Low Pretreatment CALLY Index Predicts Early Recurrence in Resected UICC Stage I Pancreatic Ductal Adenocarcinoma

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Objective: We aimed to identify the inflammation-based prognostic score (IBPS) that can be used to predict the recurrence of early-stage pancreatic ductal carcinoma (PDAC).
Methods: In this retrospective study, the data of 109 patients with Union for International Cancer Control (UICC) stage I PDAC who underwent pancreatectomy between January 2005 and December 2020 at Tokai University Hospital were assessed. The clinicopathological and risk factors for early recurrence were compared between the early (within 12 postoperative months) recurrence (ER) group (n = 29) and non-ER group (n = 80).
Results: The median overall survival (OS) durations of the ER and non-ER groups were 15.0 (95% confidence interval [CI]: 8.0–22.0) and 109.0 (95% CI: 91.4–120.9) months, respectively (p < 0.001). The patients in the ER group had a significantly poorer prognosis. Multivariate analysis showed that the C-reactive protein-albumin-lymphocyte (CALLY) index (< 4.4) (hazard ratio [HR]: 2.71, 95% CI: 1.21–6.02]), positive venous invasion (HR: 4.67, 95% CI: 1.10–19.90), tumor differentiation (moderately/poorly) (HR: 2.25, 95% CI: 2.05–13.43), and failure to complete adjuvant chemotherapy (HR: 12.50, 95% CI: 5.30–29.50) were independent risk factors for early recurrence.
Conclusions: Low pretreatment CALLY index was a useful predictor of early recurrence in patients with UICC stage I PDAC.

Key words: UICC stage I, pancreatic ductal adenocarcinoma, early recurrence, CALLY index

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related deaths in the United States of America [1]. Of gastrointestinal cancers, its prognosis is particularly poor; however, the number of patients with PDAC has been increasing in recent years, and it is expected to become the second leading cause of death by 2030 [2]. Recent advances in diagnostic imaging and other modalities have led to the early detection of PDAC [3, 4]. Patients with small PDAC tumors, with diameters of 2 cm or less, have been reported to have a good prognosis, with a 5-year survival rate of 77.9% [5]. However, patients with early-stage PDAC without lymph node metastasis tend to experience early recurrence and poor prognosis.

Although there are many reports on the risk factors for early recurrence of PDAC, including tumor size, high preoperative colorectal carcinoma antigen (CA19-9) level, positive retroperitoneal invasion, and tumor differentiation grade [6–8], few studies have focused on the risk of recurrence and prognosis of early-stage PDAC [9–12]. Recently, inflammation-based prognostic scores (IBPSs) such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), modified Glasgow prognostic score (mGPS), C-reactive protein (CRP)-to-albumin ratio (CAR), prognostic nutritional index (PNI), and CRP-albumin-lymphocyte (CALLY) index have been reported to be correlated with recurrence and prognosis in some carcinomas including PDAC [9, 13–20]. In this study, we aimed to determine the IBPS that can be used to predict the risk of early recurrence in patients with early-stage pancreatic cancer.

MATERIALS AND METHODS

Patients

This study was a retrospective study. Of the 354 patients with resectable pancreatic cancer diagnosed and resected at Tokai University in Isehara, Japan, between January 2005 and December 2020, the data of 146 patients with stage IA or IB Union for International Cancer Control (UICC) PDAC were assessed. Of these, four patients who received neoadjuvant chemotherapy, six who died from other causes, six with cancers other than adenocarcinoma, and 16 who were followed up at other hospitals were excluded, thus, we had 109 patients in the final analysis (Fig. 1). Staging was performed according to the UICC tumor-node-metastasis (TNM) classification, 8th edition [21]. The resectability of pancreatic cancer in each patient was determined according to preoperative imaging find-

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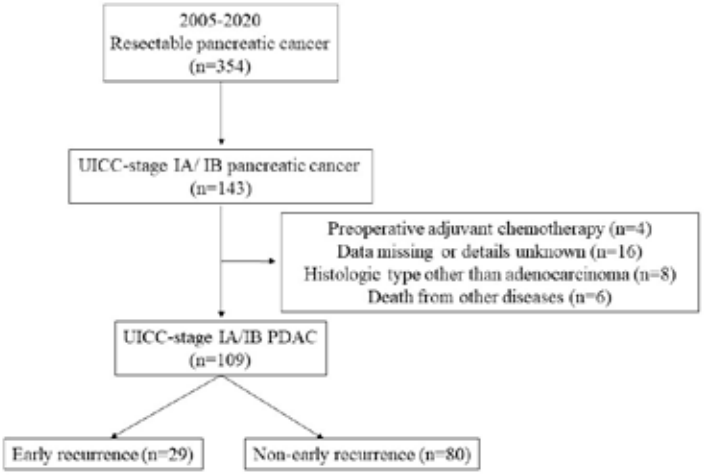

Fig. 1 Flowchart of patients with resected UICC-stage I PDAC
UICC, Union for International Cancer Control; PDAC, pancreatic ductal carcinoma

ings in accordance with the National Comprehensive Cancer Network (NCCN) guidelines [22]. Postoperative complications were evaluated using the Clavien–Dindo classification [23]. This study was approved by the Institutional Ethics Board of Tokai University Hospital (IRB No. 19R-112). The investigation conforms with the principles outlined in the Declaration of Helsinki.

Definition of early recurrence and measurement of IBPS

Some reports define early recurrence as recurrence within 6 months after surgery, whereas others define it as recurrence within 12 months. Because this study included patients with only UICC stage I PDAC, we defined early recurrence as recurrence within 12 months of surgery. We divided the patients into two groups: the early recurrence group (ER group) comprising patients who had postoperative recurrence within 12 months and the non-ER group comprising patients without postoperative recurrence within 12 months irrespective of recurrence after 12 months. The diagnosis of recurrence was made using contrast-enhanced computed tomography (CT), and liver metastasis was confirmed using contrast-enhanced magnetic resonance imaging (MRI). If CT and MRI were difficult to identify recurrence, positron emission tomography was used for diagnosis as needed.

The following IBPSs were analyzed: mGPS, as defined in previous studies [18, 19]; CRP-albumin ratio (CAR), based on a combination of CRP and albumin (Alb) levels (patients with normal levels of CRP [$\leq$ 1.0 mg/dL] and any level of Alb received a score of 0; patients with elevated CRP levels [$>$1.0 mg/L] and normal albumin levels [$>$3.5 g/L] received a score of 1; and patients with elevated CRP levels [$>$1.0 mg/L] and hypoalbuminemia [$\leq$ 3.5 g/L] received a score of 2); PNI, defined as 10 $\times$ albumin + 0.005 $\times$ total lymphocytes [24]; NLR; PLR; LMR; and CRP-albumin-lymphocyte (CALLY) index, defined as 10000 [(albumin $\times$ lymphocytes)/(CRP $\times$ 10000)] [20]. All factors were determined by blood biochemistry tests within 2 days before treatment initiation.

SURGICAL PROCEDURE

Pancreaticoduodenectomy with regional lymph node dissection was performed for pancreatic head cancer. Distal pancreatectomy with regional lymph node dissection was performed for pancreatic body and tail cancers. Until 2009, pyloric ring-preserving pancreaticoduodenectomy was performed, and from 2010 onwards, subtotal stomach preserving pancreaticoduodenectomy was performed. These two techniques do not affect the oncologic long-term prognosis. Reconstruction was performed using the modified Child procedure. Laparoscopic surgery is increasingly being performed for pancreatic cancer; it is also performed in our department. However, during the study period, laparoscopic distal pancreatectomy was performed only in one eligible patient. There were no major changes in the surgical techniques followed by our department during the study period. Moreover, neoadjuvant chemotherapy is increasingly being adopted for the treatment of resectable pancreatic cancer. During the study period, the decision to use neoadjuvant treatment was made by the attending physician, and upfront surgery was generally performed. Radiotherapy is not indicated for resectable pancreatic cancer in our department. In the present study, patients who had received preoperative adjuvant chemotherapy were excluded because of its influence on blood biochemistry test results.

Postoperative follow-up and adjuvant chemotherapy

All the patients underwent routine postoperative surveillance. Patients receiving postoperative adjuvant chemotherapy also underwent monthly tumor marker measurements (carcinoembryonic antigen [CEA] and CA19-9) for the first 6 months after surgery, every 3 months until 3 years after surgery, and every 6 months thereafter. Patients who did not receive postoperative adjuvant chemotherapy underwent tumor marker measurements every 3 months. Chest and abdominal CT scans were performed every 3 months after surgery for the first 3 years, every 6 months for the following 2 years, and annually thereafter. The choice

Table 1 Comparison of clinicopathological findings between the ER and non-ER groups

Variables	ER (n = 29)	Non-ER (n = 80)	p-value
Age, years, median (range)	73 (58–85)	68 (41–84)	0.065
Sex (Male/Female)	16/13	52/28	0.237
Location (Head/Body and tail)	17/12	48/32	0.534
Albumin (g/dL), median (range)	4.0 (2.6–4.7)	4.2 (1.6–5.0)	0.025
CRP (mg/dL), median (range)	0.26 (0.1–3.5)	0.10 (0.1–4.8)	0.038
CAR, median (range)	0.04 (0.02–1.14)	0.03 (0.02–1.18)	0.039
Neutrophil count (/μL), median (range)	3397 (1910–6842)	3379 (1845–12231)	0.964
Lymphocyte count (/μL), median (range)	1440 (457–2532)	1668 (548–2684)	0.040
Monocyte count (/μL), median (range)	291 (118–576)	291 (151–666)	0.959
Platelet count, ($\times 10^3$/μL), median (range)	210 (112–505)	204 (88–410)	0.781
mGPS (0,1/2)	27/2	77/3	0.402
PNI, median (range)	47.1 (31.5–54.3)	49.9 (25.0–60.2)	0.020
NLR, median (range)	2.4 (1.3–5.5)	2.1 (1.0–7.4)	0.211
PLR, median (range)	146.5 (86.9–597.0)	131.6 (57.2–368.6)	0.097
LMR, median (range)	4.9 (1.4–13.0)	5.7 (2.0–13.8)	0.216
CALLY index, median (range)	3.2 (0.1–9.5)	5.7 (0.1–11.5)	0.018
Total bilirubin (mg/dL), median (range)	0.6 (0.2–15.2)	0.6 (0.2–8.7)	0.293
Preoperative biliary drainage, n (%)	8 (27.6)	23 (28.8)	0.555
CEA (ng/mL), median (range)	4.7 (0.8–24.0)	3.5 (0.9–43.8)	0.234
CA19-9 (U/mL), median (range)	110.8 (1.0–930.3)	45.7 (1.0–1766.5)	0.029
Operation time (min), median (range)	323 (102–497)	281 (115–564)	0.277
Portal vein resection, n (%)	2 (6.9)	12 (15.0)	0.219
Blood loss (mL), median (range)	828 (162–2539)	546 (32–3071)	0.060
Blood transfusion (Yes), n (%)	7 (24.1)	6 (7.5)	0.025
Complication (Clavien–Dindo classification ≥ 3a)	15 (51.7)	34 (42.5)	0.261
Postoperative pancreatic fistula (Grade ≥ B)	11 (37.9)	28 (35.0)	0.474
Duration of hospitalization (day), median (range)	25 (13–63)	23 (9–132)	0.365
Tumor size (mm), median (range)	28.0 (11.0–40.0)	24.5 (1.0–38.0)	0.035
Anterior serosal invasion (positive), n (%)	15 (51.7)	24 (30.0)	0.032
Retroperitoneal invasion (positive), n (%)	20 (69.0)	57 (71.3)	0.496
Extrapancreatic nerve plexus invasion (positive), n (%)	7 (24.1)	9 (11.3)	0.088
Portal/Splenic vein invasion (positive), n (%)	4 (13.8)	14 (17.5)	0.445
Lympho-vessel invasion (positive), n (%)	25 (86.2)	51 (63.8)	0.018
Vascular invasion (positive), n (%)	27 (93.1)	55 (68.8)	0.006
Perineural invasion (positive), n (%)	26 (89.7)	59 (73.8)	0.061
Tumor differentiation (Moderately, Poorly)	23 (79.3)	35 (43.8)	0.001
Resected margin status (R1)	2 (6.9)	4 (5.0)	0.507
Adjuvant chemotherapy (Yes), n (%)	19 (65.5)	69 (86.3)	0.018
Completion of adjuvant chemotherapy, n (%)	9 (31.0)	64 (80.0)	< 0.001

ER, early recurrence; CRP, C-reactive protein; mGPS, modified Glasgow prognostic score; CAR, CRP-to-albumin ratio; PNI, prognostic nutritional index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CALLY, CRP-albumin-lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, colorectal cancer antigen.

of postoperative adjuvant chemotherapy was based on the attending physician's discretion; before 2016, gemcitabine-based chemotherapy was introduced following the result of the CONKO-001 trial [25], and since the publication of the JASPAC01 trial results, S-1 therapy has been the mainstay [26].

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS (version 26.0; New York, IBM Corporation). Chi-square and Mann–Whitney U tests were used to analyze categorical and continuous variables, respectively. Overall survival (OS) was analyzed using the Kaplan–Meier method, and statistical significance was evaluated us-

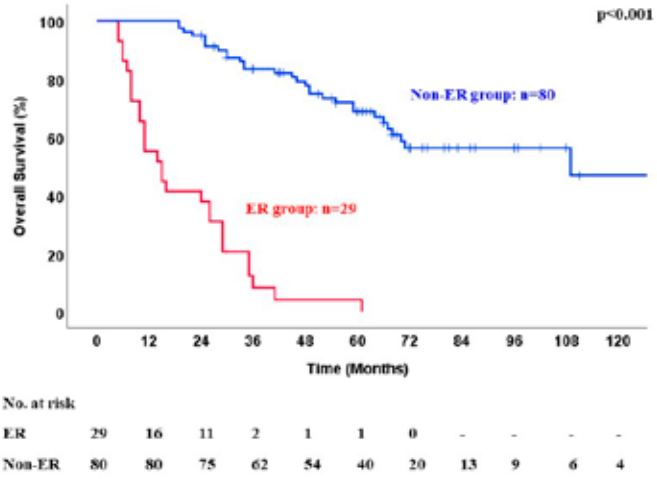

Fig. 2 Comparison of overall survival (OS) between patients with early recurrence (ER) and non-early recurrence (non-ER)

Table 2 Recurrence sites in the ER and non-ER groups

Variables	ER (n = 29)	Non-ER (n = 80)	p-value
Recurrence	29 (100)	38 (47.5)	< 0.001
Local	13 (44.8)	30 (37.5)	0.605
Liver	11 (37.9)	5 (6.3)	0.004
Peritoneum	5 (17.2)	4 (5.0)	0.174
Lung	2 (6.9)	3 (3.8)	0.459
Distant lymph node	3 (10.3)	0	0.051

ER, early recurrence

ing the log-rank test. Univariate and multivariate Cox proportional hazard regression analyses were conducted to identify the risk factors for the early recurrence of UICC stage 1 PDAC. Variables with $p < 0.05$ in univariate analyses were included in the multivariate analysis. Statistical significance was set at $p < 0.05$. The cut-off values for preoperative albumin, CRP, CEA, CA19-9, CAR, PNI, NLR, PLR, LMR, and CALLY index that could predict early recurrence were calculated using receiver operating characteristic (ROC) curves.

RESULTS

Of the 109 patients, 41 were male, and 68 were female, with a median age of 69 years (range: 41–85 years). The median observation period was 49 months (range: 5–159 months). The tumors were located in the pancreatic head in 65 patients and in the pancreatic body and tail in 44. TNM stages 1A and 1B tumors were observed in 44 and 65 patients, respectively. R0 resection was achieved in 103 patients (94.5%). As adjuvant chemotherapy, the patients received S-1 (n = 49, 45.0%), gemcitabine (n = 24, 22.0%), and gemcitabine combined with S-1 (n = 10, 9.2%). In all, 70 patients completed adjuvant chemotherapy (64.2%).

A comparison of the clinicopathological factors between the ER and non-ER groups is shown in Table 1. Preoperative CA19-9 level was significantly higher in the ER group ($p = 0.029$). There were no significant differences in serum bilirubin and preoperative biliary drainage levels. Preoperative peripheral blood tests revealed no significant differences in neutrophil, monocyte, or platelet counts. Lymphocyte counts were significantly lower in the ER group ($p = 0.040$). Preoperative serum albumin ($p = 0.025$) and CRP levels ($p = 0.038$) were significantly lower in the ER group. Regarding IBPS, the PNI ($p = 0.020$) and CALLY index ($p = 0.018$) were significantly lower and CAR was significantly higher ($p = 0.039$) in the ER group. Regarding the perioperative outcomes, the amounts of blood loss were not significantly different, but the number of blood transfusions was significantly higher in the ER group ($p = 0.025$). However, there were no significant differences in operating time or postoperative complications between the two groups. Among the histopathological factors, the values of tumor diameter ($p = 0.035$), anterior serosal invasion ($p = 0.032$), lympho-vessel invasion ($p = 0.018$), and venous invasion ($p = 0.006$) were significantly higher in the ER group; the tumors were often moderately or poorly differentiated ($p = 0.001$) in this group.

In addition, significantly more patients in the ER group failed to complete adjuvant chemotherapy ($p < 0.001$). Of the patients who did not complete chemotherapy, 20 patients relapsed early before completing adjuvant chemotherapy, 11 patients did not receive chemotherapy at the patient's request or physician's discretion, and 5 patients did not continue chemotherapy due to adverse events or poor general condition.

The 1-, 3-, and 5-year survival rates were 88.1%, 63.7%, and 52.0%, respectively, with a median survival duration of 64.0 months (95% confidence interval [CI]: 49.0–79.0). The 1-, 3-, and 5-year recurrence-free

Table 3 Predictive ability of IBPS and tumor markers for early recurrence

Variables	Cut-off value	AUC (95%CI)	Sensitivity (%)	Specificity (%)
Albumin (g/dL)	4.2	0.640 (0.519–0.761)	56.2	66.2
CRP (mg/dL)	0.20	0.619 (0.499–0.740)	59.0	67.5
CAR	0.04	0.625 (0.506–0.745)	59.0	66.8
PNI	49.0	0.647 (0.521–0.773)	65.5	70.0
NLR	2.2	0.579 (0.453–0.704)	62.1	55.0
PLR	135.9	0.604 (0.480–0.717)	58.6	55.0
LMR	5.0	0.578 (0.451–0.704)	51.7	60.0
CALLY index	4.4	0.650 (0.534–0.762)	65.5	64.3
CEA (ng/mL)	3.9	0.575 (0.447–0.703)	58.6	55.0
CA19-9 (U/mL)	58.0	0.644 (0.525–0.762)	72.4	63.7

IBPS, inflammation-based prognostic score; CRP, C-reactive protein; CAR, CRP-to-albumin ratio; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CALLY index, CRP-albumin-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, colorectal cancer antigen

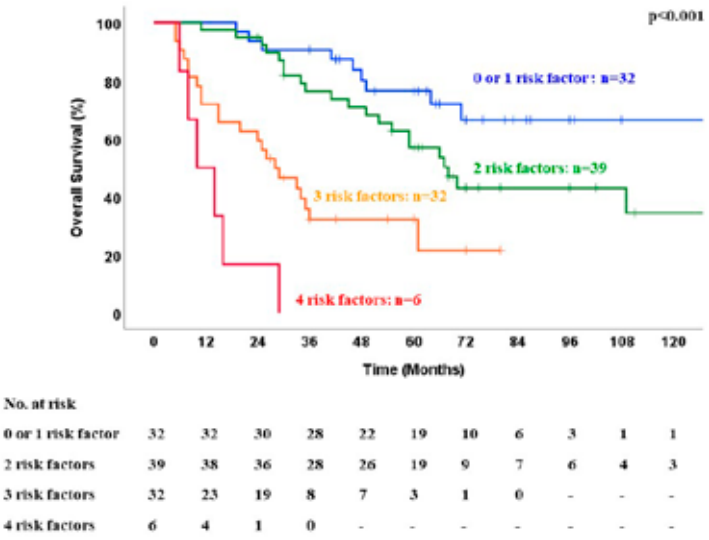

Fig. 3 Comparison of overall survival by number of risk factors for early recurrence of UICC-stage I PDAC
UICC, Union for International Cancer Control; PDAC, pancreatic ductal carcinoma

survival rates were 73.4%, 48.3%, and 38.9%, respectively, with a median recurrence-free survival duration of 36.0 months (95% CI: 17.5–54.5). The 1-, 3-, and 5-year survival rates were 55.2%, 8.3%, and 4.1% in the ER group and 100.0%, 83.4%, and 68.9% in the non-ER group, respectively. The median OS durations of the ER and non-ER groups were 15.0 (95% CI: 8.0–22.0) and 109.0 (95% CI: 91.4–120.9) months, respectively ($p < 0.001$). The patients in the ER group had a significantly poorer prognosis (Fig. 2). When comparing recurrence between the groups, liver metastasis tended to be more common in the ER group ($p = 0.004$). No significant differences were observed in other recurrence sites (Table 2).

The cut-off values for each IBPS within 12 months were calculated using ROC curves. The optimal cut-off points were defined as the points on the ROC curve plotted closest to the point in the upper-left corner. The area under the curve values were 0.640, 0.619, 0.626, 0.647, 0.579, 0.604, 0.578, 0.650, 0.575, and 0.637 for albumin, CRP, CAR, PNI, NLR, PLR, LMR, CALLY index, CEA, and CA19-9, respectively. The optimal cut-off albumin, CRP, CAR, PNI, NLR, PLR, LMR, CALLY index, CEA, and CA19-9 values were 4.2 g/dL, 0.20 mg/dL, 0.04, 49.0, 2.2, 135.9, 5.0, 4.4, 3.9 ng/mL, 58.0 U/mL, respectively (Table 3).

In the univariate analysis, the following factors were significantly associated with early recurrence: preoperative CA19-9 level (> 58.0 U/mL), CAR (> 0.04), PNI (< 49.0), and CALLY index (< 4.4); use of blood transfusion; positive anterior serosal invasion, venous invasion, and lympho-vessel invasion; tumor differentiation (moderately/poorly); absence of postoperative adjuvant chemotherapy; and failure to complete postoperative adjuvant chemotherapy. Multivariate analysis showed that CALLY index (< 4.4) (hazard ratio [HR]: 2.71, 95% CI:1.21–6.02, $p = 0.015$), positive venous invasion (HR: 4.67, 95% CI: 1.10–19.90, $p = 0.037$), tumor differentiation (moderately/poorly) (HR: 5.25, 95% CI: 2.05–13.43, $p = 0.001$), and failure to complete adjuvant chemotherapy (HR: 12.50, 95% CI: 5.30–29.50, $p < 0.001$) were independent risk factors for early recurrence (Table 4). In terms of IBPS, only the preoperative CALLY index was found to be an inde-

Table 4 Risk factors of early recurrence in UICC-stage I PDAC by univariate and multivariate analyses

Factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p-value	HR (95% CI)	p-value
Age (> 69)	1.68 (0.79–3.55)	0.176		
Sex (Female)	1.42 (0.68–2.94)	0.352		
Location (Body and tail)	1.03 (0.49–2.16)	0.938		
Albumin (< 4.2 g/dL)	1.68 (0.77–3.69)	0.196		
CRP (> 0.2 mg/dL)	1.63 (0.76–3.51)	0.210		
mGPS (2)	1.71 (0.41–7.20)	0.464		
CAR (< 0.04)	2.56 (1.22–5.36)	0.013	0.71 (0.15–3.40)	0.672
PNI (< 49.0)	2.73 (1.27–5.88)	0.010	1.87 (0.76–4.59)	0.176
NLR (> 2.2)	1.47 (0.71–3.05)	0.305		
PLR (> 135.9)	1.46 (0.70–3.06)	0.314		
LMR (< 5.0)	1.41 (0.68–2.93)	0.353		
CALLY index (< 4.4)	2.54 (1.18–5.46)	0.017	2.71 (1.21–6.02)	0.015
Total bilirubin (> 2.0 mg/dL)	2.56 (0.77–8.47)	0.125		
Preoperative biliary drainage (Yes)	1.01 (0.47–2.22)	0.970		
CEA (> 3.9 ng/mL)	1.65 (0.79–3.45)	0.186		
CA19-9 (> 58.0 U/mL)	3.73 (1.65–8.44)	0.002	1.53 (0.61–3.85)	0.371
Operation time (> 290 min)	1.61 (0.77–3.34)	0.203		
Blood loss (> 607 mL)	2.13 (0.99–4.57)	0.053		
Blood transfusion (Yes)	2.92 (1.24–6.87)	0.014	1.36 (0.51–3.62)	0.451
Portal vein resection (Yes)	0.48 (0.12–2.05)	0.326		
Clavien–Dindo classification (> 3a)	1.39 (0.67–2.88)	0.376		
Tumor size (> 20 mm)	3.01 (1.23–7.41)	0.016	1.29 (0.41–4.10)	0.661
Anterior serosal invasion (positive)	2.20 (1.06–4.57)	0.034	1.13 (0.41–3.15)	0.811
Retroperitoneal invasion (positive)	0.85 (0.86–4.72)	0.684		
Extrapancreatic nerve plexus invasion (positive)	2.02 (0.86–4.72)	0.107		
Portal vein invasion (positive)	0.77 (0.27–2.20)	0.620		
Lympho-vessel invasion (positive)	3.09 (1.07–8.87)	0.036	2.88 (0.94–8.79)	0.063
Vascular invasion (positive)	4.98 (1.18–20.95)	0.029	4.67 (1.10–19.90)	0.037
Perineural invasion (positive)	2.68 (0.81–8.87)	0.105		
Resection margin status (R1)	1.35 (0.32–5.69)	0.681		
Tumor differentiation (Moderately/Poorly)	4.01 (1.63–9.85)	0.002	5.25 (2.05–13.43)	0.001
Adjuvant chemotherapy (No)	2.91 (1.36–6.22)	0.006	0.65 (0.26–1.68)	0.377
Completion of adjuvant chemotherapy (No)	6.69 (3.03–14.76)	< 0.001	12.50 (5.30–29.50)	< 0.001

HR, hazard ratio; CI, confidence interval; mGPS, modified Glasgow prognostic score; CRP, C-reactive protein; CAR, CRP-to-albumin ratio; PNI, prognostic nutritional index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CALLY, CRP-albumin-lymphocyte; CEA, carcinoembryonic antigen; CA19-9, colorectal cancer antigen

pendent risk factor for early recurrence.

The risk factors for early recurrence identified in this study, consisting of one preoperative factor (CALLY index) and three postoperative factors (positive venous invasion, moderately to poorly differentiated adenocarcinoma, and failure to complete adjuvant chemotherapy) were combined to classify patients into groups with zero or one, two, three, or four risk factors, and the OS durations were compared. The groups with zero or one risk factor did not reach the median survival time, while the median survival times for the groups with two, three, or four risk factors were 68.0 months (95% CI: 54.8–81.2), 28 months (95% CI: 17.6–38.4) and 10 months (95% CI: 2.8–17.2), respectively. The prognosis worsened as the number of risk factors increased ($p < 0.001$) (Fig. 3).

DISCUSSION

In this study, a CALLY index of < 4.4 was the only pretreatment factor identified as a risk factor for early recurrence after radical resection for UICC stage I PDAC. Other risk factors for early recurrence includes positive vascular invasion, moderately or poorly differentiated adenocarcinoma, and failure to complete adjuvant chemotherapy. Patients with a high number of risk factors had poorer prognoses.

In approximately 80% of the PDAC cases, the tumor is unresectable at diagnosis due to locally advanced disease or distant metastasis [27, 28]. However, in recent years, advances in diagnostic imaging, including

contrast-enhanced CT and ultrasound endoscopy and the development of diagnostic tools such as circulating tumor DNA and artificial intelligence-based algorithms have enabled the diagnosis of pancreatic cancer at early stages [29–33]. According to a report published by the Japan Pancreatic Cancer Registry, the 5-year survival rates of patients with UICC stage IA and IB pancreatic cancer were 68.4% and 59.7% [34]. The 5-year survival rate of our study sample was 52.0%, with a median survival time of 64.0 months. These results are relatively favorable in pancreatic cancer, where the 5-year survival rate is still less than 20%. Thus, early PDAC detection and therapeutic interventions are crucial.

However, even patients with early-stage PDAC have a considerable risk of experiencing early postoperative recurrence and poor prognosis. In this study, relapse was reported in 29 patients (26.6%) within 12 months. Early recurrence has been reported to be associated with liver metastases [35, 36], and similarly in this study, liver metastasis was more common in the ER group. Few studies have examined the risk factors for early recurrence and prognostic factors for early-stage PDAC. In previous studies, preoperative NLR, preoperative CA19-9 levels, tumor differentiation grade, resection margin status, and use of adjuvant and neoadjuvant chemotherapy have been reported to predict poor RFS and OS in patients with early-stage PDAC [9–12].

In addition to the clinicopathological factors, we investigated whether preoperative IBPSs were risk factors for early recurrence. The correlation between cancer and inflammation was first reported by Virchow in 1863 [37]. Since then, several markers of cancer, inflammation, host immunity, and nutritional status have been identified. Various IBPSs have been reported to be associated with RFS and OS in patients with PDAC. However, few studies have reported on IBPS and the prognosis of patients with early-stage PDAC. Abe *et al.* reported that a high preoperative NLR (NLR $>$ 2.2) was a poor prognostic factor for both RFS and OS in patients with early-stage pancreatic cancer below stage IIA [9]. However, in the present study, there was no significant difference in the median NLR between the ER and non-ER groups, as some patients in the non-ER group also had high NLR.

The preoperative CALLY index is a new IBPS that was first reported by Iida *et al.* to predict prognosis after the resection of hepatocellular carcinoma (HCC) [20]. Cancer cells produce pro-inflammatory cytokines such as interleukin (IL)-6 and IL-10. CRP is produced in the liver and reflects systemic inflammation. In addition to being an indicator of infection, it has also been reported to be a prognostic marker in some cancers [38]. Albumin reflects the nutritional status of patients with cancer, whereas peripheral blood lymphocyte count reflects their immune status. In other words, the CALLY index is an immunonutritive score that combines the PNI and CRP level. Serum albumin levels and peripheral blood lymphocyte counts are reduced in patients with cancer because of their poor nutritional status and weakened immune system, whereas serum CRP levels are elevated because of an exacerbated inflammatory response. Therefore, as a patient's general condition deteriorates, the CALLY index decreases. The combination of three factors — serum CRP level, serum albumin level, and peripheral blood lymphocyte count — makes this index more reflective of a patient's cancer immunity and nutritional status than the PNI, CAR, and mGPS alone. Its prognostic value in not only HCC but also epithelial ovarian, oral cavity, and colorectal cancers has been reported [39–42]. To the best of our knowledge, this is the first report on the usefulness of the CALLY index as a prognostic factor for PDAC. The CALLY index is a useful predictor of recurrence in early-stage PDAC. However, the present study is a retrospective study of a relatively small number of patients and our results require further validation by prospective studies with patients with diverse backgrounds and treatment protocols.

Perioperative blood transfusion has been reported to be involved in poor prognostic outcomes in several cancers, including PDAC. In the present study, blood transfusion was not an independent poor prognostic factor, but was significantly performed in the ER group. Although the association between blood transfusions and poor prognosis is not yet clear, a number of potential factors have been identified that can have a significant negative impact on the host's immune system in transfusions. These immunomodulatory mediators include: leukocyte-derived mediators, platelet-derived factors, and hemolytic components such as heme and iron. It has been speculated that a patient's inflammatory and immunosuppressive state are likely to influence the immunologic response to blood transfusion [43, 44].

Pre- and postoperative adjuvant chemotherapies have become essential aspects of PDAC treatment in recent years, and many studies have reported their efficacy in improving the prognosis of patients with early-stage PDAC [10–12, 45, 46]. However, it is still unclear which patients will benefit the most from them. Patients at a high risk of early recurrence with a low preoperative CALLY index, as in the present study, require preoperative treatment, including preoperative adjuvant chemotherapy, nutritional management, and immunological intervention. In a prospective study by Tumas *et al.* of 70 patients who had undergone pancreaticoduodenectomy, increased nutritional risk was identified in 22.4%, with 41.4% ultimately diagnosed with cachexia. A high rate of nutritional impairment was identified in a cohort of patients with early-stage pancreatic cancer, including abnormal body composition phenotypes, such as a low lumbar skeletal muscle index. These factors have negative effects on postoperative outcomes [47]. A review article by Gilliland *et al.* on the perioperative nutritional management of patients with pancreatic cancer outlined four points regarding nutritional management strategies: First, patients with albumin $<$ 2.5 mg/dL or weight loss $>$10% should postpone surgery and begin aggressive nutritional supplementation. Second, patients with albumin $<$ 3 mg/dL or weight loss between 5% and 10% should receive nutrition supplementation prior to surgery. Third, postoperative enteral nutrition is the preferred intervention for total parenteral nutrition. Fourth, a multidisciplinary approach should be used for early detection of symptoms of endocrine and exocrine pancreatic insufficiency, along with the implementation of

appropriate treatment to improve the patient's quality of life (QOL) [48]. Kim *et al*. reported that the oral nutritional supplement (ONS) intervention improved the nutritional status of patients with pancreatic carcinoma and cholangiocarcinoma undergoing chemotherapy; after one course of treatment, the body weight, fat-free mass, skeletal muscle mass, body cell mass, and fat mass increased, whereas the patients who did not receive ONS showed a decrease in all indicators [49]. Combining ONS with cancer treatment is important for improving nutritional status and maintaining patients' QOL; this strategy is indispensable in the current era of pre- and postoperative adjuvant chemotherapy for PDAC.

This study had some limitations. First, this was a retrospective, single-center study with a relatively small number of patients. Second, the influence of obstructive jaundice or acute cholangitis on serum albumin and CRP levels before treatment initiation could not be completely excluded. However, in the present study, high serum CRP levels, jaundice, and preoperative biliary drainage had no prognostic impact. It may be beneficial to consider IBPS in cancers of the pancreatic body and tail, which are less susceptible to cholangitis or obstructive jaundice, before starting treatment. Finally, the lack of uniformity in postoperative adjuvant chemotherapy regimens and post-recurrence therapy due to the long research period may have led to a selection bias. Therefore, a multi-institutional prospective study is needed to clarify the clinical impact and optimal treatment strategy for early-stage PDAC.

In conclusion, low preoperative CALLY index was found to be a risk factor for early recurrence in patients with UICC stage I PDAC. Therefore, to improve the prognosis of patients with early-stage PDAC, they should be screened for low preoperative CALLY index before the start of treatment, and preoperative treatment as well as nutritional and immunological support should be provided.

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REFERENCES

1) Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022; 72: 7–33.
2) Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014; 74: 2913–21.
3) Yang J, Xu R, Wang C, Qiu J, Ren B, You L. Early screening and diagnosis strategies of pancreatic cancer: a comprehensive review. Cancer Commun (Lond) 2021; 41: 1257–74.
4) Kanno A, Masamune A, Hanada K, Maguchi H, Shimizu Y, Ueki T, *et al*. Multicenter study of early pancreatic cancer in Japan. Pancreatology 2018; 18: 61–7.
5) Furukawa H, Okada S, Saisho H, Ariyama J, Karasawa E, Nakaizumi A, *et al*. Clinicopathologic features of small pancreatic adenocarcinoma. A collective study. Cancer 1996; 78: 986–90.
6) Ono S, Adachi T, Ohtsuka T, Kimura R, Nishihara K, Watanabe Y, *et al*. Predictive factors for early recurrence after pancreaticoduodenectomy in patients with resectable pancreatic head cancer: A multicenter retrospective study. Surgery 2022; 172: 1782–90.
7) Matsumoto I, Murakami Y, Shinzeki M, Asari S, Goto T, Tani M, *et al*. Proposed preoperative risk factors for early recurrence in patients with resectable pancreatic ductal adenocarcinoma after surgical resection: A multi-center retrospective study. Pancreatology 2015; 15: 674–80.
8) Nishio K, Kimura K, Amano R, Yamazoe S, Ohrira G, Nakata B, *et al*. Preoperative predictors for early recurrence of resectable pancreatic cancer. World J Surg Oncol 2017; 15: 16.
9) Abe T, Amano H, Kobayashi T, Hanada K, Nakahara M, Ohdan H, *et al*. Preoperative neutrophil-to-lymphocyte ratio as a prognosticator in early stage pancreatic ductal adenocarcinoma. Eur J Surg Oncol 2018; 44: 1573–9.
10) Hamura R, Haruki K, Fujiwara Y, Tsunematsu M, Shirai Y, Furukawa K, *et al*. The effectiveness of adjuvant chemotherapy for stage I pancreatic cancer based on the UICC, 8th ed. Langenbecks Arch Surg 2022; 407: 3437–46.
11) Guenther M, Boeck S, Heinemann V, Werner J, Engel J, Ormanns S. The impact of adjuvant therapy on outcome in UICC stage I pancreatic cancer. Int J Cancer 2022; 151: 914–9.
12) Vega EA, Kutlu OC, Salehi O, James D, Alarcon SV, Herrick B, *et al*. Preoperative chemotherapy for pancreatic cancer improves survival and R0 rate even in early stage I. J Gastrointest Surg 2020; 24: 2409–15.
13) Kobayashi S, Karube Y, Matsumura Y, Nishihira M, Inoue T, Araki O, *et al*. Inflammatory risk factors for early recurrence of non-small cell lung cancer within one year following curative resection. World J Surg 2020; 44: 3510–21.
14) Njoku K, Ramchander NC, Wan YL, Barr CE, Crosbie EJ. Pretreatment inflammatory parameters predict survival from endometrial cancer: A prospective database analysis. Gynecol Oncol 2022; 64: 146–53.
15) Cantiello F, Russo GI, Vartolomei MD, Farhan ARA, Terracciano D, Musi G, *et al*. Systemic inflammatory markers and oncologic outcomes in patients with high-risk non-muscle-invasive urothelial bladder cancer. Eur Urol Oncol 2018; 1: 403–10.
16) Itoh S, Tsujita E, Fukuzawa K, Sugimachi K, Iguchi T, Ninomiya M, *et al*. Prognostic significance of preoperative PNI and CA19-9 for pancreatic ductal adenocarcinoma: A multi-institutional retrospective study. Pancreatology 2021; 21: 1356–63.
17) Liu Z, Jin K, Guo M, Long J, Liu L, Liu C, *et al*. Prognostic value of the CRP/Alb ratio, a novel inflammation-based score in pancreatic cancer. Ann Surg Oncol 2017; 24: 561–8.
18) McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc 2008; 67: 257–62.
19) McMillan DC. The systemic inflammation-based Glasgow prognostic score: a decade of experience in patients with cancer. Cancer Treat Rev 2013; 39: 534–40.
20) Iida H, Tani M, Komeda K, Nomi T, Matsushima H, Tanaka S, *et al*. Superiority of CRP-albumin-lymphocyte index (CALLY index) as a non-invasive prognostic biomarker after hepatectomy for hepatocellular carcinoma. HPB (Oxford) 2022; 24: 101–15.
21) Brierly JD, Gospodarowicz MK, Wittekind C. UICC TMN Classification of Malignant Tumors, 8th ed, Wiley, Hoboken New Jersey -Blackwell, 2016.
22) Tempero MA, Malafa MP, Al-Hawary M, Behrman SW, Benson AB, Cardin DB, *et al*. Pancreatic adenocarcinoma, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021; 19: 439–57.
23) Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, *et al*. The Clavien-dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250: 187–96.
24) Oyama K, Oba M, Oshima Y, Shimada H. Predicting short-term life expectancy of patients with end-stage gastric cancer using Onodera's prognostic nutritional index. Int J Clin Oncol 2021; 26: 364–9.
25) Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, *et al*. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 2013; 310: 1473–81.
26) Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, *et al*. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet 2016; 388: 248–57.
27) Zuckerman DS, Ryan DP. Adjuvant therapy for pancreatic can-

cer: a review. Cancer 2008; 112: 243–9.
28) Barugola G, Partelli S, Marcucci S, Sartori N, Capelli P, Bassi C, *et al*. Resectable pancreatic cancer: who really benefits from resection? Ann Surg Oncol 2009; 16: 3316–22.
29) Kikuyama M, Kamisawa T, Kuruma S, Chiba K, Kawaguchi S, Terada S, *et al*. Early diagnosis to improve the poor prognosis of pancreatic cancer. Cancers 2018; 10: 48.
30) Takeshita K, Kutomi K, Haruyama T, Watanabe A, Furui S, Fukushima J, *et al*. Imaging of early pancreatic cancer on multidetector roe helical computed tomography. Br J Radiol 2010; 83: 523–30.
31) Yamashita Y, Tanioka K, Kawaji Y, Tamura T, Nuta J, Hatamaru K, *et al*. Utility of contrast-enhanced harmonic endoscopic ultrasonography for early diagnosis of small pancreatic cancer. Diagnostics (Basel) 2020; 10: 23.
32) Gao Y, Zhu Y, Yuan Z. Circulating tumor cells and circulating tumor DNA provide new insights into pancreatic cancer. Int J Med Sci 2016; 13: 902–13.
33) Kenner B, Chari ST, Kelsen D, Klimstra DS, Pandol SJ, Rosenthal M, *et al*. Artificial intelligence and early detection of pancreatic cancer: 2020 summative review. Pancreas 2021; 50: 251–79.
34) Egawa S, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, *et al*. Japan Pancreatic Cancer Registry; 30th year anniversary: Japan Pancreas Society. Pancreas 2012; 41: 985–92.
35) Groot VP, Rezaee N, Wu W, Cameron JL, Fishman EK, Hruban RH, *et al*. Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg 2018; 267: 936–45.
36) Sahin IH, Elias H, Chou JF, Capanu M, O'Reilly EM. Pancreatic adenocarcinoma: insights into patterns of recurrence and disease behavior. BMC Cancer 2018; 18: 769.
37) Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420: 860–7.
38) Macciò A, Madeddu C, Gramignano G, Mulas C, Tanca L, Cherchi MC, *et al*. The role of inflammation, iron, and nutritional status in cancer-related anemia: result of a large, prospective, observational study. Haematologica 2015; 100: 124–32.
39) Müller L, Hahn F, Mähringer-Kunz A, Stoehr F, Gairing SJ, Michel M, *et al*. Immunonutritive scoring for patients with hepatocellular carcinoma undergoing transarterial chemoembolization: evaluation of the CALLY index. Cancers 2021; 13: 5018.
40) Wang W, Gu J, Liu Y, Liu X, Jiang L, Wu C, *et al*. Pretreatment CRP-albumin-lymphocyte index (CALLY index) as a prognostic biomarker of survival in patients with epithelial ovarian cancer. Cancer Manag Res 2022; 14: 2803–12.
41) Tsai YT, Ko CA, Chen HC, Hsu CM, Lai CH, Lee YC, *et al*. Prognostic value of CRP-Albumin-Lymphocyte (CALLY) index in patients undergoing surgery for oral cavity cancer. J Cancer 2022; 13: 3000–12.
42) Yang M, Lin SQ, Liu XY, Tang M, Hu CL, Wang ZW, *et al*. Association between C-reactive protein-albumin-lymphocyte (CALLY) index and overall survival in patients with colorectal cancer: from the investigation on nutrition status and clinical outcome of common cancers study. Front Immunol 2023; 14: 1131496.
43) Kanda T, Wakiya T, Ishido K, Kimura N, Nagase H, Kubota S, *et al*. Intraoperative allogeneic red blood cell transfusion negatively influences prognosis after radical surgery for pancreatic cancer: A propensity score matching analysis. Pancreas 2021; 50: 1314–1325.
44) Mavros MN, Xu L, Maqsood H, Gani F, Ejaz A, Spolverato G, *et al*. Perioperative Blood transfusion and the prognosis of pancreatic cancer surgery: Systematic review and Meta-analysis. Ann Surg Oncol 2015; 22:4382–91.
45) Turner KM, Delman AM, Ammann AM, Sohal D, Olowokure O, Choe KA, *et al*. Is there a benefit to adjuvant chemotherapy in resected, early stage pancreatic ductal adenocarcinoma? Ann Surg Oncol 2022; 29: 4610–19.
46) Narayanan S, AlMasri S, Zenati M, Nassour I, Chopra A, Rieser C, *et al*. Predictors of early recurrence following neoadjuvant chemotherapy and surgical resection for localized pancreatic adenocarcinoma. J Surg Oncol 2021; 124: 308–16.
47) Tumas J, Tumiene B, Jurkeviciene J, Jasiunas E, Sileikis A. Nutritional and immune impairments and their effects on outcomes in early pancreatic cancer patients undergoing pancreatoduodenectomy. Clin Nutr 2020; 39: 3385–94.
48) Gilliland TM, Villafane-Ferriol N, Shah KP, Shah RM, Tran Cao HS, Massarweh NN, *et al*. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. Nutrients 2017; 9: 243.
49) Kim SH, Lee SM, Jeung HC, Lee IJ, Park JS, Song M, *et al*. The effect of nutrition intervention with oral nutritional supplements on pancreatic and bile duct cancer patients undergoing chemotherapy. Nutrients 2019; 11: 1145.