A new prognostic scoring system using factors available preoperatively to predict survival after operative resection of perihilar cholangiocarcinoma

Hiroki Saito, MD, Takehiro Noji,MD, Ph.D Keisuke Okamura, MD, Ph.D Takahiro Tsuchikawa, MD, Ph.D Toshiaki Shichinohe, MD, Ph.D and Satoshi Hirano, MD. Ph.D

Department of Gastroenterological Surgery II, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

Corresponding author and reprints requested to

Takehiro Noji, M.D, Ph.D

Department of Gastroenterological Surgery II, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan.

Tel: +81-11-706-7714, fax: +81-11-706-7158

E-mail: drnoji@med.hokudai.ac.jp

Abstract

Background

Perihilar cholangiocarcinoma has one of the poorest prognoses of all cancers. However, mortality and morbidity rates after surgical resection are 0–15% and 14–66%, respectively, Additionally, the 5-year overall survival rates reported 22–40%. These findings indicate that only selected patients could achieve satisfactory beneficial effects from surgical treatment. This retrospective study sought to investigate preoperatively available prognostic factors and establish a new preoperative staging system to predict survival after major hepatectomy of perihilar cholangiocarcinoma.

Patients and methods

One hundred and twenty one consecutive patients who had undergone surgical exploration for perihilar cholangiocarcinoma were evaluated.

Results

Univariate and multivariate analysis using the identified preoperative factors revealed that four factors (Platelet-lymphocyte ratio (PLR)>150, serum C-reactive protein (CRP) levels >0.5 mg/dL, albumin levels <3.5 g/dL and carcinoembryonic antigen (CEA) levels>7.0 ng/mL) were independent prognostic factors of postoperative survival. The four preoperative factors, PLR>150, serum CRP levels >0.5 mg/dL, albumin levels <3.5 g/dL and

CEA levels>7.0 ng/mL, were allocated 1 point each. The total score was defined as the Preoperative Prognostic Score (PPS). Patients with a PPS 0, 1, 2, or 3/4 had a 5-year survival of 84.3%, 51.3%, 46.4%, and 0% respectively. There were also significant differences in the 5-year survival according to the PPS (0 vs. 1, P=0.013; 2 vs. 3/4, P<0.001). Patients with a total PPS 3/4 had dismal prognosis, with a median survival of 11.3 months.

Conclusion

A new preoperative scoring system employing PLR and serum CRP, albumin and CEA levels could predict postoperative survival resection of perihilar cholangiocarcinoma.

Introduction

Perihilar cholangiocarcinoma has one of the poorest prognoses of all cancers. Surgical resection is the only treatment option to cure perihilar cholangiocarcinoma [1-11]. However, mortality and morbidity rates after surgical resection are 0–15% and 14–66%, respectively, which are rather high compared with other cancers. Five-year overall survival rates reported from high-volume centers ranged at 22 to 40% [1-11]. These findings indicate that only selected patients could achieve satisfactory beneficial effects from surgical treatment. Therefore, it is imperative to establish a judgment standard to select patients who are good candidates for surgical treatment. Although several studies have described prognostic factors and staging systems for classification of biliary cancer, the majority of these factors are only available after surgical resection [1-4, 6-10, 12 , 13] . Many previous reports indicated that nodal metastasis was one of the strongest prognostic factors for survival of perihilar cholangiocarcinoma[8, 14-16] . However, our previous reports showed that, although nodal metastases are representative poor prognostic factors after surgery for perihilar cholangiocarcinoma, their positive predictive value in preoperative imaging study is quite low[17, 18]. Currently, no staging system using preoperatively available factors exists that can predict survival after surgical resection of perihilar cholangiocarcinoma.

Recently, several reports have indicated that the state of the Systemic Inflammatory Response (SIR) provides significant information about the prognoses of a variety of cancers [19-33]. Neutrophil–lymphocyte ratio (NLR), which reflects SIR, has been reported as a prognostic factor in gastrointestinal cancers, including intrahepatic cholangiocarcinoma [19] and colorectal cancer[20]. Platelet–lymphocyte ratio (PLR) has also been described as a prognostic factor for pancreatic cancer [21]. In perihilar cholangiocarcinoma, SIR could be a useful and preoperatively available prognostic factor to select candidates likely to benefit from surgery [34].

In the present study, we sought to investigate prognostic, clinical, hematological, surgical, and pathological factors of perihilar cholangiocarcinoma, and establish a new staging system using the newly identified and preoperatively available factors to predict survival after major hepatectomy.

Methods

Patients

This study was a retrospective analysis of a prospective database compiled by the Department of Gastroenterological Surgery II at Hokkaido University Hospital. The study protocol received Institutional Review Board approval. All participants provided their written

informed consent before treatment. Between July 1999 and October 2009, 131 consecutive patients, who had undergone surgical exploration for perihilar cholangiocarcinoma, were identified from a prospective database maintained by the department. Ten patients did not undergo tumor resection because of peritoneal implantation or extensive vascular involvement. The remaining 121 patients underwent resection with curative intent, resulting in a curative resectability rate of 92.4%, and were included in this study.

Patient's characteristics, operative procedure and operative results in this study were shown in Table 1. Tumor location was classified according to the Bismuth-Corlette classification [35]. No definite chemotherapy or radiotherapy was administered before and after surgery. All patients underwent surgical treatment in accordance with the departmental guidelines, which have been reported previously [1]. Using univariate and multivariate analyses, we investigated a wide range of clinical, hematological, surgical, and pathological factors to identify independent prognostic factors that were available preoperatively. In regards to NLR and PLR, univariate and multivariate analysis was performed for 115 patients, because six of one hundred and twenty patients missed preoperative lymphocyte counts. Then, a prognostic scoring system was established using the identified preoperatively available factors. Tumor markers were measured at the time of the preoperative hospital admission. Complete blood counts and serum CRP level were obtained after biliary drainage when

patients were afebrile and without signs of infection such as cholangitis, pneumonia, or urinary tract infection. Where more than one result was available in a factor, the results obtained closest to the date of surgery were used for analysis, on average taken 7 (range, 1–30) days before surgery. Cut-off values for each factor were selected on the basis of the maximum significant differences for survival. Preoperative biliary drainage was performed either at an outside hospital or at our institution.

Operative Procedures

According to the Bismuth-Corlette classification tumor distribution in types I, II, IIIA, IIIB, and IV was 21, 39, 21, 25, and 15 patients, respectively[35]. Hemihepatectomy with caudate lobectomy and bile duct resection were performed in all 121 patients: right hepatectomy in 77 patients and left hepatectomy in 44 patients. In 25 patients, pancreatoduodenectomy was concomitantly performed. Combined vascular resection was performed in 72 patients, including portal vein resection in 57 patients, hepatic artery resection in four patients, and both procedures in 11 patients. Operative time ranged from 426 to 1023 minutes, with a median of 639 minutes. Blood loss ranged from 515 to 8590 mL, with median of 1670 mL: red blood cell transfusion, ranging from 2 to 16 units, was required in 30 patients with a median of 5 units transfused.

Morbidity and mortality

The Clavien-Dindo classification was used for defining morbidity and mortality. Patients with postoperative complications classified as IIIa or greater in the Clavien-Dindo classification were considered as having morbidity [36].

Statistical Analysis

Statistical calculations were performed using Stat View-J 5.0 statistical software (SAS Institute, Cary, NC) and “Exact Test” produced by Prof. S. Aoki (http://aoki2.si.gunma-u.ac.jp/exact/exact.html). Results are expressed as medians. The $\chi^2$and Fisher exact probability were used where appropriate. Cumulative disease-specific survival after surgery was calculated by Kaplan- Meier method with a census date of December 2014. The log-rank test was used to compare cumulative disease-specific survival. Cox proportional hazard modeling was used for multivariate analysis. A $P<0.05$ were considered statistically significant.

Results

Pathologic Findings

Histopathologic tumor grade was determined according to the 7th International Union Against Cancer (UICC) staging system [13]. Well-differentiated carcinoma (G1) was present in 41 patients, moderately differentiated carcinoma (G2) in 64 patients, and poorly differentiated carcinoma (G3) in 16 patients. T1, T2, T3, and T4 tumors were observed in 12, 48, 32, and 29 patients, respectively. Stage I, II, IIIa, IIIb, IVa and IVb tumors were noted in 11, 38, 12, 22, 35 and 3 patient, respectively. The estimated 5-year overall survival rates for patients with Stage I, II, IIIa, IIIb and IVa/b were 77.8%, 74.5%, 63.6%, 31.4% and 27.2%, respectively. There were no differences in survival rates among patients based on their UICC stage (Figure 1.). Perineural invasion and lymph node metastasis were identified in 100 and 44 patients, respectively. Histologic invasion of the hepatic artery or the portal trunk and its major branches were seen in 9 and 43 patients, respectively. Detailed examination using serial longitudinal sections revealed 18 positive ductal margins (14.9%) containing carcinoma *in situ* and invasive cancer in 11 and 7 patients, respectively. Positive separation margins were identified in six patients. Accordingly, R0 resection was achieved in 98 patients (81.0%).

Postoperative Results and Prognostic Factors

In-hospital mortality was 4.1% (5 patients), all cases were secondary to postoperative liver failure. The 30-day mortality was 0.83% (1 patient). The 90-day mortality was 6.6% (8 patients). Postoperative complications developed in 49 patients (40.5%). The 5-year survival rate and median survival time were 44.1% and 48.2 months for all patients after resection in comparison with 47.5% and 49.5 months for the 98 patients who underwent R0 resection.

Univariate analysis using preoperative factors showed that serum carcinoembryonic antigen (CEA) levels, CA19-9 levels, albumin levels, CRP levels, PLR, and portal vein embolism were significant clinical prognostic factors. Univariate analysis using histological factors also indicated that T category, N category, perineural invasion, portal vein invasion, and surgical margins were significant prognostic factors (Table 2).

Next we performed a multivariate analysis using the six significant preoperative factors and six significant histological factors identified by univariate analysis. Multivariate analysis of the preoperative factors showed that four factors were independent prognostic factors of postoperative survival, as shown in Table 3: preoperative serum CEA levels >7.0 ng/mL (HR, 5.033; 95% CI: 2.273-11.14; P<0.001), preoperative serum albumin levels <3.5 g/dL (HR, 2.264; 95% CI: 1.140-4.497; P=0.020), preoperative serum CRP levels >0.5 mg/dL

(HR, 3.294; 95% CI: 1.799-6.032; P<0.001), and preoperative PLR >150 (HR, 2.207; 95% CI: 1.200-4.060; P=0.011). And multivariate analysis in histological factors revealed that three factors were independent prognostic factors of postoperative survival, as shown in Table 3: N category (positive) (HR, 2.908; 95%CI: 1.609–5.258; P<0.001), portal vein invasion (positive) (HR, 2.339; 95%CI: 1.114–4.912: P=0.025), and surgical margin (positive) (HR, 2.314; 95%CI: 1.099–4.872: P=0.027).

Association between PLR and Prognostic Factors

Among histopathologic factors, histopathologic grade (G2 or G3), T factor (T3 or T4), and N category had correlation with PLR (Table 4). Because six patients missed preoperative lymphocyte counts, we performed further investigation on 115 patients.

Preoperative Prognostic Scoring

One point was allocated to each preoperative factor: serum CEA levels>7.0 ng/mL, albumin <3.5 g/dL, CRP >0.5 mg/dL, and PLR >150. The total score was defined as the Preoperative Prognostic Score (PPS) (Table 5).

Figure 2a. showed that patients with PPS of 0, 1, 2, and 3/4 had a 5-year survival of 84.3%, 51.3%, 46.4% and 0% respectively. There were also significant differences of 5-year

survival according to the PPS (0 vs. 1, P=0.013; 2 vs. 3/4, P<0.001). Patients with PPS of 3/4 had a dismal prognosis; with a median survival of 11.3 months. For the reason of death of sixteen patients with PPS 3/4, eleven patients were because of tumor recurrence. Five patients were multiple liver metastases. Three patients were peritoneal recurrence. One patient was peritoneal recurrence and liver metastasis. One patient was bone metastasis and carcinomatous lymphangiosis. One patient was lymph node recurrence of hepatic hilum. Other three patients were postoperative complications. Two patients died with liver failure and one died with the rapture of false aneurism of gastroduodenal artery. Other two patients were gastrointestinal bleeding and interstitial pneumonia. Furthermore, we indicated overall survival (Figure 2b.) and disease-free survival (Figure 2c.).

Discussion

This study identified four independent factors that can be measured in the preoperative period and that could predict the prognosis of perihilar cholangiocarcinoma. Using a new preoperative scoring system employing PLR and serum CRP and albumin and CEA levels, we were able to predict survival after major hepatectomy and bile duct resection of perihilar cholangiocarcinoma. Additionally, we showed that the score correlated with the histological lymph node status, although the preoperative prediction of nodal metastasis would still be

difficult.

Several biomarkers have been used to aid in the diagnosis of cholangiocarcinoma. For perihilar cholangiocarcinoma, Juntermanns et al. reported that the preoperative serum CEA level was correlated with the tumor stage and its unresectability, and could help determine patient prognosis [37]. Some reports have suggested that the serum CEA level is an independent prognostic factor for intrahepatic cholangiocarcinoma [38-40]. Nevertheless, there are no previous reports indicating that the preoperative serum CEA level serves as an independent prognostic factor for survival.

Recently, many papers reported that SIR (NLR and PLR) is associated with the prognosis for a variety of cancers. In general, SIR reflects a local and systematic chronic inflammation, which could be caused by various types of malignancies. Riesco et al. initially reported the relationships between SIR and blood lymphocyte, monocyte, and platelet counts [22]. The Glasgow prognostic score, reported by Forrest et al. for non-small-cell lung cancer, is widely known as an indicator of SIR [23]. The gastrointestinal cancers also associated with SIR: intrahepatic cholangiocarcinoma, colorectal cancer, liver metastases of colon cancer origin, and hepatocellular cancer [19, 20, 24-26, 41]. However, only a few reports were available on perihilar cholangiocarcinoma [34, 42].

The relationship between invasive cancer and SIR is explained as follows: invasive

cancer causes tissue damage adjacent to the tumor, resulting in both a local and systemic chronic inflammatory response. Inflammation results in the release of both proinflammatory and inhibitory immunologic mediators. Interleukin (IL)-10 and transforming growth factor-β are the most important inhibitory cytokines, which can cause depressed lymphocyte function and reduced circulating lymphocyte count [27]. Lymphocytopenia is associated with other gastrointestinal malignancies, including colorectal and gastric cancer [28]. Megakaryocyte proliferation is promoted by a number of proinflammatory cytokines, including IL-1, IL-3, and IL-6, which are known to cause thrombocytosis [29, 30]. Increased platelet count is also associated with several other malignancies of the digestive system, including colorectal, gastric, esophageal, and pancreatic cancer [31-33]. Thrombocytosis and lymphocytopenia both correlate with the degree of host systemic inflammation, and the PLR is a novel marker incorporating both hematologic indices.

The CRP belongs to the family of acute phase proteins. Serum CRP level has also been thought of as a kind of SIR. It is upregulated by cytokines, such as IL-8, IL-6, and tumor necrosis factor α. In vitro studies have identified IL-6 as an autocrine growth factor of cholangiocarcinoma cell lines. In these cells, IL-6 induces the expression of the anti-apoptotic protein Mcl-1 [43-45]. Moreover, IL-6 was found to be markedly elevated in the serum of patients with cholangiocarcinoma. Remarkably, its levels dropped sharply after

resection [46]. Thus, a high CRP level might reflect an increased IL-6 level in patients with advanced cholangiocarcinoma. Increased serum CRP levels are also associated with shorter survival in patients with other malignancies of the digestive system, including perihilar cholangiocarcinoma [47].

To the best of our knowledge, only two previous reports evaluated NLR in perihilar cholangiocarcinoma [34, 42]. Only one of the previous report identified NLR as an independent prognostic factor for disease-free survival [34]. However, these two reports showed that NLR was not an independent prognostic factor in survival [34, 42]. As far as we know, this report is the first to show that PLR was a significant prognostic factor for survival. The specific reason why PLR and CRP, rather than NLR, were significant prognostic factors of survival was not clear in our study. However, like other gastrointestinal malignancies, SIR would be a significant prognostic factor for perihilar cholangiocarcinoma. Moreover, our data showed that PLR correlated with tumor extent and histopathologic grade in hilar cholangiocarcinoma, suggesting that PLR can reflect the degree of malignancy in this disease. In pancreatic cancer, one previous study reported that preoperative PLR represented a significant independent prognostic index and had prognostic value independent of tumor size and lymph node ratio[8, 14-16].

Previous reports have shown that lymph node metastases are the strongest prognostic

factors for survival in perihilar cholangiocarcinoma [8, 14-16]. Predicting the N category in the preoperative period is a very important topic in perihilar cholangiocarcinoma. Our previous reports, however, indicated that it was difficult to diagnose lymph node metastases in biliary cancer by preoperative computed tomography because even the highest positive predictive value was only 67% [17, 18]. Further, our data showed that patients with PPS 0 had satisfactory survival rates. Patients with PPS 0 should be suitable candidates compared with “surgery first” patients. On the other hand, in patients with PPS 3 and 4, it might be that preoperative chemotherapy should be given as first-line treatment, and then curative resection should be reconsidered if there is sufficient future liver remnant and no oncologically apparent contraindication during a set time period. However, there is no evidence about preoperative chemotherapy for perihilar cholangiocarcinoma.

Our scoring system for perihilar cholangiocarcinoma is simple and inexpensive, and thus, it may provide useful information in deciding the operative indications, in particular for highly advanced cases with such as UICC Stage IIIb and IVa/b. However, our study was limited to 121 the consecutive cases performed only in our institute. The evidence level provided by this retrospective analysis is relatively low. Because of the seldom tumor identity, the 10-year period from July 1999 till October 2009 would be quite long. In the future, a multicenter prospective study design to support our hypothesis should be planed.

Conclusion

A new preoperative scoring system employing PLR and serum CRP, albumin, and CEA levels could predict survival after surgical resection of perihilar cholangiocarcinoma.

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Conflict of interest statement

All authors had no financial or competing interests.

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Figure legends

Figure1. Cumulative disease-specific survival curves for patients who underwent major hepatectomy and bile duct resection according to the 7th International Union Against Cancer (UICC) staging system. There are no differences among the survival curves for each UICC stage.

Figure2a. Cumulative disease-specific survival curves for patients who underwent major hepatectomy and bile duct resection according to the preoperative scoring system.

Patients with Preoperative Prognostic Score (PPS) 0, 1 and 2 had a 5-year survival of 84.3%, 51.3% and 46.4% respectively. There were also significant differences of 5-year survival among PPS (0 vs. 1, $P=0.013$; 2 vs. 3/4, $P<0.001$).

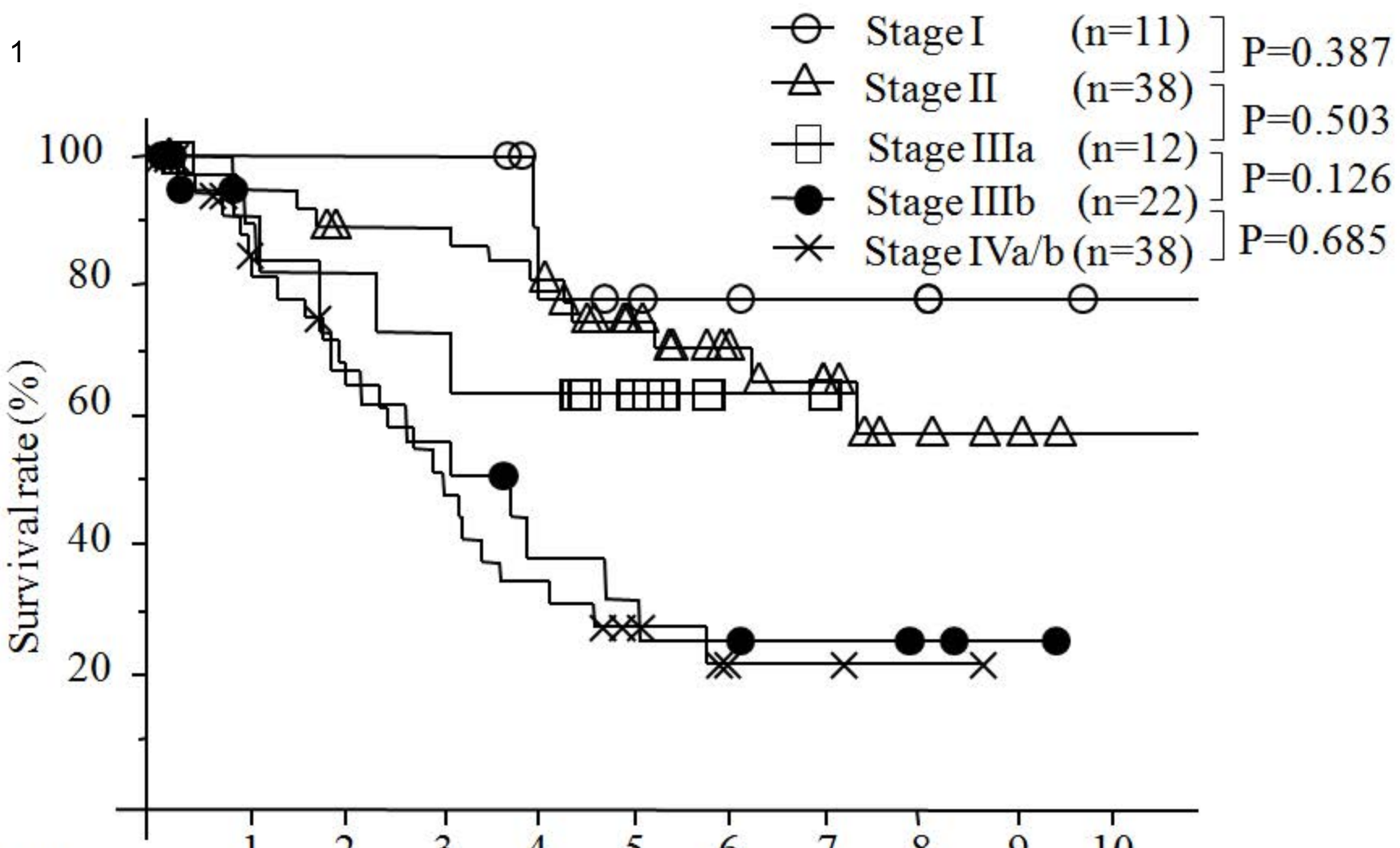
Figure2b. Cumulative overall survival curves for patients who underwent major hepatectomy and bile duct resection according to the preoperative scoring system.

Patients with Preoperative Prognostic Score (PPS) 0, 1 and 2 had a 5-year survival of 75.0%, 44.2% and 38.5% respectively. There were also significant differences of 5-year survival among PPS (2 vs. 3/4, $P<0.001$).

Figure2c. Cumulative disease-free survival curves for patients who underwent major hepatectomy and bile duct resection according to the preoperative scoring system.

Patients with Preoperative Prognostic Score (PPS) 0, 1 and 2 had a 5-year survival of 77.0%, 48.9% and 46.4% respectively. There were also significant differences of 5-year survival among PPS (0 vs. 1, $P=0.043$; 2 vs. 3/4, $P<0.001$).

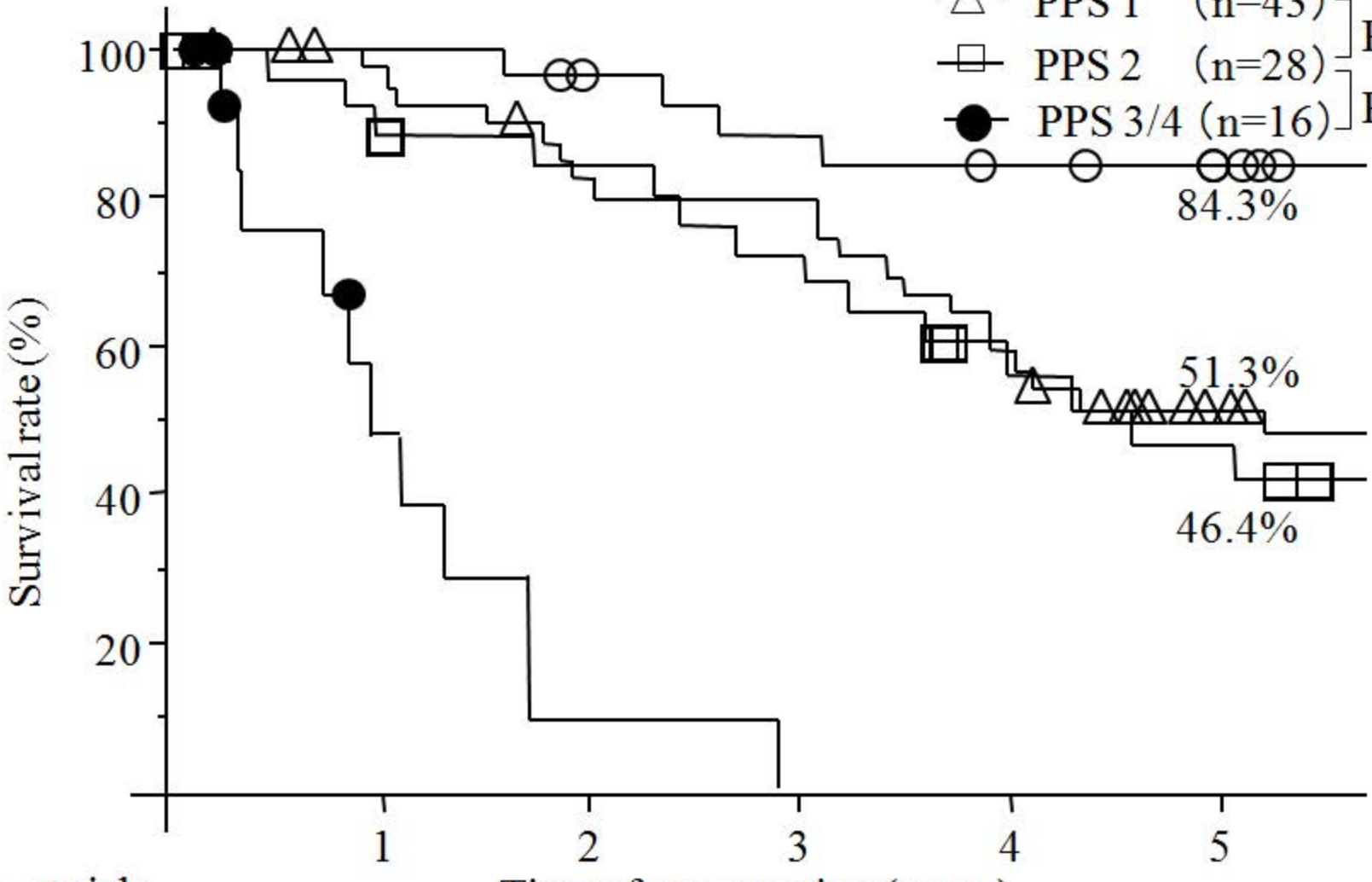
Figure 1



No. at risk

Stage I	11	11	11	6	4	1
Stage II	38	35	31	20	11	1
Stage IIIa	12	10	8	4		
Stage IIIb	22	16	10	5	3	
Stage IVa/b	38	26	15	6	2	

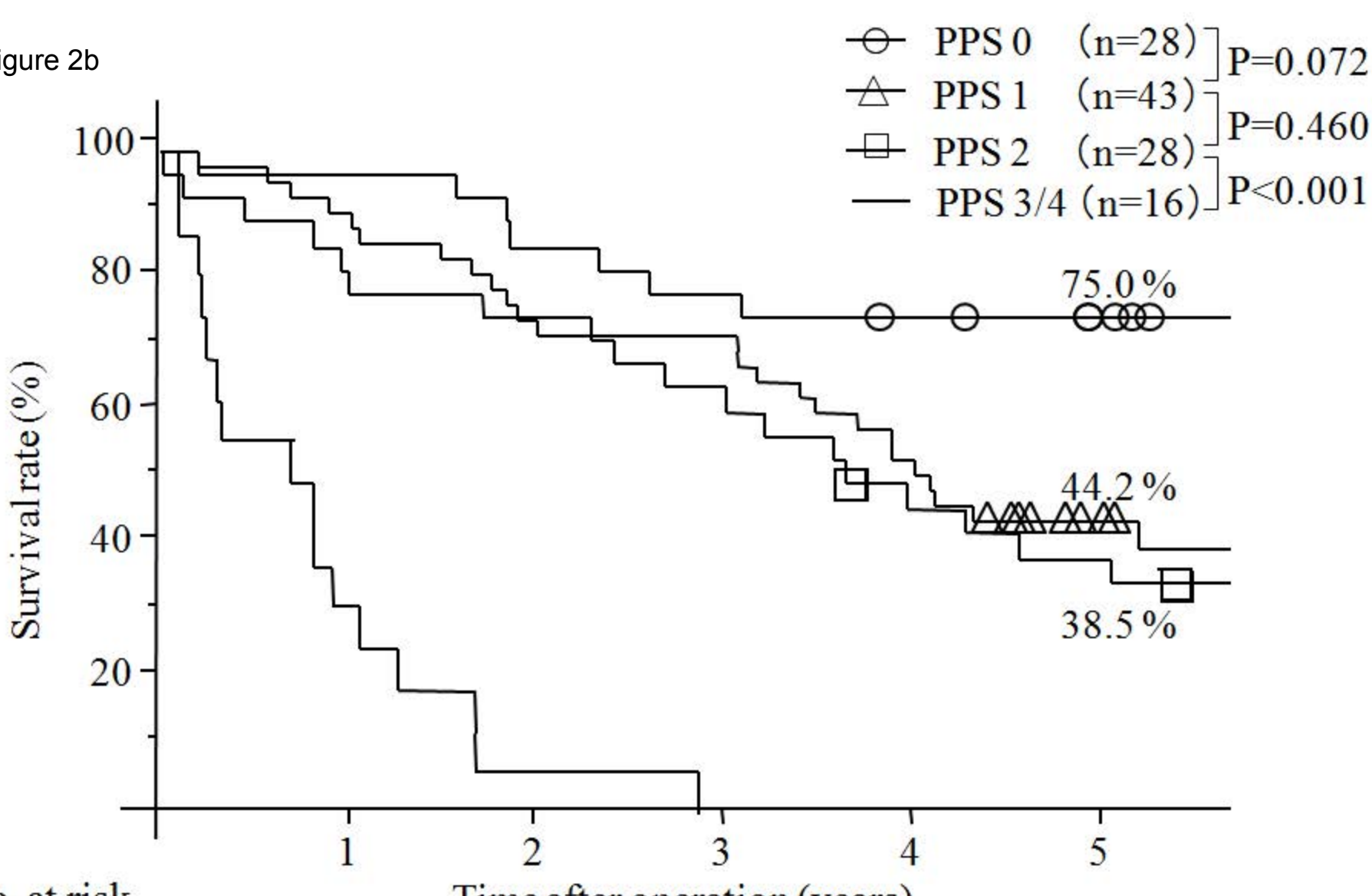
Figure 2a



No. at risk

PPS 0	28	27	24	22	20	17
PPS 1	43	39	32	31	23	13
PPS 2	28	22	21	18	12	10
PPS 3/4	16	5	1			

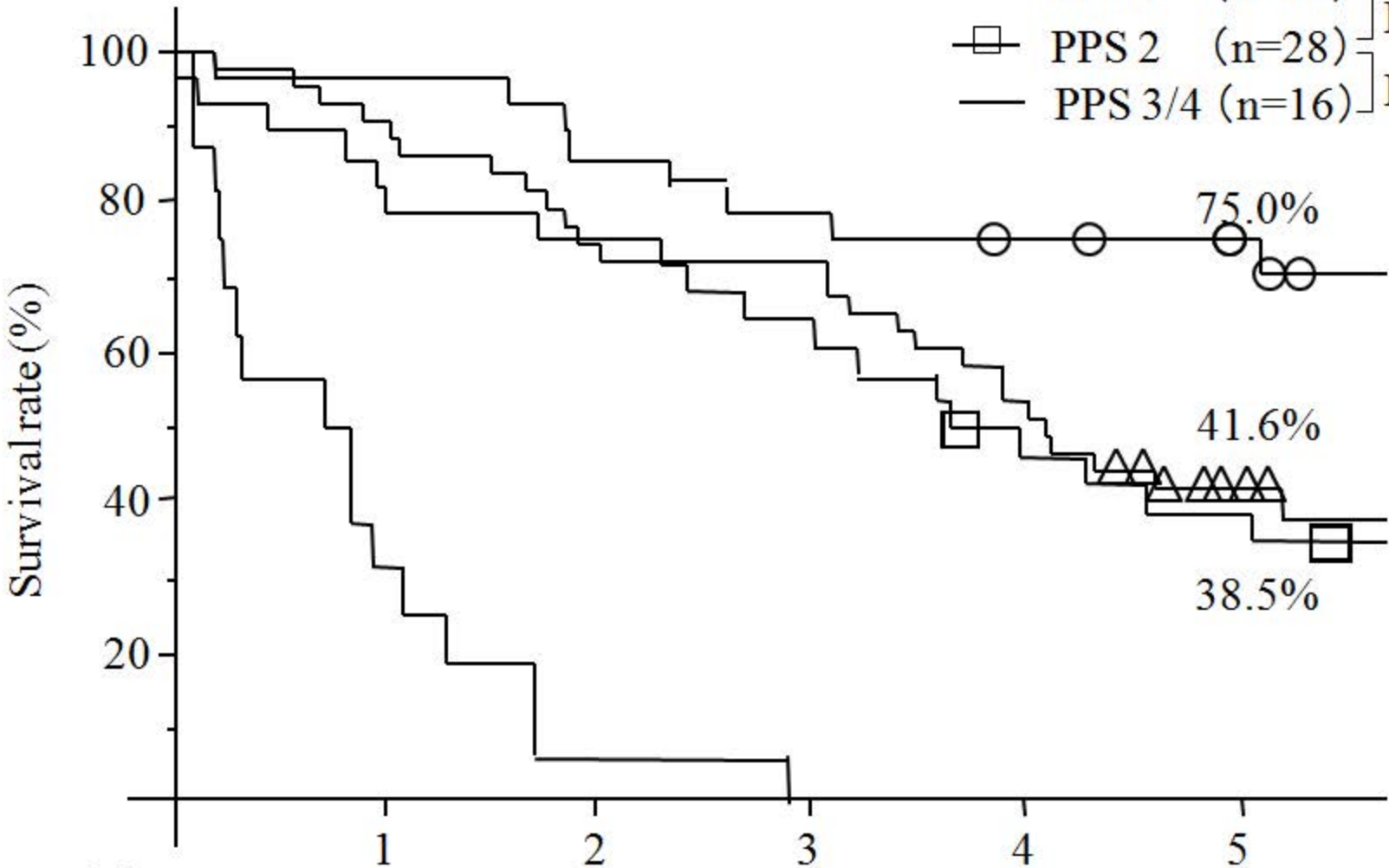
Figure 2b



No. at risk

PPS 0	28	27	24	22	20	17
PPS 1	43	39	32	31	23	13
PPS 2	28	22	21	18	12	10
PPS 3/4	16	5	1			

Figure 2c



No. at risk

PPS 0	28	27	24	22	20	17
PPS 1	43	39	32	31	23	13
PPS 2	28	22	21	18	12	10
PPS 3/4	16	5	1			

Table 1. Patients characteristics

Characteristics	N=121
Patients	
Age(y), median (range)	70 (42-82)
Gender (Male/Female)	88/33
Bismuth classification	
I	21 (17.4 %)
II	39 (32.2 %)
IIIa	21 (17.4 %)
IIIb	25 (20.6 %)
IV	15 (12.4 %)
Biliary drainage	
ENBD	62 (51.3 %)
PTBD	43 (35.5 %)
ENBD and PTBD	7 (5.8 %)
None	9 (7.4 %)
Portal vein embolization	69 (57.0 %)
ICG R15 (%), median (range)	10.2 (2-25.5)
Operative Procedure (Type of hepatectomy)	
Right hemihepatectomy (S1,5,6,7,8)	71 (58.7 %)
Right trisectionectomy (S1,4,5,6,7,8)	6 (5.0 %)
Left hemihepatectomy (S1,2,3,4)	39 (32.2 %)
Left trisectionectomy (S1,2,3,4,5,8)	5 (4.1 %)
Perioperative data	
Operative time (min), median (range)	639 (426-1023)
Blood loss (ml), median (range)	1670 (515-8590)
RBC transfusion performed	30 (24.8 %)
Morbidity (Clavien-Dindo classification≧IIIa)	49 (40.5 %)
Postoperative hospital stay (day), median (range)	38 (11-154)
In-hospital mortality	5 (4.1 %)
Concomitant resection	
Hepatic artery	15 (12.4 %)
Portal vein	68 (56.2 %)
Pancreatoduodenectomy performed	25 (20.7 %)

Residual tumor status	
R0	98 (81.0 %)
R1	23 (19.0 %)
R2	0 (0 %)
UICC (7th, 2009) pathological stage	
I	11 (9.1 %)
II	38 (31.4 %)
IIIA	12 (9.9 %)
IIIB	22 (18.2 %)
IVA	35 (28.9 %)
IVB	3 (2.5 %)
Preoperative treatment	
Chemotherapy	1 (0.83 %)
Radiation	1 (0.83 %)
Chemotherapy and radiation	1 (0.83 %)
Adjuvant therapy	
Done	21 (17.4 %)

ENBD: endoscopic nasobiliary drainage, PTBD: percutaneous transhepatic biliary drainage
ICG15R: indocyanine green retention rate at 15 min, RBC: red blood cell

Table 2. Univariate analysis of clinico-pathological factors affecting disease-specific survival

Factor		No.	3 y (%)	5 y (%)	MST (mo)	P-value
Preoperative Clinical factors						
Age						
	<70	63	76.5	59.2	88.1	0.232
	≥70	58	67.2	46.1	52.0	
Gender						
	Male	88	71.2	55.6	69.2	0.591
	Female	33	74.2	46.6	56.3	
Bismuth type						
	I or II	60	70.1	51.9	62.5	0.520
	III or IV	61	74.0	54.3	69.2	
CEA (ng/mL)						
	≤7.0	107	77.9	56.6	88.1	<0.001*
	>7.0	14	25.2	25.2	20.5	
CA19-9 (U/mL)						
	≤300	104	78.3	57.2	74.6	0.003*
	>300	17	34.4	27.5	27.6	
Albumin (g/dL)						
	<3.5	26	48.2	28.9	34.6	0.003*
	≥3.5	95	77.9	58.9	88.1	
CRP (mg/dL)						
	≤0.5	65	80.0	67.5	NA	<0.001*
	>0.5	56	61.8	34.3	44.6	
NLR						
	≤2.5	66	81.8	57.5	74.6	0.225
	>2.5	49	56.9	46.4	49.3	
PLR						
	≤150	53	85.7	62.4	NA	0.012*
	>150	62	58.3	43.8	49.3	
Biliary drainage						
	PTBD(+)	50	66.7	43.9	49.3	0.194
	PTBD(-)	71	75.5	58.9	88.1	
Portal vein embolism						
	Yes	69	66.5	42.2	46.7	0.036*

No	52	79.1	66.9	NA	
ICG15R %					
≤10	56	67.3	58.6	NA	0.551
>10	65	76.0	49.5	56.3	
Histopathological factors					
Histological grade					
G1	41	81.6	55.8	88.1	0.413
G2 or G3	80	66.7	51.3	60.8	
T category					
T1 or T2	60	86.2	63.6	NA	<0.001*
T3 or T4	61	55.2	40.3	37.1	
N category					
Negative	77	84.2	67.6	NA	<0.001*
Positive	44	49.1	25.6	34.7	
Hepatic invasion					
Yes	57	66.3	48.0	56.3	0.201
No	64	76.6	57.0	88.1	
Perineural invasion					
Yes	100	66.8	47.5	54.8	0.017*
No	21	95.0	77.2	NA	
Portal vein invasion					
Yes	43	51.1	36.1	36.1	0.001*
No	78	82.1	61.1	NA	
Hepatic artery invasion					
Yes	9	66.7	NA	36.1	0.215
No	112	72.3	54.2	69.2	
Surgical margin					
Negative or *in situ*	108	74.9	57.1	74.6	0.004*
Invasive	13	48.6	19.4	28.0	

NA, not available; 3 y, 3-year survival rate; 5 y, 5-year survival rate; *: P<0.05

MST (mo), median survival time (months); CEA, carcinoembryonic antigen

CA19-9, Carbohydrate Antigen 19-9; NLR, neutrophil-lymphocyte ratio;

PLR, platelet-lymphocyte ratio; PTBD, percutaneous transhepatic biliary drainage;

PVE, portal vein embolization; ICG15R, indocyanine green retention rate in 15 minutes.

Table 3. Multivariate analysis of significant factors affecting disease-specific survival

Preoperative factors	Hazard Ratio (95%CI)	P-value
CEA >7.0 ng/mL	5.033 (2.273-11.14)	<0.001*
CA19-9 >300 U/mL	1.000 (0.461-2.166)	0.999
Albumin <3.5 g/dL	2.264 (1.140-4.497)	0.020*
CRP >0.5 mg/dL	3.294 (1.799-6.032)	<0.001*
PLR >150	2.207 (1.200-4.060)	0.011*
Portal vein embolization: Yes	1.782 (0.990-3.503)	0.059
Histopathological factors		
T category (T3 or T4)	1.026 (0.478-2.205)	0.947
N category (Node positive)	2.908 (1.609-5.258)	<0.001*
Perineural invasion (Positive)	0.847 (0.295-2.429)	0.758
Portal vein invasion (Positive)	2.339 (1.114-4.912)	0.025*
Surgical margin (Positive)	2.314 (1.099-4.872)	0.027*

95%CI, 95% confidence interval; *P<0.05.

CEA, carcinoembryonic antigen; CA19-9, Carbohydrate Antigen 19-9;

CRP, C-reactive protein; PLR, platelet-lymphocyte ratio

Table 4. Associations between histopathologic factors and PLR

Factors		N=115	PLR>150	P-value
Histopathologic grade				
	G1	40	15	0.010*
	G2 or G3	75	47	
T category				
	T1 or T2	57	25	0.032*
	T3 or T4	58	37	
N category				
	N0	76	36	0.049*
	N1	39	26	
Hepatic invasion				
	Yes	51	29	0.571
	No	64	33	
Perineural invasion				
	Yes	94	54	0.107
	No	21	8	
Portal vein invasion				
	Yes	38	24	0.162
	No	77	38	
Hepatic artery invasion				
	Yes	7	4	0.860
	No	108	58	

NA, not available; PLR: platelet-lymphocyte ratio. *P<0.05.

Table 5. Prognostic scoring system using preoperatively available factors

Factors		Points Allocated
CEA	≤7.0 ng/mL	0
	>7.0 ng/mL	1
Albumin	≥3.5 g/dL	0
	<3.5 g/dL	1
CRP	≤0.5 mg/dL	0
	>0.5 mg/dL	1
PLR	≤150	0
	>150	1

CEA, carcinoembryonic antigen; CRP: C-reactive protein

PLR, platelet-lymphocyte ratio