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Comparison of Inflammation-based Prognostic Scores in Patients With Biliary Tract Cancer After Surgical Resection

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Abstract. *Background/Aim: Inflammation-based prognostic scores are proven prognostic biomarkers in various cancers. This study aimed to identify a useful prognostic score for patients with biliary tract cancer (BTC) after surgical resection. Patients and Methods: This retrospective study recruited 115 patients with BTC during 2010-2020. The relationship between clinicopathological variables, including various prognostic scores and overall survival (OS), was investigated using univariate and multivariate analyses. Results: BTC included 58 cholangiocarcinoma, 29 gallbladder carcinoma, 16 ampullary carcinoma, and 12 perihilar cholangiocarcinoma cases. A significant difference was detected in OS of patients with a Japanese modified Glasgow prognostic score (JmGPS) 0 (n=62) and JmGPS 1 or 2 (high JmGPS) (n=53). In the multivariate analysis, tumour differentiation (p=0.014) and a high JmGPS (p=0.047) were independent prognostic factors. Conclusion: The high JmGPS was an independent prognostic predictor after surgical resection and was superior to other prognostic scores.*

Biliary tract cancers (BTCs), which include gallbladder carcinoma (GBC), cholangiocarcinoma, and ampullary carcinoma, are relatively uncommon but lethal malignancies (1). Although it is a rare disease, the incidence of BTC has gradually increased in recent decades (1). In Japan, BTC is the sixth leading cause of cancer-related deaths, with >180,000 annual deaths (2). Currently, radical resection is the only curative treatment option for BTC; however, the high recurrence rate is a major problem (3). Moreover, BTCs are usually diagnosed at an advanced stage, and most patients, therefore, are relieved from the risk of undergoing radical resection. Though recent developments have occurred in surgical techniques and adjuvant therapy, the prognosis of BTC remains poor (4, 5). Preoperative prognostic markers for BTC could assess risk-benefit of surgery and assist in treatment stratification (6). Therefore, it is vital to identify novel, predictive biomarkers.

There is much evidence to support that the systemic inflammatory response plays an important role in the progression of various cancers (7). Measuring the inflammatory response has been subsequently refined with the use of a selective combination of C-reactive protein (CRP) and albumin. The Glasgow Prognostic Score (GPS) and modified GPS (mGPS) are preoperative inflammation-based scores for calculating the prognostic value for various malignancies (7-9). Recent studies have reported a prognostic value of the GPS/mGPS for BTC (10-12).

Additionally, other haematological components of systemic inflammation-based prognostic scores, including the neutrophil–lymphocyte ratio (NLR) (13, 14), platelet–lymphocyte ratio (PLR) (15), CRP–albumin ratio (CAR) (16, 17), and prognostic nutritional index (PNI) (18, 19), have been reported. These scores have been reported to be associated with the survival of patients with various cancers and have been used as useful prognostics markers (13-16, 20). This study aimed to evaluate the significance of inflammation-based prognostic scores and identify the most useful score in patients with BTC after surgical resection.

Patients and Methods

Patients. A total of 115 consecutive patients who underwent surgical resection with a diagnosis of BTC at the Department of Surgery, National Hospital Organization Fukuyama Medical Center between 2010 and 2020 were retrospectively reviewed. BTCs included GBC, intrahepatic cholangiocarcinoma (ICC), distal cholangiocarcinoma, ampullary carcinoma, or perihilar cholangiocarcinoma, confirmed postoperatively by pathology. The study was approved by the institutional ethical review board (number: R2-34).

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Key Words: Biliary tract cancer, inflammation-based prognostic score, modified Glasgow prognostic score, prognosis.

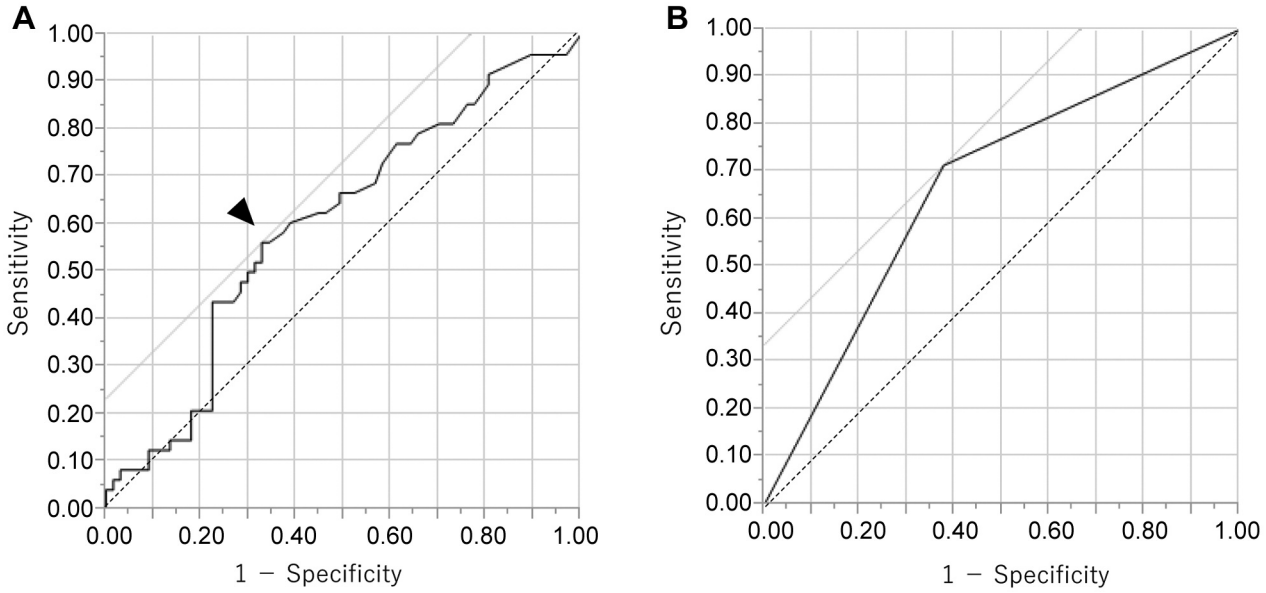

Figure 1. *(A) ROC curve for serum CRP levels in patients with biliary tract cancer after surgical resection. The arrows indicate the location on the ROC curve for the diagnostic cut-off point that minimises the misclassification of surviving and deceased patients. Cut-off of 0.4 mg/dl, sensitivity of 56.3%, specificity of 67.2%, and AUC of 0.602. (B) ROC curve for a JmGPS of 0, 1 and 2 in patients with biliary tract cancer after surgical resection. Sensitivity of 62.5%, specificity of 65.7%, and AUC of 0.641. ROC, Receiver operating characteristics; JmGPS, Japanese modified Glasgow prognostic score; AUC, area under curve; CRP, C-reactive protein.*

Data collection. The following clinicopathological factors were obtained retrospectively from patient medical records: demographic data (age at surgery and sex), laboratory data (serum levels of CRP, albumin, platelet count, neutrophil count, lymphocyte count, tumour markers), associated diseases (hypertension, diabetes, cardiac disease, and stroke), preoperative cholangitis, operative procedure (type of resection), operative blood loss, duration of operation, transfusion, tumour stage according to the Union for International Cancer Control classification (21), tumour differentiation, and postoperative adjuvant chemotherapy. Curative resection (R0) was defined as complete removal of all macroscopic tumour nodules with clear microscopic margins; R1 or R2 resections were defined as microscopic or macroscopic disease, respectively, involving at least one margin. Complications were defined according to the method described by Clavien *et al*. (22). In this study, postoperative complications were defined as grade 3 or higher complications, while postoperative mortality was defined as any death incident occurring within 30 days post-surgery.

Definition of the inflammation-based prognostic score. Peripheral venous blood samples were collected within two weeks before surgery. The inflammation-based prognostic scores, namely, the mGPS, GPS, PNI, CAR, NLR, and PLR, were calculated according to the following results: the elevated CRP level was defined according to the best predictive values calculated using receiver operating characteristics (ROC) analyses (Figure 1A). Based on this analysis, the cut-off point for CRP was 0.4 mg/dl. Toiyama *et al*. have defined the appropriate cut-off value of CRP (0.5 mg/dl) as the mGPS for the Japanese population (23-25). Considering general versatility, we used the mGPS, which was termed the Japanese modified GPS (JmGPS) in this study because there was another mGPS definition in which the cut-off point for CRP was 1.0 mg/dl (26).

The JmGPS was calculated as follows: 1) patients with an elevated CRP level (>0.5 mg/dl) and hypoalbuminemia (<3.5 g/dl) were scored as 2, 2) those with only one of the biochemical abnormalities were scored as 1, and those with no abnormalities were scored as 0 (24). The calculation for the GPS is similar to that for the JmGPS except that the elevated CRP level for the GPS is >1.0 mg/dl (9) instead of >0.5 mg/dl for the JmGPS. The CAR was calculated by dividing serum CRP levels (mg/dl) by serum albumin levels (g/l) (17). The NLR and PLR were calculated by dividing neutrophil and platelet counts by lymphocyte count, respectively (13, 14). The PNI was calculated according to the following formula: 10 × serum albumin (g/dl) + 0.05 × total lymphocyte count (per mm^3) (18, 19).

Follow-up. All patients received follow-ups routinely until December 2020. Postoperative follow-ups included medical history evaluation (symptom and physical examination), laboratory studies, and imaging examinations every 3-6 months for at least five years. Patients with lymph node metastasis or those who underwent R1/R2 resection received postoperative adjuvant chemotherapy based on TS-1 for approximately six months. Overall survival (OS) was defined as the interval between surgery and death or the last observation.

Methods used to compare inflammation-based prognostic scores and clinical variables. The relationship between clinicopathological variables, including various prognostic scores and OS, was investigated using univariate analysis. The area under the ROC curve was calculated to compare the predictive ability of each scoring system. We compared the most useful score with clinical

variables and identified independent prognostic factors associated with OS using multivariate analysis.

Statistical analyses. Data are expressed as mean±standard deviation. Univariate analysis was performed using the Mann-Whitney *U*-test and chi-squared test. Diagnostic accuracy was determined by the area under the ROC curve. The optimal cut-off values of the CAR, NLR, GPS, PLR, and PNI were determined by maximising the Youden index (sensitivity + specificity − 1) (27). The Kaplan-Meier method was used to analyse the overall survival rate, while the log-rank test was used to compare the differences between the subgroups. The univariate and multivariate analyses were performed for the prognostic factors using the Cox proportional hazards model, as significant different variables analysed using the univariate analysis were further analysed using the multiple Cox proportional hazards model. The statistical significance level was set at $p<0.05$ for all analyses. Statistical analysis was performed using JMP version 11 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. Patient characteristics are outlined in Table I. The median patient age was 75 years (range=38-92 years). BTCs included 30 intrahepatic cholangiocarcinoma, 29 gallbladder carcinoma, 28 distal cholangiocarcinoma, 16 ampullary carcinoma, and 12 perihilar cholangiocarcinoma cases. Curative resection (R0) was achieved in 95 patients (82.6%). Operative procedures consisted of cholecystectomy (n=11), liver bed resection (n=7), subsegmentectomy (n=11), sectionectomy (n=6), hemihepatectomy (n=30), trisectionectomy (n=4), hepatopancreaticoduodenectomy (n=2), pancreaticoduodenectomy (n=42), partial hepatectomy (n=1), and bile duct resection without hepatectomy (n=1). None of the patients underwent neoadjuvant chemotherapy. None of the patients underwent preoperative portal vein embolisation. Postoperative complications developed in 41 of 114 patients; these included pancreatic fistula (n=21), bile leakage (n=8), abdominal abscess (n=7), pleural effusion (n=2), abdominal bleeding (n=1), chylous ascites (n=1), and heart failure owing to arrhythmia (n=1). One patient died of heart failure owing to arrhythmia on the postoperative 18th day; thus, the mortality rate was 0.9%.

ROC analysis. Using the overall survival rate as an endpoint, the optimal cut-off value for inflammation-based markers was determined using the area under the curve (AUC) of ROC curves: i) JmGPS=1 (AUC 0.641) (Figure 1B), ii) PLR=0.12 (AUC 0.612), iii) CAR=0.10 (AUC 0.626), iv) GPS=1 (AUC 0.593), v) PNI=41.9 (AUC 0.613), and vi) NLR=2.55 (AUC 0.521). The JmGPS value was the highest (statistically significant) among inflammation-based markers.

Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after surgical resection. The median OS time was 22 months (range=1-117 months).

Table I. *Patient characteristics*.

Variables	Mean±SD or rate	Range
Age (years)	75.0±9.51	39-92
Gender (male/female)	72/43	
BMI (kg/m^2)	22.41±3.65	14.20-32.46
Preoperative laboratory data		
Albumin (g/dl)	3.77±0.53	1.70-4.80
Platelet count (×10^4/mm^3)	21.62±66.26	3.37-46.3
Neutrophil count (×10^3/mm^3)	3.81±1.92	1.01-15.39
Lymphocyte count (×10^3/mm^3)	1.59±0.72	0.48-5.80
CRP (mg/dl)	1.12±2.79	0.01-24.18
CEA (ng/ml)	6.09±13.22	0.56-113.06
CA19-9 (U/ml)	1,040.46±4,190.53	2.0-39,284.20
Inflammation-based prognostic scores		
JmGPS (0/1/2)	62/38/15	
GPS (0/1/2)	72/32/11	
NLR	2.85±2.26	0.75-14.75
PLR	158.6±85.5	41.0-561.0
CAR	0.39±1.43	0.002-14.22
PNI	45.65±6.52	22.21-62.98
Type of cancer		
Intrahepatic cholangiocarcinoma	30 (26.1%)	
Gallbladder carcinoma	29 (25.2%)	
Distal cholangiocarcinoma	28 (24.3%)	
Ampullary carcinoma	16 (13.9%)	
Perihilar cholangiocarcinoma	12 (10.4%)	
Preoperative biliary drainage (none/present)	56/59	
Preoperative cholangitis	43 (37.3%)	
Associated disease (none/present)	32/83	
Surgical procedure		
Cholecystectomy	11 (9.6%)	
Bile duct resection without liver resection	1 (0.9%)	
Type of liver resection		
Liver bed resection	7 (6.1%)	
Partial hepatectomy	1 (0.9%)	
Subsegmentectomy	11 (9.6%)	
Sectionectomy	6 (5.2%)	
Hemihepatectomy	30 (26.1%)	
Trisectionectomy	3 (2.6%)	
Pancreaticoduodenectomy	42 (36.5%)	
Hepatopancreaticoduodenectomy	2 (1.9%)	
Duration of operation (min)	458.8±172.2	124-1,049
Blood loss (ml)	774.7±1,519.9	10-13,870
Blood transfusion	15 (13.0%)	
Stage UICC 6th (0/I/II/III/IV)	3/16/49/31/16	
Curability (R0/R1/R2)	97/15/3	
Tumour differentiation (well/moderate/poor/pap/well-pap/other/unknown)	43/31/9/7/5/7/13	
Mortality	1 (0.9%)	
Postoperative adjuvant chemotherapy	78 (67.8%)	
Postoperative complication (Clavien–Dindo ≥3a) (none/present)	42/73	

BMI, Body mass index; CRP, C-reactive protein; CEA, carcinoembryonic; CA19-9, carbohydrate antigen 19-9; ASA, the American Society of Anesthesiologists; UICC, Union for International Cancer Control; HPD, hepatopancreaticoduodenectomy; PD, pancreaticoduodenectomy; CAR, C-reactive protein to albumin ratio; GPS, Glasgow prognostic score; JmGPS, Japanese modified Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrient index; SD, standard deviation.

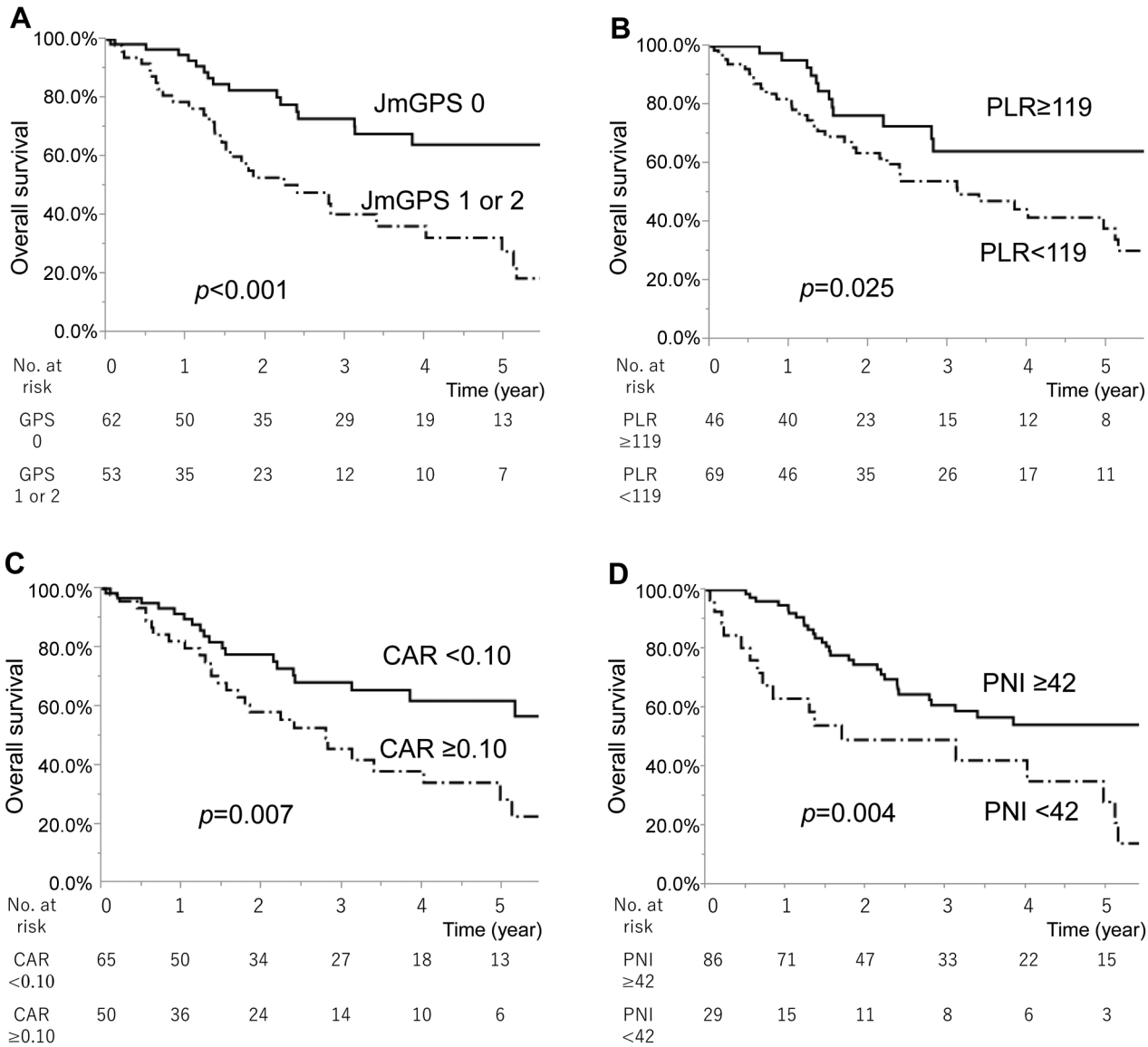

Figure 2. *The relationship between inflammation-based prognostic scores and overall survival in patients with biliary tract cancer after surgical resection. The variables are as follows: Japanese modified GPS (A), PLR (B), CAR (C), and PNI (D). GPS, Glasgow prognostic score; PLR, platelet-lymphocyte ratio; CAR, C-reactive protein-albumin ratio; PNI, prognostic nutritional index.*

The one-, three-, and five-year OS rates were 86.3%, 58.1%, and 47.0%, respectively. The relationship between the clinicopathological variables and OS rates following surgical resection is presented in Table II. In univariate analysis, the OS was significantly worse in patients with the carbohydrate antigen 19-9 level of ≥20 U/ml (p=0.004), JmGPS of 1 or 2 (high JmGPS) (Figure 2A; p<0.001), CAR of ≥0.07 (Figure 2B; p<0.001), PNI of <41.9 (Figure 2C; p<0.001), PLR of <0.12 (Figure 2D; p=0.027), preoperative cholangitis (p=0.040), tumour differentiation (p=0.004), duration of operation of ≥360 min (p=0.018), tumour stage III or IV (p=0.028), and R1 or R2 resection (p<0.001). In the multivariate analysis, tumour differentiation (p=0.024) and a high JmGPS (p=0.040) were independent and significant predictors of OS.

Association between the clinicopathologic variables and JmGPS. The relationship between clinicopathologic variables and patients with a high JmGPS is presented in Table III. Patients with a high JmGPS had a significantly higher body mass index (BMI) (p=0.020), higher incidence of preoperative

Table II. *Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after resection of biliary tract cancer.*

Variables	Univariate analysis		Multivariate analysis	
	N	*p*-Value	HR (95% CI)	*p*-Value
Age (years)				
≥75	59	0.625		
<75	56			
Gender				
Male	72	0.199		
Female	43			
BMI (kg/m^2)				
≥20	79	0.395		
<20	36			
CEA (ng/ml)				
≥9	17	0.828		
<9	98			
CA19-9 (U/ml)				
≥20	57	0.004*	1.86	0.059
<20	58		(0.97-3.64)	
Preoperative biliary drainage				
Present	59	0.827		
None	56			
Preoperative cholangitis				
Present	43	0.040*	1.27	0.434
None	71		(0.68-2.37)	
Associated disease				
Present	83	0.055		
None	32			
Type of cancer				
ICC	30	0.079		
Others	85			
Resection				
R0	97	<0.001*	1.78	0.138
R1 or R2	18		(0.82-3.70)	
Duration of operation (min)				
≥360	81	0.017*	1.41	0.375
<360	34		(0.67-3.20)	
Blood loss (ml)				
≥200	80	0.451		
<200	35			
Transfusion				
None	100	0.352		
Present	15			
Tumour stage (UICC)				
III or IV	47	0.028*	1.50	0.226
0 or I or II	58		(0.77-2.87)	
Tumour differentiation				
Well	48	0.004*	2.00	0.024*
Others	67		(1.09-3.79)	
JmGPS				
1 or 2	53	<0.001*	1.92	0.040*
0	62		(1.03-3.67)	
GPS				
1 or 2	43	0.057		
0	72			
NLR				
≥2.55	84	0.257		
<2.55	31			
PLR				
<119	69	0.025*		
≥119	46			
CAR				
≥0.10	50	0.007*		
<0.10	65			
PNI				
<42.0	39	0.004*		
≥42.0	86			
Postoperative complication (Clavien–Dindo ≥3)				
None	72	0.372		
Present	43			
Postoperative adjuvant chemotherapy				
None	37	0.390		
Present	78			

HR, Hazard ratio; CI, confidence interval; BMI, body mass index; CRP, C-reactive protein; CEA, carcinoembryonic; CA19-9, carbohydrate antigen 19-9; ICC, Intrahepatic cholangiocarcinoma; UICC, Union for International Cancer Control; CAR, C-reactive protein to albumin ratio; GPS, Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrient index. *Statistically significant.

cholangitis (p=0.045), longer duration of operation (p=0.002), higher carcinoembryonic antigen levels (p=0.025), and non-well differentiation (p=0.018) than those with JmGPS of 0 (low JmGPS).

Discussion

In our study, we demonstrated that inflammation-based prognostic scores such as the JmGPS, CAR, PLR, and PNI were associated with the prognosis of patients with BTC who underwent surgical resection. Additionally, we reported for the first time that JmGPS was an independent prognostic factor of OS in BTC patients. Though the inflammation-related marker was associated with the prognosis of various cancers, few data are available for BTCs, which are relatively rare with a poor prognosis. In a meta-analysis, it was reported that the PNI could be applied as an independent prognostic marker for patients with BTC (28) and elevated NLR and PLR values may be unfavourable prognostic factors for clinical outcomes in patients with BTC (29).

Table III. *Clinicopathological features in relation to the JmGPS*.

Variables	JmGPS 0 (n=62)	JmGPS 1 or 2 (n=53)	p-Value
Age (years)	73.7±7.9	74.1±11.2	0.813
Gender (male/female)	38/24	34/19	0.752
BMI (kg/m^2)	23.1±3.3	21.5±3.9	0.020*
Total bilirubin (mg/dl)	0.79±0.31	1.05±0.71	0.011*
Albumin (g/dl)	4.02±0.37	3.49±0.54	<0.001*
CRP (mg/dl)	0.18±0.33	2.20±3.83	<0.001*
CEA (ng/ml)	6.62±16.70	5.40±7.23	0.622
CA19-9 (U/ml)	540.1±1712.6	1606.2±5840.9	0.173
Preoperative biliary drainage			
None/present	35/27	21/32	0.072
Preoperative cholangitis			
None/present	44/18	28/25	0.045*
Associated disease			
None/present	14/48	18/35	0.175
Type of cancer			
ICC/others	19/43	11/42	0.226
Resection (R0/R1 or R2)	56/6	41/12	0.056
Duration of operation (min)	411.5±21.0	511.6±22.7	0.002*
Blood loss (ml)	625.6±936.6	938.6±1,985.6	0.271
Transfusion			
none/present	57/5	43/10	0.086
Tumour stage (UICC)			
1 or 2/3 or 4	39/23	29/24	0.374
Tumour differentiation			
Well/others	32/30	16/37	0.019*
Postoperative complication			
(Clavien–Dindo ≥3) none/present	42/20	30/23	0.218
Postoperative adjuvant chemotherapy			
none/present	22/44	13/40	0.203

BMI, Body mass index; CRP, C-reactive protein; CEA, carcinoembryonic; CA19-9, carbohydrate antigen 19-9; ICC, Intrahepatic cholangiocarcinoma; UICC, Union for International Cancer Control; JmGPS, Japanese modified Glasgow prognostic score. *Statistically significant.

The GPS has the advantage of being easily measured, routinely available, and well-standardised. In the original modified GPS or GPS, the cut-off value of CRP was defined as 1.0 mg/dl. In our study, the JmGPS was used with a CRP cut-off value of 0.5 mg/dl according to the best predictive value calculated using ROC analysis. In colorectal cancer, it has been reported that the JmGPS provided valuable prognostic information (23, 24). We showed that the JmGPS was the most accurate prognostic marker among other inflammation-based prognostic scores for patients with BTC after surgical resection.

CRP is an acute-phase protein produced in the liver, and the cytokines, such as interleukin-6, interleukin-8, and tumour necrosis factor-α, control its up-regulation (30). Elevated levels of preoperative CRP in patients with advanced cancer may be correlated with elevated cytokine levels. The systemic inflammatory response induced by cytokines leads to impaired immunity. As a result, rapid cancer progression may affect prognosis. Albumin has been used as the marker of the nutritional status of patients. A low albumin level represents poor nutritional condition and is associated with a poor prognosis.

The JmGPS determined by combining the CRP and albumin level may be correlated with a systemic inflammatory response and a progressive nutritional decline. Brozzetti *et al*. has recommended perioperative nutritional support to improve the nutritional status of patients with hepatobiliary-pancreatic carcinoma because of a high prevalence of malnutrition (31). Also, Uno *et al*. has reported that preoperative immunonutrition suppresses the perioperative inflammatory response (32). Okugawa *et al*. reported that fish oil-enriched nutrition as an anti-systemic inflammatory response nutrition intervention suppressed systematic inflammatory reaction and improved the prognosis of colorectal carcinoma patients with a high JmGPS (23). We need to further investigate the relationship between immunonutrition and inflammatory-based prognostic score for improving the management of BTC patients with a high JmGPS.

In our study, another independent prognostic factor was tumour differentiation. Previous studies reported tumour

differentiation as a predictor of survival for BTC patients who underwent curative surgery (33, 34). In our study, patients with well-differentiated tumours had significantly longer survival than those with the other non-well-differentiated tumours. This was further reaffirmed in the multivariate analysis. Patients with non-well-differentiated tumours should be carefully monitored in the postoperative follow-up for early detection of any disease recurrence.

Patients with a high JmGPS had a lower BMI, higher level of tumour marker, increased incidence of cholangitis, longer duration of surgery, and non-well-differentiated tumours than those with a low JmGPS. Our results might have been affected by advanced tumours or an increase in inflammation such as obstructive jaundice due to tumour invasions or preoperative biliary drainage.

Comparison of prognostic variables in the same cohort is very important to identify a clinically useful predictor in patients with cancer. Some studies have tried identifying prognostic factors in various cancers. However, few studies have identified and compared various prognostic factors using the same cohort. For BTCs, Fujiwara *et al*. reported that the GPS score was an independent marker of poor prognosis in patients with distal extrahepatic bile duct cancer with the same cohort (35). In a multi-institutional study, Sui *et al*. demonstrated that the GPS can be useful for predicting the postoperative outcomes of patients with ICC (36). The modified GPS was an independent prognostic factor in resected perihilar cholangiocarcinoma and was superior to the PLR, PNI, and NLR (12). Those results may support our results. However, the lymphocyte–to–monocyte ratio was reported as an independent predictor of OS in ICC patients and was superior to the GPS, mGPS, PLR, and PNI (37).

Given the retrospective design, very small sample size, and single institution-based nature of our study, certain limitations regarding our prognostic analysis should be acknowledged. The sample size limits the statistical power of the multivariate and subgroup analyses. The study was heterogeneous based on the diagnosis and type of resection. The overall survival rate of each biliary cancer (ICC, GBC, extrahepatic cholangiocarcinoma, *etc*.) was different, although statistically not significant (data not shown). Moreover, most patients underwent major resection; however, in patients with early-stage GBC, cholecystectomy or liver bed resection was commonly performed. Therefore, more prospective or multicentre studies with large patient cohorts are needed to verify our results.

In conclusion, a high JmGPS and tumour differentiation were independent prognostic risk factors of OS for BTC patients after surgical resection. Moreover, the JmGPS seemed superior to other inflammation-based prognostic scores with AUC calculated using the ROC curve. This relatively simple and inexpensive scoring system plays an important role in refining treatment stratification as well as to predict survival. Determining the indications of nutritional support as immunonutrition and a more intense follow-up are needed for patients with a high JmGPS.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

MU, KK, NT, YY, YU, TN, RH, HM, YT, SO, and MI designed the study. MI, MU, NT, and KK treated and observed the patients. MU prepared the manuscript and performed the literature search. IM corrected and revised the manuscript. All Authors read and approved the final manuscript.

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