

Modified Glasgow prognostic score as a prognostic factor for renal cell carcinomas: a systematic review and meta-analysis

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Objective: The modified Glasgow prognostic score (mGPS), a combination of C-reactive protein (CRP) and albumin levels, reflects systemic inflammation and nutritional status. This score has been shown to have prognosis value for various tumors. In the present study, we evaluated the prognostic value of mGPS for patients with renal cell carcinoma (RCC).

Methods: Literature search was conducted based on PubMed, Embase, and Cochrane Central Register of Controlled Trials up to December 2018. We pooled HRs and 95% CIs to evaluate the correlation between mGPS and survival in patients with RCC.

Results: Twelve studies comprising 2,391 patients were included in the present study for quantitative synthesis. Our studies demonstrated that higher mGPS was significantly correlated to poor overall survival (HR=4.31; 95%CI, 2.78–6.68; $P<0.001$), cancer-specific survival (HR=5.88; 95%CI, 3.93–8.78; $P<0.001$), recurrence-free survival (HR=3.15; 95% CI, 2.07–4.79; $P<0.001$), and progression-free survival (HR=1.91; 95%CI, 1.27–2.89; $P=0.002$). Subgroup analyses also confirmed the overall results.

Conclusion: mGPS could serve as a predictive tool for the survival of patients with RCC. In the different subgroups, the results are also consistent with previous results. In conclusion, pretreatment higher mGPS is associated with poorer survival in patients with RCC. Further external validations are necessary to strengthen this concept.

Keywords: modified Glasgow prognostic score, renal cell carcinoma, prognosis, meta-analysis

Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all cancers, with an estimated 403,262 new cases in the world in 2018.¹ The occurrence of RCC has been increasing over the past three decades. Approximately 67% of newly diagnosed patients are localized disease, 16% of patients present regional or distant metastases.² Although the development of treatment for localized RCC, such as radical nephrectomy or partial nephrectomy, approximately 20–40% of patients will have local or distal recurrence.³ Treatments for metastatic RCC also have developed rapidly, including cytoreductive nephrectomy, immunotherapy, or target therapy, but the clinical outcome is not encouraging.⁴

Stratifications of patients based on the risk of recurrence are important to aid decision-making, to identify further follow-up and to judge whether patients should be enrolled in adjuvant clinical trials.⁵ TNM stage and Fuhrman nuclear grade are widely served as prognostic factors, but these factors have limited accuracy.^{6,7}

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Currently, more evidence suggested that systemic inflammation is associated with disease development and progression.^{8,9} Reportedly, an increasing number demonstrated that inflammation biomarkers, such as C-reactive protein (CRP), the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR) could predict prognosis of RCC.^{10,11} Glasgow prognostic score (GPS), a combination of CRP and albumin levels, reflects systemic inflammation and nutritional status. This score has been shown to have prognosis value for various tumors including gastric cancer, non-small cell lung cancer, esophageal cancer, as well as RCC.^{12–15} Modifying GPS as modified Glasgow prognostic score (mGPS), giving a score of 1 only for an elevated CRP, has been considered as a prognostic factor for several cancers such as non-small cell lung cancer, esophageal cancer, hepatocellular carcinoma, as well as RCC.^{13,16–18} However, the prognostic value of mGPS for RCC remains unclear, and the findings of different studies are inconsistent. Therefore, it is necessary to evaluate the prognostic value of mGPS for patients with RCC by conducting a systematic review and meta-analysis.

In the present study, we evaluated the association between pretreatment mGPS and prognosis by searching available literature and pooling all outcome data.

Methods

Literatures search

We performed the study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.¹⁹ Data for this study was collected by searching PubMed, PubMed (from inception to 2018 December 15), Embase (1974 to 2018 December 14), and Cochrane Central Register of Controlled Trials (from inception to November 2018). Literature search was conducted using items about renal cell carcinoma (or carcinoma, renal cell) and mGPS (or modified Glasgow prognostic score, C-reactive protein and albumin) as keywords and Mesh terms. Moreover, we screened the reference lists of eligible studies to ensure comprehensive search. Two reviewers searched the database independently (any conflicts resolved by discussion or consulting with another one).

Inclusion and exclusion criteria

Relevant studies were required to enroll according to inclusion criteria, which are as follows: 1) population-based studies; 2) involved patients with RCC; 3) evaluated the association between mGPS and clinical outcome; 4) reported

the clinical outcome, such as overall survival (OS), cancer-specific-survival (CSS), recurrence-free survival (RFS), or progression-free survival (PFS). We excluded the following studies: 1) non-English language; 2) did not evaluate pretreatment mGPS value; 3) did not report the data of survival; 4) non-human studies. Conference abstracts were also included if data could be extracted. While for duplicated patients data, we only enrolled the most informative and recent study for analysis.

Data extraction and quality assessment

Two reviewers independently extracted the following baseline information from included studies: the name of author, study location and enrollment data, study design, treatment, number of patients, age, disease, the mGPS value, and follow-up. As for the outcome, we extracted the HR and 95% CI. The discrepancy in the data extraction was resolved by discussion or consulting with another one. For non-randomized studies, we used Newcastle–Ottawa Quality Assessment Scale for quality assessment. Studies were evaluated on three aspects including selection, comparability, and exposure/outcome. Studies with a score of no less than 7 were deemed as good quality. Studies from conference abstracts were considered as low quality.

Statistical analysis

For analysis of survival, we used HRs and 95%CI, which is the most appropriate for time-to-data events. HRs and 95%CI were extracted from included studies according to multivariable analysis. If HRs were not reported, we could estimate HRs from Kaplan–Meier curve based on the method presented by Tierney.²⁰ Heterogeneity among studies was evaluated using the Q and I² statistics. If I² statistics presented $P < 0.10$ or $I^2 > 50\%$, we used a random-effect model for analysis.²¹ To further investigate the stability of pooled results, we conducted sensitivity analyses. The possibility of publication bias was evaluated by Egger's test and Begg's test. If evidence for publication was shown, we further performed trim and fill method to estimate missing studies.²² A two-sided P -value < 0.05 was indicated a significant difference. All statistical analyses were performed using STATA version 12 (StataCorp, College Station, TX, USA).

Results

Search results

Our initial search strategy identified 278 studies, 18 of which were duplicated articles. A 187 studies were

excluded based on titles and abstracts, the remaining 73 studies were further evaluated. Ultimately, 12 studies including 2,391 patients were enrolled for final analysis after excluding irrelevant studies.^{18,23–33} A flowchart depicting the process of search strategy was illustrated in Figure 1.

Characteristics of enrolled studies

Of the enrolled 12 articles, 3 are conference abstracts^{23–25} and 3 studies are prospective studies.^{31–33} A total of 2,391 patients were enrolled from Japan, the United Kingdom, Korea, the United States, and China. Treatments include nephrectomy, immunotherapy, and target therapy. The median age of patients was not more than 70 years. The sample size ranges from 32 to 406. Most of the studies followed up for a long time, and median follow-up ranged from 12.6

months to 98 months. Nine studies evaluated the association between mGPS and OS. Four studies reported the association between mGPS and CSS. Three studies revealed the outcome of RFS and 2 studies described the PFS. The characteristics of all eligible studies are shown in Table 1. As indicated in Table 1, all studies presented in our meta-analysis were regarded as high quality except for conference abstracts.

Overall survival

A total of 9 studies involving 1,795 patients evaluated the association between mGPS and OS. The pooled results, as presented in Figure 2, revealed that higher mGPS was associated with poorer OS, the HR is 4.31 (95%CI, 2.78–6.68; $P < 0.001$). There was evidence for moderate heterogeneity among studies, $I^2 = 60.6\%$ and $P = 0.005$, so random-model was applied.

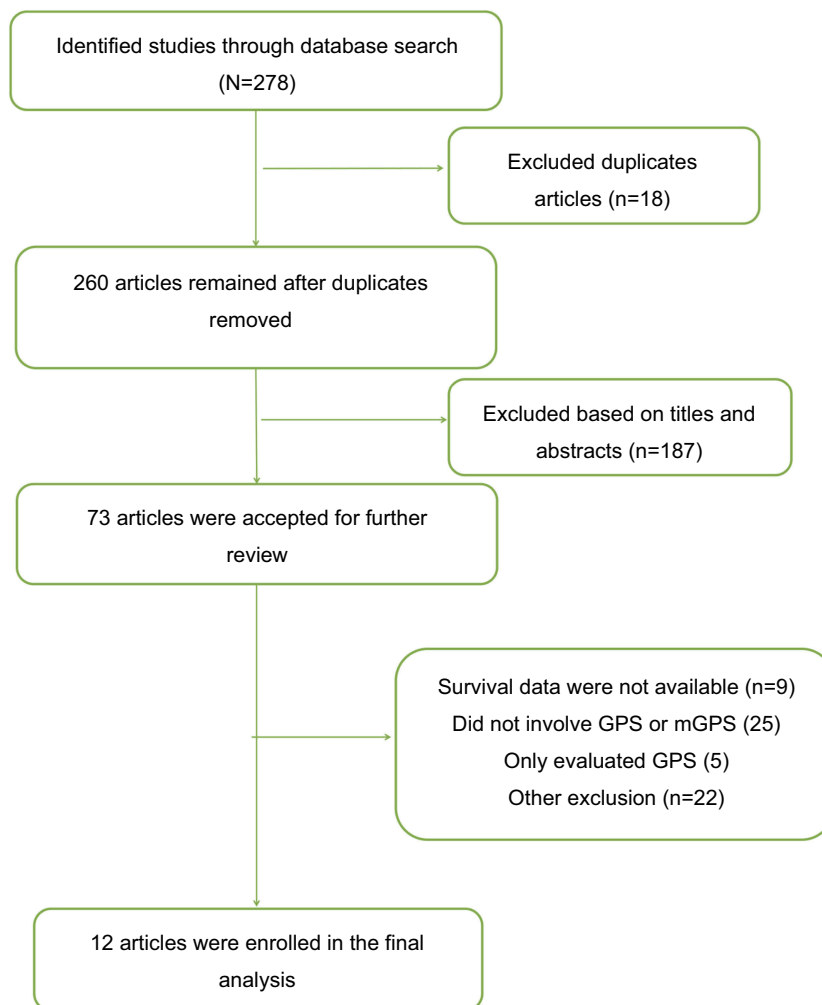


Figure 1 Flowchart of literature search.

Table 1 Characteristics of include studies

Study/pub-lished year	Enrollment date/location	Study type	Treatment	Number of patients	Age median (range) years	Tumor	mGPS	Outcomes	Follow-up median range (months)	NOS
Tsujino 2017	2005 and 2015/ Japan	Retrospective	Nephrectomy	219	mean ± SD 65.0 ± 10.8	RCC	0: 184 (84.0%) 1: 20 (9.1%) 2: 15 (6.9%)	OS CSS	Median:57	8
Ohmura 2017	October 2009 and August 2015/Japan	Retrospective	Molecular-targeted drug	32	66 (33–82)	Advanced RCC	0: 21 (65.6%) 1: 3 (9.4%) 2: 8 (25.0%)	OS PFS	NA	7
Lorentz 2017	2006 and 2016/US	NA	Nephrectomy and IVC tumor thrombectomy	117	NA	ccRCC with IVC thrombus	0: 38 (32.3%) 1: 17 (14.4%) 2: 62 (53.3%)	OS	Median (IQR) 12.6 (4.8–32.4)	Conference
Harris 2017	2005 and 2015/US	Retrospective	Targeted agent	181	64 (26–89)	mRCC	0: 92 (50.8%) 1: 36 (19.9%) 2: 53 (29.3%)	OS	NA	7
Ishihara 2016	2007 and 2014/ Japan	Retrospective	First-Line Sunitinib	71	64.0 (31–79)	mRCC	0: 53 (74.6%) 1: 10 (14.1%) 2: 8 (11.3%)	OS PFS	17.0 (2.24–65.6)	8
Cho 2016	June 1994 and July 2012/Korea	Retrospective	Radical or partial nephrectomy	388	Mean(Range) 56.0 (18–81)	Non-metastatic ccRCC	0: 327 (84.3%) 1: 38 (9.8%) 2: 23 (5.9%)	CSS RFS	44 (4–215)	8
Chen 2015	2003 to 2012/ China	Retrospective	Radical or partial nephrectomy	406	Mean(Range) 58 (24–80)	ccRCC	NA	OS	Mean (range) 63 (1–151)	7
Baum 2015	2005 and 2013/US	NA	Nephrectomy	352	Mean 58.8	Localized ccRCC	0: 267 (75.8%) 1: 38 (10.8%) 2: 47 (13.3%)	OS	Mean (range) 31.6 (0.03–84)	Conference
Tai 2014	November 2006 and January 2008/ US	Prospective	Radical nephrectomy	129	Median(IQR) 62.0 (54.0–70.0)	Localized ccRCC	0: 80 (62.0%) 1: 27 (20.9%) 2: 22 (17.1%)	RFS	Median (IQR) 25.5 (12.0–32.4)	7
Qayyum 2012	UK	Prospective	Nephrectomy	79	60(39–82)	ccRCC	0: 57 (72.2%) 1: 19 (24.0%) 2: 3 (3.8%)	CSS	93 (0.1–152)	7
Lamb 2012	March 1997 and July 2007/UK	Prospective	Nephrectomy	169	NA	ccRCC	0: 117 (69.2%) 1: 46 (27.2%) 2: 6 (3.6%)	OS CSS	Median (minimum) 98 (49)	8
Cross 2012	US	NA	Nephrectomy	248	NA	Localized ccRCC	NA	OS RFS	Mean (range) 25 (1–81)	Conference

Abbreviations: mGPS, modified Glasgow prognostic score; NOS, Newcastle–Ottawa Quality Assessment Scale; IQR, interquartile range; RCC, renal cell carcinoma; mRCC, metastatic renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; OS, overall survival; CSS, cancer-specific survival; RFS, recurrence-free survival; PFS, progression-free survival; IVC, inferior vena cava; NA, not available.

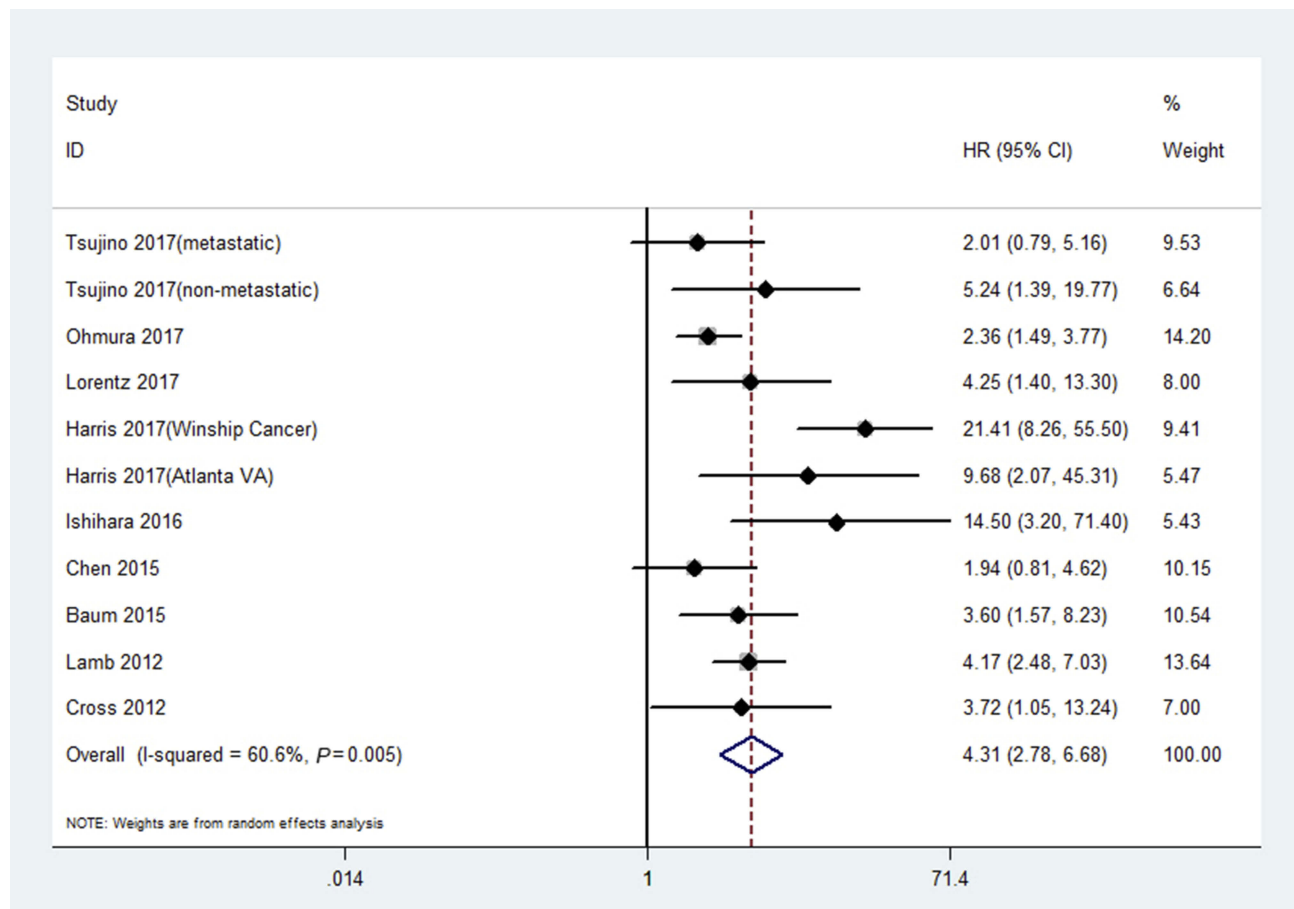


Figure 2 Association between mGPS and OS in patients with renal cell carcinoma.

Abbreviations: HR, hazard ratio; CI, confidence interval; mGPS, modified Glasgow prognostic score; OS, overall survival.

Cancer-specific survival

Regarding 4 studies comprising 855 patients reported the HRs of CSS. There was a significant association between higher mGPS and worse CSS, the pooled HR is 5.88(95% CI, 3.93–8.78; $P < 0.001$). There was no significant heterogeneity observed ($I^2 = 0\%$; $P = 0.521$; Figure 3).

Recurrence-free survival and progression-free survival

In terms of 3 studies incorporating 765 patients and 2 studies including 103 patients, we found that higher mGPS had a significantly increased risk of recurrence and progression compared with lower mGPS. The pooled HRs for RFS and PFS were 3.15(95%CI, 2.07–4.79; $P < 0.001$; Figure 4) and 1.91 (95%CI, 1.27–2.89; $P = 0.002$; Figure 5), respectively. There was also no heterogeneity among studies.

Sensitivity analysis

To further evaluate the robustness of final results, we conducted sensitivity analyses by sequentially excluding

enrolled each study. From Figure 6, we could observe that the adjusted results are consistent with previous results, which indicated the stability of our results.

Publication bias

As described in “Methods”, we used Begg’s test and Egger’s test to identify publication bias. We did not detect publication bias for OS according to Egger’s test ($P = 0.140$), while the P -value of Begg’s test is 0.029. Therefore, we used trim and fill method and did not observe publication bias. Furthermore, there was no evidence for publication bias of CSS, RFS and PFS in accordance with Egger’s test (CSS: $P = 0.787$; RFS: $P = 0.464$) and Begg’s test (CSS: $P = 1.000$; RFS: $P = 0.296$; PFS: $P = 1.000$), respectively.

Subgroup analysis

Due to obvious heterogeneity among studies, we accomplished subgroup analyses for OS stratified by pathological type, the cutoff value of mGPS, stage, and regions. While because of the small number of enrolled studies, we only

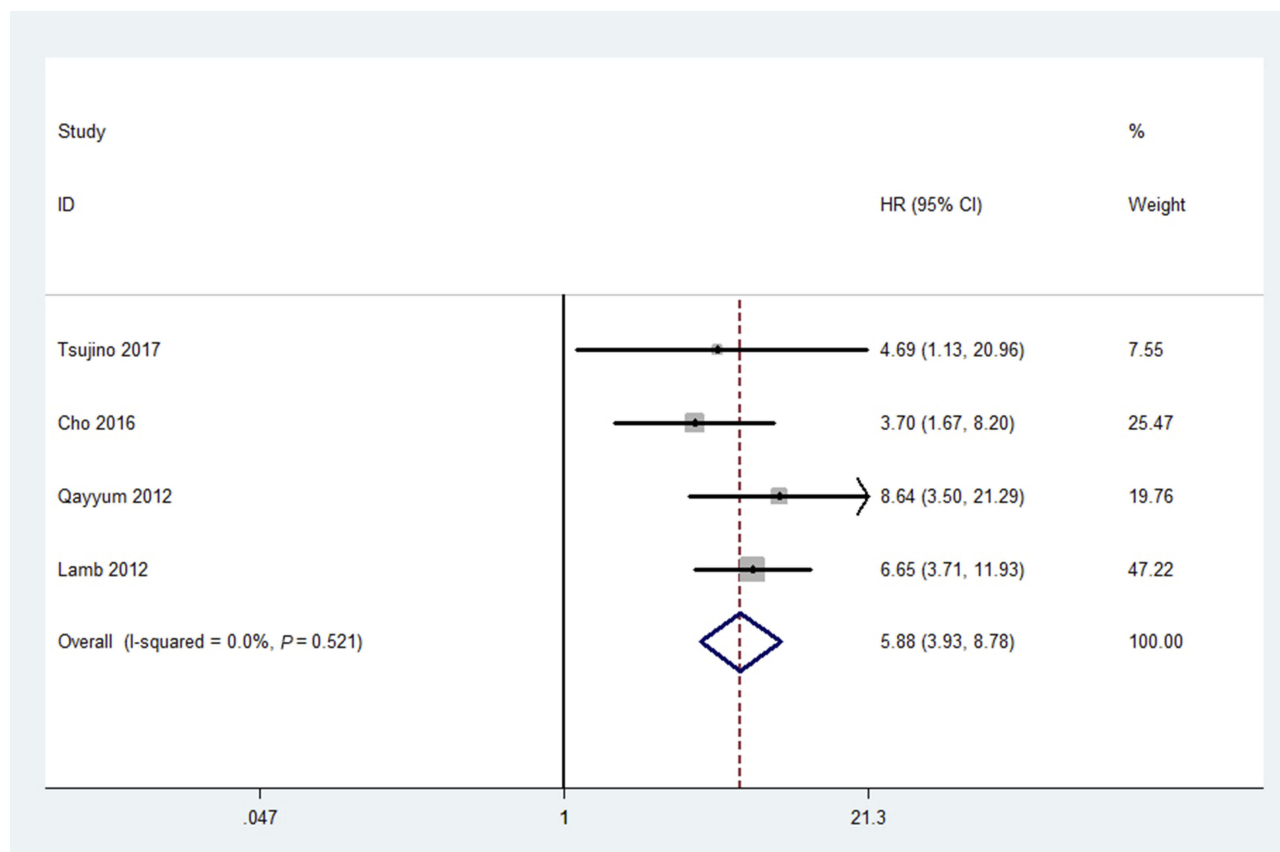


Figure 3 Association between mGPS and CSS in patients with renal cell carcinoma.

Abbreviations: HR, hazard ratio; CI, confidence interval; mGPS, modified Glasgow prognostic score; CSS, cancer-specific survival.

conducted subgroup analyses for CSS based on pathology, stage, and regions. As shown in Table 2, we demonstrated that higher mGPS had a poorer OS (HR=3.54; 95%CI, 2.48–5.06) and CSS (HR=5.99; 95%CI, 3.94–9.09) in patients with clear cell RCC. In other pathological types, higher mGPS are also associated with lower OS and CSS. Studies which used 1 and 2 as the cutoff values revealed that mGPS could serve as a prognostic factor for OS. In patients with localized RCC, increased mGPS was correlated to inferior OS (HR=3.93; 95%CI, 2.13–7.27) and CSS (HR=3.91; 95%CI, 1.94–7.86). For advanced/metastatic or all stages of RCC, there was also a significant association between mGPS and survival. The subgroup analyses based on regions show that both Asian and Western patients with higher mGPS had a decline of OS and CSS. Besides, heterogeneity was reduced in several subgroups. Detailed results of subgroup analyses are summarized in Table 2.

Discussion

Our studies pooled all eligible studies to evaluate the association between mGPS and survival in patients with

RCC. The pooled results suggested that higher mGPS was significantly linked with decreased OS and CSS and increased risk of recurrence and progression. Since there was obvious heterogeneity among studies, we carried out subgroup analyses based on pathological type, the cutoff value of mGPS, stage, and regions. We found that higher mGPS results in poorer OS and CSS in patients with clear cell RCC and other RCC. In different cutoff values, the mGPS also could be considered as a predictive factor for survival. In patients with different stages of RCC, there was also a significant association between mGPS and survival. As for patients of different regions, the pooled results are consistent with previous results. Although heterogeneity existed after subgroup analyses, it decreased in several subgroups. We also performed sensitivity analyses, and the trend of adjusted results did not alter. Besides, we also did not detect the publication bias, which indicates the reliability of our study.

It is difficult to predict the prognosis of patients with RCC because of its heterogeneous biological nature.¹⁸ TNM stage and Fuhrman nuclear grade are important

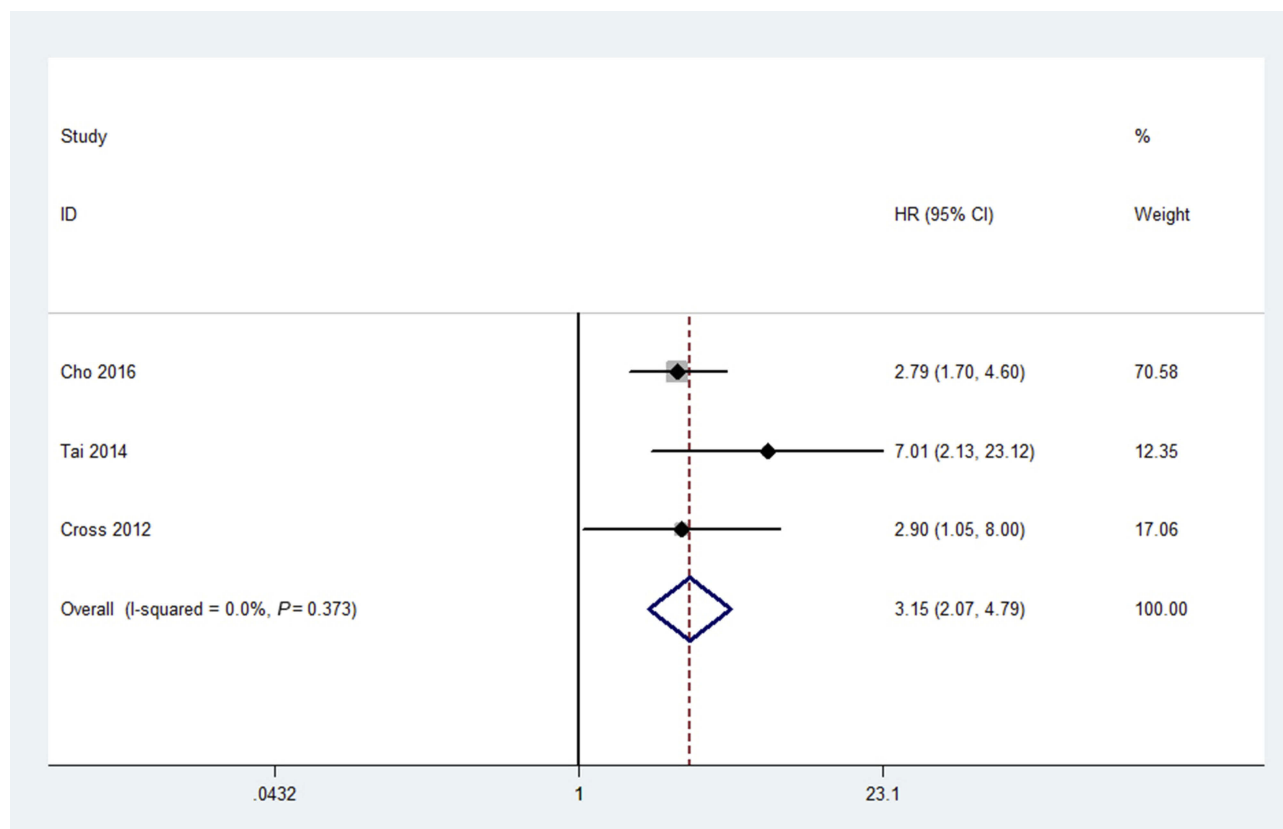


Figure 4 Association between mGPS and RFS in patients with renal cell carcinoma.

Abbreviations: HR, hazard ratio; CI, confidence interval; mGPS, modified Glasgow prognostic score; RFS, recurrence-free survival.

prognostic factors for RCC, but these factors cannot accurately predict the prognosis. An increasing number of studies searched for additional factors, suggesting cachexia, platelet count, performance status, CRP, and others, may be potential prognostic factors for patients with RCC.^{34–37}

Currently, more evidence revealed that local immune response and systemic inflammation are associated with tumor progression, metastasis, and survival of cancer patients.^{38,39} The inflammation response is characterized by white blood cells, platelets, lymphocytes, neutrophils, CRP, and albumin.³⁷ And kinds of combinations of these factors, such as NLR, PLR, GPS, and mGPS, were reported to be predictive for prognosis of cancers, including RCC.^{10–18} CRP is a typical acute-protein produced by hepatocyte, induced by cytokine especially IL-6.⁴⁰ More studies suggested that CRP is associated with prognosis of various cancers.^{10–13} Wang performed a meta-analysis and found that elevated CRP is correlated with poor prognosis in patients with RCC.³⁷ Some studies observed that RCC cells can produce IL-6, which is recognized as a promoter of tumor cells growth and functioned as an autocrine

growth factor of RCC.^{41,42} According to these evidence, we found that systemic inflammation is associated with prognosis of RCC. Furthermore, Chen et al conducted a meta-analysis and demonstrated that decreased pretreatment serum albumin levels result in poor prognosis of patients with RCC.⁴³ Albumin was reduced during chronic inflammation by immune response including CRP, increased vascular permeability for albumin, and decreased hepatic albumin synthesis.⁴⁴ Albumin levels can reflect the nutritional status of patients, malnutrition is associated with poor prognosis. Reportedly, CRP/albumin ratio, a combination of CRP and albumin, could serve as a prognostic factor of OS for patients with RCC.³⁰ GPS, originated from CRP and albumin and described by Forrest firstly, was used for predicting prognosis of non-small cell lung cancer.⁴⁵ Patients with both CRP increase (>10 mg/L) and hypoalbuminemia (<35 g/L) were defined as a score of 2. Patients with normal CRP level and albumin level were given a score of 0. Patients with either increased CRP level or hypoalbuminemia receive a score of 1. However, Proctor et al found that a low albumin level is not associated with poor survival in some cancers including bladder, prostate, renal, colorectal

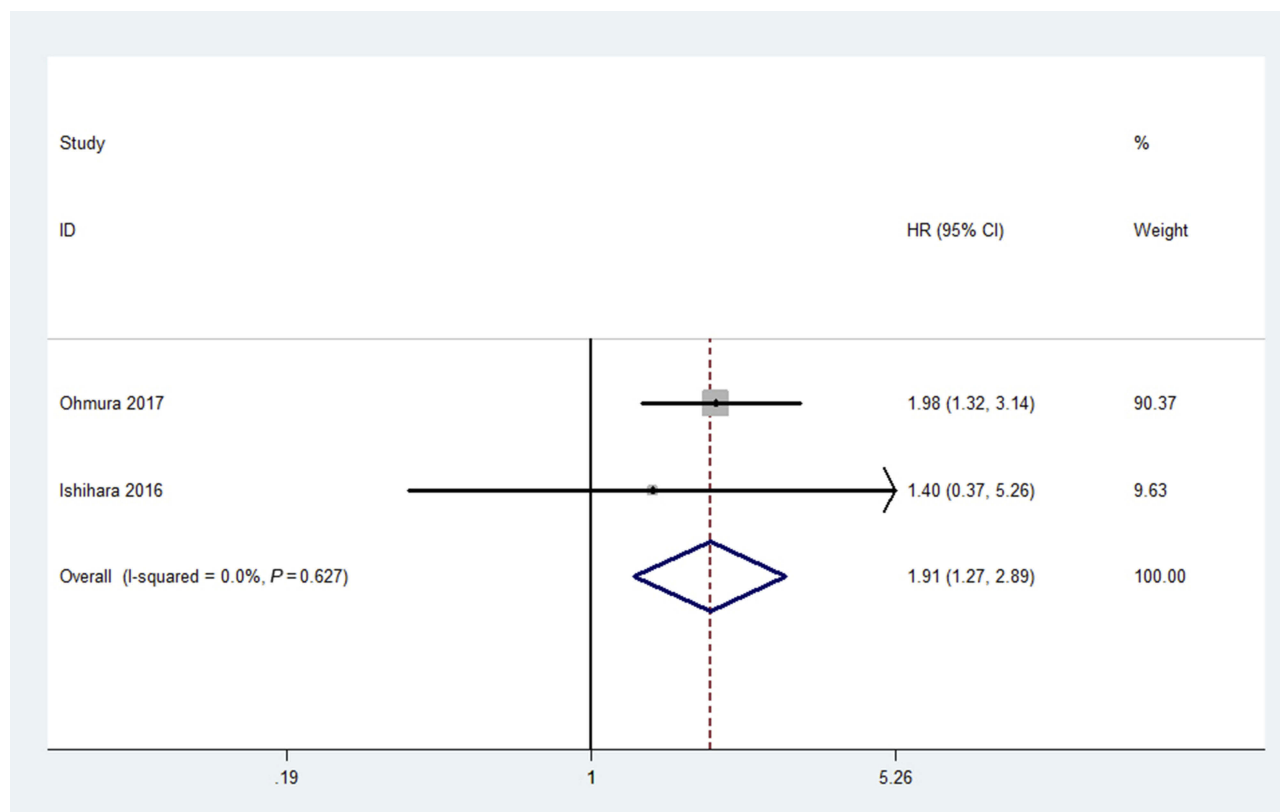


Figure 5 Association between mGPS and PFS in patients with renal cell carcinoma.

Abbreviations: HR, hazard ratio; CI, confidence interval; mGPS, modified Glasgow prognostic score; PFS, progression-free survival.

cancers and others based on a large cohort study.⁴⁶ Therefore, mGPS was modified by GPS and gave a score of 1 only for an elevated CRP, evaluating both systemic inflammation and nutrition status. As a result, the prognostic value of mGPS may be more accurate than GPS. The mGPS is easily measured, considered as a prognostic factor for various solid tumors.^{13,16–17} Based on our pooled results, we also found that higher mGPS was correlated to the poor prognosis of patients with different stages of RCC. And Tsujino et al observed that the predictive value of mGPS seems to be equivalent to those of Stage Size Grade Necrosis and University of California, Los Angeles Integrated Staging System.²⁶ Lamb et al also suggested that mGPS is at least equivalent to and independent of other current validated prognostic scoring systems for patients with RCC.³³ The mGPS, combining CRP and albumin, may provide more accurate prognostic information, and Cho revealed that mGPS is superior to CRP alone.¹⁸ To sum up, mGPS appears to be superior to other established prognostic scores and factors and could provide physicians with suggestions for patients' management. Close follow-up after treatments and optimal adjuvant therapies could be

emphasized on patients with higher mGPS. And individualized decision-making is needed with mGPS as a clinical tool to help guide therapy. Besides, further large-scale-based external validation is necessary.

However, this study is not devoid of limitations. Firstly, only 12 studies incorporating 2,391 patients were enrolled for pooled analysis, which is a small number and may limit the power of results. Further large-scale studies are necessary. Next, most studies are retrospective, increasing the risk of bias. Thirdly, the patients' baseline varied from study to study and may affect the pooled results. Although we performed subgroup analyses based on available data, some other confounders may exist and result in heterogeneity. Lastly, the measurements of CRP and albumin of enrolled studies may be different, which may also affect the final results.

Conclusion

Our study demonstrated that mGPS could serve as a predictive tool for the survival of patients with RCC. In the different subgroups, the results are consistent with previous results. In

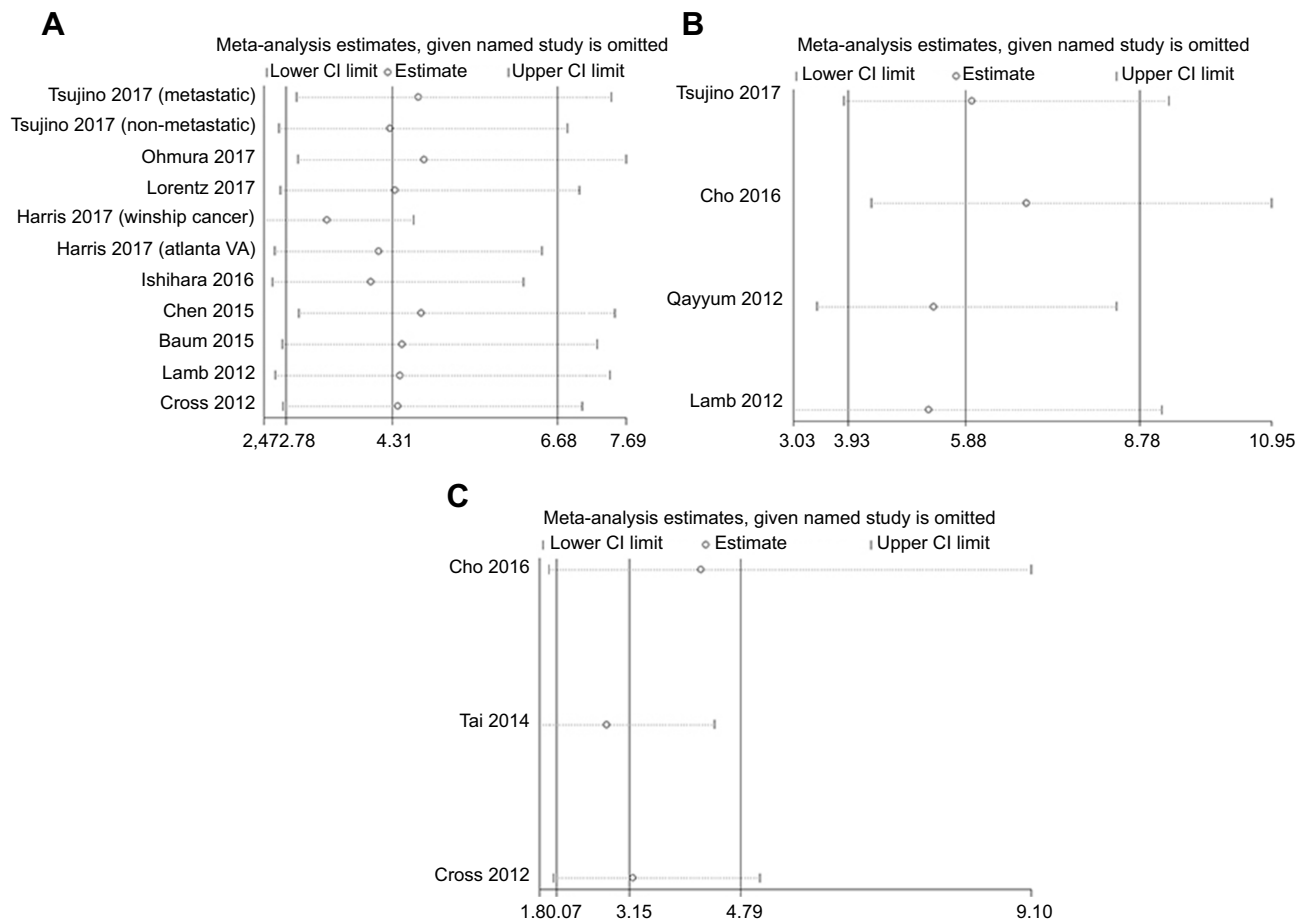


Figure 6 Sensitivity analyses of the association between mGPS and OS (A), CSS (B), and RFS (C) in patients with renal cell carcinoma. **Abbreviations:** CI, confidence interval; mGPS, modified Glasgow prognostic score; OS, overall survival; CSS, cancer-specific survival; RFS, recurrence-free survival.

Table 2 Subgroup analyses for OS and CSS

Outcome	Variable	Number of studies	Model	HR (95%CI)	I ²	P-value of heterogeneity
OS	All	9	Random	4.31 (2.78–6.68)	60.6%	P=0.005
	Pathology	Clear cell	Random	3.54 (2.48–5.06)	0%	P=0.677
	All	4	Random	5.95 (2.46–14.39)	78.2%	P<0.001
Cutoff	1	3	Random	3.01 (2.04–4.44)	23.8%	P=0.268
	2	6	Random	5.76 (2.86–11.63)	64.4%	P=0.010
Stage	Localized	3	Random	3.93 (2.13–7.27)	0%	P=0.891
	Advanced/metastatic	5	Random	5.72 (2.43–13.46)	78.0%	P<0.001
	All	2	Random	3.09 (1.49–6.43)	54.2%	P=0.139
Regions	Asia	4	Random	2.87 (1.69–4.86)	40.0%	P=0.154
	Western	5	Random	5.78 (3.24–10.30)	54.3%	P=0.053
CSS	All	4	Fixed	5.88 (3.93–8.78)	0%	P=0.521
	Pathology	Clear cell	Fixed	5.99 (3.94–9.09)	7.4%	P=0.340
	All	1	Fixed	4.69 (1.09–20.20)	-	-
Stage	Localized	2	Fixed	3.91 (1.94–7.86)	0%	P=0.781
	All	2	Fixed	7.18 (4.40–11.73)	0%	P=0.633
Regions	Asia	2	Fixed	3.91 (1.94–7.86)	0%	P=0.781
	Western	2	Fixed	7.18 (4.40–11.73)	0%	P=0.633

Abbreviations: OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval.

conclusion, pretreatment higher mGPS is associated with poorer OS, CSS, RFS, and PFS. Further external validations are necessary to strengthen this concept.

Disclosure

The authors report no conflicts of interest in this work.

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