Examination of the modified Glasgow Prognostic Score and other prognostic factors in patients undergoing hepatectomy for naïve hepatocellular carcinoma: A retrospective observational study

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Abstract

Aim: **To identify prognostic factors in patients undergoing hepatectomy for hepatocellular carcinoma (HCC), including the modified Glasgow Prognostic Score (mGPS) with a C-reactive protein (CRP) cutoff value of 0.5 mg/dl.**

Methods: **All study participants underwent hepatectomy for naïve HCC at Kindai University Hospital between January 2004 and December 2013. Their medical records were reviewed retrospectively to identify prognostic factors including the mGPS. Patients with elevated CRP levels (>0.5 mg/dl) and hypoalbuminemia (<3.5 g/dl) were assigned an mGPS score of 2 (mGPS2), those with one of these factors were allocated a score of 1 (mGPS1) and patients with neither factor were allocated a score of 0 (mGPS0). The patients were then divided into an mGPS1–2 group (including mGPS1 and mGPS2; n = 51) and an mGPS0 group (n = 150).**

Results: **There were significant differences between the groups regarding tumor diameter, PIVKA-II expression, microvascular invasion, and TNM stage. Kaplan–Meier analysis revealed that patients in the mGPS1–2 group had a significantly poorer prognosis in terms of overall survival and disease-free survival than those in the mGPS0 group. In a multivariate analysis using the Cox proportional hazards model, TNM stage and mGPS were independent prognostic factors for disease-free survival, while alpha-fetoprotein level, intraoperative blood loss, and mGPS were independent prognostic factors for overall survival.**

Conclusion: **Tumor-related factors, intraoperative blood loss, and mGPS are important prognostic factors in patients who have been treated surgically for HCC. An mGPS with a CRP cutoff value of 0.5 mg/dl is a useful prognostic factor.**

Key words: hepatocellular carcinoma; hepatectomy; modified GPS; prognostic factors

Introduction

Liver cancer is the seventh most common cancer worldwide and the third leading cause of cancer-related deaths, and is particularly prevalent in Asia [1]. Hepatocellular carcinoma (HCC) is the most frequently encountered primary liver tumor. The recent implementation of surveillance programs has enabled the early diagnosis of HCC, which has resulted in an increased likelihood of curative treatment, resulting in 5-year survival rates of up to 75% [2]. However, even patients with HCC who undergo curative hepatectomy remain at high risk of recurrence, and at least 60% of these patients experience recurrence within 5 years [3]. Moreover, there is no evidence that adjuvant chemotherapy improves outcomes in these patients.

There are currently several treatment options for

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HCC, including surgery, radiofrequency ablation, transarterial chemoembolization, and molecular targeted therapy. Treatment decisions are made after considering various tumor factors, as well as liver function and performance status, which are included in the Barcelona Clinical Liver Cancer Guidelines[4]. The Clinical Practice Guidelines for Hepatocellular Carcinoma devised by the Japan Society of Hepatology also take tumor factors and liver function into consideration[5]. Appropriate treatment is chosen by the treating clinicians, given that all therapeutic options have been proven effective[6-8]. Liver transplantation can be the most effective treatment in terms of curing the malignancy and retaining liver function, but obtaining sufficient numbers of donors and grafts for liver transplantation is difficult. Therefore, living-donor liver transplant is more common than deceased-donor liver transplant for patients with HCC, particularly in Japan[9, 10].

At our institution, we treat HCC surgically with curative intent whenever possible according to the guidelines[5]. It is recognized that there are other treatments that are effective, that recurrence is common, and that treatment is effective even after recurrence[11-13]. Therefore, we believe that the indications for surgery should be strict and that research on prognostic factors is important for the selection of effective treatments.

Prognostic factors identified in previous reports include tumor diameter, tumor number, vascular invasion, and liver function[14-16]. These factors have been incorporated into treatment guidelines and are still considered when selecting treatment[5]. Inflammation-based scoring systems are also useful for predicting prognosis in patients with HCC, such as the Glasgow Prognostic Score (GPS), the modified Glasgow Prognostic Score (mGPS), the controlling nutritional status (CONUT) score, and neutrophil-to-lymphocyte ratio[17-21]. Toiyama et al. reported the original mGPS, which has a C-reactive protein (CRP) cutoff value of 0.5 mg/dl[22]. Toiyama's mGPS has since been investigated in colorectal cancer and was found to be a prognostic factor related to disease progression[22, 23]. However, there has been no research on the prognostic value of the mGPS with a CRP cutoff value of 0.5 mg/dl for HCC.

In this study, we sought to determine the prognostic features, including the mGPS proposed by Toiyama et al., of patients undergoing surgery for HCC.

Patients and methods

The study was a retrospective analysis of pooled data from Kindai University Hospital. The study was approved by Kindai University Institutional Review Board and included on the institutional website (review board member: 29-099). Informed consent was waived because of the retrospective nature of the study, and the analyses used anonymous clinical data, which were accumulated on an opt-out basis. All patients underwent hepatic resection for naïve HCC at our institution between January 2004 and December 2013. Patients were excluded if their initial surgery was not curative according to the General Rules for Clinical and Pathological Study of Primary Liver Cancer of the Liver Cancer Study Group of Japan. Therefore, even if a tumor thrombus in a major blood vessel was removed, it was defined as non-curative according to the Japanese criteria.

Diagnosis

HCC was diagnosed using various imaging modalities, including computed tomography and magnetic resonance imaging. Tumors were diagnosed as HCC, with enhancement in the arterial phase and washout in the portal phase.

Patient follow-up

All participants underwent imaging examinations within 6 months after surgery. Subsequent examinations were performed every 6 months. All recurrences were diagnosed based on the imaging examinations.

Data collection

Clinicopathological data, including age, sex, hepatitis virus infection status (hepatitis B surface antigen or anti-hepatitis C virus antibody), history of treatment for hypertension, heart disease, or diabetes mellitus, total bilirubin, serum albumin (ALB), indocyanine green test results, platelet count, prothrombin time, CRP, alpha-fetoprotein, protein induced by vitamin K absence or antagonist II (PIVKA-II) expression, and body mass index (calculated as kg/m^2) were obtained in the month before surgery. Tumor-related factors were obtained from surgical specimens and included maximum tumor size, tumor number, microvascular invasion (MVI), degree of histological differentiation (according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer of the Liver Cancer Study Group of Japan), tumor-node-metastasis (TNM) stage, operating time, and

intraoperative blood loss.

Patients with elevated CRP levels (>0.5 mg/dl) and hypoalbuminemia (<3.5 g/dl) were allocated an mGPS score of 2 (mGPS2), those with only one factor were allocated an mGPS score of 1 (mGPS1), and patients with neither factor were allocated a score of 0 (mGPS0). The patients were then divided into mGPS1–2 (including mGPS1 and mGPS2) and mGPS0 groups.

Statistical analysis

Clinicopathological findings were compared between patients in the mGPS0 group and patients in the mGPS1–2 group using the Mann–Whitney U test. Categorical variables were compared using Fisher's exact test. The Kaplan–Meier method and the log-rank test were used to compare overall survival (OS) and disease-free survival (DFS). Univariate and multivariate analyses were performed to identify statistically significant prognostic factors using SPSS software version 21.0 (IBM Corp., Armonk, NY).

Results

A total of 201 patients with treatment-naïve HCC underwent hepatectomy at our institution between January 2004 and December 2013. The median follow-up duration was 60.2 months. There were 51 patients in the mGPS1–2 group and 150 patients in the mGPS0 group. There were no significant differences between the groups regarding total bilirubin, indocyanine green test results, or prothrombin time, all of which are indicators of liver function. However, there were significant differences in tumor diameter, PIVKA/II level, MVI, and TNM stage, which are indicators of HCC progression. Therefore, patients in the mGPS1–2 group may have had advanced HCC (Table 1).

Kaplan–Meier analysis showed that the mGPS1–2 group had poorer OS than the mGPS0 group (P =

Table 1 Clinicopathological characteristics according to the modified Glasgow Prognostic Score

Variable	mGPS1–2 group (n=51)	mGPS0 group (n=150)	P-value
Age (years)	68(36-86)	70(39-88)	0.261
Sex (male/female)	40/11	116/34	0.871
Hepatitis virus infection (yes/no)	31/20	105/45	0.224
Diabetes mellitus (yes/no)	38/13	101/49	0.338
Heart disease (yes/no)	5/46	17/133	0.762
Hypertension (yes/no)	20/31	69/81	0.399
Total bilirubin (mg/dl)	0.7(0.3-2.0)	0.7(0.2-1.7)	0.350
Albumin (g/dl)	3.4(2.6-4.8)	4.2(3.5-5.1)	<0.001*
ICG R15 (%)	14(0-61)	13(0-65)	0.116
Platelets (104/mm)	17.8(5.3-176)	16.5(4.4-35)	0.233
Prothrombin time (%)	86(59-120)	90(45-120)	0.147(t)
C-reactive protein (mg/dl)	0.81(0.02-26)	0.08(0.01-0.49)	<0.001*
Alpha-fetoprotein (ng/ml)	13.5(0-72570)	10.0(0-24627)	0.221
PIVKA II (mAU/ml)	265(0-322960)	75(0-52927)	0.005*
Maximum tumor diameter (cm)	6.8(1.5-18)	3.5(0.8-18)	<0.001*
Tumor number (single/multiple)	33/18	114/36	0.116
Microvascular invasion (yes/no)	21/30	31/119	0.004*
Degree of histological differentiation (well/other)	11/40	36/114	0.723
TNM stage (I or II/III or IV)	36/15	135/15	0.001*
Resection of two or more segments (yes/no)	30/21	69/81	0.068
Operating time (min)	255(120-945)	262(89-570)	0.891
Intraoperative bleeding (ml)	1120(5-11300)	945(5-10501)	0.623
Body mass index	22.9(17.2-31.1)	23.3(13.9-33.7)	0.216

Asterisks (*) indicate statistical significance. Chi-squared test/Mann–Whitney U test/(t): t-test. ICG, indocyanine green; mGPS, modified Glasgow Prognostic Score; PIVKA II, protein induced by vitamin K absence or antagonist II; TNM, tumor-node-metastasis

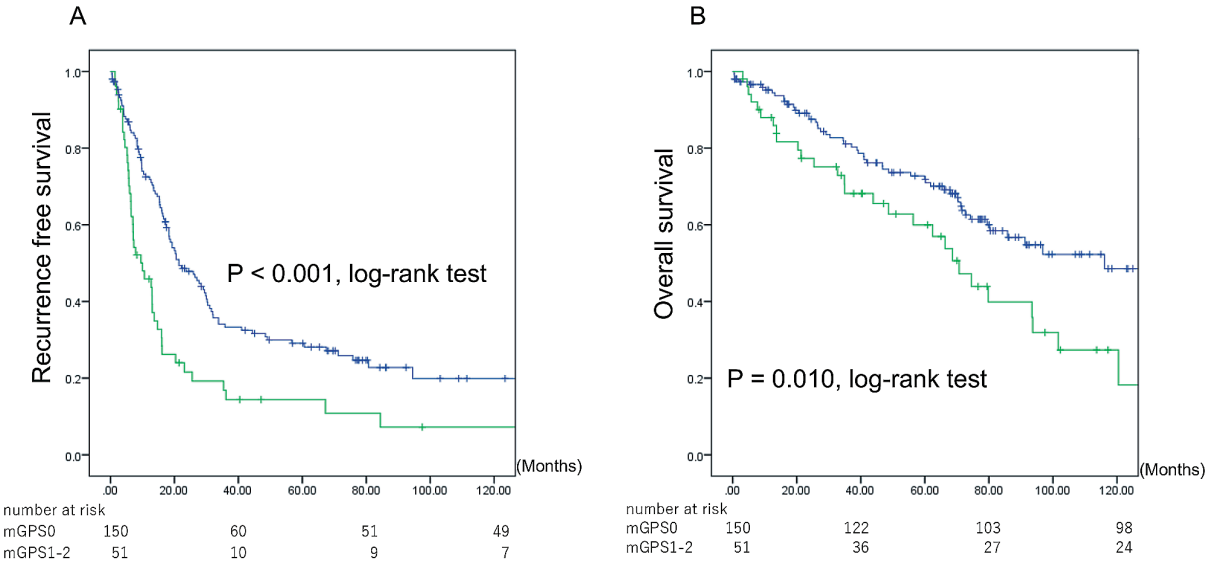

Figure 1. Kaplan–Meier analysis of (A) disease-free survival and (B) overall survival. The blue line indicates mGPS0 and the green line indicates mGPS1–2.

Table 2. Univariate and multivariate analyses of factors contributing to disease-free survival

		Univariate analysis		Multivariate analysis	
Variable	Patients, n	P-value	HR	95% CI	P-value
Age >70 years (yes/no)	90/111	0.030*	0.762	0.541–1.071	0.118
Sex (male/female)	156/45	0.901			
Hepatitis virus infection (yes/no)	136/65	0.509			
Diabetes mellitus (yes/no)	62/139	0.952			
Heart disease (yes/no)	22/179	0.070			
Hypertension (yes/no)	89/112	0.504			
Total bilirubin >1.0 mg/dl (yes/no)	32/169	0.920			
Albumin >4.0 g/dl (yes/no)	103/98	0.459			
ICG R15 >15% (yes/no)	125/71	0.451			
Platelets >15 × 104/mm (yes/no)	121/80	0.545			
Prothrombin time >80% (yes/no)	156/45	0.105			
C-reactive protein >0.5 mg/dl (yes/no)	32/169	<0.001*			
Alpha-fetoprotein >50 ng/ml (yes/no)	59/138	0.086			
PIVKA II >40 mAU/ml (yes/no)	125/67	0.607			
Maximum tumor diameter >2 cm (yes/no)	167/34	0.006*			
Tumor number (single/multiple)	147/54	<0.001*			
Microvascular invasion (yes/no)	52/149	0.007			
Degree of histological differentiation (well/other)	47/154	0.084			
TNM stage (Ⅰ or Ⅱ / Ⅲ or Ⅳ)	171/30	<0.001*	0.517	0.327–0.819	0.005*
Operating time >300 min (yes/no)	60/141	0.042*	1.278	0.900–1.813	0.170
Intraoperative bleeding >1000 ml (yes/no)	101/100	0.059			
mGPS score (1 or 2/0)	51/150	<0.001*	1.685	1.153–2.464	0.007*
Body mass index >25 (yes/no)	53/148	0.300			

Asterisks (*) indicate statistical significance. CI, confidence interval; HR, hazard ratio; ICG, indocyanine green; mGPS, modified Glasgow Prognostic Score; PIVKA II, protein induced by vitamin K absence or antagonist II; TNM, tumor-node-metastasis

0.01, log-rank test). The 5-year survival rate was 60% in the mGPS1–2 group and 71.9% in the mGPS0 group, and 10-year survival rates were 27.4% and 48.5% respectively. DFS was significantly poorer in the mGPS1–2 group; 5-year DFS rates were 14.4% in the mGPS1–2 group and 29.1% in the mGPS0 group, and 10-year DFS rates were 7.2% and 19.9%, respectively ($P < 0.001$, log-rank test; Fig 1). There were 90 recurrences of HCC in the mGPS0 group, 84 of which were intrahepatic. Of these, seven cases underwent resection. There were 40 recurrences in the mGPS1–2 group, none of which were resected. There was no significant difference between the groups regarding the treatment modality provided after recurrence.

In univariate analysis using the Cox proportional hazards model, age, CRP, maximum tumor diameter, tumor number, MVI, TNM stage, and mGPS were found to have a significant effect on DFS. CRP is one of the elements that defines the mGPS. Tumor diameter, tumor number, and MVI are the elements that define the TNM stage. Age, TNM stage, and mGPS were entered into the multivariate analysis, which revealed that TNM stage and mGPS were independent prognostic factors for DFS (Table 2). In the univariate analysis, DFS, ALB, CRP, alpha-fetoprotein, tumor number, MVI, degree of histological differentiation, TNM stage, intraoperative blood loss, and mGPS were prognostic factors for OS. However, only alpha-fetoprotein level, intraoperative blood loss, and mGPS were identified as statistically significant independent prognostic factors for OS in the multivariate analysis (Table 3).

Table 3. Univariate and multivariate analyses of factors contributing to overall survival

		Univariate analysis	Multivariate analysis		
Variable	Patients, n	P-value	HR	95% CI	P-value
Age >70 years (yes/no)	90/111	0.602			
Sex (male/female)	156/45	0.655			
Hepatitis virus infection (yes/no)	136/65	0.769			
Diabetes mellitus (yes/no)	62/139	0.565			
Heart disease (yes/no)	22/179	0.077			
Hypertension (yes/no)	89/112	0.653			
Total bilirubin >1.0 mg/dl (yes/no)	32/169	0.885			
Albumin >4.0 g/dl (yes/no)	103/98	0.009*			
ICG R15 >15% (yes/no)	125/71	0.112			
Platelets >15 × 10^4/mm (yes/no)	121/80	0.427			
Prothrombin time >80% (yes/no)	156/45	0.452			
C-reactive protein >0.5 mg/dl (yes/no)	32/169	0.001*			
Alpha-fetoprotein >50 ng/ml (yes/no)	59/138	0.011*	1.697	1.049–2.746	0.031*
PIVKA II >40 mAU/ml (yes/no)	125/67	0.420			
Maximum tumor diameter >2 cm (yes/no)	167/34	0.124			
Tumor number (single/multiple)	147/54	0.003*			
Microvascular invasion (yes/no)	52/149	<0.001*			
Degree of histological differentiation (well/other)	47/154	0.024*	0.570	0.298–1.093	0.091
TNM stage (Ⅰ or Ⅱ/Ⅲ or Ⅳ)	171/30	<0.001*	0.611	0.343–1.087	0.094
Operating time >300 min (yes/no)	60/141	0.066			
Intraoperative bleeding >1000 ml (yes/no)	101/100	0.001*	1.922	1.183–3.121	0.008*
mGPS score (1 or 2/0)	51/150	0.013*	1.644	1.001–2.698	0.049*
Body mass index >25 (yes/no)	53/148	0.311			

Asterisks (*) indicate statistical significance. CI, confidence interval; HR, hazard ratio; ICG, indocyanine green; mGPS, modified Glasgow Prognostic Score; PIVKA II, protein induced by vitamin K absence or antagonist II

Discussion

The choice of treatment for HCC recommended by the Barcelona Clinical Liver Cancer Guidelines and the Clinical Practice Guidelines for Hepatocellular Carcinoma indicated by the Japan Society of Hepatology has reached a degree of consensus[4, 5]. In these guidelines, the algorithm used to select treatment is based on both liver function and tumor factors. In general, to select surgery or radiofrequency ablation with an emphasis on local control, liver function should be Child–Pugh class A or B with no extrahepatic metastasis and no more than three tumors. Portal hypertension and vascular invasion are also considered. However, even if treatment is selected according to the algorithm, recurrence is common[3]. Therefore, additional factors are required when assessing the indications for surgery or other treatment.

Several papers have described a systemic immune-inflammation index that is not among the prognostic factors included in the algorithms recommended by the Barcelona Clinical Liver Cancer Guidelines or the Clinical Practice Guidelines for Hepatocellular Carcinoma. The two guidelines focus on liver function and cancer progression as factors in liver cancer treatment selection[4, 5]. These reports suggest that preoperative GPS, mGPS, prognostic nutrition index, neutrophil-to-lymphocyte ratio, CRP-to-albumin ratio, and CONUT score are useful prognostic factors in patients undergoing surgery for HCC[17-21, 24, 25]. These factors are also recognized as an immunonutrition index, which indicates nutritional status, immune status, and inflammation, and is closely related to tumor-associated inflammation. When cancer growth or invasion occurs, cytokines including tumor necrosis factor, interleukin (IL)-6, IL-8, and vascular endothelial growth factor are released from the cancer cells and surrounding tissues[26.] These cytokines cause tumor-related angiogenesis and immunosuppression[26]. Therefore, this index reflects the spread of cancer and is considered to be a prognostic factor independent of the degree of progression determined by imaging.

In this study, we focused on mGPS as a prognostic factor in patients undergoing hepatectomy for HCC. The mGPS is an index that contains serum ALB and CRP as elements. However, of these, only elevated CRP has been associated with the prognosis of various cancer types[27-31]. In addition, elevated CRP has been reported to be a poor prognostic factor in HCC[32, 33]. CRP is synthesized in the liver in response to inflammation and is regulated by proinflammatory cytokines such as IL-6. HCC cells have also been confirmed to produce IL-6, and a correlation has been observed between CRP and IL-6 levels[34, 35]. Furthermore, ALB is an indicator of both nutritional status and liver function and has been reported to be a prognostic factor in patients undergoing surgery for HCC. Nojiri et al. showed that hypoalbuminemia was a significant risk factor for distant recurrence of HCC[36]. Moreover, they found that the risk of distant recurrence was higher in patients with low ALB levels after treatment, even if the previous ALB value was high enough. In studies of other types of cancer, serum ALB level was found to be a predictor of poor prognosis[37-39]. However, the mechanism underlying the relationship between serum ALB and cancer prognosis is not fully understood. Nojiri and Joh reported that ALB suppresses the proliferation of HCC cells in vitro[40].

In this study, we used mGPS as an index, which has a CRP cutoff value of 0.5 mg/dl. Although there are reports on the use of this index to predict prognosis in colorectal cancer, there are none on its use in HCC[22, 23]. We found the mGPS to be a predictor of the prognosis before surgery for HCC.

We found no significant difference in total bilirubin, ICG, prothrombin time, or body mass index between the GPS0 and GPS1–2 groups but did identify a significant difference in alpha-fetoprotein levels, MVI, and TNM stage. The differences between the GPS0 and GPS1–2 groups in this study reflect the progression of liver cancer rather than a difference in liver function or nutritional status, which is consistent with the reports of Ni et al. and Kinoshita et al.[41, 42]. Ni et al. commented that this was because their subjects had a level of liver function that could tolerate surgery. In this study, we examined a similar population, and the results were concordant with those of the previous study.

Intraoperative blood loss was also identified as an independent prognostic factor. Blood loss and the need for blood transfusion during surgery are associated with a worse prognosis in patients with HCC[43, 44]. Lee et al. speculated that massive bleeding could cause cancer cells to spread, promote weakened anticancer immunity, and lead to tissue inflammation due to systemic hypoperfusion, resulting in shorter OS and DFS[43]. Furthermore, Harada at al. reported that allogeneic leukocytes in blood transfusions mediate the suppression of immune function and that transfusion-related iron overload worsens liver fibrosis and the prognosis of patients with HCC[44]. Therefore, minimizing bleeding and the need for

blood transfusion during surgery is important for improving treatment outcomes.

Conclusion

Tumor-related factors, intraoperative blood loss, and mGPS with a CRP cutoff value of 0.5 mg/dl are important prognostic factors after surgery for HCC. The mGPS value also reflects the progression of HCC. Prospective studies in which other treatments may be selected are needed to confirm the value of the mGPS and other immunonutrition indices as independent prognostic factors in HCC.

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Conflicts of interest
The authors declare that they have no conflicts of interest.

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