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SYSTEMATIC REVIEW AND META-ANALYSIS

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Prognostic Role of Glasgow Prognostic Score in Patients With Hepatocellular Carcinoma

A Systematic Review and Meta-Analysis

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Abstract: Conflicting results about the prognostic value of Glasgow Prognostic Score (GPS) in hepatocellular carcinoma (HCC) patients have been reported. We searched the available articles and performed the meta-analysis to clarify the predictive value of GPS in HCC patients' outcome.

A systematic literature search was conducted using PubMed (Medline), Embase, Cochrane Library, Web of Science, ChinaInfo, and Chinese National Knowledge Infrastructure for all years up to September 2015. Studies analyzing the relationship of GPS and survival outcome were identified. Hazard ratio (HR) with 95% confidence interval (CI) was calculated to assess the risk.

A total of 10 studies were finally enrolled in the meta-analysis. The pooled estimates demonstrated a significant relationship between elevated GPS and inferior overall survival in patients with HCC (HR = 2.156, 95% CI: 1.696–2.740, $P < 0.001$). Patients with increased GPS had a tendency toward shorter progression-free survival (HR = 1.755, 95% CI: 0.943–3.265, $P = 0.076$). And elevated GPS was found to be significantly associated with advanced Child–Pugh class (odds ratio = 25.979, 95% CI: 6.159–109.573, $P < 0.001$). The publication bias analysis revealed that there was publication bias in the meta-analysis.

Glasgow Prognostic Score may be an independent prognostic factor in patients with HCC. More well-designed studies with adequate follow-up duration are warranted.

(*Medicine* 94(49):e2133)

Abbreviations: AFP = a-fetoprotein, CI = confidence interval, CRP = C-reactive protein, GPS = Glasgow Prognostic Score, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HCVAb = hepatitis C virus antibody, HR = hazard ratio, ICG R15 (%) = indocyanine green retention rate at 15 minutes, IL = interleukin, NOS = Newcastle–Ottawa Quality Assessment Scale, OR = odds ratio, OS = overall survival, PFS = progression-free survival, Ph = P value of Q test for heterogeneity test.

Editor: Peng Qi.
Received: August 7, 2015; revised: October 23, 2015; accepted: November 1, 2015.
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This work was supported by The State Key Project on Infection Diseases of China (Grant No. 2012ZX10002016).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002133

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks as the sixth most common malignant cancer and the third most frequent cause of cancer-related mortalities worldwide.[1] Despite the dramatic advancement in the surgical techniques, loco-regional treatment options and molecular target therapy, the prognosis of HCC is still dismal compared with other solid tumors. Currently, the clinical management toward malignant cancers chiefly depends on their clinical stage. Several clinical staging systems for HCC, including American Joint Committee on Cancer staging system,[2] Barcelona Clinic Liver Cancer staging system,[3] the Okuda classification,[4] Cancer of the Liver Italian Program scoring system,[5] and the Japan Integrated Staging score [6] have already been proposed. The accuracy of all the current ongoing staging systems in predicting the patients' prognosis, however, is not satisfactory. Therefore, it is urgent to identify the prognostic index beyond the scope of current clinical staging systems to gain a rational classification of the patients according to their prognosis.

It has long been recognized that malignant cancer and chronic inflammation are closely interlinked.[7] Tumor growth and invasion to adjacent tissue can induce inflammation. The cytokines produced by the inflammatory cells and the tumor cells themselves can drastically accelerate the process of cellular proliferation, invasion, epithelial–mesenchymal transition, and vascular genesis, and therefore prompt cancer progression.[7,8] For HCC, the interrelationship is much easier to be understood as hepatitis B virus (HBV), hepatitis C virus (HCV), and ethanol are widely accepted as the etiologies of HCC. Thus, the incorporation of the inflammatory-related factors into the clinical decision making system may help us to stratify the patients at a more reasonable level. C-reactive protein (CRP), which is initially identified for its capacity to precipitate C-polysaccharide of *Streptococcus pneumonia*, is a highly sensitive and dynamic marker of systematic inflammation.[9] The secretion of CRP by the hepatocytes is mainly stimulated by the oncogenic inflammatory cytokine as interleukin (IL)-6.[10] In the meantime, hypoalbuminemia usually refers to body underperformance and poor nutrition status.[11] Glasgow Prognostic Score [(GPS); detailed in Table 1], comprising of serum CRP and albumin, has been proved to be a prognostic indicator in patients with several kinds of malignant cancers including colorectal cancer,[12] esophageal cancer,[13] gastric cancer,[14] and lung cancer.[15] For patients with HCC,

TABLE 1. The Glasgow Prognostic Score

Scoring systems	Score
CRP (≤10 mg/L) and albumin (≥35 g/L)	0
CRP (≤10 mg/L) and albumin (<35 g/L)	1
CRP (>10 mg/L) and albumin (≥35 g/L)	1
CRP (>10 mg/L) and albumin (<35 g/L)	2

CRP, C-reactive protein.

the prognostic value of GPS remains to be controversial. Horino et al[16] suggested that GPS independently predicted poorer overall survival. Meanwhile, the study by Yamamura et al[17] did not detect any significant relationship between GPS and patients' outcome. In this setting, we searched the related articles and performed the current meta-analysis to gain a thorough understanding of the prognostic role of GPS in patients with HCC.

MATERIAL AND METHODS

Literature Research

Online databases, including PubMed (Medline), Embase, Cochrane Library, Web of Science, ChinaInfo, and Chinese National Knowledge Infrastructure were searched for all years up to September 2015. Terms used in our search included: ''Glasgow Prognostic Score'' (eg, ''GPS''), ''prognosis'' (eg, ''outcome,'' ''survival,'' ''mortality,'' and ''recurrence''), and ''Hepatocellular carcinoma'' (eg, ''HCC,'' ''liver cancer,'' ''liver tumor,'' and ''liver neoplasm''). The articles should be written in English or Chinese. The reference lists of all reviewed articles were screened to identify additional related articles.

Study Inclusion/Exclusion Criteria

The inclusion criteria were as follows: the diagnosis of HCC was made based on pathologic examination or the current ongoing clinical guidelines; correlation of GPS with overall survival (OS)/progression-free survival (PFS) was presented in the article. The hazard ratios (HRs) with the respective 95% confidence interval (CI) were either directly reported or could be reconstructed by the relevant data[18] or figures in the essay[19]; and for studies with overlapping study population, only the most informative one was included. Any divergences were addressed by discussion.

Exclusion criteria were defined as: abstracts, letters, editorials, expert opinions, reviews, case reports, case series less than 5 cases; articles without sufficient reported data for determining an estimate of HR [odds ratio (OR)] and a CI; and not human-based research.

Data Extraction

The extracted data included: first author's name, year of publication, country (region) of the population studied, patients' age, sample size, gender, treatment, follow-up period, and clinicopathologic features; survival data including OS and PFS; cutoff value defining ''elevated GPS'' and number of high GPS expression. Overall survival was defined as the interval between the medical treatment and the death of patients or the last follow-up. Progression-free survival was calculated from the date of treatment to the detection of the recurrence tumor or death from any cause. In our analysis, surgical treatment was defined as surgical resection or liver transplantation. Nonsurgical treatment mainly referred to molecular target therapy, best supportive treatment, systematic chemotherapy, and loco-regional therapeutic options, such as percutaneous radiofrequency ablation, percutaneous ethanol injection, and transcatheter arterial interventional approaches.

Quality Assessment of Primary Studies

Newcastle–Ottawa Quality Assessment Scale was adopted as the appraising criteria of quality of the retrieved studies. Newcastle–Ottawa Quality Assessment Scale score ≥6 indicated high quality. Two reviewers (M-XL and X-YB) independently carried out the assessment. Consensus was finally reached through discussion when discrepancy occurred.

Statistical Analysis

The HRs and 95 % CIs were directly retrieved from the essays or were synthesized indirectly from available statistics and/or figure plots in the articles by methods reported by Parmar et al[18] and Tierney et al.[19] If several estimates were reported for the same value, the most persuading one was preferred (multivariate analysis was more advantageous than univariate analysis. And the latter one outweighed unadjusted Kaplan–Meier curve). Odds ratios and 95% CIs were used to assess the relationship between GPS and clinicopathologic parameters.

Interstudy heterogeneity among included studies was evaluated by the I^2 statistics.[20] If the I^2 was larger than 50%, implying significant statistical heterogeneity between studies, the random-effects (DerSimonian–Laird method) models was adopted; in the presence of no observable interstudy heterogeneity ($I^2 < 50\%$), the fixed-effect model was applied. All P values were 2-sided and $P < 0.05$ were considered statistical significant. Evidence of publication bias was evaluated using the Begg test [21] and Egger test.[22] ''Trim and fill'' analysis[23] was additionally performed in case that publication bias was identified. All analyses were performed using STATA statistical software package version 12.0 (STATA Corp., College Station, TX).

RESULTS

Description of the Enrolled Studies

The initial literature search yielded a total of 38 studies. After reading the titles and abstracts, 16 articles were further assessed for eligibility. Six of them were subsequently excluded: 4 studies[24–27] were removed because of their insufficient data to generate the estimate of HRs (ORs); Kinoshita et al[28,29] and Ishizuka et al[30,31] each published studies with overlapping study population. The latest ones with the most comprehensive information were admitted into the meta-analysis.[29,31] Thus, 10 studies[16,17,29,31–37] published between the year 2012 and 2015 with sample size ranging from 46 to 398 were finally enrolled into the meta-analysis. The flow chart of the literature selection was described in Figure 1.

The characteristics of the included studies were summarized in Table 2. Of them, 7 were conducted in Japan and 3 were from China. Surgical treatment was the main treatment approach in 7 of the 10 included studies. Hazard ratio and 95% CI generated by the multivariate analysis were reported directly in 9 of the enrolled cohorts. Newcastle–Ottawa Quality Assessment Scale score was above 6 in 8 cohorts.

Glasgow Prognostic Score and Overall Survival

Nine of the 10 included studies presented us with data regarding the relationship between GPS and overall survival.

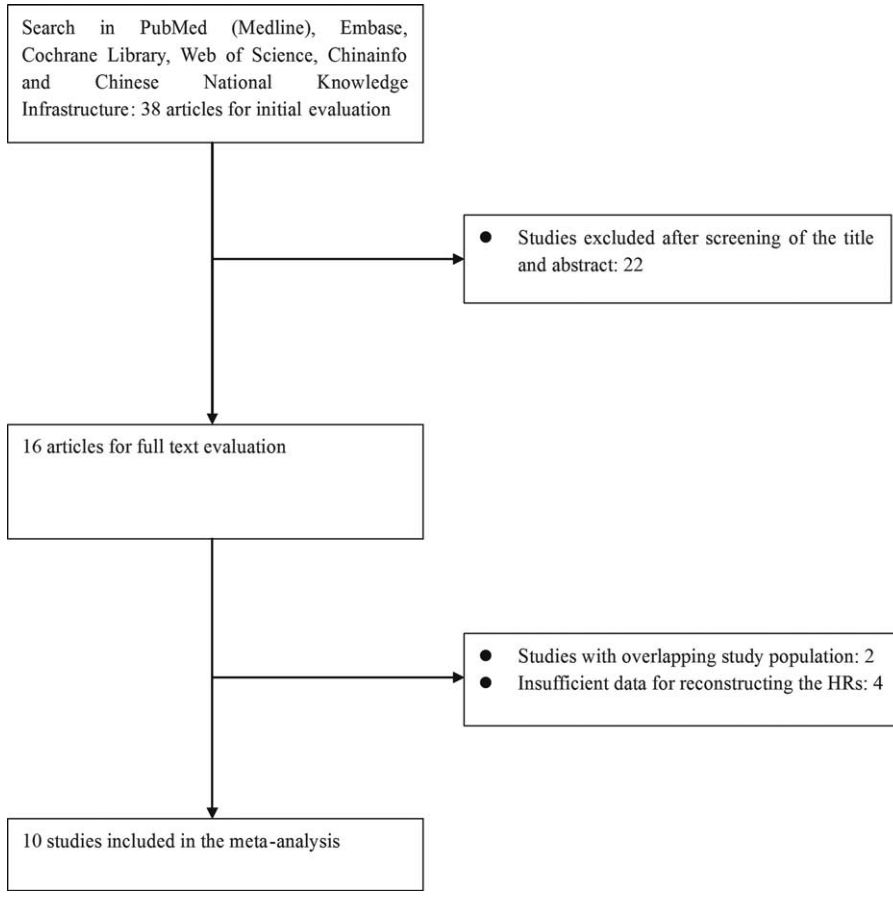

FIGURE 1. Flow chart describing the selection of eligible articles.

The pooled estimates demonstrated a significant relationship between elevated pretreatment GPS and inferior OS with heterogeneity (HR = 2.156, 95% CI: 1.696–2.740, $P < 0.001$, $I^2 = 56.2\%$, P value of Q test for heterogeneity test [(Ph) = 0.019, Figure 2; Table 3].

Subgroup analysis stratified by the main treatment (surgical versus nonsurgical), study region (China versus Japan), sample size ($\geq$200 versus <200), and cutoff value (=1 versus $\neq$1) were performed. Significant relationship between increased GPS and inferior OS were detected in all the above subgroups (Table 3).

Glasgow Prognostic Score and Progression-Free Survival

There were 4 studies presenting the information with reference to GPS and PFS. Observable heterogeneity was detected ($I^2 = 66.1\%$, Ph = 0.031, Table 3). With marginal significance, patients with elevated GPS showed a tendency toward shorter PFS (HR = 1.755, 95% CI: 0.943–3.265, $P = 0.076$, Table 3; Figure 3).

Glasgow Prognostic Score and Clinicopathologic Factors

Three of the included studies reported positive association between elevated GPS and advanced Child–Pugh class. The pooled OR of 25.979 displayed that patients with elevated GPS predisposed to be at advanced Child–Pugh class (OR: 25.979, 95% CI: 6.159–109.573, $P < 0.001$, $I^2 = 59.8\%$, Ph = 0.083, Table 3; Figure 4A). The relationship between GPS and tumor number had been reported in 4 studies. Without observable interstudy heterogeneity ($I^2 = 0\%$, Ph = 0.835, Table 3), the pooled estimates exhibited that patients with elevated GPS showed a tendency toward having multiple tumors (OR: 1.348, 95% CI: 0.965–1.882, $P = 0.080$, $I^2 = 0\%$, Ph = 0.835, Table 3; Figure 4B). But the relationship failed to gain statistical significance. And the pooled analyses showed no relationship between increased GPS and positive status of hepatitis B surface antigen (OR: 0.935, 95% CI: 0.694–1.259, $P = 0.658$, $I^2 = 0$, Ph = 0.508, Table 3; Figure 4C) as well as positive status of hepatitis C virus antibodies (OR: 1.264, 95% CI: 0.610–2.619, $P = 0.529$, $I^2 = 80.3\%$, Ph = 0.002, Table 3; Figure 4D).

Sensitivity Analyses

A single study involved in the meta-analysis was deleted each time to unveil the influence of the individual data to the wholesome result. No significant deviation from the overall results was detected.

Publication Bias

Substantial publication bias was detected in the Begg test ($Pr > |z| = 0.029$, Figure 5) and Egger test ($P > |t| = 0.007$) in the pooled estimates for OS. We further performed the ''trim and fill'' analysis. The results showed at least 1 relevant study was unpublished. The filled meta-analysis concerning OS

TABLE 2. Main Characteristics of All the Studies Included in the Meta-Analysis

First Author	Year	Study Region	Number (M/F)	Age (years)	Treatment	Follow-Up	TNM (I/II/III/IV)	Tumor Size	Tumor Number	Macrovascular Invasion (+/-)	Child–Pugh (A/B/C)	Ascites
Horino[16]	2012	Japan	283/69	63.4 ± 9.5[b]	Surgical	19 (1–69) months[a]	NR	44.6 ± 34.1 mm[b]	1.8 ± 1.4[b]	NR	258/25/0	7/276
Ishizuka[31]	2012	Japan	316/82	65.1 ± 0.5[b]	Surgical	Range: 31–793 days	NR	≤2 cm:n = 128, >2 cm:n = 270	1:n = 300, ≥2:n = 98	NR	NR	NR
Moritmoto[32]	2012	Japan	60/21	75 (34–88)[a]	Nonsurgical	Median: 19 months	12/35/34/0	NR	NR	18/63	68/13	NR
Kinoshita[29]	2013	Japan	106/44	72(43–91)[a]	Nonsurgical	18 (1–80) months[a]	21/60/48/20	NR	1:n = 76 ≥2:n = 73	15/134	106/37/6	NR
Huang[33]	2014	China	319/30	50 (13–78)[a]	Surgical	39 (3–59) months[a]	NR	5.0 (1.0–18.0) cm[a]	1:n = 252 ≥2:n = 97	125/224	335/14/0	NR
Pan[34]	2014	China	157/14	52.70 ± 12.67[b]	Surgical	41 (1–76) months[a]	96/56/19/0	5.75 ± 3.13 mm[b]	1:n = 134 ≥2:n = 37	48/123	144/27/0	19/152
Yamamura[17]	2014	Japan	91/22	66 (35–80)[a]	Surgical	29.9 (0.8–123.5) months[a]	NR	NR	NR	NR	110/3/0	NR
Okamura[35]	2015	Japan	205/51	69.5 (30–86)[a]	Surgical	36.3 (6.9–115) months[a]	I + II/III + IV:226/30	35 (9–180) mm[a]	1:n = 198 ≥2:n = 58	NR	250/6/0	NR
Zhou[36]	2015	China	199/25	53 (23–80)[a]	Nonsurgical	390 (90–1527) days[a]	44/24/123/33	9.2 (1.4–20) cm[a]	1:n = 71 ≥2:n = 153	75/149	208/16/0	NR
Abe[37]	2015	Japan	37/9	57 (45–69)[a]	Surgical	3.7 (0.1–9.6) years[a]	NR	<2 cm:n = 22 ≥2 cm:n = 24	1:n = 20 ≥2:n = 26	7/39	7/22/17	NR

Continued

First author	ICG R15 (%)	Differentiation (well/moderate/poor)	AFP (ng/mL)	HBs-Ag (+/-)	HCV-Ab(+/−)	Distal metastases (+/−)	Cutoff	NO of elevated (%)	Survival outcome	HR extraction	NOS score
Horino[16]	14.4 ± 8.8[b]	NR	NR	82/213	148/146	NR	1	72 (20.5%)	OS	R (M)	6
Ishizuka[31]	17.2 ± 0.5[b]	67/288/24	8.549 ± 3.069[b]	224/174	267/131	NR	1	242 (60.8%)	OS	R (M)	6
Moritmoto[32]	NR	NR	86 (2.0–58,9420)[a]	NR	NR	17/64	1	36 (44.4%)	OS, PFS	R (M)	6
Kinoshita[29]	NR	NR	NR	20 /130	84/66	6/143	≠1	69 (46%)	OS	R (M)	5
Huang[33]	NR	NR	357.3 (0.61–1210000)[a]	317/32	NR	NR	≠1	GPS = 0:n = 269 GPS = 1:n = 70 GPS = 2:n = 10	OS	R (M)	6
Pan[34]	NR	NR	4130.0 ± 10,926.52[b]	148/23	NR	NR	1	47 (27.5%)	OS	R (M)	6
Yamamura[17]	NR	NR	17 (1–108070)[a]	28/85	53/60	NR	1	24 (21.2%)	PFS	E (U)	5
Okamura[35]	NR	NR	15.1 (1.4–34,3422)[a]	46/210	117/139	NR	1	30 (11.7%)	OS, PFS	R (M)	6
Zhou[36]	NR	NR	25,828.4 (1.3–1210000.0)[a]	NR	NR	NR	≠1	GPS = 0:n = 99 GPS = 1:n = 101 GPS = 2:n = 24	OS	R (M)	5
Abe[37]	NR	Well/moderate: 43/Poor:3	<20.0 ng/mL:34 ≥20.0 ng/mL:12	15/31	23/23	NR	=1	32 (69.6%)	OS, PFS	R(M)	6

Hazard ratio obtained by reporting in text (R) or estimating (E). ''M'' means the HR come from multivariate analysis; ''U'' means the HR come from univariate analysis.

AFP = α-fetoprotein, HBs-Ag = hepatitis B surface antigen, HCV-Ab = hepatitis C virus antibody, HR = hazard ratio, ICG R15 = indocyanine green retention rate at 15 minutes, NOS = Newcastle–Ottawa Quality Assessment Scale, NR = not reported, OS = overall survival, PFS = progression-free survival.

[a] median (range).

[b] mean ± SD.

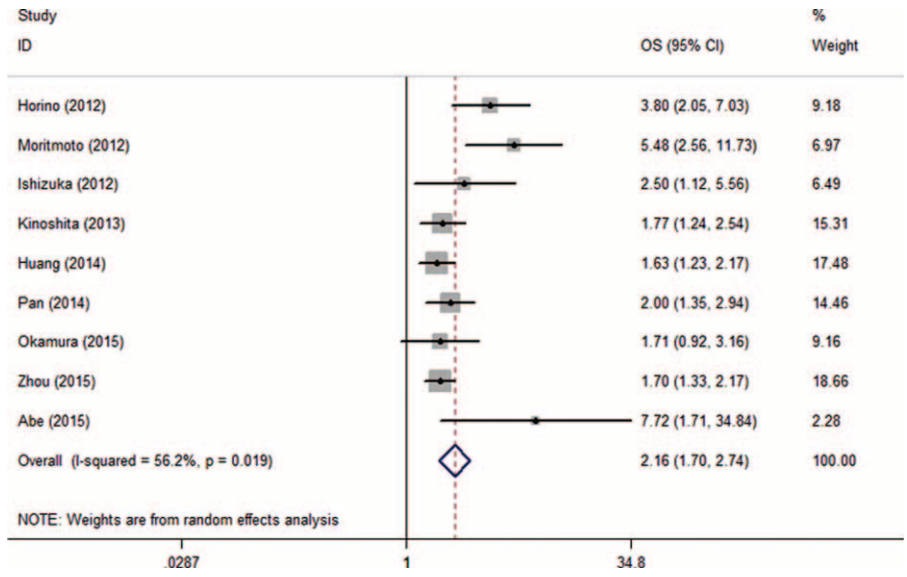

FIGURE 2. Forest plot of hazard ratio for the association between elevated Glasgow Prognostic Score and overall survival in patients with hepatocellular carcinoma with random effects model.

(HR = 2.104, 95% CI: 1.645–2.692, $P < 0.001$) upheld the strength of our pooled results.

DISCUSSION

The current meta-analysis, to our knowledge, is the first meta-analysis evaluating the prognostic value of GPS in patients with HCC. The pooled estimates of 10 studies involving 2094 patients indicated that patients with elevated GPS predisposed to have inferior survival outcome. The significant relationship between GPS and OS was detected in all the subgroup analyses stratified by the main treatment (surgical versus nonsurgical) study region (China versus Japan), sample size (≥200 versus <200), and cutoff value (=1 versus ≠1), which suggested that our results were stout. And patients with elevated GPS tended to have impaired liver function. Being based on only 2 conventional laboratory data without additional imaging techniques or histologic examinations, GPS can be a practical index for stratification of the HCC patients according to their prognosis.

The underlying biologic mechanism explaining the prognostic role of GPS in patients with HCC has not been well established. C- reactive protein secretion are usually triggered

TABLE 3. Summary of the Meta-Analysis Results

					Heterogeneity	
Analysis	**N**	**References**	**HR (95% CI)**	***P***	**I^2**	**Ph**
Overall survival	9	16, 29, 31–37	2.156 (1.696-2.740)	<0.001	56.2%	0.019
Subgroup 1:surgical	6	16, 31, 33, 34, 35, 37	1.980 (1.628–2.408)	<0.001	48.4%	0.084
Nonsurgical	3	29, 32, 36	2.217 (1.375–3.574)	0.001	76.1%	0.015
Subgroup 2:Japan	6	16, 29, 31, 32, 35, 37	2.821 (1.814–4.388)	<0.001	61.2%	0.025
China	3	33, 34, 36	1.726 (1.458–2.044)	<0.001	0	0.706
Subgroup 3:sample size ≥200	5	16, 31, 33, 35, 36	1.810 (1.530–2.142)	<0.001	42.6%	0.138
Sample size <200	4	29, 32, 34, 37	2.725 (1.607–4.622)	<0.001	69.5%	0.020
Subgroup 4: cutoff = 1	6	16, 31, 32, 34, 35, 37	2.872 (1.910–4.317)	<0.001	53.3%	0.057
Cutoff ≠ 1	3	29, 33, 36	1.691 (1.432–1.996)	<0.001	0	0.940
Progression-free survival	4	17, 32, 35, 37	1.755 (0.943–3.265)	0.076	66.1%	0.031
Clinicopathologic features			OR (95% CI)			
Child–Pugh B/C versus Child–Pugh A	3	16, 29, 37	25.979 (6.159–109.573)	<0.001	59.8%	0.083
Tumor number (multiple versus solitary)	4	29, 31, 34, 37	1.348 (0.965–1.882)	0.080	0	0.835
HBsAg positive versus HBsAg negative	5	16, 29, 31, 34, 37	0.935 (0.694–1.259)	0.658	0	0.508
HCVAb positive versus HCVAb negative	4	16, 29, 31, 37	1.264 (0.610–2.619)	0.529	80.3%	0.002

For OS, subgroup analyses were performed by treatment (surgical versus nonsurgical), study region (China versus Japan), sample size (≥200 versus <200) and cutoff value for elevated Glasgow Prognostic Score (=1 versus ≠1). Data with statistical significance were expressed in bold.

N = number of studies (cohorts), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HR = hazard ratio, OR = odds ratio, 95% CI = 95% confidence interval, Ph = *P* value of Q test for heterogeneity test.

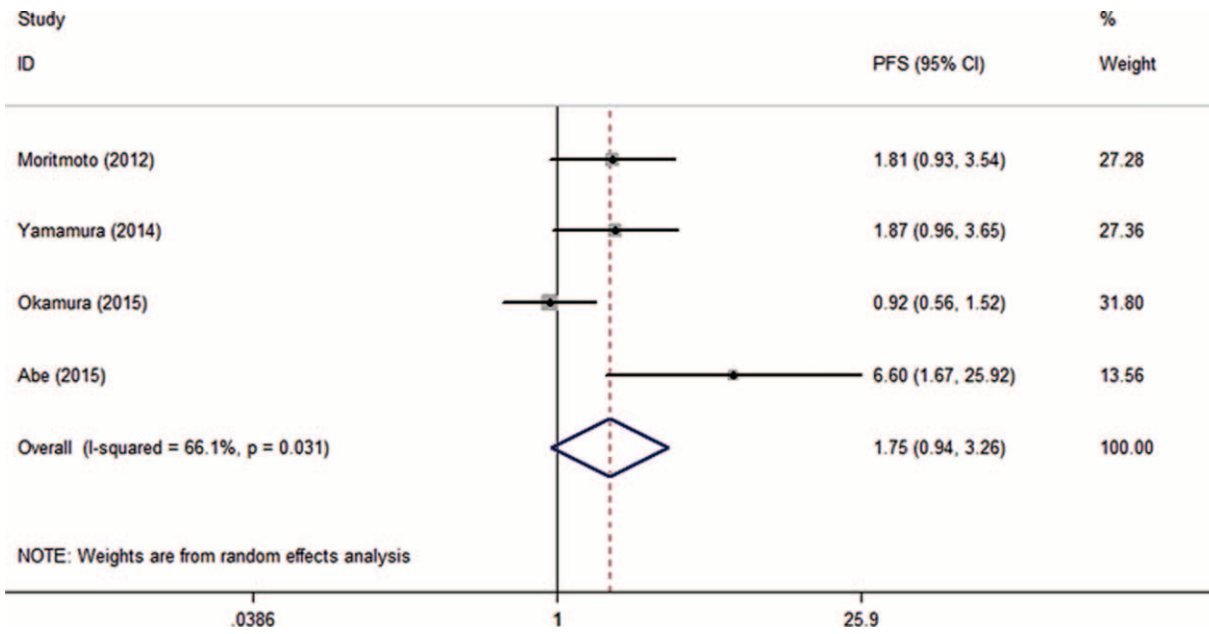

FIGURE 3. Forest plot of hazard ratio for the association between elevated Glasgow Prognostic Score and progression-free survival in patients with hepatocellular carcinoma with random effects model.

by the inflammatory cytokines, such as IL-6, IL-8, or tumor necrosis factor-α, which can in turn boost the development of HCC through facilitating cancer growth, invasion, metastasis, angiogenesis, and immunosuppression to tumor cells.[38] Increased CRP levels can act as a measure of tumor progression activity. Through a meta-analysis, Zheng et al[39] had proved that CRP was a significant predictor of poorer survival outcome in patients with HCC. The serum albumin level, which partially reflects the body function and nutrition status, has long been recognized as a prognostic factor for HCC.[40] And it has already been incorporated into several staging system such as Child–Pugh classification [41] and Cancer of the Liver Italian Program system .[5] Combining these, we can reckon that the increased GPS, incorporating elevated CRP and declined serum albumin levels, denotes enhanced neoplastic reaction and weakened body performance.

Publication bias is one of the intrinsic limitations of meta-analysis. As researches with negative results predisposed to be unpublished, the results of meta-analysis may thus be somewhat overvalued. We surmised that the publication bias may partly attribute to the statistical instability secondary to limited number of included studies. We further performed the ''trim and fill'' analysis[23]; the results of ''filled'' analysis did not change the results substantially. Regarding this, our results may also be robust.

Subgroup analysis in terms of the study region (China versus Japan) did not alter the overall results materially. As HBV and HCV are the predominant etiologies of HCC in China and Japan, respectively, our results may have implications in both HBV and HCV dominant areas to some extent. Of note, all the 10 included studies were conducted in Asian medical institutions. Although it may partially be ascribed to high burden of HCC among Asian populations,[42] doubts toward the extrapolation to Caucasian populations were also raised. It ought to be minded that the ethnic background and life styles may contribute to the variations in the patients' prognosis. Thus, the results of our meta-analysis should still be interpreted with caution when comes to the Non-Asian population. Providing these, the findings of our meta-analysis emphasize further researches studying patients from regions other than Asia to gain a comprehensive understanding of the prognostic value of GPS.

There were several other limitations of the meta-analysis. First of all, the treatment details, the baseline characteristics of the study population, and the follow-up information varied from institution to institution. These confounding factors might lead to heterogeneity. And a remarkable portion of the included studies were retrospectively performed, which was susceptible to some biases. Secondly, the HRs and 95% CIs of the study by Yamamura et al[17] were retrieved indirectly from figure plots, which was to some extent less accurate than those generated by the directly reported multivariate analyses. Thirdly, tumor recurrence and progression is a major concern in the prognosis of patients with HCC. The meta-analysis, which only took 4 studies included, found that relationship between elevated GPS and PFS only gained marginal statistical significance. It is quite possible that as more and more relevant studies publish in the future, the propensity of increased GPS toward shortened PFS may gain statistical significance. In addition, interstudy heterogeneity was observed in the meta-analysis. As metaregression analysis is best applicable for meta-analysis including more than 10 individual studies, we did not perform the metaregression analysis to figure out the source of heterogeneity. Subgroup analysis revealed that the study region (China versus Japan) and the cutoff value ($=1$ versus $\neq 1$) may explain the source of heterogeneity to some extent. The differences in the dominant etiologies along with the genetic backgrounds in China and Japan may partially explain the source of interstudy heterogeneity. No uniform cutoff value defining elevated GPS has been erected. Seven of the included studies adopted 1 as the cutoff value whereas the remaining 3 studies used cutoff value other than 1. These all could be the source of bias.

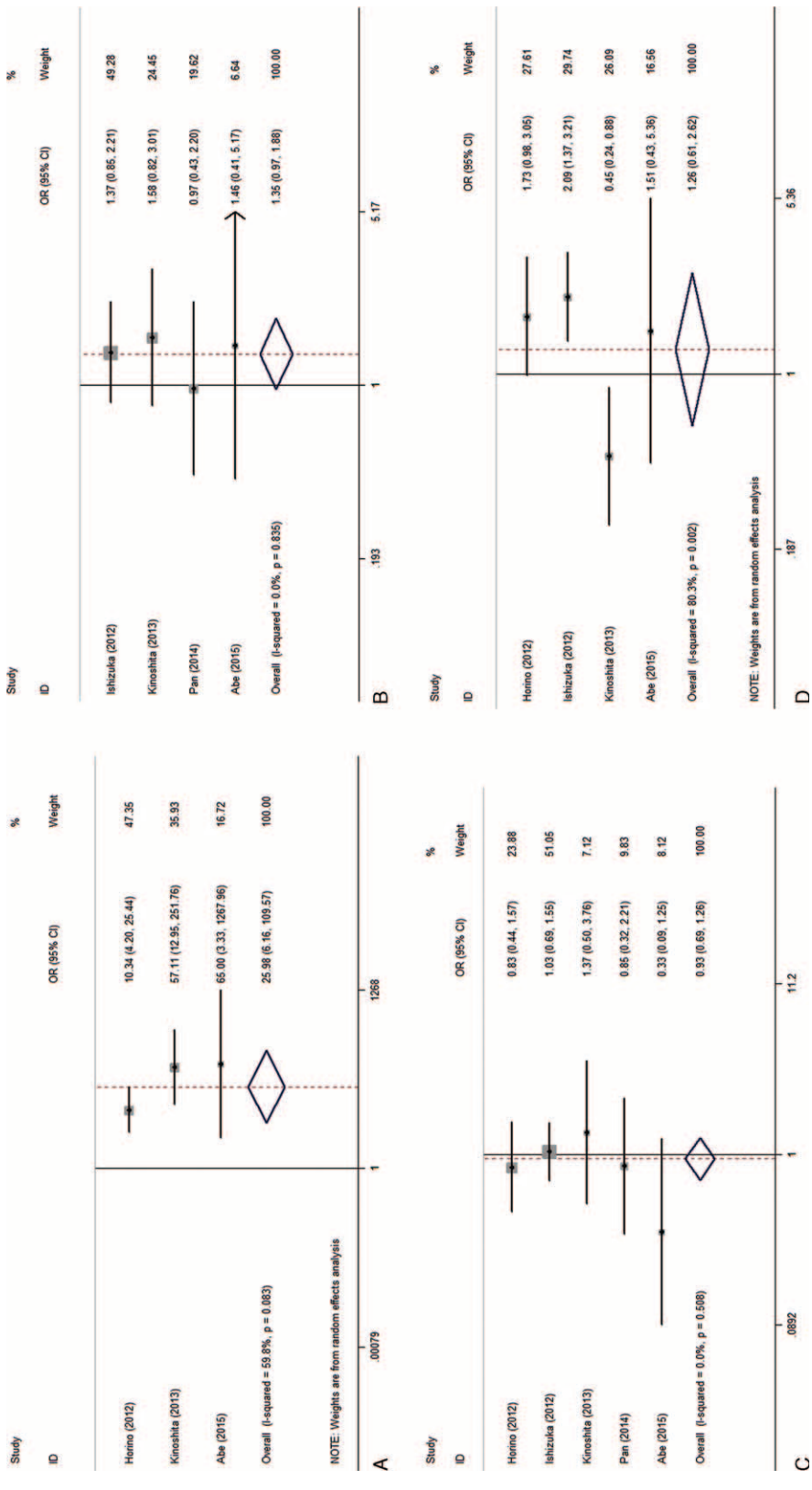

FIGURE 4. A, Forest plot of odds ratio for the association between elevated Glasgow Prognostic Score and Child–Pugh class (Child–Pugh class B and C versus Child–Pugh class A). B, Tumor number (multiple versus solitary). C, Status of hepatitis B surface antigen (positive versus negative). D, Status of hepatitis C virus antibody (positive versus negative) in patients with hepatocellular carcinoma with random effects model.

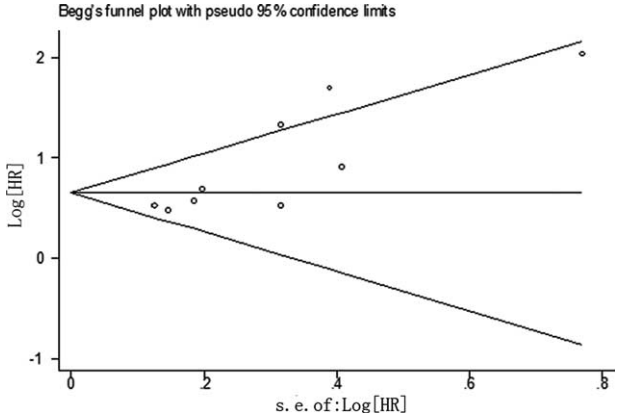

FIGURE 5. Funnel plot for elevated Glasgow Prognostic Score and overall survival in patients with hepatocellular carcinoma.

Collectively, GPS, an easily obtained and reproducible inflammatory index, is a promising prognostic factor in patients with HCC. More strictly designed studies focusing on this theme are required before GPS can move forward into routine clinical practice as a complementary prognostic factor to the current staging systems.

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