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ORIGINAL ARTICLE

Prognostic value of the Glasgow Prognostic Score in renal cell carcinoma: a meta-analysis

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Abstract
Purpose Glasgow Prognostic Score (GPS) has been reported to predict oncologic outcomes in various type of cancer. However, their prognostic value in patients with renal cell carcinoma (RCC) is unclear. In this meta-analysis, we evaluated the prognostic significance of GPS in RCC patients.
Methods We performed comprehensive searches of electronic databases to identify studies that evaluated the prognostic impact of pretreatment GPS in RCC patients. The end points were cancer-specific survival (CSS), recurrence-free/disease-free survival (RFS/DFS). Meta-analysis using random-effects models was performed to calculate hazard ratios (HRs) or odds ratios with 95 % confidence intervals (CIs).
Results Nine retrospective, observational, cohort studies involving 2096 patients were included. Seven studies evaluated CSS, and three evaluated RFS. Our results showed that higher GPS (0 vs. 1 vs. 2) was significantly predictive of poorer CSS (HR 3.68, 95 % CI 2.52–5.40, $p < 0.001$) and RFS/DFS (HR 2.83, 95 % CI 1.86–4.30, $p < 0.001$) in patients with RCC. These findings were robust when stratified by sample size, presence of metastasis, and study region. We also conducted subgroup analysis by assessment of Newcastle–Ottawa quality assessment scale (NOS) score, and the HRs were 2.708 (95 % CI 1.969, 3.725) in under 7 points group, 3.685 (95 % CI 2.516, 5.396) in over than 7 points group in CSS. Meta-regression analysis indicated that NOS score group had a significant difference in HRs ($p = 0.032$).
Conclusions Higher GPS is associated with tumor progression and is predictive of poorer survival in patients with RCC. Therefore, GPS may help to inform treatment decisions and predict treatment outcomes.

Keywords Renal cell carcinoma · Glasgow Prognostic Score · Recurrence · Survival

Introduction

Renal cell carcinoma (RCC) accounts for 2–3 % of all adult neoplasm [1]. The incidence of RCC differs geographically and has increased over the past three decades. Despite the development of treatments for RCC, such as partial or radical nephrectomy, immunotherapy, and targeted therapies, the long-term patient outcome is poor because of common local recurrence and distal metastasis [2]. Therefore, it is important to find prognostic factors that can predict the outcome of RCC patients.

The TNM staging system and Fuhrman's nuclear grade are currently the most important prognostic factors for RCC patients [3]. However, the inaccuracy of these methods for predicting clinical outcome in RCC patients has led investigators to search for other prognostic factors to predict recurrence and progression. A number of studies have reported that the host immune response, particularly the systemic inflammatory response, is associated with recurrence and progression of RCC in a manner independent of

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TNM stage or tumor grade [4, 5]. In addition, the Glasgow Prognostic Score (GPS) and the combination of C-reactive protein (CRP) and albumin levels were shown to have prognostic value for RCC patients [6–9]. However, contradictory results have been reported for the GPS in patients with RCC due to differences in study design, sample size, and other factors. Thus, it is important to perform a systematic meta-analysis to understand the prognostic value of GPS in patients with RCC.

In this study, we evaluated the prognostic role of GPS for cancer-specific survival (CSS) and recurrence-free/disease-free survival (RFS/DFS) in patients with RCC by pooling the available outcome data.

Patients and methods

Search strategy

We performed a comprehensive search of the PubMed, Cochrane Central Search library, and EMBASE databases to analyze the prognostic value of the GPS in RCC up to February 29, 2016. Searches were performed using the following MeSH headings, keywords, and text words: "Glasgow Prognostic Score" (e.g., "GPS"), "RCC" (e.g., "renal cancer," "carcinoma," renal cell," "kidney cancer," "kidney neoplasms," "clear cell carcinoma," "adenocarcinoma, clear cell," and "non-clear cell carcinoma"), and "prognosis" (e.g., "recurrence," "survival" and "outcome"). A manual search was also performed using references from relevant literature, including all of the identified studies, reviews, and editorials. Abstracts and information from conferences were also collected independently. Two researchers (SRS and DSC) independently reviewed all studies that appeared to fit the inclusion criteria and extracted data from each included study. All authors were involved in the final decision regarding the inclusion or exclusion of each study.

Study inclusion criteria and definitions

Studies were considered eligible for inclusion in the meta-analysis if they met the following criteria: (1) Treatments were limited to surveillance, surgery, targeted therapy, or immunotherapy; (2) GPS was measured before treatment, and the number of patients was reported according to the GPS value; and (3) the potential association between outcomes of RCC and GPS was analyzed. Papers in languages other than English were also included if the data could be extracted. Case reports and review articles were excluded. When patient data were reported more than once by the same institution, the most informative and recent article was included in the analysis.

GPS was defined using a selective combination of CRP and albumin levels, as described previously [10]. Patients with both an elevated CRP concentration (>10 mg/l) and hypoalbuminemia (<35 g/l) were assigned a score of 2, and patients with only an elevated CRP concentration (>10 mg/l) or hypoalbuminemia (<35 g/l) were assigned a score of 1. Patients with a normal CRP concentration and albumin level were assigned a score of 0. CSS was defined as the interval between medical treatment and death due to cancer or last follow-up. RFS/DFS was measured from the date of curative treatment until the detection of tumor recurrence.

Data extraction

The following data were extracted: (1) study information, including the names of authors, and the study region, sample size, and study duration; (2) patient characteristics including age, gender, follow-up period, and treatment methods; (3) information about RCC including tumor type, stage, and distant metastasis; (4) GPS; and (5) survival, including CSS or RFS/DFS.

Statistical analysis

Hazard ratios (HRs) were taken directly from the articles. Heterogeneity among studies was evaluated using the Cochran *Chi-square* test and quantified using I^2 statistics. A p value <0.10 was considered statistically significant for the Cochran *Chi-square* test, and an $I^2 > 50$ % indicated substantial heterogeneity among studies. Potential sources of heterogeneity were then investigated using subgroup analyses and meta-regression. Since heterogeneity was detected among the included studies, data were pooled using random-effects models with the DerSimonian Laird method. All statistical tests were two sided, and $p < 0.05$ was taken to indicate statistical significance. The possibility of publication bias was assessed using Egger's tests and visual inspection of a funnel plot. All statistical tests were performed using Stata software (version 14.0; Stata Corp., College Station, TX, USA).

Quality assessment

The quality of the included articles was assessed by two investigators independently (SRS and DSC) using the Newcastle–Ottawa quality assessment scale (NOS). Studies with an NOS score ≥7 (on a scale of 0–8) were designated as high quality. Studies from conference abstracts were defined as low quality. Any conflicts regarding the appropriate category for a study were resolved by joint discussion.

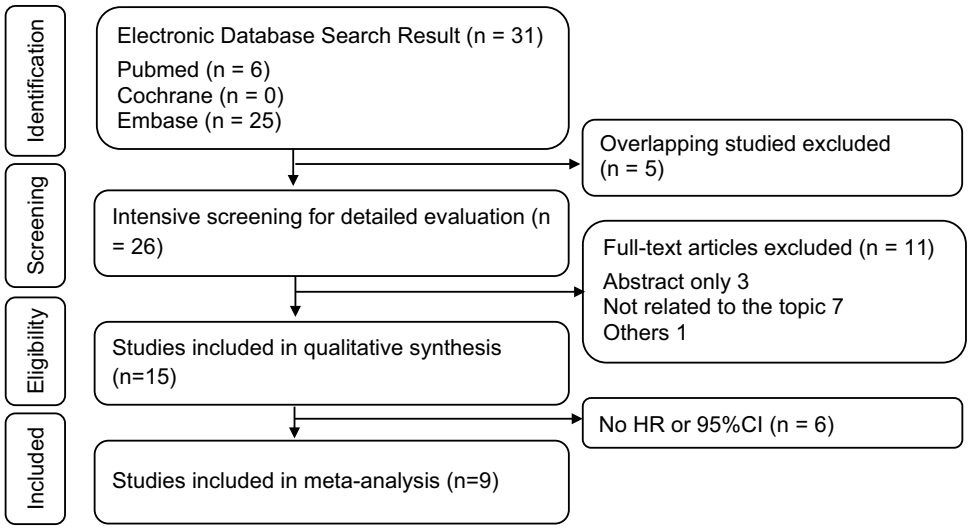

Fig. 1 Study flow diagram

Results

Study characteristics

The initial search identified 230 studies. After the title and abstract were reviewed, only 26 studies were found to have investigated the association between RCC and GPS; of these, nine retrospective studies, of 2096 RCC patients, were included in the meta-analysis after a review of the full text (Fig. 1).

The basic features of the nine studies are summarized in Table 1 [6–9, 11–14]. The median quality score of the included studies was 6 (range 5–7). Four studies were from the UK, and the rest were from the US, Austria, China, and Korea. Five of the cohort studies enrolled >150 patients, and four had <150 patients. Radical and partial nephrectomy was the only initial treatment for non-metastatic RCC in seven studies; patients in the other studies were treated using mixed therapies, including nephrectomy, immunotherapy, targeted therapy, and others.

GPS and CSS in RCC

Seven cohort studies presented data regarding the pretreatment GPS and CSS in patients with RCC. Elevated GPS was significantly associated with a shorter CSS (HR 3.68; 95 % CI 2.52–5.40, $p < 0.001$; $\chi^2 = 0.055$; $I^2 = 51.4$ %; Fig. 2a).

GPS and RFS/DFS in RCC

Three cohort studies presented data describing pretreatment GPS and RFS/DFS in patients with RCC. According to our pooled estimates, there was a significant relationship between elevated pretreatment GPS and shorter RFS/DFS (HR 2.83; 95 % CI 1.86–4.30, $p < 0.001$; $\chi^2 = 0.233$; $I^2 = 31.3$ %; Fig. 2b).

Subgroup analysis

To assess heterogeneity, subgroup analyses were performed for CSS according to sample size ($n \geq 150$ vs. $n < 150$), the presence of metastasis, NOS score (≥7 vs. <7), and study region (Western vs. Eastern countries). Subgroup analyses did not affect the prognostic impact of GPS on CSS, except NOS score. The HRs for NOS score were 2.708 (95 % CI 1.969–3.725) in the group scoring <7 and 3.685 (95 % CI 2.516–5.396) in the group scoring ≥7 points. Subgroup analyses for RFS/DFS were performed only sample size ($n \geq 150$ vs. $n < 150$) and NOS group (score of ≥7 vs. score of <7) because of the small number of included studies. Neither factor changed the prognostic potential of GPS in RFS/DFS.

Meta-regression

Meta-regression analysis indicated that the HRs of CSS differed significantly according to NOS score group ($p = 0.032$). However, no other factor had a significant impact on CSS. The results of the meta-regression analysis indicated the robustness of the findings (Table 2).

Publication bias

Analysis of publication bias revealed that the p value of the Egger's regression intercept was 0.577 (two-tailed, $p = 0.811$). A visual inspection of the symmetry graphic in the funnel plot indicated no evidence of publication bias or small-study effects (Fig. 3).

Table 1 Clinical characteristics of included studies in the meta-analysis

Study cohort	Year	Study region	Research time	Follow-up (month)	Treatment	M/F (*n*)	Age (years)	Tumor type	Distant metastasis (*n*)	GPS value	Survival analysis	HR	Adjustment variables	NOS score
Ramsey et al.	2007	United Kingdom	2001–2005	Median: 10	Curative nephrectomy:50; cytoreductive nephrectomy:48; none: 21; Immunotherapy with IFN-α and IL-2	85/35	≤60 years: 56; >60 years: 63	mRCC	119	0: 33, 1: 72, 2: 14	CSS	2.93 (95 % CI 1.88–4.55), $p < 0.001$	Hemoglobin, calcium, neutrophil count, lymphocyte percentage	6
Ramsey et al.	2008	United Kingdom	2005–2006	Median: 23 (minimum: 17)	Curative nephrectomy:13; cytoreductive nephrectomy:3; none: 7; Immunotherapy with IFN-α and IL-2	18/5	≤60 years: 9; >60 years: 14	mRCC	23	0: 8 1: 9 2: 6	CSS	2.23 (95 % CI 1.09–4.57), $p = 0.029$	Previous nephrectomy, MSKCC score, leukocyte count, IL-6, failure to complete one cycle of chemotherapy	5
Qayyum et al.	2012	United Kingdom	NA	Median: 93; range: 0.1–152	Curative nephrectomy	47/32	<65:40; >65:39	Clear cell RCC	0	0: 57 1:19 2: 3	CSS	8.64 (95 % CI 3.5–21.29), $p < 0.001$	Age, Sex, Grade, T stage, tumor necrosis, local inflammatory cell infiltrate	7

Table 1 continued

Study cohort	Year	Study region	Research time	Follow-up (month)	Treatment	M/F (*n*)	Age (years)	Tumor type	Distant metastasis (*n*)	GPS value	Survival analysis	HR	Adjustment variables	NOS score
Lamb et al.	2012	United Kingdom	1997–2007	Median: 98 (minimum: 49)	Curative nephrectomy	107/62	≤60 years: 91; >60 years: 78	Clear cell RCC	35	0: 117 1: 46 2: 6	CSS	6.65 (95 % CI 3.71–11.93), $p < 0.001$	Age, Sex, ECOG-ps, T stage, Fuhrman grade, necrosis, CRP, Kattan score, UISS, SSIGN, Leibovich	7
Tai et al.	2014	USA	2006–2008	Median: 25.5; IQR (12.0–32.4)	Curative nephrectomy	83/46	Median: 62; IQR (54.0–70.0)	Clear cell RCC	0	0: 80 1: 27 2: 22	RFS	7.012 (95 % CI 2.126–23.123), $p < 0.001$	T stage, Grade, tumor size, tumor necrosis, UISS, SSIGN, Kattan clinical scores	6
Lucca et al.	2015	Austria	2002–2014	Median: 40; IQR (17–73)	Radical and partial nephrectomy	257/173	Median: 65.5; IQR (57–73)	Clear cell RCC	0	0: 330 1: 87 2: 13	RFS (DFS)	2.32 (95 % CI 1.48–3.64), $p < 0.001$	SSIGN, PNI, NLR, MLR, PLR	7
Baum et al.	2015	USA	2005–2013	Mean: 31.6 (0.03–84)	Curative nephrectomy	352	Mean: 58.8	Clear cell RCC	0	0: 267 1: 38 2: 47	CSS	3.6 (95 % CI 1.57–8.23) $p = 0.002$	Age, sex, stage, grade	6

Table 1 continued

Study cohort	Year	Study region	Research time	Follow-up (month)	Treatment	M/F (*n*)	Age (years)	Tumor type	Distant metastasis (*n*)	GPS value	Survival analysis	HR	Adjustment variables	NOS score
Chen et al.	2015	China	2003–2012	Mean: 63 (1–151)	Radical and partial nephrectomy	406 (253/153)	Mean: 58 (24–80)	Clear cell RCC	2	NA	CSS	1.94 (95 % CI 0.81–4.62), $p = 0.153$	Age, sex, TNM stage, tumor necrosis, lymphovascular invasion, hemoglobin, calcium, CRP/albumin ratio	5
Cho et al.	2016	South Korea	June1994–July2012	Mean: 53.7 (4–215)	Radical and partial nephrectomy	388 (263/125)	Mean: 56.0 (18–81)	Clear cell RCC	0	0: 327 1: 38 2: 23	RFS CSS	2.794 (95 % CI 1.696–4.603), $p < 0.001$ 3.704 (95 % CI 1.672–8.203), $p = 0.001$	Age, gender, thrombocytosis, stage, grade, lymphovascular invasion, nephrectomy type, CRP	7

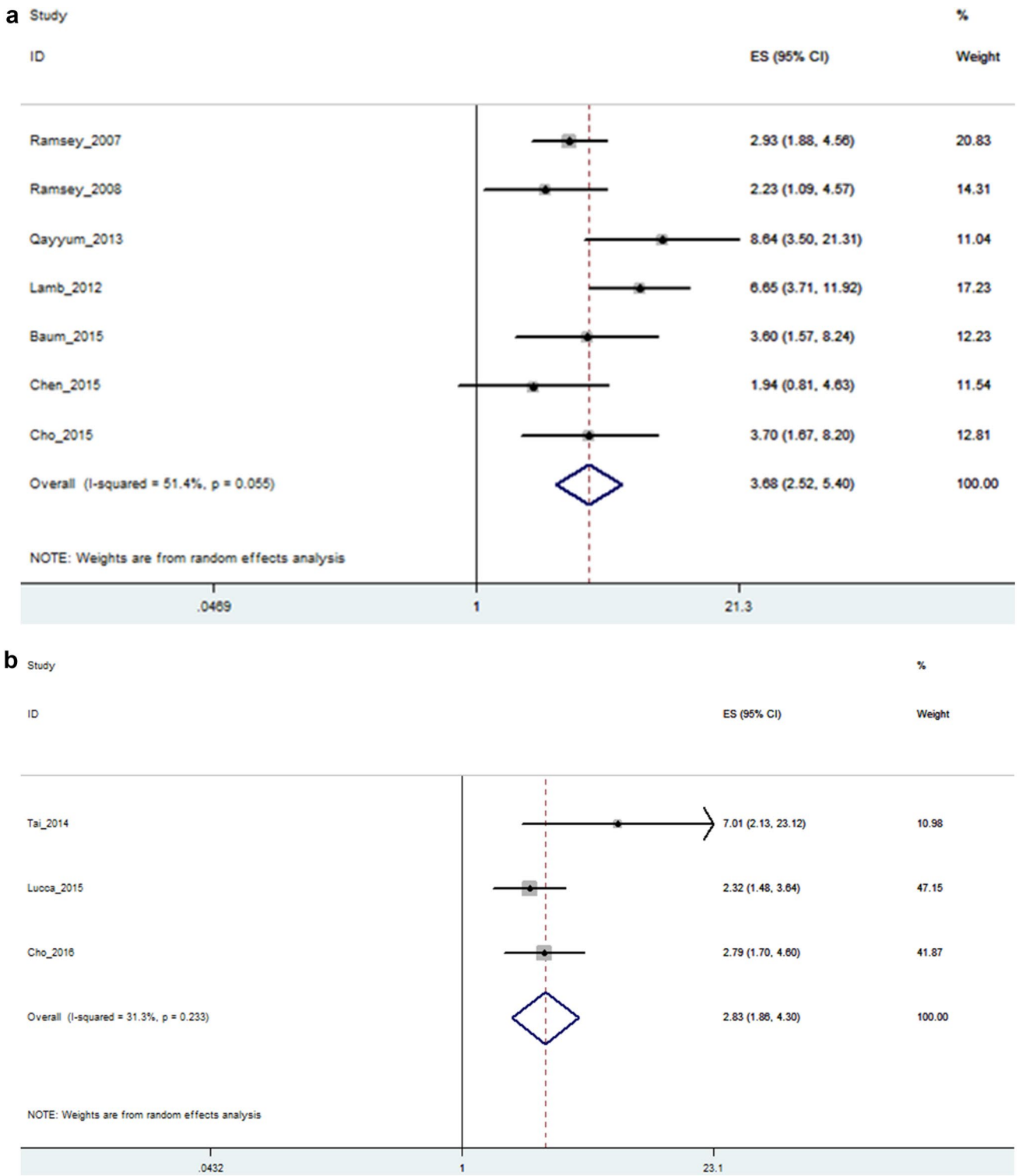

Fig. 2 Meta-analysis of the relationship between Glasgow Prognostic Score (GPS) and cancer specific survival (**a**) and recurrence-free/disease-free survival (**b**) in patients with renal cell carcinoma. Results are showed as individual and pooled HRs and 95 % CI

Table 2 Meta-regression analysis of hazard ratios in CSS

	k	Coef	SE	HR	95 % CI		*p*
No. of patients							
≥150	4	1.082	0.473	3.86	2.30	6.50	0.864
<150	3			3.56	1.85	6.88	
Presence of metastasis							
Metastasis	2	0.591	0.222	2.72	1.87	3.96	0.220
Non-metastasis				4.42	2.71	7.21	
NOS_category							
≥7	3	2.210	0.592	5.98	3.86	9.25	0.032
<7	4			2.71	1.97	3.73	
Ethnic							
Asian	2	0.669	0.315	2.75	1.46	5.17	0.432
Caucasian	5			4.08	2.54	6.56	
T stage							
T1	3	−0.002	0.006	–	–	–	0.748
T2	3	0.025	0.069	–	–	–	0.779
T3	3	0.012	0.009	–	–	–	0.390
T4	3	0.251	0.142	–	–	–	0.328

k number of observations. No. of Pt, number of total patients (1: ≥150, 0: <150). Tumor type (1: metastasis, 0: non-metastasis). NOS_category, (1: ≥7, 0: <7). Country (1: Asian, 0: Caucasian). T stage (T1 to T4) was continuous data. *p* value of random-effect meta-regression using restricted maximum likelihood (REML)

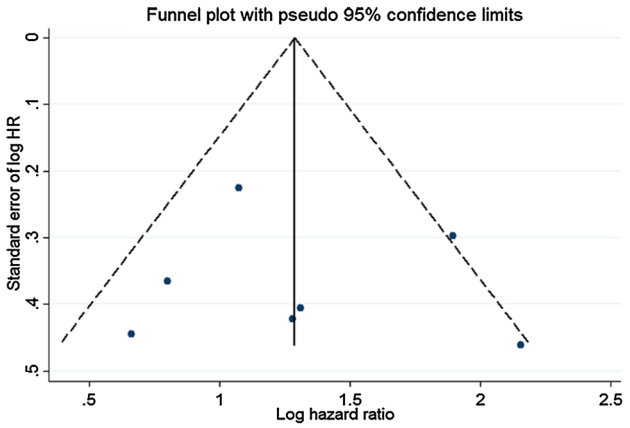

Fig. 3 Funnel plot for evaluation of publication bias or small-study effects in CSS

Discussion

Although the TNM staging system and Fuhrman's nuclear grade are the most important prognostic factors for RCC, these factors cannot accurately estimate the clinical course of patients with RCC, and many patients with the same stage or grade undergo a significantly different prognostic course. Therefore, studies have sought to identify supplementary prognostic factors for RCC, and evidence suggests that inflammation plays an important role in tumorigenesis [15, 16].

The GPS, which involves a selective combination of CRP and albumin levels, was first used in patients with advanced non-small cell lung cancer [10]. Because laboratory tests are performed routinely in patients with RCC before treatment, the GPS could be used as a simple, easy, and convenient measure of the systemic inflammatory response. Importantly, the GPS has a prognostic role in several types of cancer, including RCC [6–9, 17–19].

To the best of our knowledge, the current study is the first meta-analysis to comprehensively and systematically estimate the relationship between GPS and the clinical outcome of patients with RCC. The results suggested that elevated GPS was related not only to an increased risk of cancer recurrence in localized RCC, but also to disease progression or reduced CSS in advanced RCC. Therefore, multifactorial approaches should be used during the treatment of RCC patients, including radical or cytoreductive nephrectomy, immunotherapy, and targeted therapy, particularly in patients with higher GPS prior to treatment. Since there was moderate heterogeneity among the included studies, we also performed subgroup analyses of the studies that assessed CSS based on sample size, the presence of metastasis, NOS score, and study region. No subgroup analysis was significant except for that regarding the NOS score. Therefore, the results suggest that GPS is a promising prognostic factor that could help clinicians make appropriate treatment decisions and estimate the clinical outcome of patients with RCC.

We tried to identify the cause of heterogeneity observed among the included studies using meta-regression analysis and found that NOS score ($p = 0.032$) and the presence of metastasis ($p = 0.220$) were responsible for the moderate heterogeneity in CSS. It is inevitable that studies reporting a lower NOS score are more likely to show statistical heterogeneity. Although there was no significant difference according to the presence of metastasis in the meta-regression, GPS had superior prognostic value in patients with non-metastatic RCC compared with those with metastatic RCC. We also performed subgroup analyses of studies that assessed RFS/DFS and detected mild heterogeneity. However, the impact of subgroup analysis was weak in RFS/DFS because of the small number of studies; therefore, further evaluations are needed.

The funnel plot analysis showed relative symmetry in the meta-analysis, suggesting a low possibility of publication bias. Therefore, the results showed that there was an association between a higher GPS value and poorer prognosis in patients with RCC.

Because of the limited data in the included studies, we did not conduct pooled analysis on the correlation between high GPS and the clinicopathological features of RCC. As reported previously, a higher GPS is closely associated with more aggressive tumor behavior and poorer patient prognosis. This suggests that there could be a significant association between GPS, pathological tumor features, and other known RCC risk factors. Nevertheless, more clinical studies focusing on these relationships are necessary to help us better understand how GPS influences the prognosis of patients with RCC.

The current study had several limitations. First, although nine studies containing 2096 cases were included in the analysis, few studies were included in the subgroup analyses for CSS, and the subgroup analyses for RFS/DFS lacked data. In addition, this meta-analysis also ignored the potential effects of unpublished data [20]. Second, the study design, clinical characteristics of the included patients, and follow-up durations varied among studies. As a result, heterogeneity could not be eliminated completely and might have interfered with the results of the combined analysis. Third, we could not eliminate individual patient factors, such as smoking or alcohol consumption, which may affect the GPS by inducing systemic inflammation, and by extension could also influence patient prognosis.

Conclusions

The results of this meta-analysis encourage the routine use of GPS to predict recurrence, progression, and survival in patients with RCC, independent of the tumor stage, therapeutic intervention, and geographical area. In conclusion, this meta-analysis demonstrated that a higher GPS is closely associated with tumor progression and poor prognosis in patients with RCC. Therefore, GPS is a simple, highly available, and robust prognostic marker in patients with RCC.

Authors' contribution SR Shim was involved in protocol/project development, manuscript editing, data analysis; SJ Kim and SI Kim were involved in data management; DS Cho wrote the manuscript and analyzed the data.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study formal consent is not required.

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