World J Surg (2021) 45:279–290
https://doi.org/10.1007/s00268-020-05797-4

ORIGINAL SCIENTIFIC REPORT

Prognostic Utility of the Glasgow Prognostic Score for the Long-Term Outcomes After Liver Resection for Intrahepatic Cholangiocarcinoma: A Multi-institutional Study

Kenta Sui[1] · Takehiro Okabayashi[1] · Yuzo Umeda[2] · Masahiro Oishi[3] · Toru Kojima[4] · Daisuke Sato[5] · Yoshikatsu Endo[6] · Tetsuya Ota[7] · Katsuyoshi Hioki[8] · Masaru Inagaki[9] · Tadakazu Matsuda[10] · Ryuji Hirai[11] · Masashi Kimura[12] · Takahito Yagi[2] · Toshiyoshi Fujiwara[2]

Accepted: 8 September 2020 / Published online: 28 September 2020

Abstract

Objective The usefulness of the modified Glasgow prognostic score (GPS) as a prognostic tool remains unclear for patients undergoing curative surgery for intrahepatic cholangiocarcinoma (ICC). Therefore, this study investigated the prognostic usefulness of the GPS for patients who underwent ICC surgery.

Method All ICC patients who had a curative-intent hepatectomy at 17 institutions between 2000 and 2016 were included. The correlation was assessed between the preoperative GPS and the baseline characteristics of the patients, histopathological parameters, surgical parameters, and the postresection overall survival (OS).

Result There were 273 patients who met the eligibility criteria between the years 2000 and 2016. The postoperative OS rates at 1, 3, and 5 years were 83.8%, 56.3%, and 41.5%, respectively (median OS, 47.7 months). A multivariate analysis revealed the factors that were associated with a worse OS, which included an increased GPS (hazard ratio = 1.62; 95% confidence interval [CI]: 1.01–2.53; $P = 0.03$), an elevated carcinoembryonic antigen level (hazard ratio = 1.60; 95% CI: 1.06–2.41; $P = 0.02$), an elevated carbohydrate antigen 19–9 level (hazard ratio = 1.55; 95% CI: 1.05–2.30; $P = 0.03$), undifferentiated carcinoma (hazard ratio = 2.41; 95% CI: 1.56–3.67; $P < 0.01$), and positive metastasis to the lymph nodes (hazard ratio = 2.54; 95% CI: 1.76–3.67; $P < 0.01$). In ICC patients after a hepatectomy, an elevated GPS was associated with poorer OS, even if the tumour factors that affected GPS were eliminated by propensity-score matching.

Conclusion Preoperative GPS can be useful to predict the postoperative outcomes of ICC patients. Therefore, this relatively simple and inexpensive scoring system can be utilized to further refine patient stratification as well as to predict survival.

✉ Yuzo Umeda
y.umeda@d9.dion.ne.jp

[1] Department of Gastroenterological Surgery, Kochi Health Sciences Center, Kochi, Japan

[2] Department of Gastroenterological Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

[3] Department of Surgery, Tottori Municipal Hospital, Tottori, Japan

[4] Department of Gastroenterological Surgery, Okayama Saiseikai General Hospital, Okayama, Japan

[5] Department of Surgery, Hiroshima Citizens Hospital, Hiroshima, Japan

[6] Department of Surgery, Himeji Red Cross Hospital, Himeji, Japan

[7] Department of Surgery, National Okayama Medical Center, Okayama, Japan

[8] Department of Surgery, Fukuyama City Hospital, Fukuyama, Japan

Introduction

Primary liver cancer is one of the top four causes of cancer-related deaths [1]. Among primary liver cancers, intrahepatic cholangiocarcinoma (ICC) develops when neoplastic transformation turns bile duct cholangiocytes into intrahepatic tumour cells [2]. ICC accounts for 5%–30% of primary malignancies in the liver and is second only to hepatocellular carcinoma [2, 3]. The main standard curative treatment for ICC is still resection [4, 5]. Unfortunately, patients receiving a hepatectomy for ICC continue to have unsatisfactory prognoses due to the high locoregional recurrence and/or distant metastases [5, 6]. Additionally, the mortality rate of patients with ICC is high possibly owing to the late diagnosis and limited accuracy of diagnostic and prognostic biomarkers [5, 6].

Cancer development factors can include immune response and chronic inflammation [7]. Carcinogenesis incidence has been increasing, but it is not clear whether the increase is due to improved screening programs, including the rising use of cross-sectional imaging, leading to more diagnoses, or an uptick in risk factors and comorbidities, such as cirrhosis. Recently, the inflammatory biomarkers platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and neutrophil-to-lymphocyte ratio were shown to predict long-term outcomes for several cancers [8–11]. Actually, a stage of the TNM classification, surgical margin, lymph node metastases, blood vessel permeation, and differentiation grade are included in a factor to predict the survival of patients in ICC. But each factor is usually detected only after during the operation or the operation. Moreover, among patients with ICC, those with choledochal cysts, primary sclerosing cholangitis, hepatolithiasis, or parasitic infection with chronic biliary inflammation had an elevated risk to develop biliary tract cancer [7, 12]. Therefore, the relationship between overall survival (OS) and the nutritional, inflammatory, or immunological status suggests that the oncologic outcome may be related to the biological status of the patient.

The link connecting prognosis and biological status has primarily been evaluated only in small groups of ICC patients receiving conservative palliative therapy [13, 14]. Accordingly, owing to the absence of high-quality clinical data, this study evaluated the association between OS and pretreatment biological status, focusing on the Glasgow prognostic score (GPS) in a multi-facility ICC patient cohort that received curative surgery. It was intended to identify a new tool for patient risk stratification and clinical decision making.

Patients and methods

Study design

This retrospective study assessed the clinical importance of preoperative nutritional, inflammatory, and immunological status on long-term outcomes using the data of patients with clinically resectable ICC treated from January 2000 to December 2016 at 17 institutions in Japan: Okayama University Hospital, Okayama Saiseikai General Hospital, Hiroshima Citizens Hospital, Kochi Health Sciences Center, Himeji Red Cross Hospital, National Fukuyama Medical Center, Tottori Municipal Hospital, Tenwakai Matsuda Hospital, National Okayama Medical Center, Fukuyama City Hospital, Himeji St. Maria Hospital, Matsuyama Municipal Hospital, Sumitomo Besshi Hospital, Onomichi Municipal Hospital, National Iwakuni Medical Center, Himeji Central Hospital, and Kobe Red Cross Hospital. The surgical management was determined by a multidisciplinary tumour board at each institution. Subjects meeting any of the following criteria were excluded: 1) insufficient records about pathology and immunolological assessment; or 2) lack of follow-up data. Blood tests were performed within 2 weeks before surgery, and ICC was confirmed by histopathological examinations done postoperatively.

This study conformed to the Declaration of Helsinki on Human Research Ethics standards and was approved by the Okayama University Hospital Institutional Ethics Board (number 1701–026). Since this study was retrospective in nature, there was no written informed consent from the investigated patients. All data were blinded before analysis.

Clinicopathological data, biochemical parameters, and the GPS

The clinical demographic data of patients, including age, sex, history of viral hepatitis, levels of carbohydrate antigen 19–9 (CA19-9), and levels of carcinoembryonic antigen (CEA), were collected from the medical records at each institution. Hepatitis B (HBV) and C (HCV) viruses were tested for in all patients by HB antigen and HCV antibodies. In positive tests, PCR was used to examine the viral nucleic acid in sera. The GPS was determined by combining the preoperative serum *C*-reactive protein

[9] Department of Surgery, National Fukuyama Medical Center, Fukuyama, Japan

[10] Department of Surgery, Tenwakai Matsuda Hospital, Okayama, Japan

[11] Department of Surgery, Himeji Saint Mary's Hospital, Himeji, Japan

[12] Department of Surgery, Matsuyama City Hospital, Matsuyama, Japan

(CRP) and albumin levels. Elevated CRP levels (> 10.0 mg/d*L*) are worth one point, and hypoalbuminemia (< 3.5 g/d*L*) is also worth one point in the GPS. Only one biochemical abnormality had a score of 1, and those without elevated CRP nor hypoalbuminemia scored zero points [15]. The prognostic nutritional index (PNI) formula uses the serum albumin and the number of the total lymphocyte count: PNI = (10 × serum albumin (g/d*L*)) + (0.005 × total lymphocyte count). Chest radiography, an upper gastrointestinal tract endoscopy, abdominal ultrasonography, contrasting computed tomography (CT), and magnetic resonance imaging were included in the routine investigations. Positron emission tomograms were performed on patients in whom the liver or metastasis out of the liver was doubted by clinical or radiation inspection. A preoperative diagnosis of ICC was made based on the clinical and radiological results as well as considering elevated serum marker levels. The histopathology of the specimen removed surgically was performed by the expert pathologists of each facility independently. Pathological characteristics such as the diameter of tumour, the number of tumours, the existence of the capsule, the tumour part, surgical margin, blood vessel permeation, metastases to the lymph nodes, hepatitis, and cirrhosis were recorded, and the pathologists determined the degree of tumour differentiation.

Assessments

The prognostic factors after the intent-to-cure resection for ICC that were evaluated included the age, sex, tumour size, type of surgery, pathological findings, neoadjuvant therapy, adjuvant therapy, and physio-biological parameters including the GPS. Follow-up was conducted after surgery at three-month intervals for two years and then varying by patient and institution between 2 and 4 times per year thereafter. MRI or contrast-enhanced CT was done once every 6 months. If tumour recurrence or metastasis was suspected, imaging was performed as needed and further investigation was done as indicated. The length of OS was counted from the surgery date until death related to ICC. Deaths not related to ICC were censored at the final follow-up. After having adjusted a known factor to entangle using the multivariate Cox proportion hazard model, the influence of the physiological biological value of the preprocessing as the continuous variable of the OS: A CEA level was examined, preoperative CA19-9 level and a convalescence nomogram were established in the GPS, the neutrophilic/lymphocyte ratio (NLR), the lymphocyte/monocyte ratio (LMR), and the preoperative prognostic nutrition index. The discrimination in the logistic model equation was decided using a receiver operating characteristic (ROC) curve and calculating a coincident indicator. Moreover, propensity score matching matched the patients with a zero GPS (the GPS0 group) with the controls, i.e. patients with a GPS of 1 or 2 (the GPS1/2

Table 1 Main characteristics of 273 patients in study registry 2010–2016

Variable of interest	All patients (n = 273)
Age, mean (±SD)	70 (±9.4)
Median (range)	70 (42–88)
Gender, female/male, number	109/194
(%)	(39%/71%)
Body mass index, mean (±SD)	22.6 (±3.8)
Median (range)	22.1 (14.0–38.9)
Preoperative laboratory data, median (range)	
Total bilirubin, mg/d*L*	0.7 (0.3–12.7)
Albumin, g/d*L*	4.2 (2.2–5.2)
C-reactive protein, mg/d*L*	0.2 (0.0–22.0)
Glasgow prognostic score	0 (0–2)
Neutrophil/lymphocyte ratio	2.3 (0.4–15.9)
Lymphocyte/monocyte ratio	4.5 (0.7–34.3)
Prognostic nutritional index	42.0 (22.0–52.0)
CEA, ng/mL	2.9 (0.0–210.0)
CA19-9, U/mL	39.1 (0.2–148620.0)
Etiology of hepatic disease, number (%)	
HCV antibody positive	43 (16%)
HBs antigen positive	16 (6%)
Operative demographics (%)	
Localization [peripheral type]	176 (64%)
Major hepatectomy*	198 (73%)
Extra hepatic bile duct resection	74 (27%)
Blood loss volume (mL), median (range)	650 (0–22200)
Pathological demographics	
Tumour size (cm), median (range)	4 (1–17)
Periductal infiltration, number (%)	39 (14%)
Undifferentiated adenocarcinoma, number (%)	53 (19%)
Portal venous infiltration, number (%)	121 (44%)
Hepatic arterial invasion, number (%)	16 (6%)
Hepatic vein infiltration, number (%)	77 (28%)
Lymph node metastasis, number (%)	77 (28%)
Intrahepatic metastasis, number (%)	40 (15%)
Positive surgical margin, number (%)	68 (25%)
Peri-operative therapy, number (%)	
Neoadjuvant therapy	6 (2%)
Adjuvant therapy	106 (39%)

HB hepatitis B virus, *HCV* hepatitis C virus, *CEA* preoperative serum carcinoembryonic antigen level, *CA19-9* preoperative serum carbohydrate antigen 19–9 level

*Resection of 3 or more segment of the liver

Table 2 Association of overall survival with clinicopathological characteristics in ICC patients

Demographics	Univariate			Multivariate		
	n	HR (95% CI)	*p*	HR	95% CI	*p*
Gender						
Female	109					
Male	164	1.05 (0.59–2.08)	0.826			
Age						
< 70	137					
≥ 70	136	1.69 (0.85–3.34)	0.064			
GPS						
GPS 0	210					
GPS 1/2	63	3.59 (1.49–8.67)	0.001	1.62	1.04–2.53	0.033
NLR						
< 2.6	162					
≥ 2.6	111	1.44 (1.06–2.49)	0.016	0.92	0.63–1.34	0.650
LMR						
≥ 3.7	186					
< 3.7	87	1.44 (1.03–2.43)	0.022	1.05	0.71–1.57	0.790
PNI						
≥ 40	160					
< 40	113	1.96 (1.17–3.32)	0.035	0.81	0.55–1.19	0.290
CEA						
< 5 ng/mL	204					
≥ 5 ng/mL	69	2.62 (1.17–5.81)	0.001	1.60	1.06–2.41	0.024
CA19-9						
< 40 U/mL	152					
≥ 40 U/mL	121	3.56 (1.75–7.23)	0.001	1.55	1.05–2.30	0.028
Localization						
Peripheral	176					
Perihilar	97	2.58 (1.26–5.27)	0.001	0.63	0.37–1.05	0.073
Surgery						
Non-major hepatectomy	75					
Major hepatectomy	198	1.94 (0.91–4.13)	0.101			
Extra hepatic bile duct resection						
Not performed	199					
Performed	74	2.21 (1.05–4.66)	0.001	0.98	0.58–1.65	0.930
Blood loss volume						
< 500 mL	114					
≥ 500 mL	159	1.33 (0.67–2.63)	0.194			
Tumour size						
< 5 cm	176					
≥ 5 cm	97	1.73 (0.86–3.48)	0.005	1.34	0.90–1.98	0.150
Periductal infiltration						
Absent	234					
Present	39	1.55 (0.61–3.93)	0.726			
Differentiation						
Differentiated	220					
Undifferentiated	53	1.83 (0.80–4.18)	0.006	2.41	1.56–3.67	0.001
Portal venous infiltration						
Absent	152					

Table 2 continued

Demographics	Univariate			Multivariate		
	n	HR (95% CI)	*p*	HR	95% CI	*p*
Present	121	1.93 (0.97–3.84)	0.004	1.03	0.72–1.48	0.880
Hepatic artery invasion						
Absent	257					
Present	16	2.78 (0.60–12.9)	0.475			
Lymph node metastasis						
Absent	196					
Present	77	7.57 (2.79–20.5)	0.001	2.54	1.76–3.67	0.001
Intrahepatic metastasis						
Absent	232					
Present	40	1.71 (0.69–4.21)	0.065			
Surgical margin						
Negative	205					
Positive	68	2.63 (1.14–6.07)	0.001	1.42	0.97–2.08	0.075

HR hazard ratio, *CI* confidence interval, *GPS* Glasgow prognostic score, *NLR* neutrophil/lymphocyte ratio, *LMR* lymphocyte/monocyte ratio, *PNI* prognostic nutritional index, *CEA* preoperative serum carcinoembryonic antigen level, *CA19-9* preoperative serum carbohydrate antigen 19–9 level

group) considering four variables (tumour size, CA19-9 levels, ICC location, and extra hepatic bile duct resection) that we speculated might influence the outcomes of radical surgery.

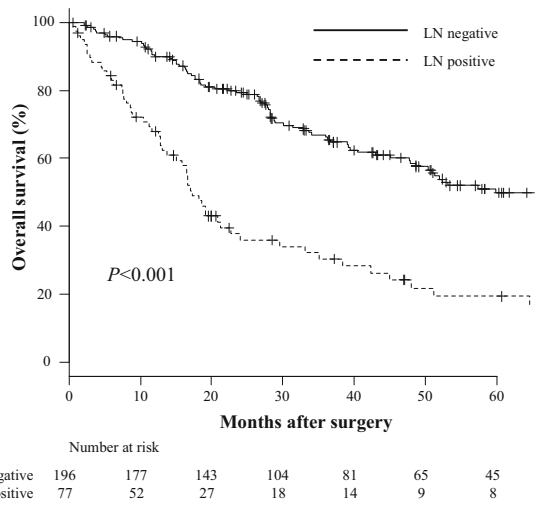
Statistical analysis

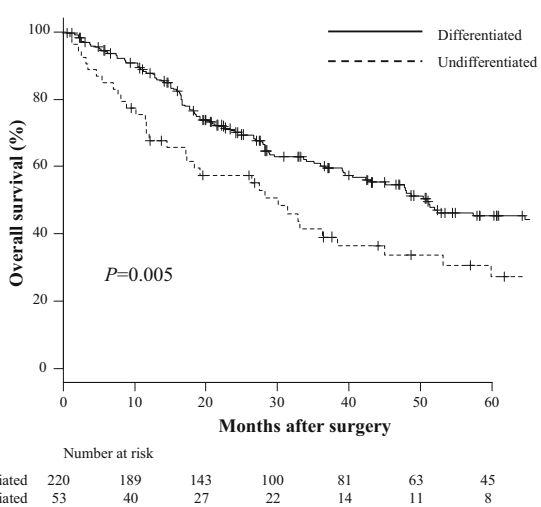
Patient characteristics were compared by a Chi-squared test or Fisher's exact test for the categorical variables and using a *t*test for the continuous variables. The Kaplan–Meier method was used to estimate survival, and those estimates were compared using a log-rank test. Those patients who could not be followed up with were censored by the date of the previous follow-up. A Cox proportional-hazards model multivariate regression analysis determined how presurgical clinicopathological variables affected OS. For this analysis, clinical variables showing values of $p < 0.05$ in univariate analyses were entered into multivariate analysis. The propensity score was made with a logistic regression model using preoperative variables suspected of being correlated with poor outcomes. The model was established by including all significant pre- and peri-operative variables. These variables included tumour size, CA19-9 levels, location of the ICC (i.e. alternative to the ICC with hilum invasion), and extra hepatic bile duct resection. Both GPS0 and GPS1/2 patient groups did a 1:1 nearest available match of the logit of the propensity score with a 0.20 width calliper of the score's standard deviation. Stated *P* values are two-sided, with a statistically significant alpha level of 0.05. Analyses were done with SPSS software (SPSS; Chicago, IL). The nomograms were created with R software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

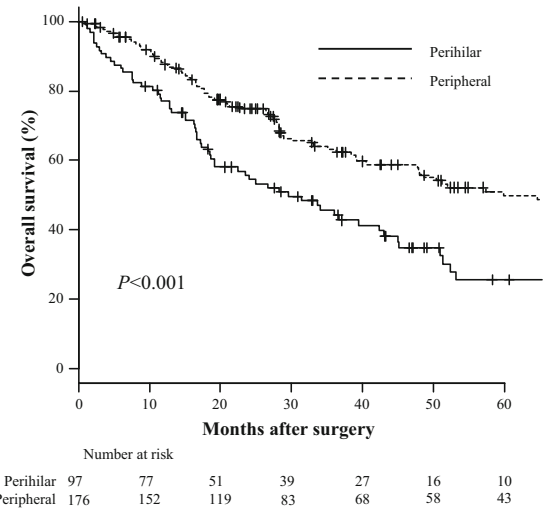
Results

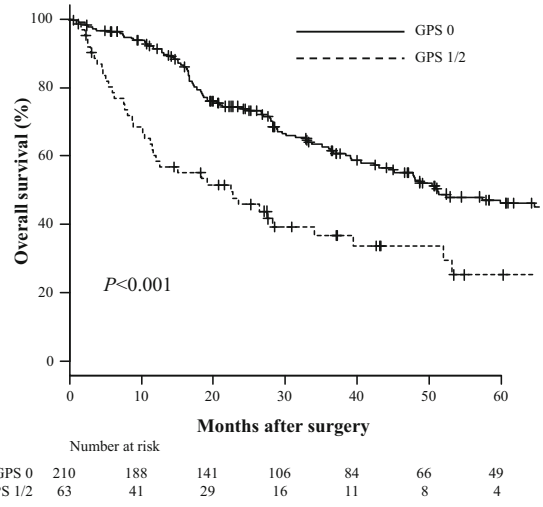
Clinicopathological patient characteristics

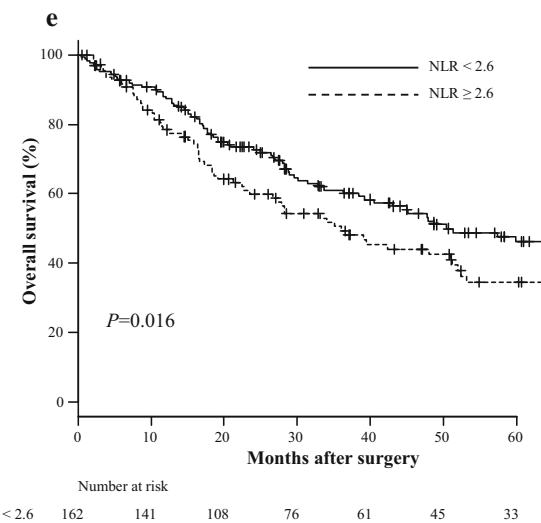
Of the 398 ICC patients in the primary cohort who underwent a liver resection, 273 were included in this study and 125 were rejected for not meeting the criteria for inclusion. Table 1 summarizes the included patient's clinicopathological features (194 men [71%]; median age 70 [range, 42–88] years). CEA was elevated (>5 ng/mL) in 69 patients (25.3%), and CA19-9 was elevated (>35 U/mL) in 131 patients (48.0%). Hepatitis B and hepatitis C were confirmed in 16 (5.9%) and 43 (15.8%) ICC patients, respectively. Major hepatectomies were performed on 198 (73%) patients for ICC, and extra hepatic bile duct resection with hepaticojejunostomy was performed on 74 (27%) patients (Table 1). The median resected ICC size was 4 cm (range, 1–17 cm), and 53 (19.4%) ICC patients had pathologically undifferentiated adenocarcinoma. Surgical resection with intent-to-cure was the operative aim for all patients, of whom 39 (14.3%) patients were pathologically positive for periductal infiltration, 121 (44.3%) for portal venous infiltration, 16 (5.8%) for hepatic arterial invasion, and 77 (28.2%) for hepatic vein infiltration.

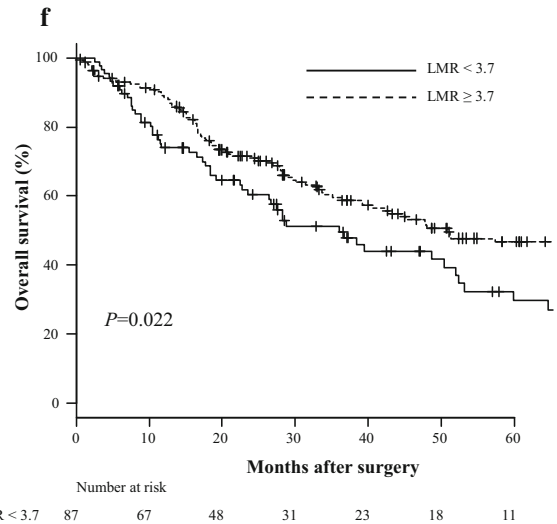

a
LN negative
LN positive
Overall survival (%)
P<0.001
Months after surgery
Number at risk
LN negative 196 177 143 104 81 65 45
LN positive 77 52 27 18 14 9 8


b
Differentiated
Undifferentiated
Overall survival (%)
P=0.005
Months after surgery
Number at risk
Differentiated 220 189 143 100 81 63 45
Undifferentiated 53 40 27 22 14 11 8


c
Perihilar
Peripheral
Overall survival (%)
P<0.001
Months after surgery
Number at risk
Perihilar 97 77 51 39 27 16 10
Peripheral 176 152 119 83 68 58 43


d
GPS 0
GPS 1/2
Overall survival (%)
P<0.001
Months after surgery
Number at risk
GPS 0 210 188 141 106 84 66 49
GPS 1/2 63 41 29 16 11 8 4


e
NLR < 2.6
NLR ≥ 2.6
Overall survival (%)
P=0.016
Months after surgery
Number at risk
NLR < 2.6 162 141 108 76 61 45 33


f
LMR < 3.7
LMR ≥ 3.7
Overall survival (%)
P=0.022
Months after surgery
Number at risk
LMR < 3.7 87 67 48 31 23 18 11

◀**Fig.1** Kaplan–Meier overall survival curves according to the baselines of status of lymph node metastasis **(a)**, tumour differentiation **(b)**, tumour location **(c)**, the Glasgow prognostic score **(d)**, neutrophil/lymphocyte ratio **(e)**, lymphocyte/monocyte ratio **(f)**, and prognostic nutritional index **(g)**

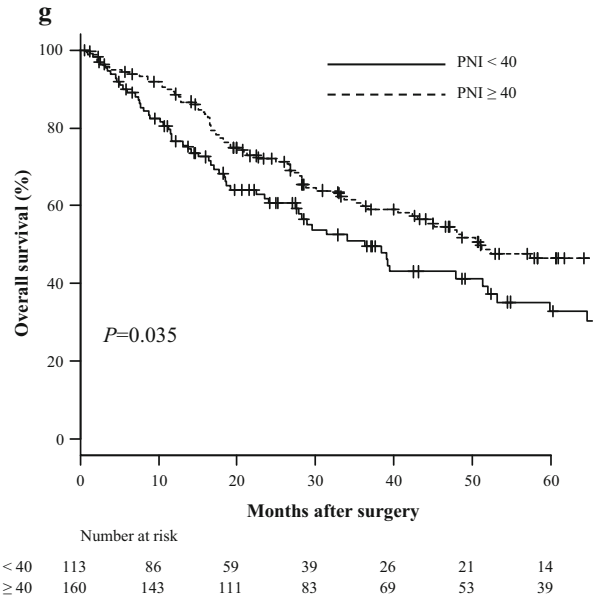


Fig.1 continued

Association of OS with clinicopathological characteristics in ICC patients

The associations between the clinicopathological characteristics and OS are shown in Table 2. Univariate associations of clinicopathological demographics revealed that higher GPS, increasing NLR, reduced LMR, decreasing PNI, elevated CEA and CA19-9 tumour markers, the tumour being situated in the perihilar region, the presence of extra hepatic bile duct resection, a larger tumour size, undifferentiated ICC type, positive metastasis to the lymph nodes, microvascular invasion, and positive surgical margin all were significantly associated with a worse outcome. A multivariate analysis showed an association between the following factors and a worse OS: an increased GPS (hazard ratio = 1.62; 95% CI: 1.04–2.53; P = 0.03), elevated CEA levels (hazard ratio = 1.60; 95% CI: 1.06–2.41; P = 0.02), elevated CA19-9 levels (hazard ratio = 1.55; 95% CI: 1.05–2.30; P = 0.03), undifferentiated carcinoma (hazard ratio = 2.41; 95% CI: 1.53–3.67; P< 0.01), and positive metastasis to the lymph nodes (hazard ratio = 2.54; 95% CI: 1.76–3.67; P< 0.01). In contrast, sex, age, NLR, LMR, PNI, localization of the tumour, type of surgery, blood loss volume, tumour size, periductal infiltration, microvascular invasion, surgical margin status, and additional peri-operative therapy (neoadjuvant and/or adjuvant treatment) did not have a significant association with worse outcomes (Table 2).

Survival

Patients were followed up with until October 2019; the follow-up period varied between 0.5 and 160.9 months. The median follow-up period was 27.6 months (mean follow-up, 37.0 months). The cohort's median overall survival was 47.7 months, with 1-, 3-, and 5-year overall survival rates of 83.8%, 56.3%, and 41.5%, respectively. Obviously, elevated levels of tumour markers, positive metastasis to the lymph nodes, and undifferentiated carcinoma all had worse survival rate associations. From the view point of preoperative physio-biological status, interestingly, positive lymph node metastasis (Fig. 1a), undifferentiated tumour (Fig. 1b), perihilar lesion (Fig. 1c), elevated GPS (Fig. 1d), increasing NLR (Fig. 1e), lower LMR (Fig. 1f), and decreasing PNI (Fig. 1g) were associated with reduced survival.

Analysis after propensity-score matching

On the entire cohort characteristics in this series, the proportion of cases that received a major liver resection together with biliary reconstruction was larger in the GPS1/2 group (P = 0.001) than in the GPS0 group (P = 0.006). The GPS0 group's OS was better than the GPS1/2 group (Fig. 1d). Age, sex, hepatitis viral status, and serum CEA levels had no significant differences between the GPS0 and GPS1/2 groups (Table 3). Presurgical serum CA19-9 levels were significantly higher in the GPS1/2 group (Table 3). The GPS1/2 group's tumour size was significantly higher. The surgery type performed was significantly different between the two groups, with a major hepatectomy performed in 67.6% of patients in the GPS0 group compared to 88.9% of patients in the GPS1/2 group (Table 3). The GPS1/2 group had significantly higher blood loss (median, 945 mL *vs.* 620 mL in the GPS0 group, P = 0.041) and rate of extra hepatic bile duct resection (41.3% *vs.* 22.9% in the GPS0 group), possibly owing to the tumour location (i.e. a peri-hilar-type in 31.4% of the GPS0 group *vs.* 49.2% of the GPS1/2 group; Table 3). The administration of neoadjuvant and/or adjuvant treatment was not significantly different, with only 2.2% of all the included patients receiving neoadjuvant treatment, 39.0% of the GPS0 group received adjuvant therapy, and 38.1% of the GPS1/2 group received adjuvant therapy. In addition, the two groups had no significant difference in pathological findings: carcinoma differentiation, the presence of macrovascular invasion, lymphatic permeation, metastasis to the lymph nodes nor surgical margin status (Table 3).

Table 3 Characteristics of patients before and after propensity score matching

Characteristics	All Pt			Propensity matched Pt	
	GPS 0 $n = 210$	GPS 1/2 $n = 63$	p	GPS 0 $n = 63$	p
Clinical demographics, number (%)					
Female	109 (42.4)	20 (31.7)	0.14	31 (49.2)	0.07
Age ≧ 70	99 (47.1)	37 (58.7)	0.12	33 (52.4)	0.59
Blood chemistry, number (%)					
HBs antigen positive	15 (7.1)	1 (1.6)	0.13	5 (7.9)	0.21
HCV antibody positive	35 (18.2)	8 (14.0)	0.55	6 (9.5)	0.57
CEA ≥ 5 ng/mL	48 (22.9)	21 (33.3)	0.10	16 (25.4)	0.43
CA19-9 ≥ 40 U/mL	86 (41.0)	35 (55.6)	0.04	35 (55.6)	1.00
Operative demographics, number (%)					
Major hepatectomy*	142 (67.6)	56 (88.9)	0.01	50 (79.4)	0.22
EHBDR	48 (22.9)	26 (41.3)	0.01	26 (41.3)	1.00
Blood loss volume ≥ 500 mL	115 (54.8)	44 (69.8)	0.04	34 (54.0)	0.10
Pathological demographics, number (%)					
Tumour size ≥ 5 cm	63 (30.0)	34 (54.0)	0.01	34 (54.0)	1.00
Perihilar type	66 (31.4)	31 (49.2)	0.01	32 (50.8)	1.00
Periductal infiltration	31 (14.8)	8 (12.7)	0.84	10 (15.9)	0.80
Undifferentiated type	37 (17.6)	16 (25.4)	0.20	8 (12.7)	0.11
Portal venous infiltration	88 (41.9)	33 (52.4)	0.15	33 (52.4)	1.00
Hepatic arterial invasion	13 (6.2)	3 (4.8)	1.00	6 (9.5)	0.49
Hepatic vein infiltration	57 (27.1)	20 (31.7)	0.52	26 (41.3)	0.36
Lymph node metastasis	57 (27.1)	20 (31.7)	0.52	21 (33.3)	1.00
Intrahepatic metastasis	31 (14.8)	9 (14.3)	1.00	9 (14.3)	1.00
Positive surgical margin	48 (22.9)	20 (31.7)	0.18	22 (34.9)	0.85
Peri-operative therapy, number (%)					
Neoadjuvant therapy	3 (1.4)	3 (4.8)	0.14	2 (3.2)	1.00
Adjuvant therapy	82 (39.0)	24 (38.1)	1.00	20 (31.7)	0.58

Pt patients, *HB* hepatitis B virus, *HCV* hepatitis C virus, *CEA* preoperative serum carcinoembryonic antigen level, *CA19-9* preoperative serum carbohydrate antigen 19–9 level, *EHBDR* extra hepatic bile duct resection

*Resection of 3 or more segment of the liver

The GPS was significantly associated with the tumour size, CA19-9 levels, anatomic location of the primary cancer, and the resection of the extra hepatic bile duct when the demographic data were stratified as GPS0 and GPS 1/2. Propensity score matching yielded a final cohort of 126 patients (63 patients in each group) who were eligible for further analyses. After matching, the GPS0 group had better OS than the GPS1/2 group did (Fig. 2). In the GPS0 group, the median OS was 50.9 months, with 1-, 3-, and 5-year OS rates of 92.0%, 57.1%, and 44.7%, respectively. The GPS1/2 group had a median OS of 22.4 months, with 1-, 3-, and 5-year OS rates of 58.5%, 36.7%, and 25.2%, respectively ($P < 0.001$). The multivariate analysis revealed that higher age, GPS, localization of the tumour, undifferentiated carcinoma, and positive metastasis to the lymph nodes were independent risk factors leading to poorer OS (Table 4). Currently, the postoperative prognosis for ICC patients is primarily based on the pathological examination according to the TNM staging system. Importantly, stage classification of a disease is essential before the surgical treatment to make a diagnosis based on the pretreatment information of the ICC. R software was used to create a prognostic nomogram (Fig. 3). The C-index of the nomograms for OS was 0.725, using the preoperative physio-biological parameters of GPS, CEA, and CA19-9.

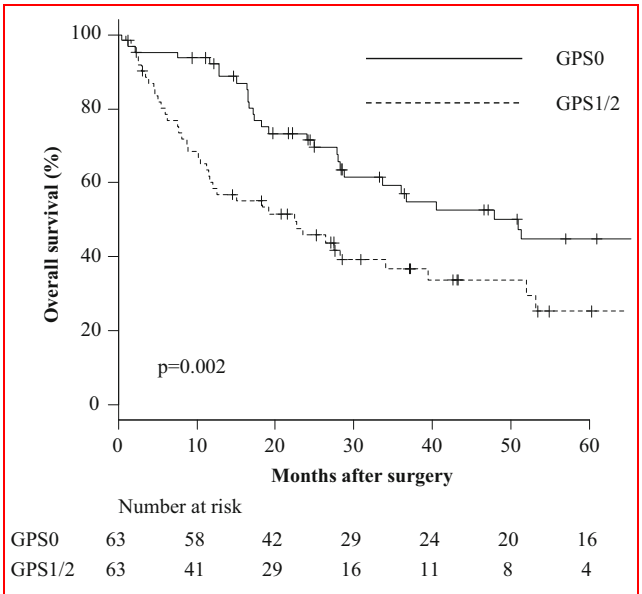


Fig.2 Kaplan–Meier analysis of the overall survival after propensity score matching according to baseline GPS

Discussion

This study demonstrated that the GPS (calculated from preoperative serum albumin and CRP levels) can help predict ICC patient survival after a curative resection. The GPS is a known prognostic factor for various cancers and is frequently an indicator of tumour size, TNM classification, and lymph node metastasis [16, 17]. Therefore, to eliminate the effect of other prognostic factors, the cohort in the present study was matched for four factors: tumour size, CA19-9 level, anatomic location of the primary cancer, and extra hepatic bile duct resection, all of which were prognostic factors on univariate analysis for OS and were associated with the GPS. Upon propensity score matching, the GPS showed itself to be a prognostic independent factor under multivariate analysis. As far as we are aware, this large-scale cohort study is the first to show that the GPS is an independent prognostic factor for ICC patients [18].

Cancer is a complex disease due to the cells intrinsic and extrinsic processes [19]. Systemic inflammation along with malnutrition status are well-established factors that are

Table 4 Association of overall survival with clinicopathological characteristics in ICC patients after propensity score matching

Demographics	Univariate			Multivariate		
	n	HR (95% CI)	*p*	HR	95% CI	*p*
Gender						
Female	51					
Male	75	1.37 (0.50–3.78)	0.431			
Age						
< 70	56					
≥ 70	70	2.43 (0.88–6.73)	0.033	1.83	1.11–3.02	0.018
GPS						
GPS 0	63					
GPS 1/2	63	2.96 (1.05–8.40)	0.016	2.49	1.49–4.17	0.001
CEA						
< 5 ng/mL	89					
≥ 5 ng/mL	37	2.01 (0.67–6.05)	0.052			
CA19-9						
< 40 U/mL	56					
≥ 40 U/mL	70	2.08 (0.78–5.53)	0.057			
Localization						
Peripheral	63					
Perihilar	63	5.77 (1.88–17.7)	0.001	3.13	1.39–7.14	0.006
Surgery						
Non-major hepatectomy	20					
Major hepatectomy	106	6.92 (1.43–33.5)	0.003	1.71	0.68–4.26	0.250
Extra hepatic bile duct resection						
Not performed	74					
Performed	52	2.99 (1.03–8.66)	0.006	0.65	0.29–1.45	0.300
Blood loss volume						

Table 4 continued

Demographics	Univariate			Multivariate		
	n	HR (95% CI)	*p*	HR	95% CI	*p*
< 500 mL	48					
≥500 mL	78	1.53 (0.56–4.19)	0.162			
Tumour size						
< 5 cm	58					
≥ 5 cm	68	0.98 (0.37–2.63)	0.544			
Periductal infiltration						
Absent	18					
Present	108	1.72 (0.47–6.31)	0.860			
Differentiation						
Differentiated	102					
Undifferentiated	24	6.30 (1.19–33.3)	0.001	3.13	1.82–5.39	0.001
Portal venous infiltration						
Absent	60					
Present	66	1.84 (0.68–5.03)	0.290			
Hepatic artery invasion						
Absent	117					
Present	9	0.93 (0.15–6.00)	0.180			
Lymph node metastasis						
Absent	85					
Present	41	10.5 (1.95–56.6)	0.001	2.85	1.72–4.72	0.001
Intrahepatic metastasis						
Absent	108					
Present	18	1.15 (0.31–4.26)	0.205			
Surgical margin						
Negative	84					
Positive	42	2.42 (0.77–7.64)	0.035	1.38	0.83–2.30	0.210

correlated with a poor prognosis in various tumours. The proliferation, angiogenesis, and metastasis of a tumour are closely associated with its related inflammation responses [20]. CRP, an acute phase protein thought to be a predictor of infection, is induced by pro-inflammatory cytokines after being synthesized in the liver. Elevated CRP levels can also be seen during tumour metastasis. Albumin, a protein that circulates in the plasma, can additionally be part of the inflammatory response. Therefore, the GPS may be an indicator of the potential inflammatory status in the body. Furthermore, both inflammation and malnutrition are known to associate with a lower quality of life as well as having negative effects on the treatment effectiveness of patients with cancer [21]. The GPS can show the inflammatory and nutritional status of patients during their treatment as a variable that can be quantified continuously. This study shows that a higher GPS can be a useful and remarkable predictor of poorer OS in ICC patients who underwent a liver resection.

On multivariate analysis after propensity score matching, positive metastasis to the lymph nodes and histopathological undifferentiated carcinoma were both independent pathological prognostic factors. However, these factors were only available from specimens obtained after resection. An evaluation before surgical treatment is essential, and it is important to make a diagnosis based on preoperative information about the ICC, especially because some investigators assert that ICC is a systemic disease and should be treated with systemic therapy [22]. We believe that patients with ICC are at high risk of poor outcomes after medical management and should be identified using simple baseline clinical and laboratory parameters. Accordingly, the results here show that high GPS patients might need adjuvant therapy to increase the chance of prolonging life expectancy even though surgery is the only

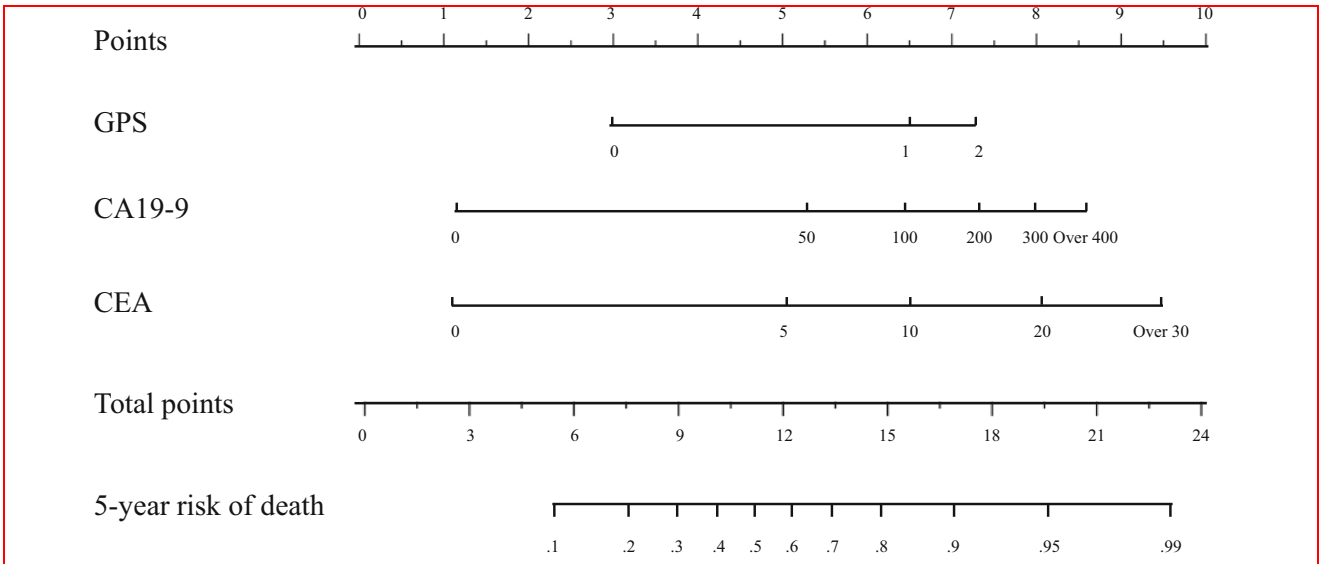


Fig.3 Predictive nomograms of overall survival in ICC patients following a resection; *C*-index = 0.725. *GPS* Glasgow prognostic score, *CEA* carcinoembryonic antigen *CA19-9* carbohydrate antigen 19–9

potential curative treatment for localized biliary tract cancer [23].

The cohort sample size was a factor which limits our subgroup analyses but was well-characterized and diverse considering the associations between the key prognostic factor, i.e. the GPS, and the long-term outcomes after surgical treatment for patients with ICC. Some other limitations in the study included the retrospective nature of the work and the fact that the patients were enrolled from multiple institutions in Japan, where the risk factors are different from those of patients in Western countries considering the carcinogenesis of ICC [24]. In addition, we did not analyse the change in trends of postoperative GPS, because the follow-up protocol was different between participating facilities. Moreover, patients who had underwent a curative resection were the only ones included in our study. A convalescence nomogram of the ICC was established by the combination of GPS, CEA, and CA19-9. This nomogram was highly predictive, similar to the classification system for conventional TNM stages of ICC. Nevertheless, despite the aforementioned limits, the finding of this study focuses on the protocol design and most suitable allocation of the treatment plan based on the individual characteristics of each ICC patient.

To date, the prognosis for ICC uses the complex pathological TNM classification and is postoperatively assessed. The GPS system is a biochemically simple test using preoperative serum CRP and albumin levels. This study showed that GPS, a novel and easily administered inflammation examination, had strong prognostic capability for ICC patients who underwent a curative resection. A high GPS is a negatively correlated biomarker for the overall survival of ICC patients after a hepatectomy. Accordingly, using the GPS to improve the accuracy of the preoperative prognosis may aid in the appropriate selection of patients for surgical treatment.

Acknowledgements The authors thank their colleagues who contributed to data collection for this study: Kazuyasu Kobayashi (Sumitomo Besshi Hospital), Toshihiro Murata (Onomichi Municipal Hospital), Hideki Aoki (National Iwakuni Medical Center), Yasuhiko Ishida (Himeji Central Hospital), and Nobuhiro Ishido (Kobe Red Cross Hospital). The authors wish to thank Dr. Tomokazu Fuji and Kazuhiro Yoshida for giving technical assistance.

Funding This study was financially supported by the Japan Society for the Promotion of Science (JSPS), Grant Number 19K09217 to Yuzo Umeda.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

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