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Preoperative Platelet to Albumin Ratio Predicts Outcome of Patients with Cholangiocarcinoma

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Abstract. *Background: The purpose of this study was to evaluate the prognostic index of the preoperative platelet to albumin ratio (PAR) in patients who underwent primary resection for cholangiocarcinoma. Patients and Methods: A total of 59 patients were divided into two groups: those with PAR ≥72.6×10^3 or <72.6×10^3 according to the area under the receiver operating characteristics curve. Results: PAR was significantly inversely associated with overall (OS) and disease-free (DFS) survival on univariate analysis. PAR showed significance on multivariate analysis for OS (hazard ratio=6.232, 95% confidence interval=1.283-30.279, p=0.023), along with tumor differentiation (p=0.009), nodal involvement (p=0.001), intraoperative blood loss (p=0.001), and serum carcinoembryonic antigen (CEA) (p=0.012). High PAR was also significantly associated poor DFS on multivariate analysis (hazard ratio(HR)=4.422, 95% confidence interval(CI)=1.168-16.732, p=0.029), along with tumor differentiation (p=0.009). Conclusion: PAR is a useful prognostic index for OS and DFS in patients with cholangiocarcinoma after primary resection. By accumulating cases prospectively, this new index may be a reference for use before neoadjuvant chemotherapy.*

Cholangiocarcinoma is characterized by tumor aggressiveness with limited choices of curative treatment (1); it has an extremely poor prognosis with a high mortality rate all over the world. Most cases are found to be unresectable as a result of cancer progression. The median survival time (MST) of patients with unresectable cholangiocarcinoma is only 3-6 months (2). In resectable cases, the 5-year overall survival for those with stage 3 cholangiocarcinoma is only 10% (3). Even for margin-negative resection cases, the MST after curative resection is reported to be 46 months (4). Recently, several studies for cholangiocarcinoma, including neoadjuvant or adjuvant chemotherapy, have been published (5, 6). To select an effective therapeutic strategy, accurate preoperative estimation of the prognosis is important. Some reports have emphasized the importance of preoperative platelet count and postoperative prognosis, including cancer-specific mortality (7, 8). Moreover, other reports imply that a low serum albumin level is associated with a poor postoperative outcome (9, 10). Therefore, in order to make an index reflecting both these factors, we analyzed the relation between the platelet to albumin ratio (PAR) and postoperative prognosis. To our best knowledge, this is the first study that has analyzed the significance of PAR for cholangiocarcinoma. In the current study, we evaluated the correlation between long-term postoperative outcomes of the patients with cholangio-carcinoma and PAR.

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Key Words: Cholangiocarcinoma, bile duct neoplasm, prognosis, surgery.

Patients and Methods

Between 2010 and 2014, 60 patients with primary cholangio-carcinoma underwent primary tumor resection. Although this seems a small sample size, this is because of the rarity of this disease and short-term observation due to its poor prognosis.

Depending on tumor localization, we performed hepatic resection for perihilar cholangiocarcimona, and pancreaticoduodenectomy for distal bile duct cancer at Jikei University Hospital, Tokyo, Japan. Of these, there was no case for which hepato-pancreatico-duodenectomy was performed. We conducted a retrospective review of a maintained database of patients who were histologically diagnosed with primary cholangiocarcinoma. Of these, one patient was excluded as having cholangitis after postoperative pathological diagnosis, leaving the remaining 59 cases for this study. This study was approved by the Ethics Committee of Jikei University School of Medicine (approval number: 27-177 (8062)). Our Ethics Committee conforms to the provisions of the Declaration of Helsinki. The detailed pathological factors were based on the seventh edition of the Union for International Cancer Control TNM Classification (11). All excised specimens were diagnosed as adenocarcinoma at the Department of Pathology, Jikei University Hospital, Tokyo, Japan. The laboratory

data were collected shortly before the operation was determined. All patients underwent operation without neoadjuvant chemotherapy.

We investigated the relation between clinicopathological variables and overall (OS) and disease-free (DFS) survival after curative primary resection by univariate and multivariate analyses. Glasgow Prognostic Score (GPS) was determined as previously described (12). The neutrophil to lymphocyte ratio (NLR) (13), platelet to lymphocyte ratio (PLR) (14), prognostic nutrition index (PNI) (15), and C-reactive protein to albumin ratio (CAR) (16) were calculated on the basis of previous studies. PAR was defined as the platelet count divided by serum albumin level as we previously reported for pancreatic cancer (17). The cut-off values of these inflammation-based prognostic scores were classified into two groups for the log-rank test and Cox proportional regression model based on receiver operating characteristic (ROC) curve analysis using 3-year survival. Recurrence of cholangiocarcinoma was defined as a local or distant metastatic tumor that was newly found by ultrasonography, computed tomography, or magnetic resonance imaging with or without an increase in serum carcinoembryonic antigen (CEA).

We analyzed the relationship between clinicopathological variables including inflammation-based prognostic scores and survival after hepatic or pancreatic resection for cholangiocarcinoma by univariate and multivariate analysis of the following 16 factors: tumor stage, differentiation, size, nodal involvement, resection margin status, preoperative biliary drainage, localization of tumor, operative time, intraoperative blood loss, serum CEA, GPS, NLR, PLR, PNI, CAR, and PAR. We also evaluated the relationship between PAR and clinicopathological variables by univariate analysis. In the current study, carbohydrate antigen 19-9 (CA19-9) was not included. Although the serum CA19-9 level was useful for diagnosis or follow-up on recurrence, the level of CA19-9 did not necessarily reflect the prognosis in this study.

For both perihilar and distal cholangiocarcinoma, liver function was Child-Pugh classification A or B.

Statistical analysis. Continuous variables are expressed as the median and interquartile range. Categorical variables are expressed as absolute numbers. Univariate analyses for categorical data were performed using chi-square tests or Fisher's exact test. The area under the ROC curve (AUC) was calculated to determine the cut-off value for each prognostic score. The OS and DFS rates were determined by the Kaplan–Meier method, using Graphpad PRISM ver. 6.07 (GraphPad Software, Inc., La Jolla, CA, USA). Comparisons of OS and DFS were performed using the log-rank test for univariate analysis and the Cox proportional regression model with backward elimination stepwise approach for multivariate analysis, using SPSS 23.0 (IBM Corp., Armonk, NY, USA). *p*-Values were considered statistically significant when less than 0.05.

Results

Patient characteristics. Table I lists patient characteristics. Among the study population, the median age was 69 years (25 to 75 percentile of 62.5-73.5 years), and 42 patients were male. A majority, 67.8% of patients, had stage II or III cholangiocarcinoma. Median OS and DFS after surgery for cholangiocarcinoma with curative intent were 22.8 and 18 months, respectively, and 3-year survival rates were 49.3% and 32.3%, respectively.

Table I. *Patient characteristics (n=59).*

Factor	Median or number	Range (IQR)
Age (years)	69	62.5-73.5
Gender (male:female)	42:17	
Disease-free survival (years)	1.5	0.7-2.0*
Overall survival (years)	1.9	1.3-2.9*
White blood cell count ($\times10^3$/ml)	6.6	5.0-7.9
Neutrophil count ($\times10^3$/ml)	4.1	2.9-5.0
Lymphocyte count ($\times10^3$/ml)	1.5	1.3-2.0
Platelet count ($\times10^3$/ml)	220	188-274
Serum albumin (g/dl)	3.9	3.4-4.2
Serum CRP (mg/l)	0.2	0.1-0.5
Serum CEA (/ml)	46.0	19.5-106.0
PLR	149.4	106.2-191.8
NLR	2.4	1.7-3.8
PNI	46.0	41.3-49.8
CAR	0.05	0.02-0.13
PAR ($\times10^3$)	60.6	44.3-74.5

IQR: Interquartile range; CEA: carcinoembryonic antigen; PLR: platelet to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; GPS: Glasgow prognostic score; PNI: prognostic nutritional index; CAR: CRP to albumin ratio; PAR: platelet to albumin ratio; *95% confidence interval.

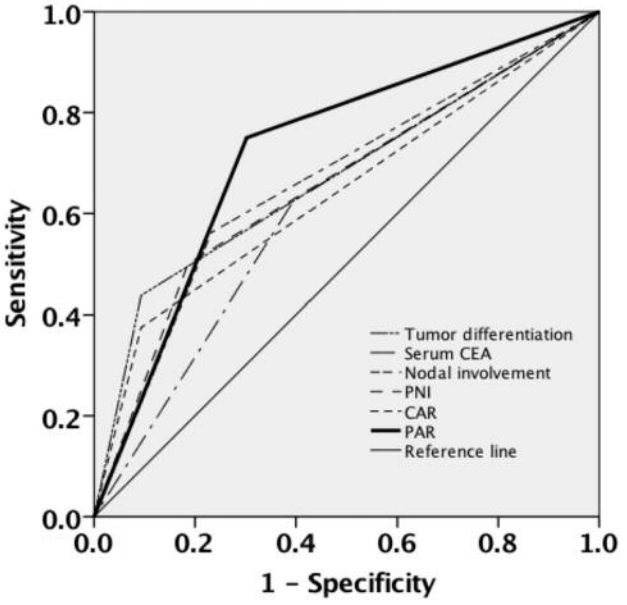

Figure 1. *The receiver operating characteristics (ROC) analysis of study factors. The platelet to albumin ratio (PAR) had the highest area under the curve value (0.709±0.08, p=0.002) compared to other prognostic scores as independent risk factors.*

Relationship between clinical variables and OS. The relationship between clinicopathological variables, including inflammation-based prognostic scores and OS, are shown in Table II. In univariate analysis, significant prognostic factors

Table II. *Univariate and multivariate analysis of clinicopathological variables in relation to overall survival.*

			Univariate analysis		Multivariate analysis	
Factor	Subgroup	N	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Tumor stage	II, III/I	40/19	2.788 (1.057-7.353)	0.038		n.s
Tumor size (mm)	≥30.5/<30.5 mm	41/18	1.878 (0.652-5.410)	0.242		n.s
Tumor differentiation	Poor	11	10.06 (2.394-42.26)	0.002	3.238 (1.349-7.771)	0.009
	Moderate	30	1.596 (0.452-5.635)			
	Well (ref)	18				
Nodal involvement	Positive/negative	19/40	3.498 (1.134-10.79)	0.029		0.001
Resection margin status	Positive/negative	13/46	1.535 (0.485-4.856)	0.466		n.s
Preoperative biliary drainage	Positive/negative	16/43	1.218 (0.410-3.621)	0.723		n.s
Tumor localization	Extrahepatic/intrahepatic	35/24	1.772 (0.677-4.638)	0.244		n.s
Operative tme	≥427/<427 min	47/12	2.869 (0.962-8.561)	0.059		n.s
Intraoperative blood loss	≥845/<845 ml	30/29	2.664 (1.001-7.091)	0.049	1.001 (1.000-1.002)	0.001
Serum CEA	≥3.25/<3.25 U/ml	27/32	2.846 (1.094-7.406)	0.032	6.051 (1.484-24.669)	0.012
GPS	1, 2/0	11/48	2.943 (0.787-11.01)	0.109		n.s
NLR	≥5.41/<5.41	5/54	1.427 (0.542-3.760)	0.471		n.s
PLR	≥134/<134	38/21	1.495 (0.559-3.996)	0.423		n.s
PNI	≥43/<43	42/17	0.282 (0.092-0.858)	0.026		n.s
CAR	≥0.061/<0.061	31/28	2.836 (1.070-7.516)	0.036		n.s
PAR	$\geq 72.6\times10^3/<72.6\times10^3$	16/43	3.534 (1.160-10.77)	0.026	6.232 (1.283-30.279)	0.023

CI: Confidence interval; extrahepatic: perihilar and distal bile duct carcinoma; intrahepatic: intrahepatic cholangiocarcinoma, cholangiocellular carcinoma, combined hepatocellular and cholangiocarcinoma; CEA: carcinoembryonic antigen; GPS: Glasgow prognostic score; HR: hazard ratio; NLR: neutrophil to lymphocyte ratio; n.s.: not significant; PLR: platelet to lymphocyte ratio; PNI: prognostic nutritional index; CAR: C-reactive protein to albumin ratio; PAR: platelet to albumin ratio.

of poor patient survival consisted of tumor stage (p=0.0038), tumor differentiation (p=0.002), nodal involvement (p=0.029), intraoperative blood loss (p=0.049), serum CEA (p=0.032), PNI (p=0.026), CAR (p=0.036), and PAR (p=0.026). In multivariate analysis, independent risk factors of poor patient survival consisted of poor tumor differentiation (p=0.009), nodal involvement (p=0.001), high intraoperative blood loss (p=0.001), high serum CEA (p=0.012), and high PAR (p=0.023). ROC curves were calculated for survival status at the 3-year follow-up, and the AUC values were compared to assess cut-offs for each prognostic score as independent risk factors (Table III). The PAR had the highest AUC value (0.709±0.08, p=0.002) compared to other prognostic scores as independent risk factors (Figure 1).

Table III. *Comparison of the area under the curve (AUC) between prognostic scores.*

Factor	AUC	95% CI	*p*-Value
Tumor differentiation	0.678±0.08	0.517-0.838	0.002
CEA	0.674±0.37	0.522-0.826	0.032
Nodal involvement	0.604±0.08	0.440-0.769	0.029
PNI	0.652±0.08	0.488-0.816	0.026
CAR	0.633±0.08	0.475-0.791	0.036
PAR	0.709±0.08	0.563-0.856	0.002

AUC: Area under the Receiver Operating Characteristics curve; CI: confidence interval; CEA: carcinoembryonic antigen; CAR: C-reactive protein to albumin ratio; PNI: prognostic nutritional index; PAR: platelet to albumin ratio.

Relationship between clinical variables and DFS. The relationship between clinical variables and DFS are shown in Table IV. In univariate analysis, significant risk factors for cancer recurrence consisted of tumor stage (p=0.0327), tumor differentiation (p=0.004), serum CEA (p=0.011), PNI (p=0.016), and PAR (p=0.020). In multivariate analysis, poor tumor differentiation (p=0.009) and high PAR (p=0.029) remained independent risk factors for cancer recurrence.

Univariate analysis of clinical variables in relation to PAR. The relationship between clinical variables and PAR are shown in Table V. The group with a high PAR ($\geq 72.6\times10^3$) group had advanced tumor stage (p=0.048), higher PLR (p=0.008) and lower PNI (p=0.008).

Relationship between PAR and survival. In univariate analysis, the high PAR ($\geq 72.6\times10^3$) group had a poor median OS (28.4 months, p=0.0025) and DFS (23.1 months, p=0.003) (Figure 2); 3-year OS was 49.3% and 93.1% for the high and low PAR groups, respectively.

Table IV. *Univariate and multivariate analysis of clinicopathological variables in relation to disease-free survival.*

			Univariate analysis		Multivariate analysis	
Factor	Subgroup	N	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Tumor stage	II,III/I	40/19	2.913 (1.092-7.771)	0.0327		n.s
Tumor size (mm)	≥30.5/<30.5 mm	41/18	1.822 (0.636-5.221)	0.264		n.s
Tumor differentiation	Poor	11	10.77 (2.525-45.96)	0.004	2.711 (1.279-5.747)	0.009
	Moderate	30	1.652 (0.466-5.857)			
	Well (ref)	18	1			
Nodal involvement	Positive/negative	19/40	2.887 (0.972-8.569)	0.056		
Resection margin status	Positive/negative	13/46	1.258 (0.416-3.808)	0.684		n.s
Preoperative biliary drainage	Positive/negative	16/43	1.228 (0.411-3.668)	0.713		n.s
Tumor localization	Extrahepatic/intrahepatic	35/24	1.534 (0.580-4.056)	0.389		n.s
Operative tme	≥427/<427 min	47/12	1.335 (0.856-2.133)	.		n.s
Intraoperative blood loss	≥845/<845 ml	30/29	2.509 (0.949-6.635)	0.064		n.s
Serum CEA	≥3.25/<3.25 U/ml	27/32	3.510 (1.327-9.288)	0.011		n.s
GPS	1,2/0	11/48	3.846 (0.957-15.46)	0.058		n.s
NLR	≥5.41/<5.41	5/54	1.576 (0.584-4.254)	0.369		n.s
PLR	≥134/<134	38/21	1.709 (0.626-4.667)	0.295		n.s
PNI	≥43/<43	42/17	0.247 (0.079-0.771)	0.016		n.s
CAR	≥0.061/<0.061	31/28	2.612 (0.991-6.885)	0.052		n.s
PAR	$\geq 72.6\times10^3/<72.6\times10^3$	16/43	3.789 (1.227-11.70)	0.020	4.422 (1.168-16.732)	0.029

CI: Confidence interval; extrahepatic: perihilar and distal bile duct carcinoma; intrahepatic: intrahepatic cholangiocarcinoma, cholangiocellular carcinoma, combined hepatocellular and cholangiocarcinoma; CEA: carcinoembryonic antigen; GPS: Glasgow prognostic score; HR: hazard ratio; n.s.: not significant; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; PNI: prognostic nutritional index; CAR: C-reactive protein to albumin ratio; PAR: platelet to albumin ratio.

Table V. *Univariate analysis of clinical variables in relation to preoperative platelet-to-albumin ratio (PAR).*

Factor		PAR		*p*-Value (univariate)
		$<72.6\times10^3$ (n=43)	$\geq 72.6\times10^3$ (n=16)	
Tumor stage	I, II/III	17/26	2/14	0.048
Tumor size	<30.5/≥30.5 mm	13/30	5/12	0.940
Tumor differentiation	Well/moderate/poor	13/23/7	5/7/4	0.706
Nodal involvement	Negative/positive	30/13	10/6	0.595
Resection margin status	Negative/positive	34/9	12/4	0.737
Preoperative biliary drainage	Negative/positive	32/11	11/5	0.663
Operation	PD/HRx	20/23	4/12	0.135
Operative time	<427/≥427 min	11/32	1/15	0.101
Intraoperative blood loss	<845 ml/≥845 ml	23/20	6/10	0.275
Serum CEA	<3.25/≥3.25 U/ml	24/19	8/8	0.690
GPS	0/1, 2	36/7	12/4	0.444
NLR	<5.41/≥5.41	28/15	7/9	0.137
PLR	<134/≥134	32/11	6/10	0.008
PNI	≥43/<43	7/36	8/8	0.008
CAR	>0.061/≥0.061	26/17	6/10	0.115

PD: Pancreaticoduodenectomy; HRx: hepatic resection; CEA: carcinoembryonic antigen; GPS: Glasgow prognostic score; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; PNI: prognostic nutritional index; CAR: C-reactive protein to albumin ratio; PAR: platelet to albumin ratio.

Discussion

The correlation between inflammation and each stage of cancer progression, such as carcinogenesis, promotion, progression and metastasis, has been reported (18, 19). In addition, several reports demonstrate a relationship between postoperative prognosis and systemic inflammation-based prognostic score such as GPS, modified GPS (20), NLR, PLR, PNI, and CAR. However, the relationships between these prognostic scores and therapeutic outcomes in cholangiocarcinoma have not been clarified.

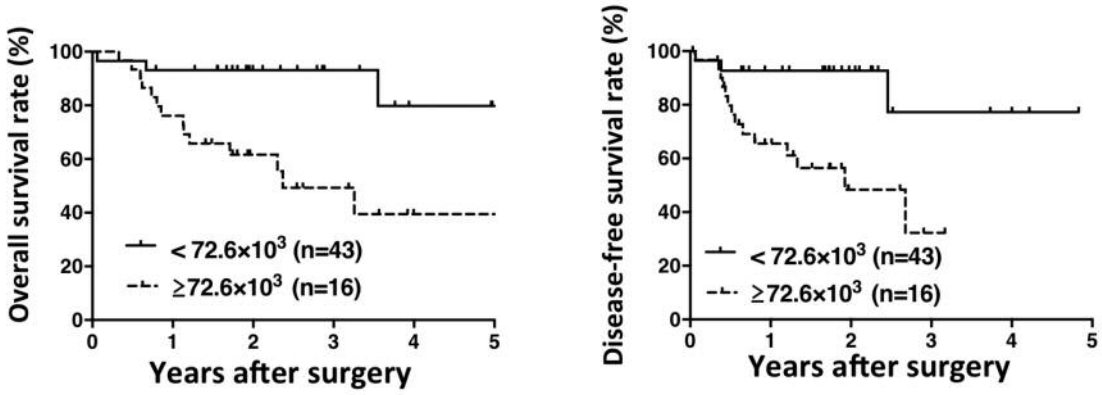

Figure 2. *The relationship between platelet-to-albumin ratio (PAR) and survival. The group with a high PAR (≥72.6×10^3) had a significantly poorer median overall survival (28.4 months, p=0.0025) and disease-free survival (23.1 months, p=0.003).*

Some reports demonstrated that thrombocytosis, defined as a platelet count over 300-450×10^6/l, was the significant risk factor in colorectal cancer (21-23). The most commonly expressed reasons for this correlation were induction of inflammation and protection from immune system surveillance (24). Platelets contain several types of cytokines that induce systemic inflammation such as interleukin 6 (IL6), transforming growth factor-β (TGF-β), nuclear factor-kappa B, and platelet-derived growth factor (PDGF) (25). These cytokines increase with thrombocytosis and affect cancer progression (19). Specifically, IL6 plays an important role in carcinogenesis and cancer progression (26); these severely worsen a patient's prognosis. In addition, PDGF activates cancer-associated fibroblasts, which play an active role in cell proliferation, production of anti-apoptotic signals and tumor progression (27, 28). Cancer-associated fibroblasts are highly prevalent in cholangiocarcinoma, therefore, a high serum platelet count would seem to affect the condition of patients with cholangiocarcinoma (29).

The relationship between hypoalbuminemia and short life expectancy in patients with cancer has also been broadly recognized (30). Hypoalbuminemia is seen in patients with malnutrition and cachexia, increasing the risk of anticancer agent-induced toxicity. Furthermore, systemic inflammation suppresses albumin synthesis in hepatocytes by the production of cytokines. Hypoalbuminemia is also associated with failure of various immune system components (31) and helps tumor cells to progress.

In summary, because PAR reflects both the platelet count and serum albumin level, it seems to be a useful index for patients with cholangiocarcinoma after primary resection. PAR also has other advantages. The platelet count and serum albumin level are usually examined at every institution before surgery without excessive cost. Furthermore, PAR can easily be calculated dividing the platelet count by the serum albumin level. Limitations of the current study include its retrospective design with potential biases. By accumulating data prospectively, the benefit of neoadjuvant chemotherapy before resection for cholangiocarcinoma may be clarified by PAR.

Conflicts of Interest

No Author has any conflicts of interest to declare in regard to the current study.

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