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Original Article

Comparison of the prognostic value of C-reactive protein-based prognostic scores in patients with hepatitis B virus-related hepatocellular carcinoma

Jian-Qiang Wang[1], Pi-Guang Cheng[1], Meng-Yu Li[2], Lian-Mei Ma[3]

[1]Department of General Surgery I, The People's Hospital of Binzhou, No. 551, Yellow-River Seventh Street, Binzhou 256603, People's Republic of China; [2]Department of General Surgery III, The People's Hospital of Binzhou, No. 551, Yellow-River Seventh Street, Binzhou 256603, People's Republic of China; [3]Department of Pediatrics, The Affiliated Hospital of Binzhou Medical University, No. 661, Yellow-River Second Street, Binzhou 256603, People's Republic of China

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Abstract: Objectives: C-reactive protein (CRP) based prognostic scores including the modified Glasgow Prognostic Score (mGPS), prognostic index (PI) and CRP/albumin ratio have been reported to be associated with survival in cancer patients. The aim of this study was to compare the prognostic value of these CRP-based prognostic scores in patients with hepatitis B virus-related hepatocellular carcinoma (HCC). Methods: A total of 203 patients diagnosed with HCC were respectively evaluated between January 2005 and December 2012. Patients were divided according to the modified Glasgow prognostic score (mGPS), prognostic index (PI) and CRP/albumin ratio. The receiver operating curves (ROC) were generated and the area under the curve (AUC) was calculated to compare the discriminatory ability of each prognostic score. Significant prognostic factors associated with overall survival (OS) were identified using univariate and multivariate analyses. Results: The median follow-up period was 19.0 months and three-year OS of all patients was 29.7%. The mGPS, CRP/Albumin ratio, CLIP score and vascular invasion were independent prognostic indicators for OS in the multivariate analysis. The mGPS consistently had a higher AUC value at 6 mo (0.771), 12 mo (0.775), and 24 mo (0.673) in comparison with other CRP-based scores. Conclusions: The mGPS is an independent factor for OS in patients with HBV-related HCC and is superior to the other CRP-based prognostic scores. The mGPS could be used in combination with conventional stage system to predict survival in these patients.

Keywords: Prognostic score, the modified Glasgow prognostic score, CRP/albumin ratio, prognostic index, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies worldwide and the third leading cause of cancer-related deaths, with an age-adjusted worldwide annual incidence of 5.5-16 persons per 100,000 population [1-3]. The chronic hepatitis viral (HBV) infection is the main causal factor in the development of HCC in the world, especially in China [3]. More than 50% of HCC arise in the context of chronic liver disease [3, 4]. In contrast to other malignant tumors, both the tumor burden and patient's liver function could influence the prognosis of HCC [5, 6]. The 5-year overall survival (OS) rate for HCC patients was only about 5-6% [7] and a proportion of patients will develop local relapse and/or distant metastases, who had have a poorer prognosis. Therefore, identifying easily obtainable factors with prognostic value in HCC patients may help improve their clinical outcomes.

It is recognized that not only the intrinsic properties of cancer cells influence the progression of cancer, but also the host-related factors. Investigators have demonstrated that the presence of a systemic inflammation response, as evidenced by an elevated C-reactive protein (CRP) concentration, is associated with poor outcome in patients with various types of cancer, including HCC [8-10]. Recently, several studies have shown that CRP-based prognostic scores including the modified Glasgow

Table 1. Baseline characteristics of patients (N=203)

Characteristic	
Age (median, years)	55 (37-79)
Sex (male/female)	155/48
White cell count ($\times 10^9$/L)	7.3 (2.5-19.5)
Neutrophil count ($\times 10^9$/L)	4.6 (1.4-13.7)
AST (U/L)	50.5 (18.7-405.9)
ALT (U/L)	48.5 (11.0-375.8)
AFP (ng/mL)	19622.2 (2.5-795863.2)
TB (mmol/L)	16.5 (3.2-186.0)
Albumin (g/L)	37.5 (22.8-48.1)
CRP (mg/L)	4.1 (0.2-86.4)
Hemoglobin (g/dL)	138 (85-176)
PLT ($\times 10^9$/L)	241 (95-608)
Maximal tumour diameter (mm)	64 (25-185)
Tumor number (solitary/multiple)	69/134
TNM stage (I/II/III/IV)	20/58/89/36
Child-Pugh grade (A/B)	181/22
CLIP score (0/1/2/3/4/5)	15/52/83/46/7
BCLC stage (A/B/C)	9/109/85
mGPS (0/1/2)	130/48/25
PI (0/1/2)	115/74/14
CRP/Albumin ratio	0.14 (0.02-2.16)

Abbreviations: AST, asparate aminotransferase; ALT, Alanine aminotransferase; AFP, Alpha-fetoprotein level; TB, total bilirubin; CRP, C-reactive protein; PLT, platelet; CLIP, Cancer Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer; mGPS, modified Glasgow prognostic score; PI, Prognostic Index.

Prognostic Score (mGPS), the prognostic index (PI) and CRP/albumin ratio had a prognostic role in HCC patients [11, 12]. These CRP-based prognostic scores could be useful markers in clinical practice considering that they are easily accessible, inexpensive and quite simple tools. However, it has not been clear which CRP-based prognostic score is the most important prognostic factor in HCC patients. Therefore, this study aimed to compare the prognostic value of these CRP-based prognostic scores (mGPS, PI, and CRP/albumin ratio) in patients with HBV-related HCC.

Materials and methods

Patient characteristics

Patients with HBV positive who were newly diagnosed HCC at the Affiliated Hospital of Binzhou Medical University between January 1st, 2005 and December 31st, 2012 were enrolled. The medical records were retrospectively reviewed. A total of 203 HCC patients with HBV positive were finally included in the study and evaluated. The research was approved by the Institutional Review Board of the Affiliated Hospital of Binzhou Medical University, and written informed consent was obtained.

The diagnosis of HCC was based on the diagnostic criteria for HCC applied by the American Association for the Study of the Liver guidelines [13]. HCC was diagnosed by at least two radiologic images which showed the characteristic features of HCC or one radiologic image showing characteristic features of HCC accompanied persistent elevated serum alpha-fetoprotein (AFP ≥400 ng/mL) or histopathologic evidence. Tumor-related variables, such as the maximum tumor diameter, tumor number and vascular invasion were also evaluated. The Barcelona Clinic Liver Cancer (BCLC) stage and Cancer Liver Italian Program (CLIP) score were calculated based on these imaging data and other obtained variables.

Treatment and patient's follow-up

The criteria for surgical resection were presence of solitary lesion, no main portal vein trunk involvement, no distant metastasis and Child-Pugh grade A. Radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI) with/without transcatheter arterial chemoembolization (TACE) was performed for patients with lesions <3 cm in size and <3 in number. Transcatehter arterial chemoembolization (TACE) or lipiodol-transcatheter arterial infusion (TAI) was performed in patients with more than four lesions or larger than 3 cm in size. Systemic chemotherapy or targeted therapy including sorafenib was administered to patients with distant metastasis and preserved liver function.

All patients were carefully followed after the initial treatment. Physical examination, abdominal CT scans and blood tests for AFP and liver function were performed at three month intervals during the first two years, then every 6 months. The date of last follow-up was September 2015.

CRP-based prognostic scores

Complete blood samples were obtained for CRP, serum albumin, total bilirubin (TB), alanine aminotransferase (ALT), asparate aminotrans-

Table 2. Univariate and multivariate analysis of prognostic factors for overall survival in hepatitis B virus-related HCC patients

Variable	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	*P* value
Age (≤55/>55 years)	0.562		
Sex (male/female)	0.008		
WBC (≤11/>11×10^9/L)	0.023		
PLT (≥200,000/<200,000/dL)	0.838		
Hemoglobin (12/<12 g/dL)	0.236		
TB (≤20.5/>20.5 mmol/L)	<0.001		
AST (≥2/<2× normal limit)	0.118		
ALT (≥2/<2× normal limit)	0.027		
Albumin (≥35/<35 g/L)	<0.001		
CRP (<10/≥10 mg/L)	<0.001		
AFP (≥400/<400 ng/ml)	<0.001		
ALP (≤110/>110 IU/L)	0.189		
LDH (≥170/<170 U/L)	0.238		
mGPS (0/1/2)	<0.001	3.763 (1.677-8.443)	0.001
PI (0/1/2)	<0.001		
CRP/Albumin ratio (<0.21/≥0.21)	<0.001	2.887 (2.011-4.144)	0.007
Child-Pugh grade (A/B)	0.027		
CLIP score (0-2/3-5)	<0.001	1.986 (1.028-2.478)	0.021
BCLC stage (A/B/C)	<0.001		
Tumor number (solitary/multiple)	0.017		
Vascular invasion (absent/present)	<0.001	1.969 (1.179-3.287)	0.010
Maximal tumor diameter (≥50/<50 mm)	<0.001		
TNM stage (I-II/III-IV)	<0.001		

Abbreviations: HR, hazards ratio; 95% CI, 95% confidence interval; WBC, white blood cell; PLT, platele; TB, total bilirubin; AST, asparate aminotransferase; ALT, Alanine aminotransferase; CRP, C-reactive protein; AFP, Alpha-fetoprotein level; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; mGPS, modified Glasgow prognostic score; PI, Prognostic Index; CLIP, Cancer Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer.

ferase (AST), white blood cell count (WBC), platelet count (PLT) and AFP at the time of diagnosis before any treatment modality was given. The mGPS was calculated using CRP and serum albumin levels. A score of 2 indicated elevated CRP (>10.0 mg/L) and low albumin (<35 g/L), a score of 1 indicated elevated CRP (>10.0 mg/L) without hypoalbuminemia and 0 indicated normal CRP with or without hypoalbuminemia [14]. The PI combines CRP and white cell count. Patients with both elevated CRP (>10.0 mg/L) and elevated white cell count (>11×10^9/L) were allocated a score of 2. A score of 1 indicated that elevated CRP (>10.0 mg/L) with normal white cell count or elevated white cell count (>11×10^9/L) with normal CRP and 0 indicated normal CRP and normal white cell count [12, 15]. The CRP/albumin ratio was calculated from the CRP level divided by the serum albumin level [16-18]. No patients showed clinical signs of severe infection at the time of diagnosis in this study.

Statistical analysis

Categorical variables are presented as the number and continuous variables are presented as the median and range. The OS was calculated from the date of the diagnosis to the date of death or censored at the date of final follow-up. Survival analyses were carried out by the Kaplan-Meier method and differences in survival rates between the groups were compared by a log-rank test. Variables that were significant in the univariate analysis (P<0.10) were included into multivariate Cox proportional hazard model. The optimal cut-off level of CRP/albumin ratio was determined by a receiver operating characteristics (ROC) curve. The area under the curve (AUC) was also calculated to evaluate the discriminatory ability of each prognostic scores. The statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). All tests were two-sided and a P value <0.05 was considered statistically significant.

Results

Patient characteristics

The clinicopathological characteristics of the patients are described in **Table 1**. The median age of the whole cohort was 55 (range 37-79) years. The majority of the patients were males

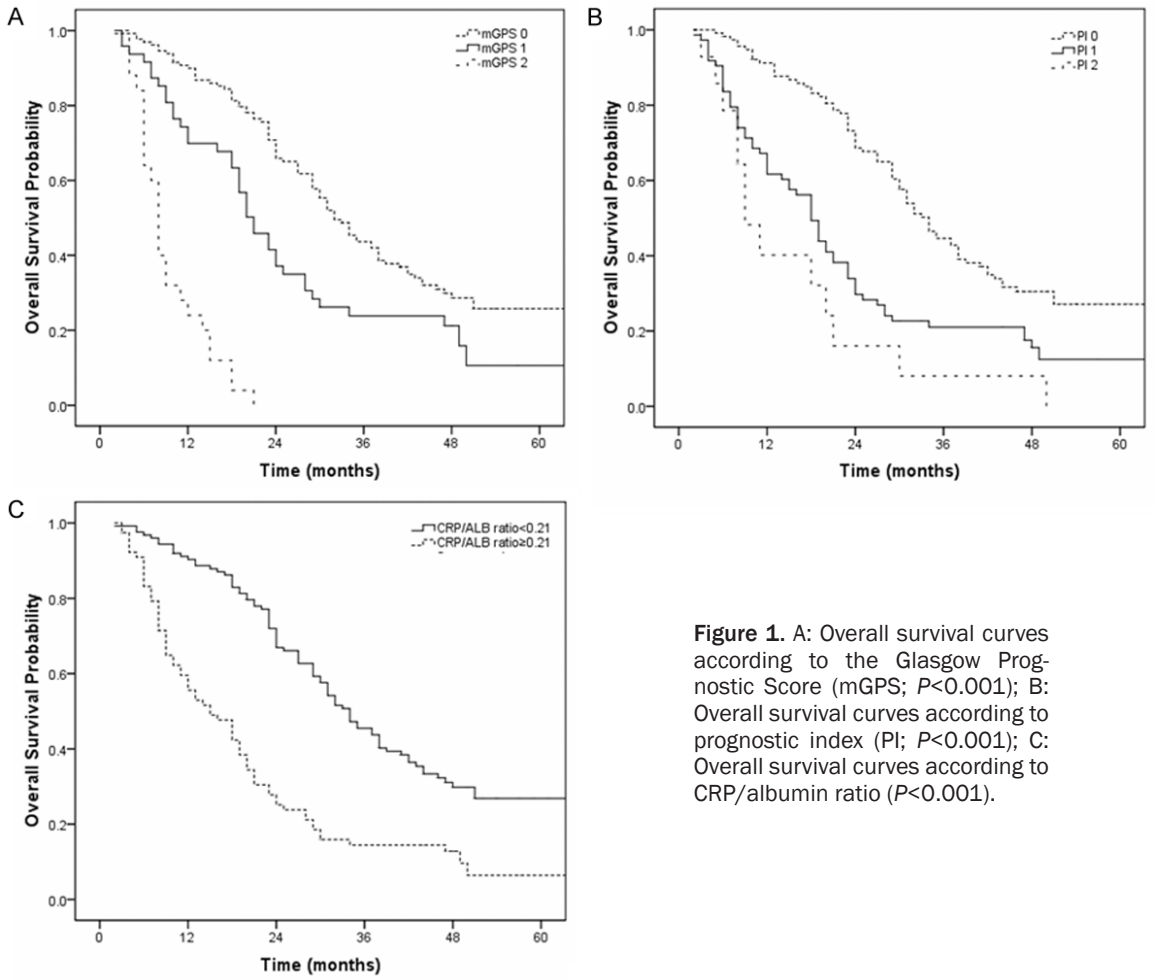

Figure 1. A: Overall survival curves according to the Glasgow Prognostic Score (mGPS; *P*<0.001); B: Overall survival curves according to prognostic index (PI; *P*<0.001); C: Overall survival curves according to CRP/albumin ratio (*P*<0.001).

(n=155, 76.4%) and 181 patients (89.2%) had a good liver functional reserve with Child-Pugh A grade. Seventy-eight patients (38.4%) were classified as stage I/II. Surgical liver resection was administered in 23 (11.3%) patients, TACE or RFA were performed in 156 (76.8%) patients.

In this study, forty-eight patients (23.6%) had hypoalbuminemia (serum albumin <35 g/L) and73 (36.0%) patients had an elevated CRP level (>10 mg/L). One hundred and thirty patients (64.0%) had a mGPS of 0, 48 patients (23.6%) had a mGPS of 1 and 25 patients (12.3%) had a mGPS of 2, respectively. One hundred and fifteen patients (56.7%), seventy-four patients (36.5%) and fourteen patients (6.9%) allocated to PI 0, 1 and 2, respectively. The median CRP/Albumin ratio was 0.14 (range, 0.02-2.16) and the optimal cutoff levels for CRP/Albumin ratio was 0.21 for OS according the ROC curves.

Survival analysis and prognostic factors

The median follow-up period was 19.0 (ranging from 2 to 80 months) months. During the follow-up, 151 patients had died of cancer. The one-, two-, and three-year OS of the whole cohort was 75.5%, 48.8%, and 29.7% respectively. The median OS was 24.0 months.

The univariate and multivariate analyses of prognostic factors for OS are shown in **Table 2**. The univariate analysis revealed that sex, WBC, TB, ALT, serum albumin, CRP level, AFP, mGPS, PI, CRP/Albumin ratio, Child-Pugh grade, CLIP score, BCLC stage, tumor number, vascular invasion, maximal tumor diameter, TNM stage were significantly associated with OS. In this study, increasing mGPS and PI were significantly correlated with gradual decrease in OS for HCC patients. The 3-year OS rates for patients with mGPS score of 0, 1, 2 were 43.6%, 23.8%, 0.4%, respectively (*P*<0.001; **Figure 1A**). The

Table 3. Comparison of the areas under the curves for the CRP-based prognostic scores

Period	AUC	95% CI	*P* value
6 months' follow-up			
mGPS	0.771	0.658-0.885	<0.001
PI	0.756	0.653-0.858	<0.001
CRP/Alb ratio			
Continuous	0.712	0.601-0.824	0.001
Dichotomized	0.707	0.599-0.816	0.001
12 months' follow-up			
mGPS	0.775	0.694-0.856	<0.001
PI	0.726	0.647-0.804	<0.001
CRP/Alb ratio			
Continuous	0.754	0.675-0.833	<0.001
Dichotomized	0.740	0.662-0.819	<0.001
24 months' follow-up			
mGPS	0.673	0.601-0.746	<0.001
PI	0.658	0.582-0.734	<0.001
CRP/Alb ratio			
Continuous	0.665	0.590-0.740	<0.001
Dichotomized	0.675	0.601-0.750	<0.001

Abbreviations: AUC, area under the curve; 95% CI, 95% confidence interval; mGPS, modified Glasgow prognostic score; PI, Prognostic Index.

3-year OS rates for patients with PI of 0, 1, 2 were 44.6%, 21.0%, 0.8%, respectively (P< 0.001; **Figure 1B**). Compared to patients with a CRP/Albumin ratio <0.21, the OS rates were significantly poorer in patients with a CRP/Albumin ratio ≥0.21 (3-year OS: 14.4% vs. 43.7%, P<0.001; **Figure 1C**).

Variables that were statistically significant in a univariate analysis were included further into a multivariate analysis. The multivariate analysis of these significant variables revealed that the mGPS (hazard ratio [HR] 3.763, 95% confidence interval [CI] 1.677-8.443, P=0.001), CRP/Albumin ratio (HR 2.887, 95% CI 2.011-4.144, P=0.007), CLIP score (HR 1.986, 95% CI 1.028-2.478, P=0.021) and vascular invasion (HR 1.969, 95% CI 1.179-3.287, P=0.010) were independent factors affecting OS in HCC patients (**Table 2**).

Prognostic validity of the CRP-based prognostic scores

ROC curves were calculated for the survival status at the 6-, 12-, and 24-month follow-up examinations, and the AUC values were used to compare the prognostic validity of each CRP-based prognostic score (**Table 3**; **Figure 2**). The mGPS consistently had a higher AUC value at 6 month (0.771), 12 month (0.775), and 24 month (0.673) in comparison with other CRP-based prognostic scores.

Discussion

To our best knowledge, this is the first study to evaluate the prognostic value of CRP-based prognostic scores (mGPS, PI, and CRP/Albumin ratio) in HBV-related HCC patients. This study demonstrated that the mGPS was an independent marker of poor prognosis in these patients and was superior to PI and CRP/Albumin ratio in terms of prognostic ability for OS.

The process of carcinogenesis in HCC patients was associated with inflammation [19, 20]. As the predominant etiology of HCC, HBV infection accounted for over 80% of the caseload in East Asia [21, 22]. It is increasingly recognized that host inflammatory response, evidenced by an elevation of the serum CRP level, has an important role in development and prognosis of HBV-related HCC patients [23-26]. CRP is one of the acute phase inflammatory mediators synthesized predominantly by hepatocytes under the control of interleukin-6. Elevated CRP levels were associated with an increased risk for several types of malignancies and could influence prognosis [27, 28]. The mechanism that system inflammation influenced inversely cancer survival may be associated with immune dysfunction, nutritional decline, angiogenesis, up-regulation of growth factors [29, 30].

The CRP-based prognostic scores (mGPS, PI, and CRP/Albumin ratio) were based on limited laboratory data and they could be simple, conventionally available, and well standardized tools in HCC patients. The mGPS, which combined both elevated levels of CRP (>10 mg/L) and hypoalbuminemia (<35 g/L), could be indicative of underlying systemic inflammatory response and a nutritional decline. Proctor et al. suggested that mGPS could be included in routine assessment of all patients with cancer by a retrospective analysis of 27,031 cancer patients [12]. The concept of CRP/Albumin ratio was first proposed by Fairclough et al [18]. Akiyoshy et al. revealed that CRP/Albumin ratio was an independently prognostic factor in HCC patients [16]. In this study, the univariate analy-

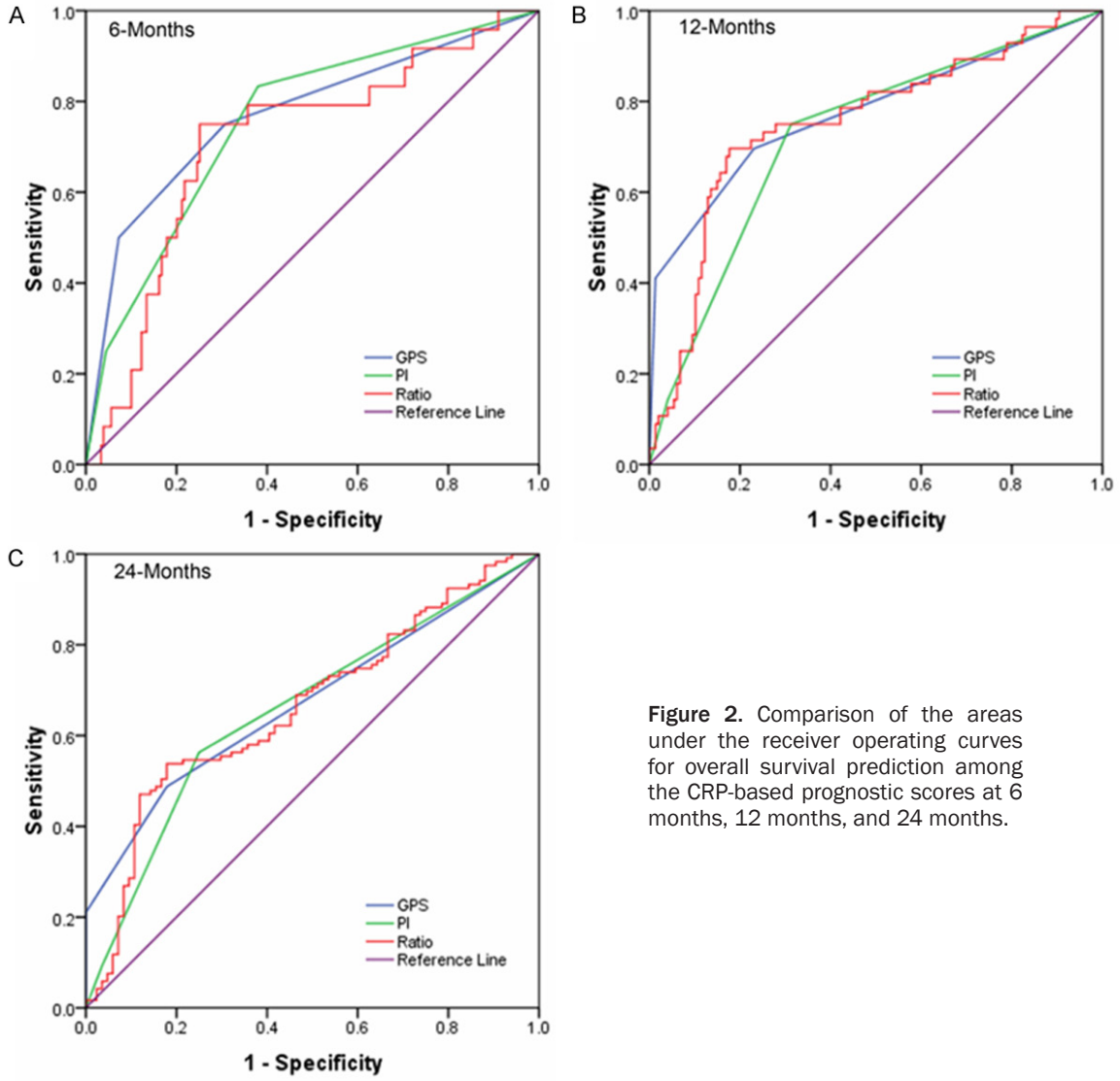

Figure 2. Comparison of the areas under the receiver operating curves for overall survival prediction among the CRP-based prognostic scores at 6 months, 12 months, and 24 months.

sis showed that mGPS, PI and CRP/Albumin ratio had a prognostic role in OS of HBV-related HCC patients. The multivariate analysis demonstrated that mGPS and CRP/Albumin ratio were independently associated with the OS. Our results were consistent with previous studies [11, 12, 31]. Kinoshita et al [11] compared the prognostic value of these inflammation scores in 150 HCC patients with various TNM stages and revealed that GPS was an independently prognostic marker of poor prognosis in HCC patient. There were several possible mechanisms to explain the prognostic value of CRP-based prognostic scores in cancer patients. Firstly, the sustained systemic inflammatory response could create conditions that favor tumor growth, angiogenesis, invasion, and metastases through recruitment of regulatory T lymphocytes and chemokines, activation of IL-6 and angiogenic factors and chemokines. IL-6 is an important pro-inflammatory cytokine during the development of cancer and closely correlates with elevation of the CRP in HCC patients [16]. The change of microenvironment could induce subversion of adaptive immune response, and aberration of response to chemotherapy drugs [32]. Secondly, the existence of hypoalbuminemia, often secondary to a systemic inflammatory response, reflect a state of impaired immunity and poor nutrition [33] and could also reduce patient tolerance to treatment-related toxicities [34].

To further evaluate the discrimination ability of the CRP-based prognostic scores, the ROC analysis was performed to compare the AUC

value. The mGPS had a higher AUC value than other markers (6 months: 0.771; 12 months: 0.775; 24 months: 0.673). The current study revealed that mGPS was superior to other CRP-based prognostic scores in terms of prognostic ability for OS in HBV-related HCC patients. Our results were consistent with previous studies. Proctor et al. undertook retrospective analyses of 27,031 cancer patients and reported that mGPS had the greatest AUC when compared with other inflammation-based prognostic scores [12]. Notably, our findings might have important value in the therapy of HCC. Patients with an elevated mGPS may benefit from anti-inflammatory therapy or nutritional support [35].

In this study, the independently prognostic factors of OS were CLIP scores, vascular invasion, mGPS and CRP/Albumin ratio. No major difference was found, in the multivariate analysis of this study, in predictive factors of OS in HBV-related HCC patients [3].

There are several inevitable limitations in this study. First, this study was a single-center retrospective study, which inevitably leaded to confounding and bias. Second, there was heterogeneity in the treatments for HBV-related HCC patients in this study. At last, the patient population in this study was based on HBV-related HCC. Whether these preliminary results could be applied to Western populations required further study. Therefore, a large-scale and multiple-center prospective validation study is needed to confirm the preliminary results.

In conclusion, our study revealed that mGPS is an independently prognostic factor of OS in patients with HBV-related HCC and is superior to the other CRP-based prognostic scores in terms of prognostic ability. The mGPS, as an easily obtainable and objective biomarker, could be used in combination with the conventional staging system to predict survival in these patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Lian-Mei Ma, Department of Pediatrics, The Affiliated Hospital of Binzhou Medical University, No. 661, Yellow-River Second Street, Binzhou 256603, People's Republic of China. Tel: +86-543-3256544; Fax: +86-543-3256544; E-mail: malianmbinzhou@sina.com

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