Prognostic Significance of the Modified Glasgow Prognostic Score in Patients With Pancreatic Cancer: A Meta-Analysis

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Abstract

Background: The prognostic value of the modified Glasgow prognostic score (mGPS) in patients with pancreatic cancer is controversial, based on previous studies. Therefore, this meta-analysis aimed to explore the relationship between mGPS and prognosis in pancreatic cancer.

Methods: The databases PubMed, Web of Science, Embase, and the Cochrane Library were searched to identify eligible studies. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to estimate the associations between mGPS score and survival outcomes.

Results: A total of 26 studies with 5198 patients were included in this meta-analysis. In a pooled analysis, elevated mGPS predicted poorer overall survival (OS; HR = 1.98, 95% CI, 1.65-2.37, $P < .001$). In addition, elevated mGPS was also significantly associated with worse progression-free survival (PFS), disease-free survival (DFS), and cancer-specific survival (CSS; HR = 1.95, 95% CI, 1.36-2.80, $P < .001$). Subgroup analyses confirmed a significant association between mGPS and survival outcomes.

Conclusions: Our meta-analysis demonstrated that high mGPS was correlated to worse OS, PFS, DFS, and CSS in patients with pancreatic cancer. Therefore, mGPS could be employed as an effective prognostic factor for pancreatic cancer in clinical practice.

Introduction

Pancreatic cancer is a lethal disease and is characterized as one of the most malignant tumors.[1] As estimated by the GLOBO-CAN 2018 study,[2] 458 918 cases would be diagnosed with pancreatic cancer, and 432 242 cases will die of the disease worldwide in 2018. The global mortality rate coincides with the incidence rate of pancreatic cancer, which emphasizes poor prognosis.[3] Pancreatic cancer is usually diagnosed at an advanced stage and the median overall survival (OS) is <12 months, and the 5-year OS rate is approximately 5%.[4] Therapeutic strategies for pancreatic cancer include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. These treatment methods have improved outcomes during the past years.[5] However, patients with pancreatic cancer could also develop chemoresistance because of a lack of efficient predictive and prognostic markers.[3,6,7] Therefore, to improve the survival of patients with pancreatic cancer, it is important to identify novel and available prognostic biomarkers.

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Recently, growing evidence has shown that tumor-elicited inflammation, immune cells, and inflammatory cytokines play critical roles in pancreatic cancer development, progression, and metastasis.[8,9] An increasing number of studies have focused on the prognostic role of inflammatory parameters in various cancers.[10] These indicators include the neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, systematic inflammatory index, and the modified Glasgow prognostic score (mGPS). The mGPS is based on serum albumin (Alb) and C-reactive protein (CRP) and is scored as mGPS 0, 1, and 2.[11] Previous studies have validated the prognostic value of mGPS in various solid tumors, including small cell lung cancer,[12] biliary tract cancer,[13] renal cell carcinoma (RCC),[11] and soft-tissue sarcoma.[14] A variety of studies have also investigated the prognostic significance of mGPS in patients with pancreatic cancer; however, the results were inconsistent.[15-40] Therefore, we carried out a meta-analysis to assess the association between mGPS and survival outcomes in patients with pancreatic cancer.

Materials and Methods

Literature Search Strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[41] A literature search was performed using PubMed, Web of Science, Embase, and the Cochrane Library. The search terms were as follows: "modified Glasgow prognostic score," "mGPS," "pancreatic neoplasm," "pancreatic cancer," and "pancreatic carcinoma." Only literature published in English was considered. The search was updated on May 10, 2020. The reference lists of selected studies were checked to identify potential inclusions. All related data were extracted from previously published studies; therefore, no ethical approval or informed consent was necessary for this meta-analysis.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) diagnosis of pancreatic cancer pathologically or histologically confirmed; (2) CRP and Alb measured from peripheral blood samples before treatment; (3) mGPS scored as the following method: patients with Alb ≥ 3.5 g/dL and CRP ≤ 1 mg/dL are defined as mGPS 0, patients with Alb ≥ 3.5 g/dL and CRP > 1 mg/dL or Alb < 3.5 g/dL and CRP ≤ 1 mg/dL are defined as mGPS 1, and patients with Alb < 3.5 g/dL and CRP > 1 mg/dL are defined as mGPS 2; (4) the hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) of survival outcomes including OS, progression-free survival (PFS), disease-free survival (DFS), and cancer-specific survival (CSS) supplied in studies or sufficient data were provided; (5) full-text articles published in English. The exclusion criteria were as follows: (1) case reports, reviews, letters, or comments; (2) studies with insufficient information for meta-analysis; (3) overlapping studies; and (4) animal studies.

Data Extraction and Quality Assessment

Two independent investigators (W.F. and R.W.) reviewed eligible studies and extracted data. Any disagreements were resolved by discussion with a third reviewer (T.W.) until consensus was reached. The following information was extracted: name of the first author; year of publication; country; sample size; study period; ethnicity; sex; treatment; follow-up; number of patients with mGPS 0, 1, and 2; and survival outcomes. The HRs and 95%CIs were calculated based on mGPS 1 to 2 versus mGPS 0. For studies that reported HRs for mGPS 1 and 2 separately, we combined these 2 groups into a single group and calculated a combined HR to analyze the prognostic role of the overall elevated GPS as previously reported.[42,43] Overall survival was the primary outcome of interest. Progression-free survival, DFS, and CSS were secondary outcomes. The methodological qualities of the included studies were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS)[44] by 2 independent investigators (K.W. and S.Y.). The total NOS scores are in the range of 0 to 9. Studies with NOS scores ≥6 were regarded as of high quality.

Statistical Analysis

The HRs and 95% CIs were used to estimate the associations between mGPS score and survival outcomes. Heterogeneity among studies was evaluated using Cochran Q test and Higgins I^2 statistic. When the Q test ($P < .10$) or the I^2 test (>50%) indicated significant heterogeneity, a random-effect model would be used to combine the data. Otherwise, a fixed-effect model was applied. Subgroup analysis was performed to detect the source and for further investigation. Sensitivity analysis was carried out to evaluate the robustness of the data by omitting one study at a time. Publication bias was examined using Begg rank correlation test. All analyses were performed using Stata version 12.0 software (STATA Corp). Value of $P < .05$ was considered statistically significant.

Results

Search Results

The initial literature search retrieved 205 studies in total (Figure 1). Of these studies, 151 duplicate records were excluded, and 54 studies were screened by titles and abstracts. Then, 19 articles were removed after title and abstract examination, and 35 studies remained for full-text evaluation. After carefully reviewing the full text, 9 articles were excluded for the following reasons: 7 studies without sufficient data for this meta-analysis, 1 study enrolled overlapping patients, and 1 study did not measure pretreatment mGPS. Finally, 26 studies were included in this meta-analysis.[15-40] The literature selection process is shown in Figure 1. In the included studies, one study[18] recruited 2 independent cohorts of patients receiving chemotherapy or surgical resection, and the HRs and 95% CIs were separately given for these 2 cohorts. These 2 cohorts were independently analyzed and labeled as Stotz(A) and Stotz(B).
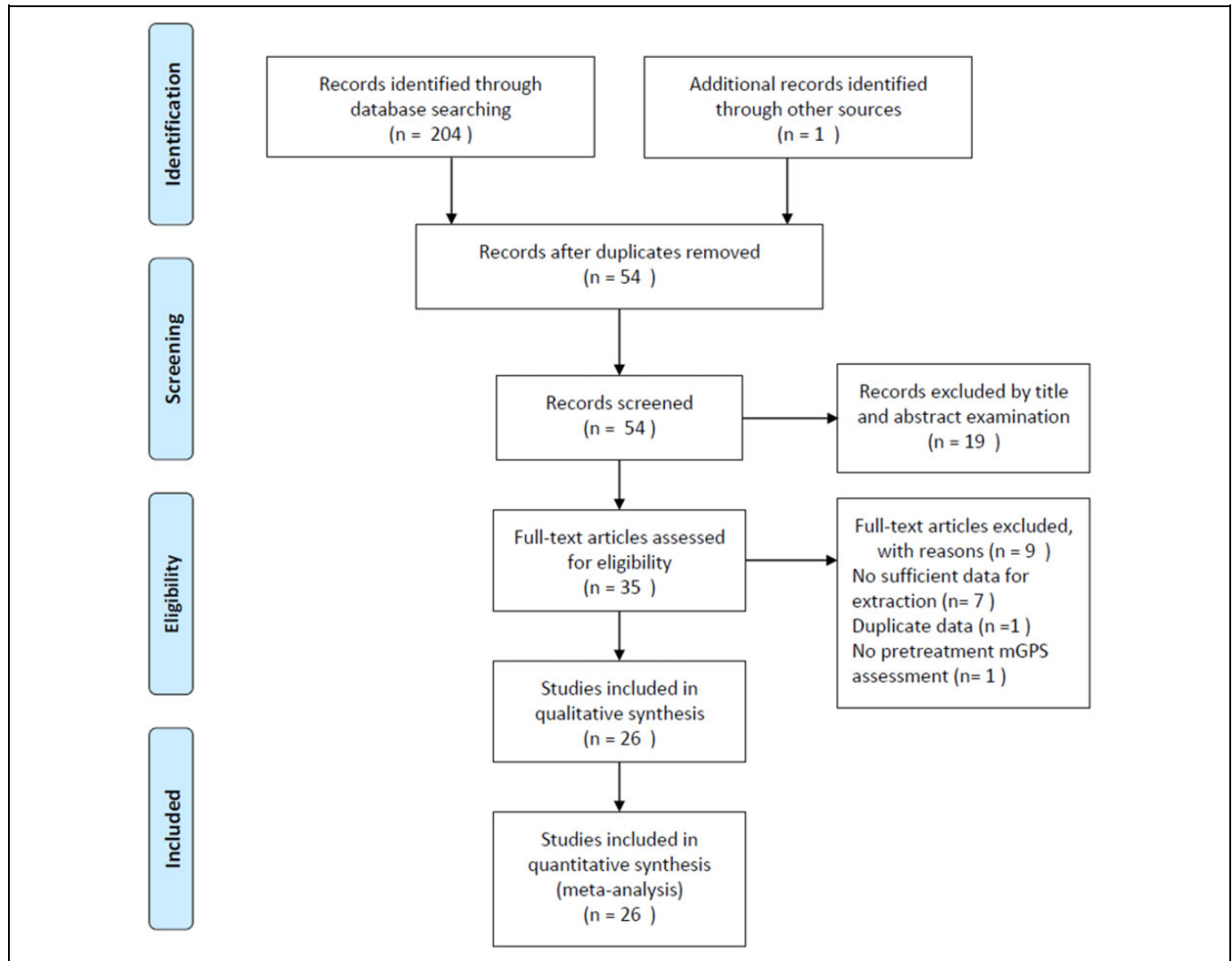
Figure 1. Flowchart of the study selection procedure in the meta-analysis.

Therefore, 27 cohorts from 26 studies were included in this meta-analysis.

Characteristics of the Included Studies

The included studies were published from 2012 to 2019, with a total of 5198 cases. The sample sizes ranged from 25 to 807, with a median value of 172. The included studies were conducted in 8 countries, including Japan (n = 16),[20-22,24,25,27,29-32,35-40] China (n = 4),[17,23,26,28] Austria (n = 2 cohorts),[18] Australia (n = 1),[19] the United Kingdom (n = 1),[15] Greece (n = 1),[33] Italy (n = 1),[16] and Korea (n = 1).[34] A total of 24 studies with 4651 patients[15-17,19-34,36-40] provided data on the correlation between mGPS and OS. Seven cohorts presented the data on the prognostic value of mGPS for PFS, DFS, and CSS, including 3 for PFS,[29,30,38] 2 for DFS,[31,35] and 2 for CSS.[18] The major characteristics of the enrolled studies are summarized in Table 1. The NOS scores ranged from 6 to 8, and the median value was 7, which suggested that all eligible studies were of high quality.

Association Between mGPS and OS

A total of 24 cohort studies consisting of 4651 patients[15-17,19-34,36-40] reported the HRs and 95% CIs for the relationship between mGPS and OS in pancreatic cancer. A random-effects model was applied due to significant heterogeneity ($I^2 = 68.1\%$, $P < .001$, Table 2; Figure 2A). The pooled data demonstrated that pretreatment mGPS was significantly associated with OS, and patients with high mGPS had shorter survival durations (HR = 1.98, 95% CI, 1.65-2.37, $P < .001$, Table 2; Figure 2A). Subgroup analysis was performed according to ethnicity, treatment, and sample size. The combined data indicated that mGPS remained a significant prognostic factor for OS irrespective of ethnicity (Table 2; Figure 2B) or sample size (Table 2; Figure 2D). In addition, a high mGPS was also

Table 1. Characteristics of Studies Included in the Present Meta-Analysis.

Author	Year	Country	Sample size	Study duration	Ethnicity	Sex (M/F)	TNM stage	Treatment	Follow-up median (months)	mGPS (0/1/2)	Outcomes	NOS score
Jamieson[15]	2012	The United Kingdom	173	1997-2009	Caucasian	93/80	I-III	Surgical resection	27	95/37/41	OS	8
La Torre[16]	2012	Italy	101	2003-2009	Caucasian	53/48	I-IV	Surgical resection	19	37/20/25	OS	7
Wang[17]	2012	China	177	2006-2010	Asian	120/57	I-IV	Mixed	31.33	115/46/16	OS	7
Stotz(A)[18]	2013	Austria	261	2004-2010	Caucasian	103/158	III-IV	Chemotherapy	5	117/115/29	CSS	7
Stotz(B)[18]	2013	Austria	110	2004-2010	Caucasian	51/59	I-III	Surgical resection	18	73/21/16	CSS	8
Martin[19]	2014	Australia	124	2008-2012	Caucasian	66/58	III-IV	Chemotherapy	12	46/26/52	OS	7
Inoue[20]	2015	Japan	440	2008-2012	Asian	249/191	I-IV	Mixed	18.7	367/49/24	OS	7
Kasuga[21]	2015	Japan	61	2009-2013	Asian	40/21	IV	Chemotherapy	6.3	NA	OS	6
Imaoka[22]	2016	Japan	807	2001-2013	Asian	473/334	I-IV	Mixed	15.8	620/153/34	OS	7
Wu[23]	2016	China	233	2011-2014	Asian	156/77	III-IV	Chemotherapy	4.4	NA	OS	6
Yamada[24]	2016	Japan	379	2002-2014	Asian	228/151	I-IV	Surgical resection	15.1	189/80/36	OS	7
Iino[25]	2017	Japan	47	2010-2015	Asian	24/23	III-IV	Chemotherapy	NA	35/5/7	OS	6
Liu[26]	2017	China	386	2010-2015	Asian	238/148	I-IV	Mixed	8.7	121/242/13	OS	8
Matsumoto[27]	2017	Japan	25	2007-2013	Asian	14/11	I-IV	Surgical resection	36.3	20/2/3	OS	8
Xiao[28]	2017	China	66	2012-2013	Asian	30/36	III-IV	Chemotherapy	NA	39/11/16	OS	6
Abe[29]	2018	Japan	329	1996-2014	Asian	198/131	I-III	Surgical resection	NA	282/27/20	OS, PFS	8
Asama[30]	2018	Japan	72	2006-2016	Asian	40/32	III-IV	Chemotherapy	8	52/11/9	OS, PFS	8
Fujiwara[31]	2018	Japan	188	2000-2015	Asian	115/73	I-IV	Surgical resection	28.9	140/21/27	OS, DFS	7
Ikuta[32]	2018	Japan	38	2011-2018	Asian	20/18	III-IV	Chemotherapy	39.8	30/7/1	OS	7
Christos[33]	2019	Greece	226	2004-2015	Caucasian	124/102	I-IV	Surgical resection	23.1	NA	OS	6
Hwang[34]	2019	Korea	203	Jan-Dec 2016	Asian	116/87	IV	Chemotherapy	21.5	137/19/47	OS	8
Ichikawa[35]	2019	Japan	176	2005-2015	Asian	116/60	III-IV	Chemotherapy	To Dec 2017	157/13/6	DFS	8
Ikuta[36]	2019	Japan	136	2005-2017	Asian	76/60	I-IV	Surgical resection	16.8	NA	OS	6
Kubo[37]	2019	Japan	119	2009-2017	Asian	66/53	I-III	Chemoradiotherapy	NA	NA	OS	6
Matsumoto[38]	2019	Japan	66	2013-2014	Asian	44/22	IV	Chemotherapy	12.7 (1.8-21.1)	NA	OS, PFS	6
Nakagawa[39]	2019	Japan	172	2006-2015	Asian	102/70	I-III	Surgical resection	To December 2017	NA	OS	7
Shimizu[40]	2019	Japan	83	2008-2014	Asian	57/26	IV	Chemotherapy	NA	44/28/11	OS	6

Abbreviations: CSS, cancer-specific survival; DFS, disease-free survival; F, female; M, male; mGPS, modified Glasgow Prognostic Score; NA, not available; NOS, Newcastle Ottawa Scale; OS, overall survival; PFS, progression-free survival.

Table 2. Subgroup Analysis of the Studies Reporting the Association of mGPS and Prognosis in Pancreatic Cancer.

Stratified analysis	Number of studies (cohorts)	Number of patients	Effects model	HR (95% CI)	P	Heterogeneity I^2 (%)	P
OS							
Total	24	4651	Random	1.98 (1.65-2.37)	<.001	68.1	<.001
Ethnicity							
Asian	20	4027	Random	2.11 (1.68-2.65)	<.001	71.7	<.001
Caucasian	4	624	Fixed	1.59 (1.35-1.89)	<.001	0	.812
Treatment							
Surgical resection	9	1729	Fixed	2.01 (1.71-2.38)	<.001	42.1	.087
Chemotherapy	10	993	Random	2.06 (1.45-2.93)	<.001	73.7	<.001
Mixed	4	1810	Random	2.28 (1.48-3.52)	<.001	79.0	.003
Chemoradiotherapy	1	119	–	1.03 (0.60-1.77)	.915	–	–
Sample size							
<175	14	1283	Random	2.01 (1.51-2.69)	<.001	67.0	<.001
≥175	10	3368	Random	1.98 (1.55-2.51)	<.001	71.5	<.001
PFS/DFS/CSS							
Total	7	1202	Random	1.95 (1.36-2.80)	<.001	74.8	.001
Ethnicity							
Asian	5	831	Fixed	2.33 (1.84-2.94)	<.001	38.1	.167
Caucasian	2	371	Fixed	1.14 (0.90-1.45)	.284	0	.711
Treatment							
Surgical resection	3	627	Random	1.75 (1.01-3.05)	.048	84.4	.002
Chemotherapy	4	575	Random	2.26 (1.24-4.10)	.007	72.2	.013
Sample size							
<175	3	248	Random	2.32 (0.90-5.99)	.083	82.9	.003
≥175	4	954	Random	1.89 (1.27-2.83)	.002	71.7	.014

Abbreviations: CI, confidence interval; CSS, cancer-specific survival; DFS, disease-free survival; HR, hazard ratio; mGPS, modified Glasgow prognostic score; OS, overall survival; PFS, progression-free survival; TNM, tumor–node–metastasis.

associated with poor OS in patients receiving surgical resection, chemotherapy, and mixed treatment (Table 2; Figure 2C).

Correlation Between mGPS and PFS/DFS/CSS

Seven cohorts with 1202 patients[18,29-31,35,38] provided data on the prognostic effect of mGPS in PFS/DFS/CSS. There was significant heterogeneity ($I^2 = 74.8\%$, $P = .001$, Table 2; Figure 3A); therefore, a random-effects model was selected. The pooled HR and 95% CI were HR = 1.95, 95% CI = 1.36-2.80, $P < .001$ (Table 2; Figure 3A), indicating that a higher mGPS was significantly correlated with poor PFS/DFS/CSS. Subgroup analysis was also carried out, stratified by ethnicity, treatment, and sample size. The results of the subgroup analysis showed that a high mGPS was correlated with inferior PFS/DFS/CSS in Asian patients (HR = 2.33, 95% CI, 1.84-2.94, $P < .001$, Table 2; Figure 3B), in patients receiving surgical resection (HR = 1.75, 95% CI, 1.01-3.05, $P = .048$) and receiving chemotherapy (HR = 2.26, 95% CI, 1.24-4.10, $P = .007$; Table 2; Figure 3C) and in studies with a sample size ≥175 (HR = 1.89, 95% CI, 1.27-2.83, $P = .002$, Table 2; Figure 3D).

Sensitivity Analysis

To assess the stability of the pooled results, sensitivity analysis was performed by sequentially omitting individual study. The pooled HRs for OS (Figure 4A) and PFS/DFS/CSS (Figure 4B)

were not substantially changed, indicating the reliability of our results.

Publication Bias

Begg funnel plot was used to evaluate the potential publication bias for OS and PFS/DFS/CSS. As shown in Figure 5, there was no significant publication bias for OS (Begg test, $P = .385$) or for PFS/DFS/CSS (Begg test, $P = .085$).

Discussion

The prognostic role of mGPS for patients with pancreatic cancer has been explored in many previous studies,[15-40] with the conflicting results presented. Therefore, we aggregated data from 26 eligible studies comprising 5198 patients. Our meta-analysis showed that a high mGPS (score 1-2) was associated with worse OS and PFS/DFS/CSS in pancreatic cancer. To further investigate the association between mGPS and survival in various patient groups, subgroup analysis was conducted, and the data showed that mGPS remained a significant prognostic factor for OS, irrespective of ethnicity or sample size. In addition, a high mGPS was correlated with inferior PFS/DFS/CSS in Asian patients, in patients undergoing surgical resection and receiving chemotherapy. Taken together, our meta-analysis indicated that an elevated mGPS was correlated with poor survival outcomes in patients with pancreatic cancer.
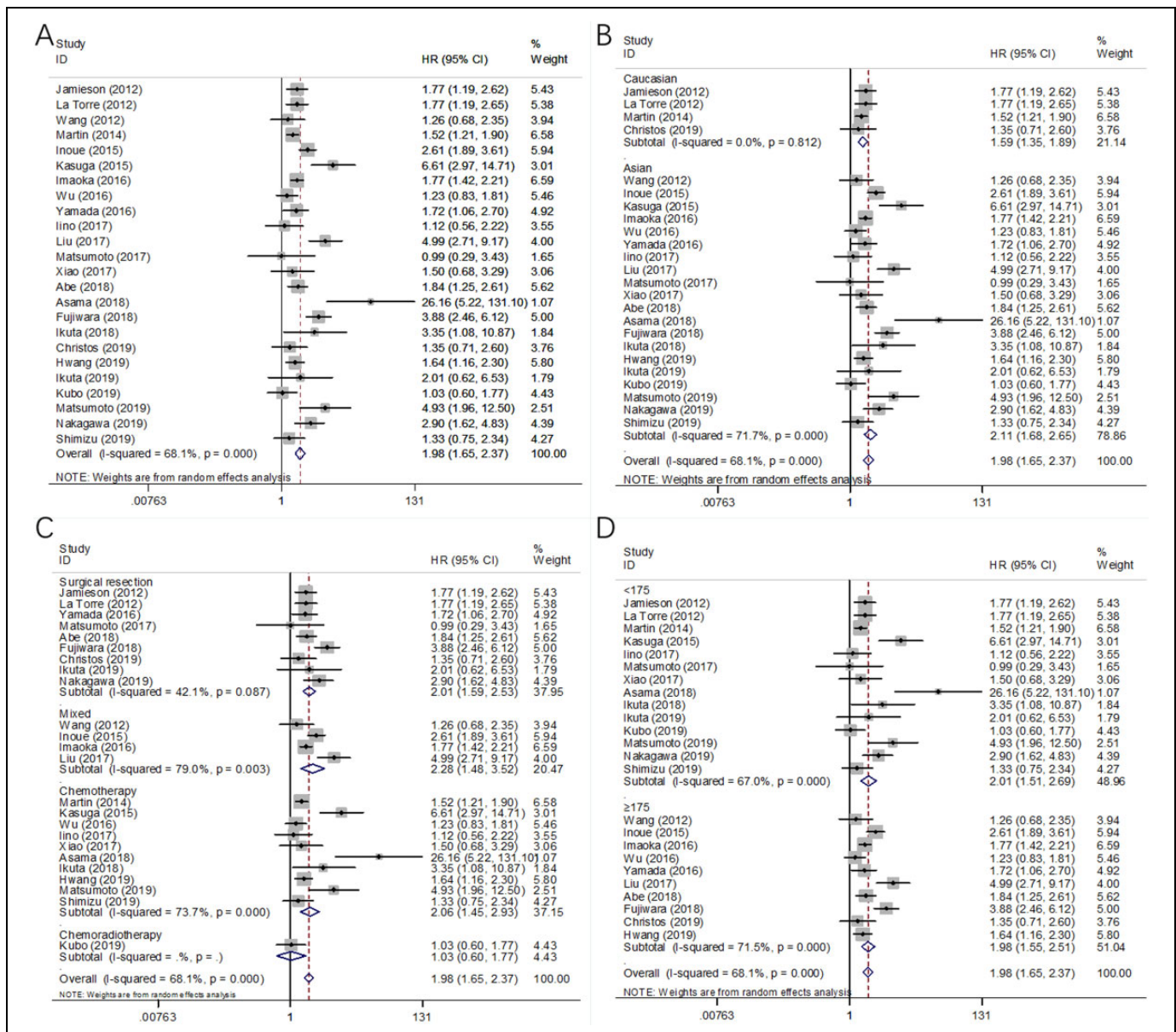
Figure 2. Forest plots of the significant correlation of modified Glasgow prognostic score with overall survival in pancreatic cancer: (A) in total patients, (B) subgroup analysis stratified by ethnicity, (C) subgroup analysis stratified by treatment method, and (D) subgroup analysis stratified by sample size.

Moreover, the reliability of the results was confirmed by quality assessments, sensitivity analysis, and publication bias tests. To the best of our knowledge, the current study was the first meta-analysis to explore the prognostic role of mGPS in pancreatic cancer.

The survival of patients with cancer is associated with nutritional status, and approximately one-third of cancer-related deaths are attributed to malnutrition rather than cancer.[45,46] In recent years, much attention has been paid to the prognostic effect of combinational nutritional parameters, such as mGPS, which is derived from Alb and CRP in peripheral blood. Briefly, patients with lower Alb and high CRP levels scored a high mGPS. The mechanisms of association between mGPS

and poor survival could be explained by the following aspects. First, Alb is a major protein in the blood. Serum Alb is an objective indicator of nutritional status, and hypoalbuminemia is reflective of malnutrition in patients with cancer. Albumin is also regarded as an acute-phase protein and is downregulated in inflammation.[47] Current evidence has shown that serum Alb is associated with anticancer activity, for example, its antioxidant effect.[48] When hepatocytes generate Alb normally in patients with cancer, they are more resistant to disease and tumor growth.[49] Therefore, reduced serum Alb level is a predictor of poor prognosis in various cancers, including urothelial carcinoma,[50] colorectal cancer,[51] and non-small cell lung cancer.[52] Second, CRP is a common acute-phase serum protein
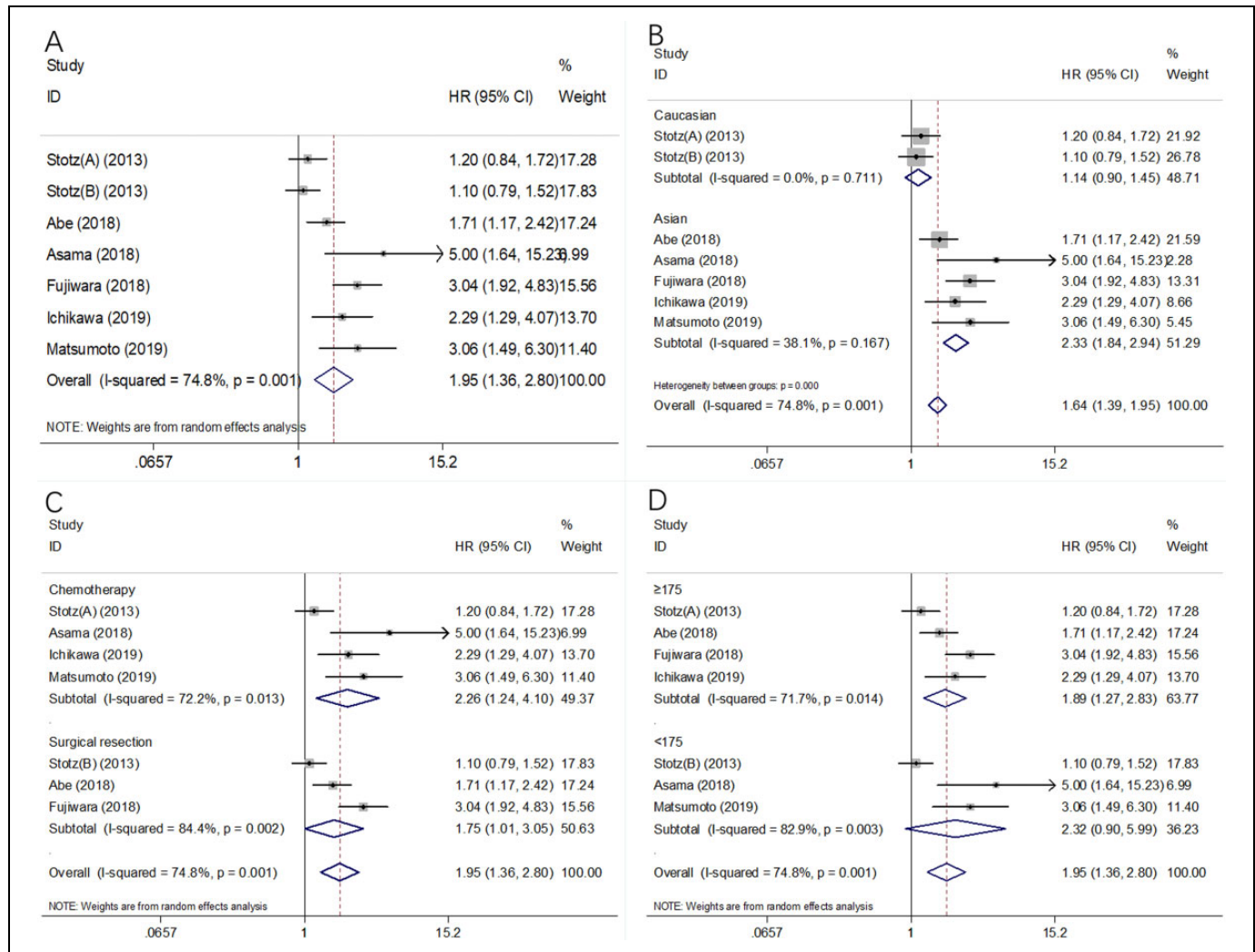
Figure 3. Forest plots of the significant correlation of mGPS with PFS/DFS/CSS in pancreatic cancer: (A) in total patients, (B) subgroup analysis stratified by ethnicity, (C) subgroup analysis stratified by treatment method, and (D) subgroup analysis stratified by sample size. CSS indicates cancer-specific survival; DFS, disease-free survival; mGPS, modified Glasgow prognostic score; PFS, progression-free survival.
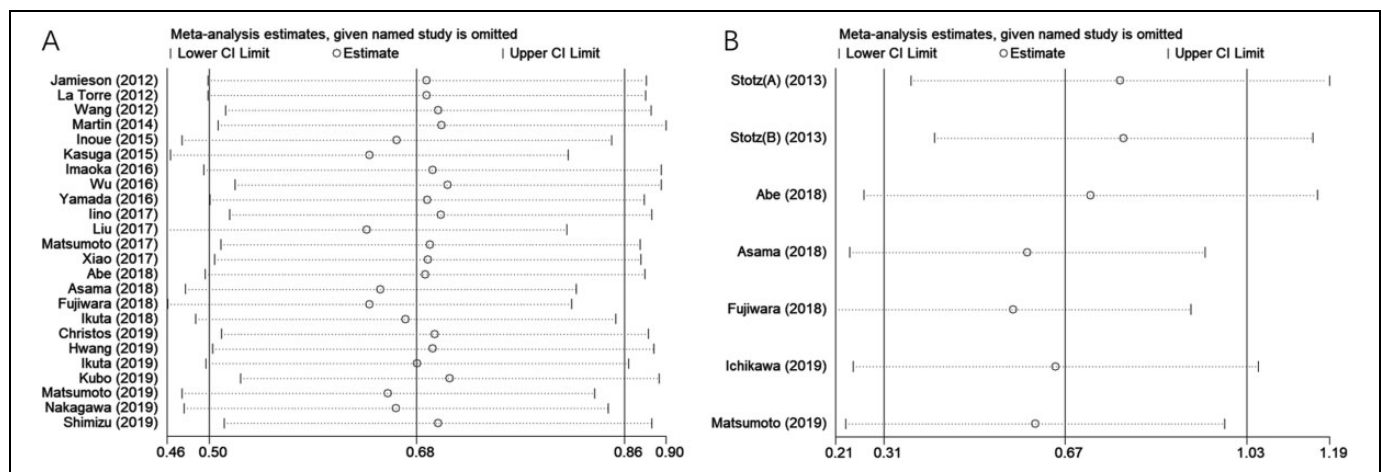

Figure 4. Sensitivity analysis of included studies for association between mGPS and (A) OS and (B) PFS/DFS/CSS in pancreatic cancer. CSS indicates cancer-specific survival; DFS, disease-free survival; mGPS, modified Glasgow prognostic score; OS, overall survival; PFS, progression-free survival.
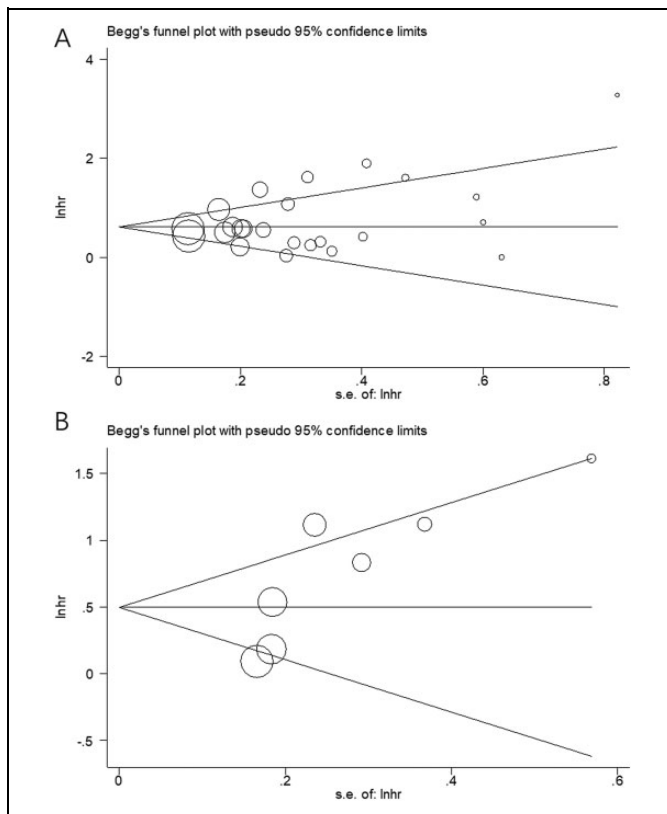
Figure 5. Publication bias tested by Begg funnel plot. (A) Begg test for OS, $P = .385$; (B) Begg test for PFS/DFS/CSS, $P = .085$. CSS indicates cancer-specific survival; DFS, disease-free survival; OS, overall survival; PFS, progression-free survival.

that is synthesized by liver cells.[53] Cancer cells secrete inflammatory cytokines, which strongly stimulate CRP production in liver.[54] Previous studies indicated that high levels of serum CRP were significantly associated with poor OS in patients with cancer.[55-57] The mGPS enables better appreciation of systemic inflammation or malnutrition through changes in Alb and CRP levels. The high mGPS is indicative of low Alb and high CRP, which usually suggests malnutrition and severe systemic inflammation in patients with pancreatic cancer. Thus, mGPS, as a combinational index of Alb and CRP, is efficient in prognostication of survival in patients with cancer. Patients with high mGPS usually have poor survival outcomes.

A variety of meta-analyses have also investigated the prognostic value of mGPS in solid tumors.[58-61] A meta-analysis incorporating 12 studies with 2391 patients showed that higher mGPS significantly correlated with worse OS, CSS, recurrence-free survival, and PFS in patients with RCC.[60] Subgroup analyses also confirmed the overall results. Moreover, another meta-analysis demonstrated that elevated mGPS predicted poorer OS in patients with lung cancer.[58] A recent meta-analysis by Zhang et al[62] showed that OS was worse in patients with an mGPS of 1 and 2 compared with those with a score of 0 in patients with gastric cancer. In the current meta-analysis, our findings on pancreatic cancer were in accordance with the results of other types of cancer. In addition, the subgroup

analysis also confirmed the consistent prognostic efficiency of mGPS in different subpopulations. In the present meta-analysis, only English studies were included to guarantee the availability of all eligible publications to investigators. English publications are available to most investigators around the world, and the data of included studies can also be extracted and examined. Notably, publications in non-English language were not selected, which may contribute to heterogeneity in this meta-analysis.

This meta-analysis has several limitations. First, all of the included studies were retrospective, which may have introduced selection bias in this meta-analysis. Second, the heterogeneity among the included studies was significant. Although we adopted a random-effects model to calculate the pooled data. The inherent heterogeneity among retrospective studies may still exist. Third, the relationship between mGPS and clinicopathological features in pancreatic cancer could not be analyzed due to insufficient information in recruited studies. Fourth, most eligible studies are from Asian countries, especially Japan, which decreases the study's significance to the global community. The results may be applicable to Asian patients with pancreatic cancer. Therefore, further large-scale prospective studies are necessary to validate our results.

Conclusions

In summary, our meta-analysis demonstrated that high mGPS correlated with worse OS, PFS, DFS, and CSS in patients with pancreatic cancer. Therefore, mGPS could be employed as an effective prognostic factor for pancreatic cancer in clinical practice.

Authors' Note

Wen Fu, Kun Wang, and Shan Yan made equal contribution and are co-first authors. T.W. collected and analyzed the data and wrote the article; W.F., K.W., S.Y., X.W., B.T., and J.C. collected and analyzed the data; R.W. and T.W. revised the whole article. All authors reviewed the final article. All authors read and approved the final manuscript.

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