Prognostic value of the pretreatment Glasgow prognostic score or modified Glasgow prognostic score in patients with advanced cancer receiving immune checkpoint inhibitors: A systematic review and meta-analysis

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Abstract. The Glasgow prognostic score (GPS) and modified GPS (mGPS) have value in evaluating the prognosis of patients receiving immune checkpoint inhibitors (ICIs). However, with the continuous emergence of new research, the predictive value of GPS and mGPS for immunotherapy deserves further validation. The aim of the present study was to explore the predictive value of GPS or mGPS on the progression-free survival (PFS) and overall survival (OS) of patients with advanced cancer receiving ICIs. Eligible studies were systematically searched using the PubMed, Embase, Cochrane library and Web of Science databases until November 2022. Published data were extracted and the hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled. A total of 18 studies with 1,355 patients were included in the present study. Patients were divided into the low GPS/mGPS (0) and high GPS/mGPS (1/2/1-2) groups. Overall, the high GPS group had a shorter OS (HR, 2.88; 95% CI, 2.06-4.03) with high heterogeneity, and a shorter PFS (HR, 2.08; 95% CI, 1.55-2.78) with low heterogeneity, compared with the low GPS group. Sensitivity analysis showed that the results were stable and the heterogeneity was significantly reduced from 56.4 to 30.3% after excluding one study. Subgroup analyses by score showed that GPS 1, GPS 2 and GPS 1-2 all had a poorer OS than GPS 0, with low heterogeneity. Overall, the high mGPS group had a poorer OS (HR, 2.56; 95% CI, 1.76-3.72) with low heterogeneity, and a poorer PFS (HR, 2.55; 95% CI, 1.81-3.60) with high heterogeneity, compared with the low mGPS group. The combined effect size was consistent but the heterogeneity was not eliminated after sensitivity analysis. Subgroup analyses by country and score also showed that the country had no effect on the results and that mGPS 1, mGPS 2 and mGPS 1-2 had a poorer PFS than mGPS 0. Therefore, high GPS and mGPS may be effective biomarkers for predicting the survival of patients with cancer receiving ICIs. Patients with high GPS and mGPS may be considered for supportive treatment; however, large prospective trials are needed to validate these findings.

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Introduction

In recent years, more research evidence on immunotherapy has been emerging in the field of oncology. Immune checkpoint inhibitors (ICIs) have demonstrated notable efficacy in both perioperative and advanced cancer treatment (1,2). Nevertheless, the problems of hyper-progression and serious adverse reactions after receiving immunotherapy cannot be ignored (3,4). At present, the expression level of programmed death ligand-1 (PD-L1) is the main predictive biomarker for immunotherapy. However, a study has found that a small proportion of patients with negative PD-L1 expression remain sensitive to immunotherapy (5). In addition, there is still a lack of unified standards for the detection method of PD-L1. The prognostic value of tumor mutational burden (TMB) as a biomarker for immunotherapy has been

validated in clinical studies and using real-world data (6,7). However, due to the lack of a unified detection standard, the inability to fully reflect the tumor immune microenvironment, the differences between different tumor types and the limitations of dynamic changes, the application of TMB is limited (6). Therefore, PD-L1 expression and TMB cannot predict the prognosis and efficacy of immunotherapy fully and effectively. It is therefore imperative to explore new predictive markers for identifying patients with a potentially poor prognosis at an earlier stage and to provide supportive treatment to improve treatment outcomes to further expand the population benefiting from immunotherapy.

The value of inflammatory markers and nutritional status in evaluating tumor prognosis has gradually become a research hotspot. Specifically, the prognostic scoring systems based on inflammatory markers, such as the Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), immuno-inflammatory index (SII), lymphocyte-to-monocyte ratio (LMR) and prognostic nutritional index (PNI), have been shown to have predictive value in the prognosis of anti-tumor therapy (3,8-10). The GPS, originally proposed by Forrest *et al* (11), is a scoring system based on a combination of C-reactive protein (CRP) and albumin levels. Albumin is a biomarker of nutritional status (12), whereas CRP is a sensitive indicator of the inflammatory response and has also been shown to promote the formation of an immunosuppressive tumor microenvironment and the growth of tumor cells (13). CRP can be used as an independent prognostic factor for a variety of malignant tumors such as gastric and pancreatic cancer (14,15). Recently, CRP has also been found to predict the efficacy of programmed cell death protein 1 (PD-1) treatment (16). Hypoalbuminemia is a manifestation of cachexia in patients with advanced tumors and severe inflammatory damage can also lead to hypoalbuminemia. Decreased albumin can weaken the ability of cells to activate immunity and antioxidant (17,18). Thus, the GPS combines the two indicators, CRP and albumin, to more effectively evaluate the prognosis of patients with tumors.

The GPS criteria are as follows: CRP elevation (CRP >10 mg/l) combined with hypoalbuminemia (albumin <35 g/l) is assigned a score of 2, only one abnormality is assigned a score of 1 and a score of 0 is assigned when both indicators are normal (19). In 2007, McMillan *et al* (20) refined the scoring system to create the modified GPS (mGPS). The improved scoring system emphasizes that individuals with elevated CRP and normal albumin are scored as 1 point. Studies have shown that the mGPS system is more effective in reflecting systemic inflammatory responses than isolated inflammatory indicators (21,22). GPS and mGPS have gradually been proven to have value in evaluating the prognosis of patients receiving immunotherapy (23,24). However, with the continuous emergence of new research, the predictive value of GPS and mGPS for immunotherapy deserves further validation.

In the present study, the literature on the association between GPS or mGPS and the prognosis of patients with advanced cancer receiving immunotherapy was reviewed, and a meta-analysis was conducted to demonstrate the role of GPS or mGPS in predicting overall survival (OS) or progression-free survival (PFS).

Materials and methods

Preferred reporting items for systematic reviews and meta-analyses (PRISMA). The present study was performed in accordance with the PRISMA guidelines (25). The protocol for the systematic review and meta-analysis was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/view/CRD42023396079, no. CRD42023396079).

Literature search. The PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane library (https://www.cochranelibrary.com/) and Web of Science (www.webofscience.com) databases were systematically searched by three independent researchers, searching literature from the inception of the databases to November 2022. The following key words were used: ('Glasgow prognostic score' OR 'GPS' OR 'modified Glasgow prognostic score' OR 'mGPS') AND ('immune checkpoint inhibitors' OR 'PD-L1 inhibitor' OR 'PD-1 inhibitor') AND ('neoplasms' OR 'carcinoma'). Full database search strategies can be viewed in Supplementary materials 1. Other sources were also included, such as relevant articles found in the review article (26).

Study selection. The inclusion criteria were as follows: i) Studies on patients with advanced cancer that cannot be cured by local treatment receiving ICIs; ii) studies that calculated the GPS or mGPS before ICI treatment; iii) studies reporting clinical outcomes such as OS and/or PFS; and iv) studies with hazard ratio (HR) with 95% confidence interval (CI) data available. Reviews, case reports, letters, studies not in English or with insufficient data were excluded.

Data extraction. The following data were extracted from each individual study: Country, cancer type, study design type, ICIs, sample size, line of treatment, patient sex, patient age, analysis model, GPS or mGPS, follow-up time, endpoint and HRs with 95% CIs for OS and PFS. If both univariate and multivariate results were available, priority was given to the multivariate results.

Quality assessment. The Newcastle-Ottawa Scale (NOS) was applied to assess the quality of studies (27). The total score of NOS ranges from 0 to 9 based on its assessment items. In total, two reviewers assessed each study independently and reached a consensus after discussion.

Statistical analysis. Patients were divided into low GPS/mGPS (0) and high GPS/mGPS (1/2/1-2) groups, with a cut-off value of 0. Studies containing two HRs (such 0 vs. 1 and 0 vs. 2) were included in the meta-analysis as two independent findings. The outcomes were reported as pooled HRs with 95% CIs for OS and PFS. The pooled results were examined by random-effects models. $P<0.05$ or $I^2>50\%$ was considered to indicate high heterogeneity. Subgroup analysis was used to analyze the sources of heterogeneity. A sensitivity analysis was performed using the leave-one-out sensitivity method to evaluate the robustness of the combined results and to identify the studies that contributed significantly to

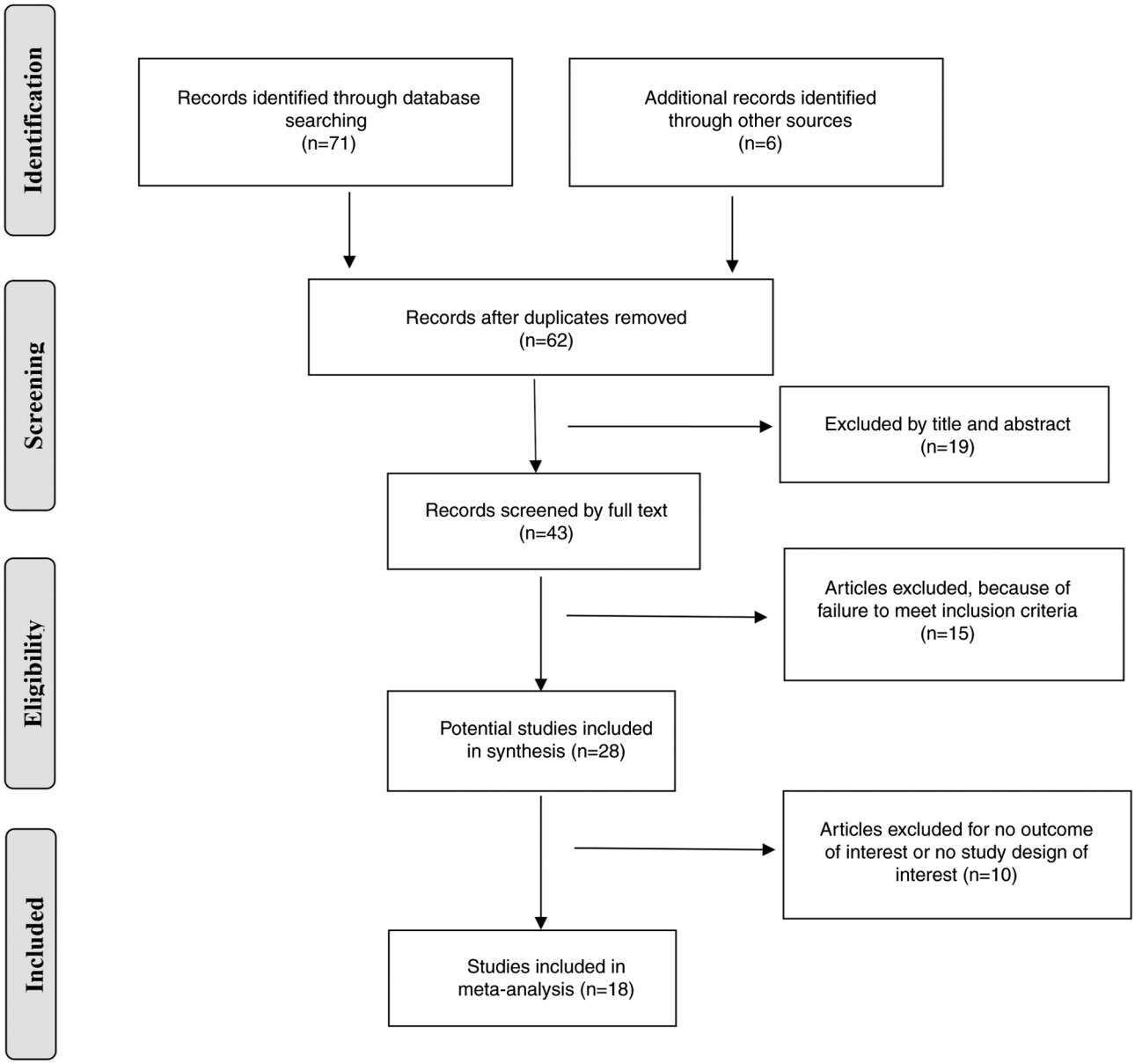

Figure 1. Flow chart of the literature search and screening process.

heterogeneity. A graphical funnel plot and Egger's test was used to evaluate publication bias. Statistical analyses were conducted using Stata 14.0 (StataCorp LP).

Results

Study identification and selection. The literature retrieval and screening process is shown in Fig. 1. After initial searches in the PubMed, Web of Science, Medline, Embase and Cochrane Library databases, 71 relevant publications were screened, and 6 additional records were identified through other sources. Subsequently, after omitting duplicate records and eliminating by title and abstract, detailed screening was conducted on the remaining 43 records. In total, 15 studies that did not meet the inclusion criteria and 10 studies with no outcome of interest were excluded. Finally, 18 studies (28-45) involving 1,355 patients were included in the present meta-analysis.

Characteristics and quality assessment. All included studies were retrospective and published between 2020 and 2022. In 9 studies that reported GPS, 8 were from Asian countries (5 from Japan, 2 from Korea and 1 from China), 8 reported the HR of OS and 7 reported the HR of PFS. In 9 studies that reported mGPS, 4 were from Asian countries (all from Japan), while 5 were from European or American countries, 8 reported the HR of OS and 8 reported the HR of PFS. The NOS scores of all included studies were ≥5. The study characteristics are presented in Table SI.

Prognostic value of GPS on survival outcomes. The pooled results of 8 studies involving 12 sets of data (28-35) revealed that a high GPS in patients receiving ICIs resulted in a poorer OS than a low GPS (HR, 2.88; 95% CI, 2.06-4.03), with high heterogeneity (Fig. 2). Sensitivity analysis showed that heterogeneity was significantly reduced (I^2 reduced from 56.4 to 30.3%) after the study by Kasajima *et al* (34) was excluded,

Table I. GPS subgroup analysis for OS and mGPS subgroup analysis for PFS.

A, GPS for OS

Subgroup	Number of studies	HR (95% CI)	P-value	Heterogeneity, P-value (I^2), %
Score				
1 vs. 0	4	2.18 (1.46-3.25)	<0.001	0.219 (32.1)
2 vs. 0	4	5.03 (3.17-7.99)	<0.001	0.619 (0.0)
1-2 vs. 0	4	1.88 (1.46-2.42)	<0.001	0.143 (44.7)

B, mGPS for PFS

Subgroup	Number of studies	HR (95% CI)	P-value	Heterogeneity, P-value (I^2), %
Region				
Asian	3	2.60 (1.62-4.16)	<0.001	0.899 (0.0)
Non-Asian	5	2.61 (1.65-4.11)	<0.001	0.001 (67.9)
Score				
1 vs. 0	6	1.55 (1.17-2.05)	0.002	0.391 (4.0)
2 vs. 0	6	3.74 (2.02-6.91)	<0.001	0.011 (66.5)
1-2 vs. 0	2	2.92 (1.33-6.41)	0.007	0.793 (0.0)

All results were obtained using Cochran's Q-test and I^2 statistics. OS, overall survival; PFS, progression-free survival; GPS, Glasgow prognostic score; mGPS, modified GPS; HR, hazard ratio; CI, confidence interval.

indicating that this study markedly contributed to heterogeneity (Fig. S1A). Subgroup analyses were conducted by the GPS value. GPS 1 [from 4 studies (29-32); HR, 2.18; 95% CI, 1.46-3.25], GPS 2 [from 4 studies (29-32); HR, 5.03; 95% CI, 3.17-7.99] and GPS 1-2 [from 4 studies (28,33-35); HR, 1.88; 95% CI, 1.46-2.42] were all found to be associated with a worse OS compared with GPS 0, with low heterogeneity. No subgroup analysis by country was performed because seven studies were from Asian populations and only one study was from Australia. All subgroup analyses are shown in Table I.

The pooled results of 7 studies involving 10 sets of data (30-36) showed that a high GPS resulted in a poorer PFS in patients receiving ICIs than a low GPS (HR, 2.08; 95% CI, 1.55-2.78), with low heterogeneity (Fig. 2). The combined effect size was consistent after eliminating any of the studies, indicating that the results had a good robustness (Fig. S1B).

The funnel plots for GPS in OS and PFS are shown in Fig. 3A and B. The Egger's tests (OS, P=0.896; PFS, P=0.989) indicated that no notable publication bias existed.

Prognostic value of mGPS on survival outcomes. The pooled results of 8 studies involving 14 sets of data (37-44) showed that a high mGPS resulted in a shorter OS in patients receiving ICIs than a low mGPS (HR, 2.56; 95% CI, 1.76-3.72), with high heterogeneity (Fig. 4). The combined effect size remained consistent after excluding any one study, which indicated that the results were stable (Fig. S2A).

The pooled results of 8 studies involving 14 sets of data (38-45) showed that a high mGPS resulted in a shorter PFS in patients receiving ICIs than a low mGPS (HR, 2.55; 95% CI, 1.81-3.60), with high heterogeneity (Fig. 4). Sensitivity analysis and subgroup analysis by country and mGPS value were performed to analyze the sources of heterogeneity. The combined effect size was consistent but the heterogeneity was not eliminated after sensitivity analysis (Fig. S2B). Subgroup analysis by country showed that a high mGPS in Asians from 3 studies (38,44,45) and non-Asians from 5 studies (39-43) was associated with a shorter PFS time than a low mGPS (HR, 2.60; 95% CI, 1.62-4.16; and HR, 2.61; 95% CI, 1.65-4.11), and the non-Asian subgroup still had high heterogeneity (I^2=67.9%). Subgroup analysis by score indicated that an mGPS of 1 (n=6 studies) (38-43), an mGPS of 2 (n=6 studies) (38-43) and an mGPS of 1-2 (n=2 studies) (44,45) was associated with a poorer PFS than mGPS 0 (HR, 1.55; 95% CI, 1.17-2.05; HR, 3.74; 95% CI, 2.02-6.91; and HR, 2.92; 95% CI, 1.33-6.41, respectively), and the mGPS 2 subgroup still had high heterogeneity (I^2=66.5%). All subgroup analysis results are shown in Table I.

The funnel plots for mGPS in OS and PFS were symmetrical, indicating no publication bias (OS, P=0.670; PFS, P=0.941; Fig. 5A and B).

Discussion

GPS and mGPS have been shown to have prognostic value in multiple cancer types and different treatment stages (46,47). Although other inflammatory indicators, such as NLR, PLR, PNI and SII, have some predictive value, they lack a comprehensive assessment of nutritional status and are less consistent across cancer types. Specifically, Yamanouchi *et al* (48) evaluated the effects of inflammatory and nutritional indicators such as GPS, NLR and PNI on the prognosis of patients with metastatic breast cancer,

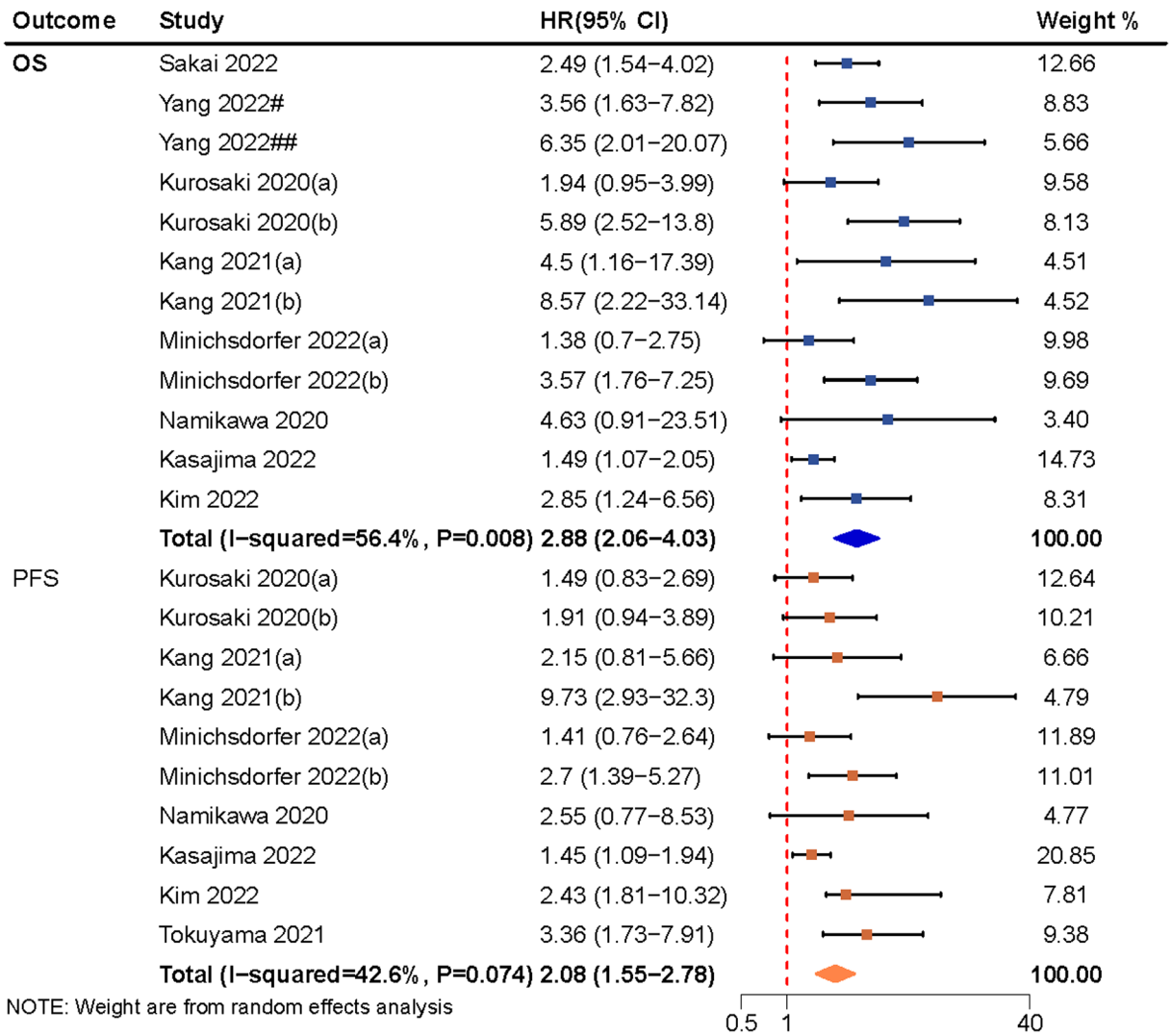

Figure 2. Forest plots of the HRs and 95% CIs for OS (blue dots) and PFS (orange dots) by GPS in patients treated with immune checkpoint inhibitors. [(a)] Univariate analysis results and [(b)] multivariate analysis results of the same study, respectively; [#] and [##] represent 1 vs. 0 and 2 vs. 0 subgroups in the same study, respectively. HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival; GPS, Glasgow prognostic score.

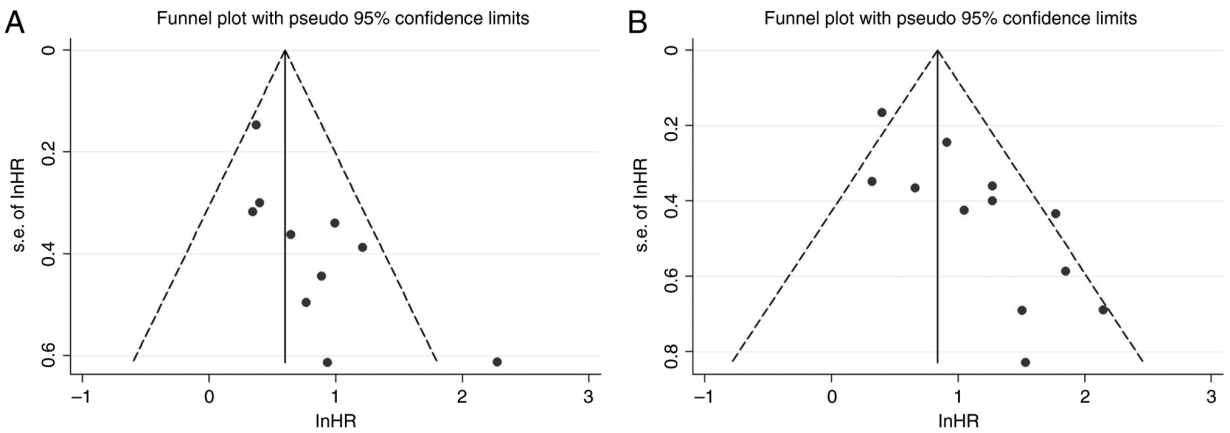

Figure 3. Funnel plots of Glasgow prognostic score for (A) progression-free survival and (B) overall survival. s.e. standard error; lnHR, natural logarithm of the hazard ratio.

and only GPS was indicated to be an independent predictor of OS. GPS was also shown to be an independent indicator of prognosis in patients with hepatocellular carcinoma, and was superior to other inflammatory prognostic scores in terms of prognostic power (49). Shimoyama *et al* (50) evaluated the prognostic value of 17 inflammatory markers

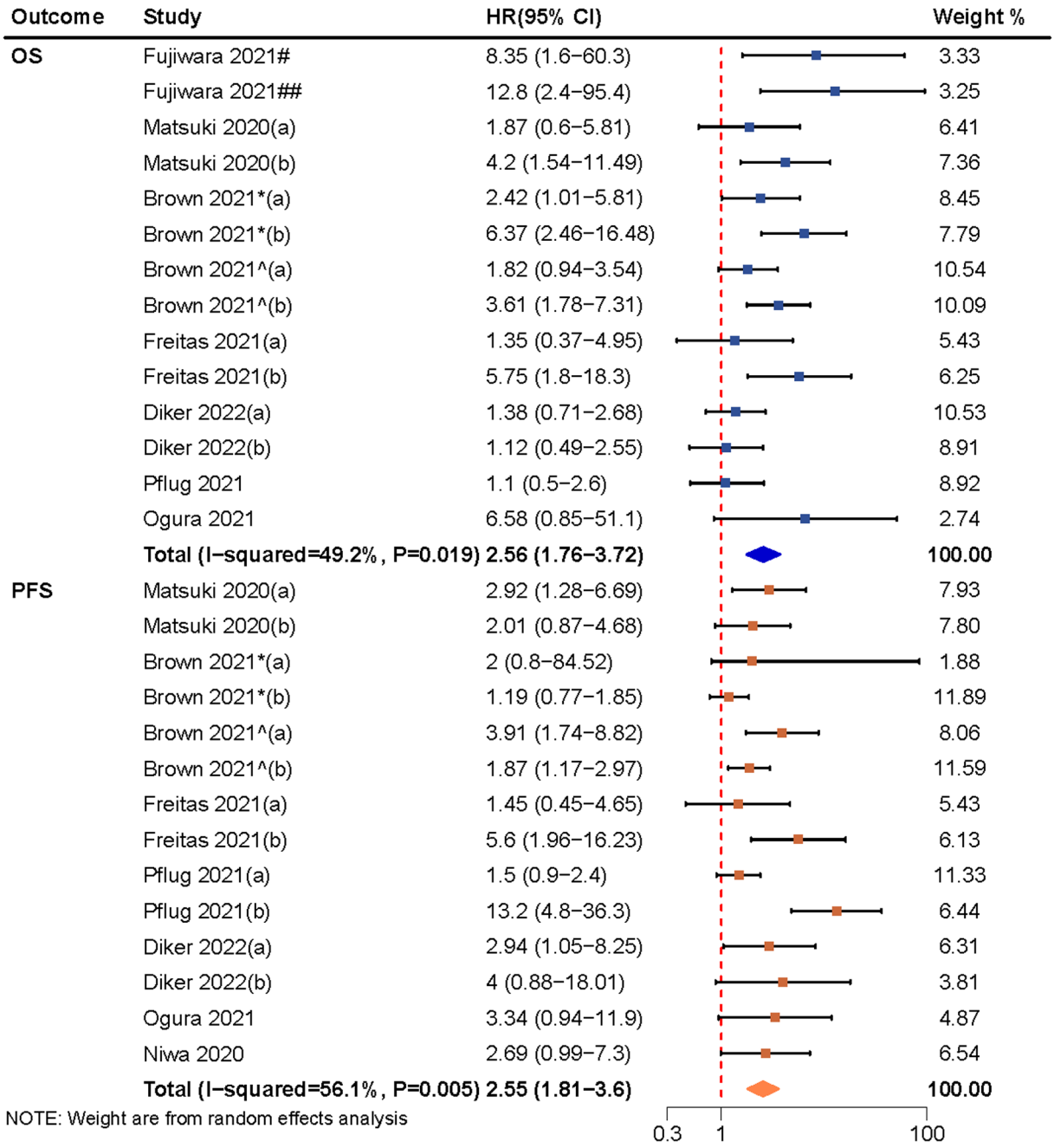

Figure 4. Forest plots of the HRs and 95% CIs for OS (blue dots) and PFS (orange dots) by mGPS in patients treated with immune checkpoint inhibitors. [(a)] Univariate analysis results and [(b)] multivariate analysis results of the same study; [#] and [##] represent 1 vs. 0 and 2 vs. 0 subgroups in the same study, respectively; [*] and [^] represent different studies conducted by the same author in the same year. HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival; mGPS, modified Glasgow prognostic score.

in patients with advanced or recurrent gastric cancer who received opdivo and found that mGPS had the strongest association with patient outcome. GPS or mGPS also have the characteristics of being cheap, convenient and easy to obtain, and have great application potential (46).

The present meta-analysis, which included data from 18 studies involving 1,355 patients with cancer, assessed the association between GPS or mGPS and survival in patients receiving ICIs. The results indicated that a higher GPS or mGPS contributed to poorer survival in patients with cancer, and subgroup analyses also demonstrated that patients with GPS or mGPS 1 and GPS or mGPS 2 exhibited poorer OS and PFS than those with GPS 0. However, due to the heterogeneity of some of the data, caution is required in interpreting these results.

GPS, based on CRP and albumin levels, has been proven to have independent prognostic value in various cancer types in previous years (46,51). CRP and albumin are sensitive and reliable indicators that reflect the inflammatory state and immune nutritional status of a cancer population, and have been widely confirmed as biomarkers of poor prognosis in cancer (46). CRP is an acute phase response protein that can serve as a biomarker for infection and tissue damage (52). CRP can promote an inflammatory response (53), thereby

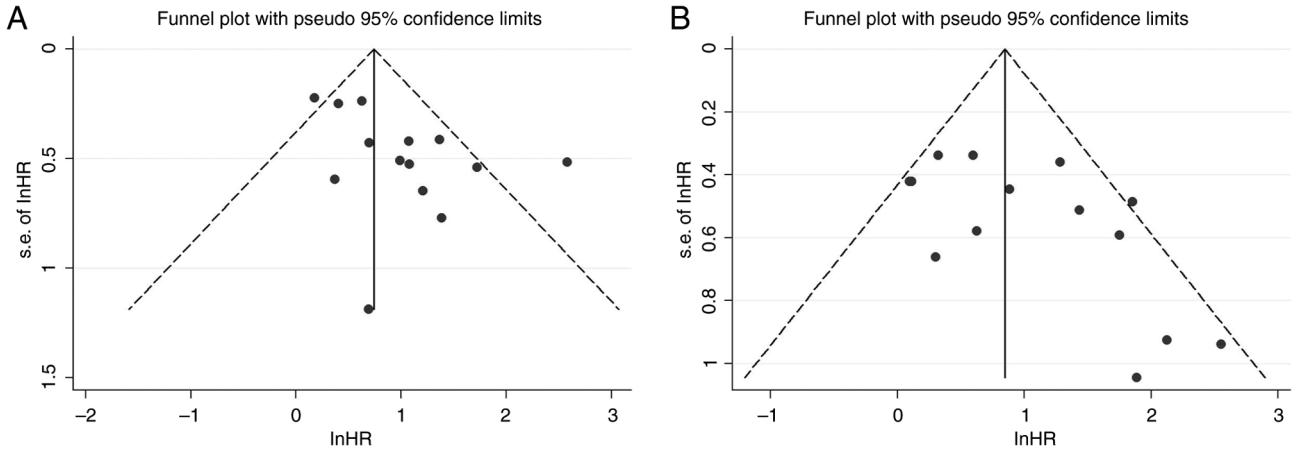

Figure 5. Funnel plots of modified Glasgow prognostic score for (A) progression-free survival and (B) overall survival. s.e. standard error; lnHR, natural logarithm of the hazard ratio.

inhibiting immune function and promoting tumor proliferation and metastasis (54). At the same time, CRP can also suppress the immune response, accelerate tumor migration and tumor microenvironment formation (54), which may weaken the role of ICIs. Previous studies have found that CRP can directly inhibit T cells and dendritic cells (55,56), thereby affecting the action of ICIs by impacting innate and acquired immunity in patients with cancer. The CRP level before treatment can not only predict the therapeutic effect of ICIs (57), but can also predict the survival of patients with advanced urothelial cancer or non-small cell lung cancer receiving immunotherapy (58,59). The serum albumin level is a notable indicator of nutritional status, and low albumin levels are a manifestation of malnutrition and poor general status (60). Hypoproteinemia reflects poor nutritional status and chronic inflammation, and can serve as a biomarker for cancer prognosis (61). Studies have identified serum albumin as a potential biomarker for evaluating the efficacy of ICIs, whether alone or in combination with chemotherapy (61,62). The results of the present study showed that a high GPS was associated with unfavorable OS and PFS, suggesting poor survival outcomes for patients treated with ICIs, regardless of hypoproteinemia or elevated CRP. However, the OS results were heterogeneous. Sensitivity analysis showed that the study by Kasajima *et al* (34) contributed significantly to heterogeneity. The study was divided into GPS 1-2 and GPS 0 groups, with a tumor type of non-small cell lung cancer, treatment regimen of pembrolizumab or altezomumab monotherapy and a treatment line of second-line or subsequent-line therapy (34). There were no significant differences in clinical features between the study by Kasajima *et al* (34) and other included studies. The heterogeneity in the OS results was reduced after subgroup analysis based on the scores. This may be due to the subgroups being divided reasonably, which makes the studies within each subgroup more homogeneous in certain key features. The grouping of different GPSs is likely to be the main cause of heterogeneity.

Extensive evidence suggests that weight loss and poor physical fitness are related to systemic inflammatory responses in advanced cancer (3,63,64). Significant inflammatory response can lead to hypoalbuminemia (65), and cancer-related inflammation can impair albumin synthesis by altering cytokine production and thereby increasing microvascular permeability (66). Therefore, hypoalbuminemia is more likely to be secondary to elevated CRP levels. There is growing evidence that inflammation has a role in cancer development, and that inflammation may also be accelerated by the cancer itself due to increased catabolism and malnutrition (67,68). McMillan *et al* (20) revised the GPS to mGPS to more accurately predict the prognosis of various cancer types. mGPS weakens the effect of albumin, emphasizing the importance of CRP. GPS 0 is determined by the CRP and albumin levels, but mGPS 0 is determined by CRP alone, regardless of albumin levels (20). For mGPS 1, elevated CRP is rated as 1 even if albumin levels are normal (20), but GPS 1 includes patients with hypoalbuminemia who do not have elevated CRP levels. The rating criteria for GPS 2 and mGPS 2 are the same and both combine high CRP and hypoproteinemia, which may indicate strong systemic inflammation and poor nutritional status. The results of the present study demonstrated that mGPS, like GPS, can serve as a predictor of OS and PFS in cancer populations receiving immunotherapy. However, there was high heterogeneity in the PFS data. Sensitivity analysis did not identify any study that had a notable impact on heterogeneity. After subgroup analysis by country and score, significant heterogeneity still existed, suggesting that the present analysis failed to fully explain the source of heterogeneity and further exploration and verification are needed.

The evaluation of GPS or mGPS only requires routine blood tests, which is low cost, highly standardized and suitable for clinical promotion. The evaluation can be adapted to different cancer types or population characteristics, while other static indicators lack such optimization space. For example, mGPS further improves the predictive sensitivity and specificity of GPS by adjusting the critical value of CRP and albumin. The cut-off values may vary across different diseases and even within different cohorts of the same disease. Therefore, cut-off values can be determined clinically according to actual disease conditions, such as tumor type and ethnicity. Compared with PD-L1 and TMB, which focus on the local characteristics of tumors, the core advantages of GPS and mGPS lie in their comprehensiveness,

universality and economy, and are more suitable for widespread clinical promotion and the construction of a comprehensive prognostic evaluation system. GPS or mGPS can be used in combination with immunotherapy-related markers to provide multidimensional information. For example, a high inflammatory state may impair efficacy in patients with high PD-L1 expression, and the combination of GPS or mGPS and PD-L1 detection may optimize patient stratification. Systemic inflammation may indirectly regulate immunotherapy response by affecting intestinal flora, and GPS or mGPS can be used as a proxy indicator of systemic inflammation in comprehensive analysis.

The present study has some limitations. First, the included studies were retrospective and showed notable methodological diversity. Second, although subgroup and sensitivity analyses were performed, heterogeneity was not completely eliminated. Heterogeneity may be caused by multiple factors, such as tumor type, ICI regimens, treatment lines, the diversity of the study population and an inconsistent follow-up time. The small number of studies within subgroups also resulted in insufficient statistical power to accurately assess differences between subgroups. Third, the absence of patient-level data may limit the assessment of certain baseline characteristics and affect the interpretation of results. Therefore, there is still a need to design clinical studies to further validate the relevance of GPS and mGPS in predicting the survival of each patient with cancer. In particular, further research is needed on specific factors, such as differences in the effectiveness of interventions in different populations.

In conclusion, high GPS or mGPS, that is, either high CRP or low albumin, may have adverse effects on the OS and PFS of patients with cancer receiving ICIs. In clinical practice, patients can be risk stratified according to GPS or mGPS prior to immunotherapy, thereby enhancing patient management and improving treatment outcomes. Future prospective cohort studies are needed to validate the results of the present study, and further studies in combination with other prognostic markers are needed to improve the prediction accuracy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LZ, LH and TL conceived and designed this study. LZ, TL and LH conducted the literature screening. TL and LL performed the statistical analysis. LZ and LH wrote the manuscript. LH and JN were responsible for the interpretation of data and revised the manuscript. LZ, TL and LH checked and confirmed the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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