








## ORIGINAL ARTICLE

# The impact of C-reactive protein-albumin-lymphocyte (CALLY) index on the prognosis of patients with distal cholangiocarcinoma following pancreaticoduodenectomy

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## Abstract

**Aim:** The C-reactive protein (CRP)-albumin-lymphocyte (CALLY) index is a novel inflammation-based biomarker, which has been associated with long-term outcomes in patients with hepatocellular carcinoma. We aimed to investigate whether the CALLY index can predict the prognosis for distal cholangiocarcinoma after pancreaticoduodenectomy.

**Methods:** The study comprised 143 patients who had undergone primary pancreaticoduodenectomy for distal cholangiocarcinoma between 2002 to 2019. The CALLY index was defined as (albumin × lymphocyte)/ (CRP × 10<sup>4</sup>). We investigated the association of CALLY index with disease-free survival and overall survival by univariate and multivariate analyses.

**Results:** Eighty-seven (61%) patients had a preoperative CALLY index <3.5. In multivariate analysis, obstructive jaundice drainage ( $P < .01$ ), poorly differentiated tumor ( $P < .01$ ), and CALLY index <3.5 ( $P = .02$ ) were independent predictors of disease-free survival, while obstructive jaundice drainage ( $P < .01$ ), poorly differentiated tumor ( $P < .01$ ), and CALLY index <3.5 ( $P = .02$ ) were independent predictors of overall survival.

**Conclusion:** The CALLY index may be an independent and significant indicator of poor long-term outcomes in patients with distal cholangiocarcinoma after pancreaticoduodenectomy, suggesting the importance of comprehensive assessment for inflammatory status.

## KEYWORDS

CALLY index, distal cholangiocarcinoma, pancreaticoduodenectomy

[Correction added on 19 January 2023, after first online publication: The copyright line has been corrected.]

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## 1 | INTRODUCTION

Distal cholangiocarcinoma accounts for 30%–40% of cholangiocarcinoma.<sup>1</sup> Currently, the only curative treatment for distal cholangiocarcinoma is resection including pancreaticoduodenectomy. Despite advances in perioperative management, instruments, and surgical techniques, the 5-year survival rate after radical resection is reported to be 30%–40% due to the high recurrence rate.<sup>2</sup> Therefore, it is critically important to identify better risk assessment of distal cholangiocarcinoma for recurrence and survival for clinical decision-making.

Host inflammatory response is considered a hallmark of cancer. Accumulating evidence suggests that the host inflammatory response plays an important role in the development, progression, and metastasis of cancer.<sup>3</sup> Various preoperative inflammation-based prognostic markers, such as neutrophil-lymphocyte ratio (NLR),<sup>4</sup> platelet-lymphocyte ratio (PLR),<sup>5</sup> and C-reactive protein (CRP)-albumin ratio (CAR),<sup>6</sup> have been reported to predict long-term survival in cancer patients. However, few reports have described prognostic markers for distal cholangiocarcinoma.

The CRP-albumin-lymphocyte (CALLY) index was developed as a new inflammation-based biomarker and was first proposed by Iida et al.<sup>7</sup> In patients with hepatocellular carcinoma, the CALLY index has been associated with recurrence-free as well as overall survival, and was superior to other inflammation-based biomarkers, including NLR and PLR.<sup>8</sup> Therefore, we hypothesized that the CALLY index can be better prognostic marker in distal cholangiocarcinoma. In the present study, we retrospectively investigated the prognostic association of the CALLY index with survival in patients with distal cholangiocarcinoma who underwent pancreaticoduodenectomy.

## 2 | PATIENTS AND METHODS

### 2.1 | Patient selection

Subjects of this retrospective study were distal cholangiocarcinoma patients who underwent pancreaticoduodenectomy at the Department of Surgery, The Jikei University Hospital, Tokyo, Japan, between April 2002 to June 2019. Distal cholangiocarcinoma included distal bile duct cancer and ampullary cancer. We excluded patients with concomitant hepatic resection, postoperative mortality, and unavailable data, leaving the remaining 143 patients enrolled in this study.

As validation sets, we used a combined cohort of 99 patients who underwent pancreaticoduodenectomy for distal cholangiocarcinoma at The Jikei University Katsushika Medical Center ( $n = 8$ ), Department of Digestive Surgery, Kawaguchi Municipal Medical Center ( $n = 23$ ), and The Jikei University Daisan Hospital ( $n = 66$ ) between April 2002 to June 2019.

We retrospectively reviewed a prospectively maintained database of patients. Patients were followed until death or the end of follow-up. The study was approved by the Institutional Ethics Committee of the Jikei University School of Medicine [27-177(8062)]

and conformed to the provisions of the Declaration of Helsinki, as revised in Fortaleza, Brazil, October 2013.

### 2.2 | Treatment and follow-up

During the period, preoperative chemotherapy was not administered to patients with distal cholangiocarcinoma. Basically, pancreaticoduodenectomy with D2 lymph node dissection was performed with some exceptions. The pancreas was transected at the level of the portal vein according to the anterior artery-first approach. The bile duct was dissected at the common hepatic duct. The bile duct stump was evaluated by frozen-section diagnosis and resection of hilar bile duct was added in case of positive for ductal margin stump. Reconstruction was performed using the modified Child method, with Braun anastomosis. In patients with positive ductal margin by permanent pathological diagnosis, chemo-radiation therapy (5-fluorouracil + 50.4 gray radiation) targeting the ductal stump was performed.<sup>9</sup> Since 2007, adjuvant chemotherapy with S-1 was administered to patients with distal cholangiocarcinoma after radical resection with some exceptions.<sup>10,11</sup>

Tumor-Nodes-Metastasis (TNM) classification was based on the pathology according to the Union for International Cancer Control 7th Edition.<sup>12</sup> After surgery, all patients were evaluated every 3 months, and follow-up contrast-enhanced computed tomography was performed every 6 months. For recurrence, chemotherapy including gemcitabine ( $\pm$  cisplatin) or S-1 was given according to the patient's status.

### 2.3 | Measurement of the CALLY index and other inflammatory responses

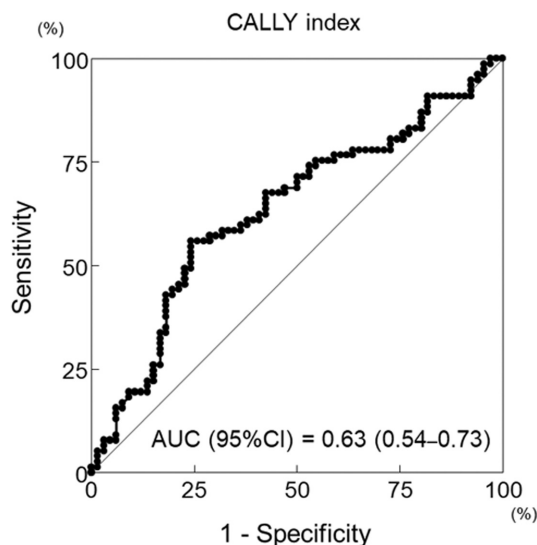
The CALLY index was defined as the preoperative serum albumin value multiplied by the peripheral lymphocyte count and divided by the serum CRP value multiplied by 10000  $[(\text{Albumin} \times \text{Lymphocyte}) \div (\text{CRP} \times 10^4)]$  and which was assessed within 7 days before surgery.<sup>7,8</sup>

We also assessed NLR, PLR, and CAR within 7 days before surgery. As previously described, NLR was calculated as absolute neutrophil count divided by absolute lymphocyte count.<sup>4</sup> PLR was calculated as absolute platelet count divided by absolute lymphocyte count.<sup>5</sup> CAR was calculated as serum CRP level divided by serum albumin.<sup>6</sup>

The cut-off value of each marker was determined according to receiver operating characteristics (ROC) analysis using survival status at the 3-year follow-up. Values of CALLY index  $<3.5$ , NLR  $>2.2$ , PLR  $>170$ , and CAR  $>0.05$  were considered to reflect high inflammatory status (Figure 1; Figure S1).

### 2.4 | Analyses of predictors for recurrence and overall survival

First, we investigated the relationship between clinicopathologic variables of patients with distal cholangiocarcinoma who underwent



**FIGURE 1** Receiver operating characteristic (ROC) curve of C-reactive protein-albumin-lymphocyte (CALLY) index for survival status at the 3-year follow-up (area under ROC = 0.63, 95% confidence interval 0.54–0.73). The cutoff value of the CALLY index was 3.5 (sensitivity = 53.3%, specificity = 75.6%)

pancreaticoduodenectomy and the CALLY index. The variables included the following: sex (male or female), age (years), body mass index ( $\text{kg}/\text{m}^2$ ), obstructive jaundice drainage (yes or no), preoperative administration of antibiotics (yes or no), preoperative nutritional support (yes or no), total bilirubin level ( $\text{mg}/\text{dl}$ ), carbohydrate antigen 19–9 (CA19–9) ( $\text{U}/\text{ml}$ ), type of tumor (ampullary cancer or distal bile duct cancer), duration of operation (min), intraoperative blood loss (ml), intraoperative blood transfusion (red blood cell or fresh frozen plasma), intraoperative albumin use (yes or no), maximum tumor size (mm), TNM stage (I to IV), tumor differentiation (poorly or well/moderate), residual tumor status (R1 or R0), postoperative complication (yes or no), adjuvant chemotherapy (yes or no), NLR, PLR, and CAR.

Next, we investigated the relationship between clinicopathologic variables and disease-free survival, as well as overall survival after pancreaticoduodenectomy for distal cholangiocarcinoma by univariate and multivariate analyses. The univariate and multivariate Cox regression model initially included sex (male vs. female), age ( $\geq 65$  vs.  $< 65$  years), body mass index ( $\geq 25$  vs.  $< 25 \text{ kg}/\text{m}^2$ ), obstructive jaundice drainage (yes vs. no), CA19–9 ( $\geq 70$  vs.  $< 70 \text{ U}/\text{mL}$ ), duration of operation ( $\geq 480$  vs.  $< 480$  min), intraoperative blood loss ( $\geq 700$  vs.  $< 700 \text{ mL}$ ), intraoperative blood transfusion (yes vs. no), maximum tumor size ( $\geq 27$  vs.  $< 27 \text{ mm}$ ), TNM stage (III and IV vs. I and II), tumor differentiation (poorly vs. well/moderate), residual tumor status (R1 vs. R0), postoperative complication (yes or no), adjuvant chemotherapy (yes or no), NLR ( $> 2.2$  vs.  $\leq 2.2$ ), PLR ( $> 170$  vs.  $\leq 170$ ), CAR ( $> 0.05$  vs.  $\leq 0.05$ ), and CALLY index ( $< 3.5$  vs.  $\geq 3.5$ ). Intraoperative blood transfusion included red blood cell or fresh frozen plasma transfusion. Backward elimination was conducted with a threshold  $P$  of .05 to select variables for the final models.

Next, using validation sets, we performed the same analysis for the relationship between the CALLY index and disease-free survival, as well as overall survival.

**TABLE 1** Baseline characteristics ( $n = 143$ )

Variables	Median (interquartile range) or ratio
Sex, male	66 (46%)
Age, years	68 (60–73)
Body mass index, $\text{kg}/\text{m}^2$	22 (20–25)
Obstructive jaundice drainage, yes	100 (70%)
Preoperative administration of antibiotics, yes	17 (12%)
Preoperative nutritional support, yes	4 (3%)
Total bilirubin, $\text{mg}/\text{dl}$	1.1 (0.7–1.9)
CA19–9, $\text{U}/\text{ml}$	44 (19–108)
Type of tumor	
Ampullary cancer	82 (57%)
Distal bile duct cancer	61 (43%)
Duration of operation, min	510 (437–566)
Intraoperative blood loss, ml	740 (439–1250)
Intraoperative blood transfusion, yes	26 (18%)
Red blood cell transfusion, yes	24 (17%)
Fresh frozen plasma transfusion, yes	9 (6%)
Intraoperative albumin use, yes	33 (23%)
Maximum tumor size, mm	9 (3–25)
TNM stage	
I	51 (36%)
II	56 (39%)
III	27 (19%)
IV	9 (6%)
Tumor differentiation, poorly	27 (19%)
Residual tumor status, R1	17 (12%)
Postoperative complication, yes	50 (35%)
Adjuvant chemotherapy, yes	95 (69%)
NLR	2.4 (1.6–3.4)
PLR	165 (117–225)
CAR	0.07 (0.02–0.26)
CALLY index	2.4 (0.5–8.9)

Abbreviations: CA19–9, carbohydrate antigen 19–9; CALLY index, C-reactive protein-albumin-lymphocyte index; CAR, C-reactive protein-albumin ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; TNM, Tumor-Nodes-Metastasis.

Finally, we assessed the statistical interaction between CALLY index ( $< 3.5$  vs.  $\geq 3.5$ ) and the treatment period (before 2012 vs. after 2012), using the Wald test in the multivariate-adjusted Cox proportional regression model for disease-free as well as overall survival.

## 2.5 | Statistical analysis

Statistical analyses were performed using STATA/SE (STATA Statistical Software, version 14.2; Stata Corp., College Station, TX, USA). A

two-sided  $\alpha$  level of 0.05 was used. Continuous variables are expressed as medians and interquartile ranges (IQR), while categorical variables are expressed as absolute numbers. Clinical datasets were compared using the Mann-Whitney U-test or chi-square test, as appropriate. Univariate and multivariate Cox proportional hazards regression models were used to estimate hazard ratio (HR) for disease-free and overall survival. Cumulative survival probabilities were estimated using the Kaplan-Meier method and compared using the log-rank test.

### 3 | RESULTS

#### 3.1 | Patient characteristics

Patient characteristics are outlined in Table 1. Among 143 patients, 82 (57%) patients had ampullary cancer, and 61 (43%) patients had distal bile duct cancer. During the median follow-up time of 3.5 years (IQR, 1.6–6.9 years) for all censored patients, 65 of 143 patients experienced recurrence (45%), and the median time to recurrence following pancreaticoduodenectomy was 2.5 years (IQR, 0.7–6.5). The 5-year disease-free and overall survival rates in patients with distal cholangiocarcinoma who underwent pancreaticoduodenectomy were 31% and 37%, respectively.

Among the 143 patients, 87 (61%) patients had a preoperative CALLY index  $<3.5$ . In Kaplan-Meier analyses, CALLY index  $<3.5$  was associated with worse disease-free ( $P < .01$ , Figure 2A) and overall survival ( $P < .01$ , Figure 2B).

#### 3.2 | Univariate and multivariate analyses of clinicopathological variables associated with disease-free survival after pancreaticoduodenectomy for distal cholangiocarcinoma

Table 2 shows the association of the clinicopathological variables with disease-free survival after pancreaticoduodenectomy for distal cholangiocarcinoma. In univariate analysis, disease-free survival was significantly associated with obstructive jaundice drainage ( $P < .01$ ), CA19-9  $\geq 70$  U/mL ( $P = .04$ ), maximum tumor size  $\geq 27$  mm ( $P = .02$ ), TNM stage III or IV ( $P = .04$ ), poorly differentiated tumor ( $P < .01$ ), R1 resection ( $P = .03$ ), CAR  $>0.05$  ( $P < .01$ ), and CALLY index  $<3.5$  ( $P < .01$ ). In multivariate analysis, obstructive jaundice drainage ( $P < .01$ ), poorly differentiated tumor ( $P < .01$ ), and CALLY index  $<3.5$  [HR 2.13, 95% confidence interval (CI) 1.15–3.86,  $P = .02$ ] were independent predictors of disease-free survival.

#### 3.3 | Univariate and multivariate analyses of clinicopathological variables associated with overall survival after pancreaticoduodenectomy for distal cholangiocarcinoma

Table 3 shows the association of the clinicopathological variables with overall survival after pancreaticoduodenectomy for distal cholangiocarcinoma. In univariate analysis, overall survival was significantly associated with age  $\geq 65$  ( $P = .02$ ), obstructive jaundice

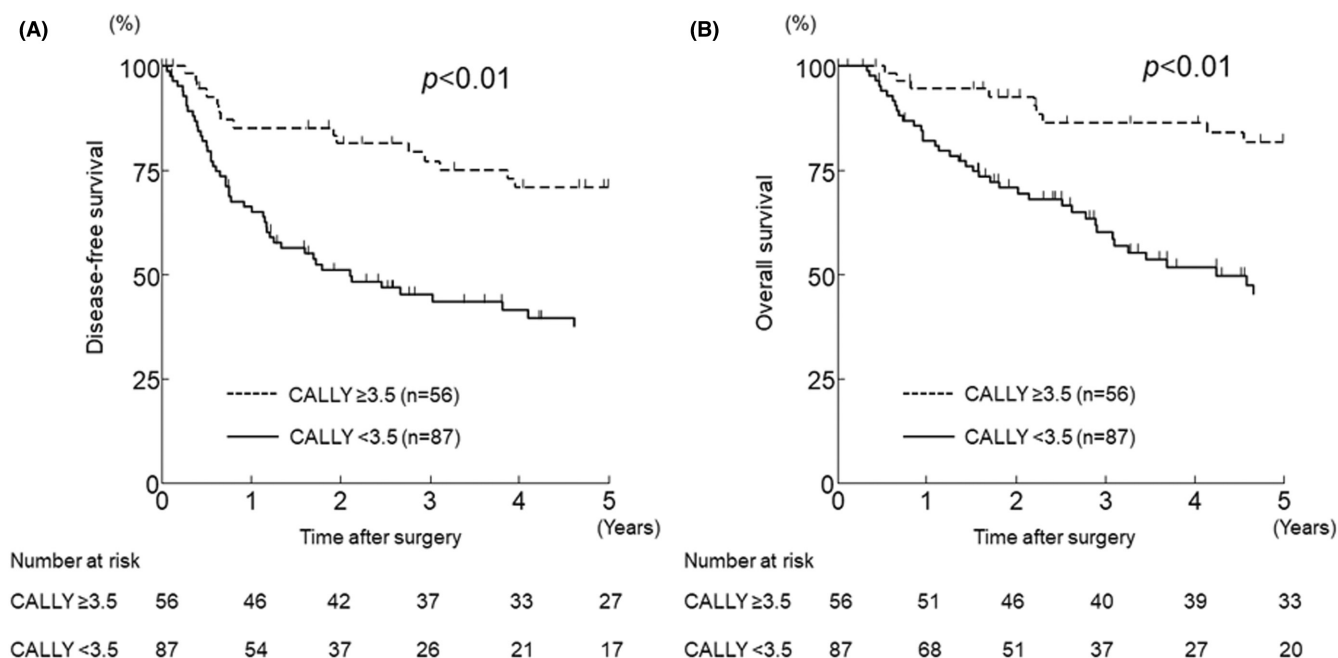


FIGURE 2 Kaplan-Meier curves of disease-free survival (A) and overall survival (B) after pancreaticoduodenectomy for distal cholangiocarcinoma. The C-reactive protein-albumin-lymphocyte (CALLY) index  $<3.5$  was associated with worse disease-free survival ( $P < .01$ ) and overall survival ( $P < .01$ )

**TABLE 2** Univariate and multivariate analyses of clinicopathologic variables in relation to disease-free survival following pancreaticoduodenectomy for distal cholangiocarcinoma (n = 143)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value <sup>a</sup>
Sex, male	1.20 (0.68–2.11)	.53		NS
Age, ≥65 year	1.46 (0.87–2.47)	.15		NS
Body mass index, ≥25 kg/m <sup>2</sup>	1.35 (0.78–2.36)	.29		NS
Obstructive jaundice drainage, yes	7.31 (2.93–18.23)	<.01	7.10 (2.55–19.75)	<.01
CA19-9, ≥70 U/mL	1.66 (1.02–2.72)	.04		NS
Duration of operation, ≥480 min	1.52 (0.91–2.55)	.11		NS
Intraoperative blood loss, ≥700 mL	1.60 (0.96–2.66)	.07		NS
Intraoperative blood transfusion, yes	1.38 (0.75–2.54)	.30		NS
Maximum tumor size, ≥27 mm	1.92 (1.12–3.28)	.02		NS
TNM stage, III or IV	1.76 (1.03–3.02)	.04		NS
Tumor differentiation, poorly	3.75 (2.18–6.45)	<.01	2.92 (1.64–5.20)	<.01
Residual tumor status, R1	1.99 (1.06–3.74)	.03		NS
Postoperative complication, yes	1.19 (0.71–1.98)	.51		NS
Adjuvant chemotherapy, yes	1.31 (0.79–2.17)	.30		NS
NLR, >2.2	1.43 (0.87–2.35)	.16		NS
PLR, >170	1.10 (0.67–1.80)	.70		NS
CAR, >0.05	2.75 (1.57–4.81)	<.01		NS
CALLY index, <3.5	3.07 (1.71–5.50)	<.01	2.13 (1.15–3.86)	.02

Abbreviations: CA19-9, carbohydrate antigen 19-9; CALLY, C-reactive protein-albumin-lymphocyte; CI, confidence interval; HR, hazard ratio; NS, not significant; TNM, Tumor-Nodes-Metastasis.

<sup>a</sup>The multivariate Cox regression model initially included sex (male vs. female), age (≥65 vs. <65 years), body mass index (≥25 vs. <25 kg/m<sup>2</sup>), obstructive jaundice drainage (yes vs. no), CA19-9 (≥70 vs. <70 U/mL), duration of operation (≥480 vs. <480 min), intraoperative blood loss (≥700 vs. <700 mL), intraoperative blood transfusion (yes vs. no), maximum tumor size (≥27 vs. <27 mm), TNM stage (III or IV vs. I or II), tumor differentiation (poorly vs. well or moderate), residual tumor status (R1 vs. R0), postoperative complication (yes vs. no), adjuvant chemotherapy (yes vs. no), NLR (>2.2 vs. ≤2.2), PLR (>170 vs. ≤170), CAR (>0.05 vs. ≤0.05), and CALLY index (<3.5 vs. ≥3.5). Backward elimination was conducted with a threshold P of .05 to select variables for the final models.

drainage ( $P < .01$ ), maximum tumor size  $\geq 27$  mm ( $P = .04$ ), TNM stage III or IV ( $P = .01$ ), poorly differentiated tumor ( $P < .01$ ), adjuvant chemotherapy ( $P < .01$ ), CAR  $> 0.05$  ( $P < .01$ ), and CALLY index  $< 3.5$  ( $P < .01$ ). In multivariate analysis, obstructive jaundice drainage ( $P < .01$ ), poorly differentiated tumor ( $P < .01$ ), and CALLY index  $< 3.5$  (HR 2.07, 95% CI 1.11–3.89,  $P = .02$ ) were independent predictors of overall survival.

As secondary analyses, given the advances in distal cholangiocarcinoma treatment, we assessed the prognostic association of the CALLY index in strata of the treatment period (before 2012 vs. after 2012). The prognostic association of the CALLY index was not significantly modified by the treatment period ( $P$  for interaction = .96 for disease-free survival, and  $P$  for

interaction = .30 for overall survival in strata of the treatment period) (Tables S1 and S2).

### 3.4 | Association of CALLY index with clinicopathological variables

Table 4 shows the clinicopathological variables according to the CALLY index. In univariate analysis, older age ( $P = .04$ ), obstructive jaundice drainage ( $P < .01$ ), high serum bilirubin level ( $P = .02$ ), large tumor size ( $P = .02$ ), advanced TNM stage ( $P = .01$ ), poorly differentiated tumor ( $P < 0.01$ ), high NLR ( $P < 0.01$ ), and high CAR ( $P < 0.01$ ) were positively associated with CALLY index  $< 3.5$ .

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value <sup>a</sup>
Sex, male	0.88 (0.51–1.55)	.67		NS
Age, ≥65 year	2.07 (1.15–3.75)	.02		NS
Body mass index, ≥25 kg/m <sup>2</sup>	1.09 (0.59–2.03)	.78		NS
Obstructive jaundice drainage, yes	6.17 (2.46–15.48)	<.01	5.70 (2.04–15.95)	<.01
CA19-9, ≥70 U/mL	1.35 (0.80–2.30)	.26		NS
Duration of surgery, ≥480 min	1.30 (0.76–2.21)	.34		NS
Intraoperative blood loss, ≥700 mL	1.50 (0.88–2.56)	.14		NS
Intraoperative blood transfusion, yes	1.69 (0.94–3.05)	.08		NS
Maximum tumor size, ≥27 mm	1.83 (1.04–3.22)	.04		NS
TNM stage, III or IV	2.18 (1.26–3.78)	.01		NS
Tumor differentiation, poorly	4.81 (2.77–8.36)	<.01	3.48 (1.95–6.21)	<.01
Residual tumor status, R1	1.58 (0.77–3.22)	.21		NS
Postoperative complication, yes	0.92 (0.52–1.61)	.77		NS
Adjuvant chemotherapy, yes	1.10 (0.64–1.87)	.74		NS
NLR, >2.2	1.53 (0.90–2.61)	.12		NS
PLR, >170	1.24 (0.74–2.09)	.42		NS
CAR, >0.05	3.00 (1.65–5.44)	<.01		NS
CALLY index, <3.5	3.05 (1.66–5.60)	<.01	2.07 (1.11–3.89)	.02

**TABLE 3** Univariate and multivariate analyses of clinicopathologic variables in relation to overall survival following pancreaticoduodenectomy for distal cholangiocarcinoma (n = 143)

Abbreviations: CA19-9, carbohydrate antigen 19-9; CALLY, C-reactive protein-albumin-lymphocyte; CI, confidence interval; HR, hazard ratio; M, Metastasis; N, Nodes; NS, not significant; T, Tumor.

<sup>a</sup>The multivariate Cox regression model initially included sex (male vs. female), age (≥65 vs. <65 years), body mass index (≥25 vs. <25 kg/m<sup>2</sup>), obstructive jaundice drainage (yes vs. no), CA19-9 (≥70 vs. <70 U/mL), duration of operation (≥480 vs. <480 min), intraoperative blood loss (≥700 vs. <700 mL), intraoperative blood transfusion (yes vs. no), maximum tumor size (≥27 vs. <27 mm), TNM stage (III or IV vs. I or II), tumor differentiation (poorly vs. well or moderate), residual tumor status (R1 vs. R0), postoperative complication (yes vs. no), adjuvant chemotherapy (yes vs. no), NLR (>2.2 vs. ≤2.2), PLR (>170 vs. ≤170), CAR (>0.05 vs. ≤0.05), and CALLY index (<3.5 vs. ≥3.5). Backward elimination was conducted with a threshold P of .05 to select variables for the final models.

### 3.5 | External validation analyses of the CALLY index associated with disease-free survival as well as overall survival after pancreaticoduodenectomy for distal cholangiocarcinoma

Among the 99 patients, 61 (62%) patients had a preoperative CALLY index <3.5. In Kaplan–Meier analyses, CALLY index <3.5 was associated with worse disease-free (P = .03, [Figure 3A](#)) and overall survival (P < .01, [Figure 3B](#)).

## 4 | DISCUSSION

In the present study, we found that the CALLY index <3.5 was associated with worse disease-free as well as overall survival in patients with distal cholangiocarcinoma who underwent

pancreaticoduodenectomy. In multivariate analysis, the CALLY index exhibited superior prognostic ability compared to the NLR, PLR, and CAR. The validity of the CALLY index was confirmed even in the external validation analyses by setting the cut-off value as 3.5. Our results suggest the importance of comprehensive assessment for inflammatory status.

The CALLY index, a newly proposed prognostic biomarker for liver function, immune system status, and inflammatory component of the tumor microenvironment, was calculated using serum CRP concentration, serum albumin concentration, and peripheral lymphocyte count.<sup>7,8</sup> Despite the use of three factors, the formula used is simple and allows easy calculation. Owing to its relatively long half-life, serum albumin concentration is widely used for indicating nutrition and hepatic functional reserve.<sup>13</sup> Peripheral lymphocyte count is a surrogate marker of immunocompetence, as lymphocytes play a role in tumor immunity to suppress carcinogenesis.<sup>14</sup> CRP is



an acute-phase protein, and the production of CRP is independently carried by interleukin-6 in the liver.<sup>15</sup> Decreases in albumin and increases in CRP fluctuate in response to exacerbations of inflammation in cancer tissue. Taken together, the CALLY index can be considered to reflect the systemic inflammatory response to cancer more sensitively as this index included three essential components of systemic inflammation and immunity.

NLR has been considered to reflect increasing in chemokine/cytokine production that promotes tumor cell proliferation, tumor invasiveness, and angiogenesis.<sup>15</sup> Similar to NLR, PLR has been reported to be associated with chronic inflammation that promotes cancer progression.<sup>16</sup> CAR may reflect systemic inflammation in the micro-environment of cancer, and CAR has been reported to parallel tumor progression.<sup>17,18</sup> Several previous studies investigated the survival association of those well-established biomarkers such as NLR, PLR, and CAR in patients with distal cholangiocarcinoma.<sup>4–6</sup> There have been only a few studies on the CALLY index in patients with cancers, and this is the first study of the CALLY index in patients with distal cholangiocarcinoma. In addition, none of these studies have evaluated the efficacy of the CALLY index with other biomarkers in multivariate analyses.<sup>7,8</sup> In our study, multivariate analysis showed that the CALLY index exhibited superior prognostic ability compared to

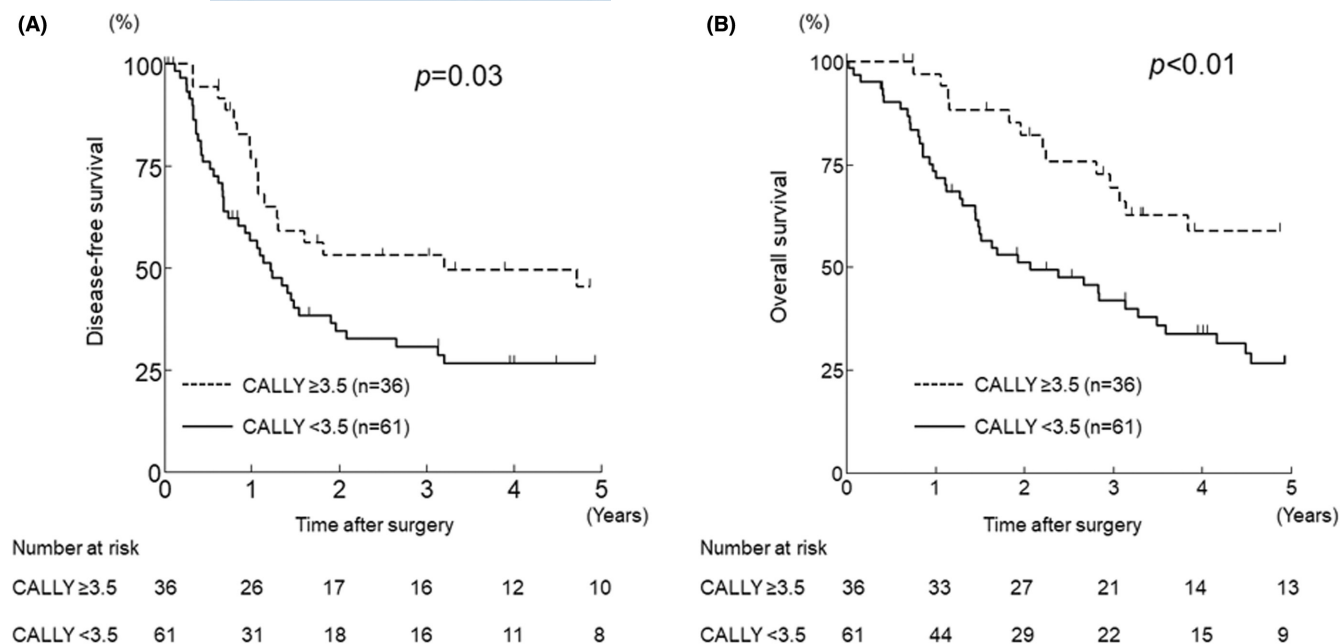
the NLR, PLR, and CAR in patients with distal cholangiocarcinoma. The potential reason for these findings was that the CALLY index can evaluate systemic inflammatory response more comprehensively than each inflammatory biomarker including NLR, PLR, and CAR. NLR and PLR consist of peripheral blood cell counts, while CAR is a CRP-based biomarker. Several studies indicated that both white blood cell-based and CRP-based biomarkers are important in the prediction of long-term outcomes.<sup>4–6,13–18</sup> Moreover, a study suggested the better prognostic utility of a combined biomarker of NLR and CRP.<sup>19</sup> Thus, a comprehensive assessment of the systemic inflammatory response using CALLY index may provide better prognostic utility in cancer patients.

Although the current study supports a prognostic role of the CALLY index in patients with distal cholangiocarcinoma, the mechanisms underlying the associations of low CALLY index with poor prognosis remain unclear. In this study, low CALLY index was associated with obstructive jaundice, high serum bilirubin, large tumor size, advanced TNM stage, poorly differentiated tumor, high NLR, and high CAR. Our findings suggest the CALLY index reflects nutritional status and especially high inflammatory status due to cancer progression and aggressiveness. Conventionally, tumor-related factors, including tumor size, TNM classification system,

**TABLE 4** Comparison of the clinicopathological variables between the two groups classified by CALLY index in patients with distal cholangiocarcinoma (n = 143)

Variables	CALLY index <3.5 (n = 87)	CALLY index ≥3.5 (n = 56)	P-value
Sex, male	66 (76%)	37 (66%)	.20
Age, years	70 (61–75)	65 (59–71)	.04
Body mass index, kg/m <sup>2</sup>	22 (20–25)	22 (21–25)	.72
Obstructive jaundice drainage, yes	70 (80%)	30 (54%)	<.01
Total bilirubin, mg/dl	1.5 (0.8–2.5)	1 (0.7–1.5)	.02
CA19-9, U/ml	57 (19–125)	36 (20–86)	.17
Duration of operation, min	510 (437–566)	500 (427–603)	.92
Intraoperative blood loss, ml	730 (428–1218)	740 (450–1370)	.66
Intraoperative blood transfusion, yes	18 (21%)	8 (14%)	.33
Maximum tumor size, mm	30 (23–45)	25 (19–40)	.02
TNM stage			
I	25 (29%)	26 (46%)	.01
II	33 (38%)	23 (41%)	
III	20 (23%)	7 (13%)	
IV	9 (10%)	0 (0%)	
Tumor differentiation, poorly	23 (26%)	4 (7%)	<.01
Residual tumor status, R1	11 (13%)	6 (11%)	.72
Postoperative complication, yes	27 (31%)	23 (41%)	.24
Adjuvant chemotherapy, yes	40 (49%)	19 (34%)	.08
NLR	2.7 (2.0–3.8)	1.8 (1.4–2.7)	<.01
PLR	174 (123–233)	156 (102–208)	.06
CAR	0.16 (0.08–0.63)	0.013 (0.011–0.026)	<.01

Abbreviations: CA19-9, carbohydrate antigen 19-9; CALLY index, C-reactive protein-albumin-lymphocyte index; CAR, C-reactive protein-albumin ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; TNM, Tumor-Nodes-Metastasis.



**FIGURE 3** Kaplan-Meier curves of disease-free survival (A) and overall survival (B) after pancreaticoduodenectomy for distal cholangiocarcinoma in the external validation analyses the C-reactive protein-albumin-lymphocyte (CALLY) index  $< 3.5$  was associated with worse disease-free survival ( $P = .03$ ) and overall survival ( $P < .01$ )

poor differentiation, and obstructive jaundice have been associated with tumor burden and prognosis,<sup>20</sup> and surgical indications are decided based on the degree of these cancer statuses. Because the CALLY index is associated with tumor-related factors as well as inflammation-based markers, it is probably a better prognostic predictor than NLR, PLR, and CAR. With high accuracy, accessibility, and cost-effectiveness, the CALLY index can provide useful tumor-related as well as inflammation-based information for the prediction of prognosis and optimization of planning therapeutic strategy.

The present study has limitations. First, it was a retrospective study and the potential bias could not be completely excluded. Especially, there might be potential bias in the protocol for adjuvant chemotherapy, because patients with R1 resection received adjuvant chemotherapy (65%) more frequently than patients with R0 resection (39%) ( $P = .04$ , data not shown). However, we included both adjuvant chemotherapy and residual tumor status in the multivariate analyses and revealed that both variables were not significant predictors for disease-free survival and overall survival in the multivariate analyses. Although we validated our findings using external validation cohorts of multi-centers, our sample size was still limited. Therefore, the prognostic value of the CALLY index should be further validated in large-scale studies. Second, data were acquired over 17 years, during which period, the treatment of cholangiocarcinoma has considerably evolved. Given the advances in cholangiocarcinoma treatment, we conducted stratified analyses according to the treatment period. However, the prognostic association of the CALLY index was not significantly modified by the treatment period.

In conclusion, the CALLY index, which is calculated using the serum CRP level, serum albumin level, and lymphocyte count, can be

a predictor of long-term outcomes in patients with distal cholangiocarcinoma following pancreaticoduodenectomy. Our result suggests that the CALLY index is a promising stratification tool for patients with distal cholangiocarcinoma.

## DISCLOSURE

**Author contributions:** MT, KH, and TI developed the main concept and designed the study. MT, TT, YT, YS, KF, TW, SO, TU, YN, and TO were responsible for acquisition of clinicopathological data. MT, KH, and MY performed data analysis and interpretation. MT, KH, and TI drafted the manuscript. TT, YT, YS, KF, TW, and SO contributed to editing and critical revision for important intellectual contents.

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**Conflict of Interest:** The authors declare that they have no conflicts of interest.

**Ethics Approval:** This study protocol was approved by the Ethics Committee of The Jikei University School of Medicine (#27-177). Patients were given an opportunity to opt out of this study through public announcements.

**Informed Consent:** All informed consent was obtained from the subject(s) and/or guardian(s).

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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