90% in both groups. Patients with distal cholangiocellular carcinoma showed high frequency of bile culture positive (88%) and slightly high CRP (1.44 ± 2.14) rather

Table I. Patient characteristics (n=84).

Patient characteristic	Data
Age (years)	68.1±8.7
Sex	Male, 63 (75%) Female, 21 (25%)
Diagnosis	Ampullary carcinoma, 27 (32.1%) Distal cholangiocellular carcinoma, 57 (67.9%)
Operative procedure	PPPD, 74 (88.1%) SSPPD, 7 (8.3%) PD, 3 (3.6%)
Complication (≥CDIII)	Anastomotic leakage, 31 (36.9%) Intra-abdominal abscess, 2 (2.4%) Bleeding, 2 (2.4%) Pneumonia, 2 (2.4%) Liver abscess, 1 (1.2%) Anaphylactic shock, 1 (1.2%)

CD, Clavien-Dindo; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy.

than ampullary carcinoma (70% and 0.60±0.64, respectively), but with no statistically significant difference (P=0.06 and 0.051, respectively). Other preoperative biochemical variables and operative parameters including operative times, blood loss volumes, the incidence of transfusion or portal vein resection were comparable between the 2 groups. There was no significant difference in UICC TNM stage, NLR and GPS, however patients with ampullary carcinoma showed higher level of PNI rather than distal cholangiocellular carcinoma with statistically significant difference. The complication rate over grade III in CD classification and postoperative hospital stays were comparable between the 2 groups.

Next, the patients were divided into 2 groups depending on the presence of complication or not for evaluating risk factor of postoperative complication. The 39 patients with postoperative complications of CD classification grade III or higher were assigned to the major complications group. The remaining 45 patients were assigned to the non-major complications group. The clinical characteristics of each group are summarized in Table III. Preoperative biochemical variables, including platelet count and total bilirubin, alkaline phosphatase, gamma-glutamyltransferase, albumin, and CRP levels, were comparable between the 2 groups. There were no significant differences in mean operative times, blood loss volumes, the incidence of blood transfusions or portal vein resection, UICC TNM stage, the frequencies of biliary drainage and bile culture positive. The major complications group had a significantly higher neutrophil count (P<0.05), NLR (P<0.01), and BMI (P<0.01) than the non-major complications group. In contrast, the lymphocyte count was significantly lower in the major complications group than in the non-major complications group (P<0.05). Other indicators, such as the PNI and the GPS, did not

differ significantly between the 2 groups. Understandably, the postoperative hospital stay was statistically long in the major complications group rather than in the non-major complications group.

Variables for which significant differences were identified in the univariate analysis were further analyzed using ROC curve analysis to determine the optimal cut-off values. The optimal cut-off value for the NLR was 2.0 [area under curve (AUC), 0.72; Fig. 1A]. The optimal cut-off value for the BMI was 23.0 kg/m² (AUC, 0.67; Fig. 1B). The optimal cut-off values for the neutrophil count and lymphocyte count were 2,727 (AUC, 0.67) and 1,870 (AUC, 0.59), respectively. These parameters were included in the multivariate logistic regression analysis. A BMI of >23.0 kg/m² (OR: 3.83, 95.0% CI: 1.35-11.83; P=0.011) and a NLR of >2.0 (OR: 6.77, 95.0% CI: 2.44-21.13; P<0.001) were independent risk factors for major postoperative complications (Table IV).

Discussion

The present study highlights the usefulness of the NLR in predicting postoperative major complications after PD in patients with distal cholangiocarcinoma, providing surgeons with important information. Surgeons sometimes confront the situation that patients with biliary carcinoma experience acute cholangitis immediately prior to surgery. Acute cholangitis activates inflammatory responses, whilst suppressing immunological and nutritional responses, resulting in elevated neutrophil counts and CRP levels and reduced lymphocyte counts and albumin levels. In such cases, antibiotic treatment or biliary drainage (stenting) were performed. However, we do not know how long we should wait for the patient's condition to improve. Our findings suggest that surgeons may be able to determine treatment strategies based on the NLR.

Over the past few decades, many studies (14-18,23-25) have reported that the risk factors for postoperative complications after PD include a soft pancreatic texture, a small pancreatic duct diameter, a high BMI, preoperative biliary drainage, operative blood loss, and sarcopenia. However, the patients enrolled in these studies have included a mixture of those with distal cholangiocarcinoma and pancreatic head cancer. Andrianello *et al* (13) reported that the postoperative morbidity rate was significantly higher in patients with distal cholangiocarcinoma than in those with pancreatic ductal adenocarcinoma (75.9% vs. 52.1%, respectively; P<0.01). Preoperative variables [e.g., the incidence of jaundice (94.4% vs. 72.0%, respectively; P<0.01) and biliary stent insertion (79.6% vs. 54.4%, respectively; P<0.01)] also differed significantly between the 2 groups. In this study, we compared patients with ampullary carcinoma and those with distal cholangiocellular carcinoma. Both groups showed the same frequencies of biliary drainage (93% vs. 98%, respectively; P=0.212). Concerning bile juice infection, slightly higher incidence was observed in patients with distal cholangiocellular carcinoma (88%) compared to patients with ampullary carcinoma (70%), however the frequency of postoperative complications was observed equally between 2 groups (44% vs. 52%; P=0.493).

Finally, a high NLR and a high BMI were extracted as independent risk factors for postoperative complications after PD for

Table II. Characteristics of patients with ampullary carcinoma and patients with distal cholangiocellular carcinoma.

Variable	Ampullary carcinoma (n=27)	Distal cholangiocellular carcinoma (n=57)	P-value
Age (years)	65.8±10.3	69.2±7.7	0.092
Sex (M/F)	18/9	45/12	0.704
Total bilirubin (mg/dl)	0.87±0.62	1.02±0.61	0.326
ALP (U/l)	448.6±65.9	546.6±45.3	0.224
GTP (U/l)	149.8±53.1	267.7±6.6	0.071
Platelets, x10 ⁴ /μl	26.2±10.3	24.6±6.6	0.385
Neutrophils/μl	3,261±1,228	3,504±1,269	0.411
Lymphocytes/μl	1,558±552	1,437±479	0.308
Albumin (g/dl)	3.79±0.07	3.62±0.05	0.066
CRP (mg/dl)	0.60±0.64	1.44±2.14	0.051
BMI	21.94±3.35	22.43±3.39	0.541
Biliary drainage (+)	25 (93%)	56 (98%)	0.212
Bile culture positive	19 (70%)	50 (88%)	0.060
Operation time (min)	505±130	537±117	0.263
Blood loss (ml)	1,293±1,142	1,196±899	0.682
Transfusion (+)	7 (26%)	10 (18%)	0.379
PV resection (+)	1 (4%)	6 (11%)	0.259
Stage			0.195
IA	7	5	
IB	3	8	
IIA	4	18	
IIB	12	24	
III	0	0	
IV	1	1	
NLR	2.40±1.60	2.68±1.32	0.392
PNI	45.64±4.82	43.36±4.39	0.034
GPS			0.388
0	16	26	
1	9	22	
2	2	9	
Complication (≥CDIII)	14 (52%)	25 (44%)	0.493
Postoperative hospital stay (days)	25.4±17.7	26.9±20.7	0.743

M, male; F, female; ALP, alkaline phosphatase; BMI, body mass index; CD, Clavien-Dindo classification; CRP, C-reactive protein; GPS, Glasgow prognostic score; γGTP, γ-glutamyl transferase; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; PV, portal vein.

distal cholangiocarcinoma. Yamashita *et al* (26) reported that a BMI of ≥ 25.0 kg/m² is an independent risk factor for clinically relevant pancreatic fistulas after PD for pancreatic ductal adenocarcinoma. The authors speculate that this may be because the pancreas of patients with a high BMI contains a large fatty component, which results in a fragile parenchyma (so called 'soft pancreas') (27-29). It seems acceptable that the BMI threshold in our study was lower than that of the Yamashita *et al* (26) study because pancreatic exocrine function is well preserved in patients with cholangiocarcinoma compared to those with pancreatic ductal adenocarcinoma (30).

In the last decade, the NLR has emerged as an attractive proxy to characterize systemic inflammatory status. Several studies (1,3,31) have suggested that a high NLR is a poor

prognostic marker because neutrophilia accelerates tumor vessel angiogenesis and lymphopenia diminishes immune protection against tumor invasion. Therefore, a high NLR is associated with favorable tumor conditions. However, the reason why the NLR is concerning for postoperative complications may be related to quite different mechanisms. The mechanisms underlying associations between systemic inflammation and postoperative complications remain to be elucidated. Josse *et al* (10) reported that a high NLR of >2.3 correlated with postoperative complications, specifically anastomotic leakage and not infections, in patients with colorectal cancer. Kudo *et al* (32) reported an association between the perioperative NLR and postoperative complications, specifically infections, in patients with colorectal cancer. Considering

Table III. Comparison between clinical characteristics and perioperative outcomes between the major and non-major complications groups.

Variable	Major complications group (n=39)	Non-major complications group (n=45)	P-value
Age (years)	69.2±8.5	67.3±8.9	0.325
Sex (M/F)	30/9	33/12	0.704
Total bilirubin (mg/dl)	0.86±0.10	1.06±0.65	0.131
ALP (U/l)	491.7±55.2	535.4±51.4	0.563
GTP (U/l)	232.5±45.1	227.5±42.0	0.935
Platelets, x10 ⁴ /μl	24.1±7.5	26.0±8.4	0.293
Neutrophils/μl	3,758±1,138	3,138±1,290	0.023
Lymphocytes/μl	1,353±375	1,582±576	0.037
Albumin (g/dl)	3.68±0.06	3.67±0.06	0.905
CRP (mg/dl)	1.15±1.57	1.18±2.06	0.943
BMI	23.3±3.67	21.35±2.80	0.007
Biliary drainage (+)	38 (97%)	43 (96%)	0.639
Bile culture positive	33 (85%)	36 (80%)	0.580
Operation time (min)	535±130	519±115	0.553
Blood loss (ml)	1,359±1,201	1,119±743	0.282
Transfusion (+)	11 (28%)	6 (13%)	0.090
PV resection (+)	1 (3%)	6 (13%)	0.060
Stage			0.327
IA	5	7	
IB	6	5	
IIA	13	9	
IIB	15	21	
III	0	0	
IV	0	2	
NLR	3.04±1.46	2.21±1.26	0.007
PNI	43.54±4.82	44.58±4.46	0.306
GPS			0.846
0	19	23	
1	14	17	
2	6	5	
Postoperative hospital stays (days)	38.3±21.9	16.1±9.1	<0.0001

M, male; F, female; ALP, alkaline phosphatase; BMI, body mass index; CRP, C-reactive protein; GPS, Glasgow prognostic score; γGTP, γ-glutamyl transferase; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; PV, portal vein.

these findings, one potential explanation is that subclinical inflammation (e.g., latent cholangitis) may be exaggerated by surgery in a second attack. Excessive postoperative systemic inflammatory response syndrome causes a cytokine storm that results in microcirculatory disturbances in whole organs. In this study, the most common complication was anastomotic leakage. Nakanishi *et al* (33) reported that systemic inflammatory responses modified endothelial function. An inability of the endothelium to produce nitric oxide and prostacyclin could result in depletion of the vasodilator and antithrombotic properties of the vascular endothelium. Yao *et al* (34) also reported that a high NLR was associated with vascular thrombosis. Thus, a high NLR seems to drive microvascular impairment, which is unfavorable for wound healing.

A value of 2.0, as determined by ROC curve analysis, was selected as the threshold for the NLR in this study. This value was relatively low compared to that reported in the literature (5.0) (1). We speculate that this may be because systemic inflammatory responses need to be sustained for a prolonged period and with sufficient power to influence prognosis compared to postoperative complications. Other studies (8,29) have reported thresholds of 2.3 for postoperative complications in colorectal surgery. It is reasonable that the threshold is 2.0 for PD and 2.3 for colorectal surgery because PD is a more invasive procedure than colorectal surgery.

A high preoperative NLR of >2.0 is a novel indicator for identifying patients at high risk of postoperative complications

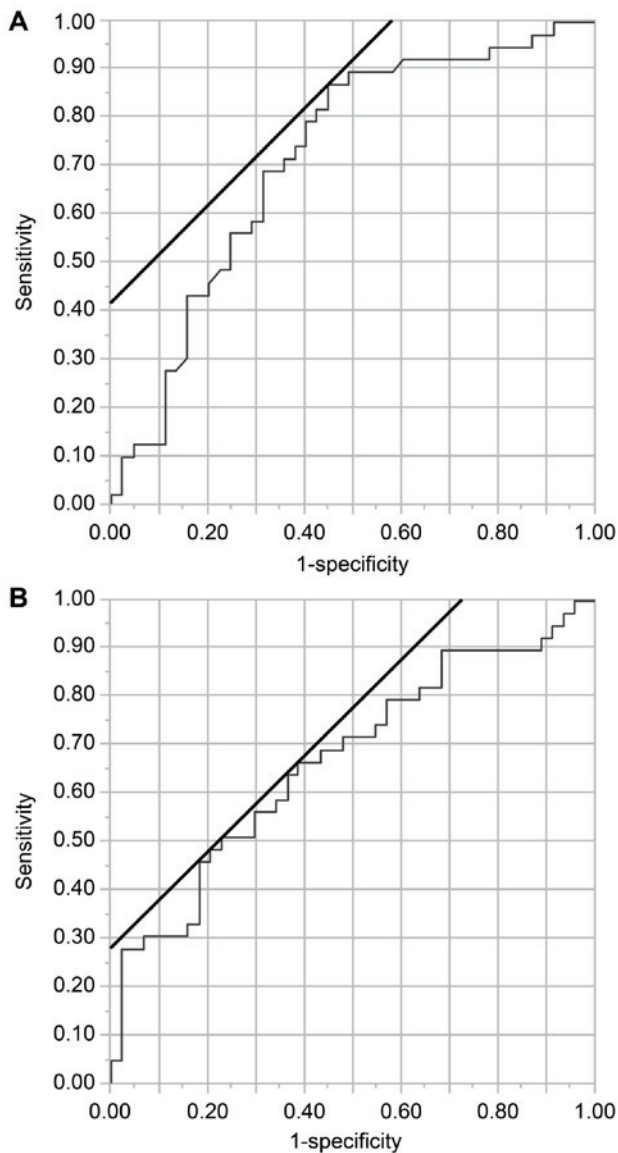


Figure 1. Receiver operating characteristic curve analysis of (A) the neutrophil-to-lymphocyte ratio and (B) the body mass index. The cut-off values were defined as those which corresponded to the points situated furthest away from the reference line.

after PD. As the NLR can be calculated from routine blood test results, it is cost effective and a convenient biomarker for surgeons to determine the best time to operate or to select different strategies for positive surgical outcomes.

This study has several limitations associated with its single-center retrospective design, limited sample size, and 8-year enrollment period. Although the perioperative management and surgical procedures have remained relatively constant, the skills and experiences of the surgeons were not included in the analysis. As cholangiocarcinoma is a rare disease, large multicenter studies would be desirable to validate our findings in a prospective manner.

In conclusion, a high NLR and a high BMI are risk factors of morbidity after PD in patients with distal cholangiocarcinoma. To our knowledge, this is the first study to report the effectiveness of the NLR for predicting postoperative complications in the pancreato-biliary field. Based on our findings, aggressive therapeutic intervention and/or waiting for a reduction in the

Table IV. Multivariate logistic regression analysis of the influence of clinical parameters on postoperative complications.

Variable	OR	95% CI	P-value
Neutrophil >2,727	2.08	0.68-6.49	0.201
Lymphocyte <1,870	2.70	0.44-22.81	0.290
NLR >2.0	6.77	2.44-21.13	<0.001
BMI >23.0 kg/m ²	3.83	1.35-11.83	0.011

BMI, body mass index; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio.

NLR are recommended for reducing morbidity in patients with distal cholangiocarcinoma and a high preoperative NLR.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YK designed this study and wrote the whole draft of the manuscript. TK and HT contributed to the preparation of the clinical data. NN and SE contributed to analysis the data. KI contributed to the preparation of documents for the local ethics committee and search literatures. MW supervised the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Kitasato University School of Medicine (Kitasato, Japan). Research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Patient consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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