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REVIEW

The prognostic value of pretreatment Glasgow Prognostic Score in patients with esophageal cancer: a meta-analysis

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Objectives: To examine the predictive role of Glasgow Prognostic Score (GPS) on long-term survival in esophageal cancer.

Method: Comprehensive searches of electronic databases were performed to identify potential studies that evaluated the prognostic value of pretreatment GPS in esophageal cancer patients. We combined the hazard ratios (HRs) with 95% confidence intervals (CIs) to assess the association of GPS with overall survival (OS), disease-free survival (DFS) and cancer-specific survival (CSS).

Results: A total of 21 studies including 6115 patients were analyzed. Compared with patients with GPS 0, patients with elevated GPS had poorer OS (HR =2.12, 95% CI: 1.83–2.45, $P<0.001$) and CSS (HR =2.16, 95% CI: 1.56–2.98, $P<0.001$); but no significant relationship was observed between the elevated GPS and DFS (HR=2.14, 95% CI:1.00–4.61, $P=0.051$). Subgroup analysis outcomes were similar to overall analyses.

Conclusion: Pretreatment GPS could serve as a valuable factor in predicting the prognosis of patients with esophageal cancer. More well-designed prospective studies are warranted to confirm our findings.

Keywords: esophageal cancer, Glasgow Prognostic Score, survival, meta-analysis

Introduction

Esophageal cancer is the third most common malignant tumor and the fourth cause of cancer-related mortality in China.[1] Esophageal cancer mainly comprises two pathology subtypes, esophageal squamous-cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Despite of the advances in detection and treatment of esophageal cancer, its prognosis remains poor because patients were often diagnosed with the advanced stage. An ideal method that could predict the prognosis of esophageal cancer would be of great clinical significance.

A number of studies have reported that systemic inflammatory response is significantly associated with the prognosis of several kinds of cancers.[2] Inflammatory factors including Glasgow Prognostic Score (GPS) have been proven to play an important role in tumor progression and metastasis.[3–6] As an easily obtained inflammatory factor based on the serum C-reactive protein (CRP) and albumin levels, GPS was put forward in 2003 by Forrest et al for the first time and has been demonstrated to be predictors in the long-term survival of several neoplasms including gastric cancer, colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer and

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esophageal cancer.[7–11] The GPS was calculated as: a score of 0 for normal CRP (<10.0 mg/L) and albumin (>35.0 g/L) levels, 1 for either an abnormal CRP (>10.0 mg/L) or abnormal albumin level (<35.0 g/L) and 2 for both abnormal CRP (>10.0 mg/L) and abnormal albumin (<35.0 g/L) levels.[11]

The role of pretreatment GPS on survival outcomes of esophageal cancer has also been explored by several studies, however, no consensus has been reached. To our knowledge, there exists no meta-analysis to confirm the value of GPS in predicting prognosis of esophageal cancer. Thus, the aim of our study was to provide a synthetic analysis of the role of GPS in esophageal cancer and to verify the prognostic significance and clinical relevance of GPS in esophageal cancer patients.

In this study, we evaluated the predictive value of pretreatment GPS for overall survival (OS), disease-free survival (DFS) and cancer-specific survival (CSS) in patients with esophageal cancer by pooling the available data.

Methods

Search strategy

A systematic search was performed in PubMed, the Cochrane Library, EMBASE (via OVID) and Web of Science from January 1, 1966 to October 31, 2018 to identify potential studies that explored the prognostic role of GPS in esophageal cancer.

The search strategy used both with MeSH terms and free-text words to increase sensitivity. The following search terms were used: “esophagus”, “esophageal”, “cancer”, “carcinoma”, “tumor”, “neoplasm”, “Glasgow prognostic score”, “GPS”, “C-reactive protein” and “serum albumin”. Moreover, the references cited in the included articles were explored for additional publications.

We evaluated all searched results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The publication language was limited to English. We screened titles and abstracts to identify related studies, and then full texts were evaluated carefully.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) articles investigating the relation of GPS and prognosis for esophageal cancer patients; (2) C-reactive protein and serum albumin levels were collected before any treatment such as the chemoradiotherapy, surgery and neoadjuvant chemoradiotherapy; (3) full text papers published in English; (4) the outcome of interest included OS, DFS or CSS with hazards ratios (HRs) and corresponding 95% confidence intervals (CIs).

The following exclusion criteria were used: (1) letters, editorials, expert opinions, case reports, and reviews; (2) nonhuman studies; (3) if data sets were duplicated or overlapped, only the most recent information was included.

Data collection

Data were extracted by two researchers (Yan Wang and Pengfei Li) independently. Any disagreement was resolved through team discussion until consensus reached. Data were retrieved from each article by using an excel sheet (Microsoft Corporation). The following information was extracted from all included studies: the first author of the study, publication year, country, study period, study design, number of patients, female-male ratio, pathology type, treatment, follow up period, tumor-node-metastasis (TNM) stage and HR with 95% confidence interval (CI) of each long-term outcome.

We calculated the pooled HRs from each study in multivariate models whenever available if no multivariate statistic was reported then HRs from univariate analyses were used. HRs would be calculated from the Kaplan-Meier curves according to the methods reported by Tierney et al if they could not be obtained directly from the articles.[12] The first author and the publication year were used for identification.

Statistical analyses

For each study, the HR with 95% CI was used to estimate the prognostic value of GPS on the long-term survival of esophagus cancer patients. If groups comparing GPS 2 with 0 and 1 with 0 were both reported then the former one was used for synthesis in the forest plot. Statistical heterogeneity between studies was evaluated using Cochran’s Q test and Higgins I^2 statistic; and significant heterogeneity was defined as $P<0.10$ and/or $I^2>50\%$.[13] The random-effects model was used to calculate the pooled effect estimates when significant heterogeneity was observed, otherwise the fixed-effects model was applied. The robustness of the pooled results was confirmed by a sensitivity analysis in which the data of an individual study was removed each time. Publication bias was evaluated by Begg’s funnel plot and Egger’s linear regression

tests. When publication bias was observed presenting a $P<0.05$, the nonparametric trim and fill method was applied to re-estimate a corrected effect size after adjustment for publication bias.[14] All analyses were performed according to the PRISMA guidelines and by STATA (version 12.0; Stata Corporation).[15]

Quality assessment

The quality of the included studies was assessed with the NOS (Newcastle-Ottawa quality assessment scale). Studies earned a score of 6 or higher were regarded as high-quality studies. Quality assessment was conducted by two independent researchers (Yutian Lai and Kun Zhou).

Results

Literature selection process

The initial searching yielded 481 records from the four electronic databases, with no additional publications discovered. After duplicates removed, a total of 215 records were screened. Finally, 21 studies investigating the prognostic role of GPS in esophageal cancer patients met our criteria and were enrolled.[4–6,11,16–32] (Figure 1)

Characteristics of included studies

The characteristics of these 21 studies were summarized in Table 1. The majority of the studies were from Asian countries. All of the studies were retrospective observational studies except for a randomized controlled trial (RCT) from Japan. The sample size ranged from 48 to 1135 patients. All enrolled patients received esophagectomy in 13 studies and in another 3 studies patients were treated with chemotherapy and radiotherapy, while patients in the remained 5 studies were treated with mixed therapies. Only one study did not provide the HR with 95% CI and the crude HR with 95% CI was estimated from the corresponding Kaplan-Meier curve. These

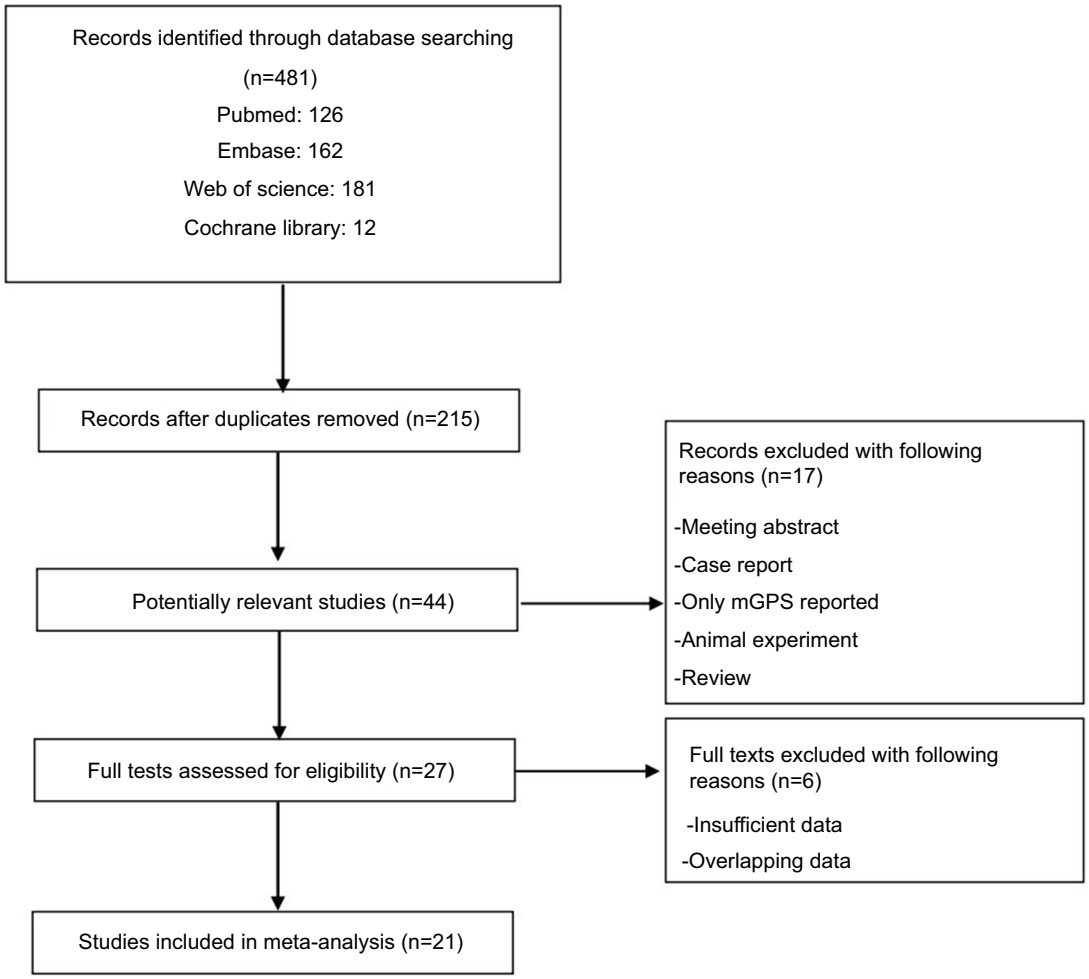


Figure 1 Flow diagram of the literature review.

Table 1 Basic characteristics of all studies included

First author	Publishing year	Country	Study period	Study design	Sample size	Gender (F/M)	Pathology type	Treatment	Follow up (months) Median	TNM	Types of outcomes	GPS value (0/1/2)	Source of HR	NOS score
Liu et al[4]	2015	China	2006–2008	ROS	326	43/283	SCC	Surg (+CT/RT)	45	NR	CSS	187/97/42	R	6
Liu et al[5]	2016	China	2004–2010	ROS	260	43/217	SCC	Surg	40.5 (2–91)	I-IV	OS/DFS	220/39/1	R	6
Okuno et al[6]	2017	Japan	2000–2006	RCT	131	12/119	SCC	CT+RT	NR	II-IV	OS	56/48/27	R	6
Vashist et al[11]	2011	Germany	1994–2007	ROS	424	NR	SCC/AC	Surg	NR	I-IV	OS/DFS	229/148/47	R	6
Wang et al[16]	2012	Taiwan, China	2002–2007	ROS	271	10/261	SCC/AC	Mixed	30 (5–81)	I-IV	OS	NA	R	6
Kimura et al[17]	2016	Japan	2002–2011	ROS	142	11/131	SCC	CT+RT	NR	III-IV	CSS	72/42/28	R	6
Hirahara et al[18]	2015	Japan	2006–2014	ROS	141	14/127	SCC	Surg	NR	I-III	OS	109/23/9	R	6
Lindenman et al[19]	2017	Austria	2003–2011	ROS	167	24/143	SCC/AC	Surg	23	NR	OS	118/41/8	R	7
Feng et al[20]	2014	China	2005–2008	ROS	493	73/420	SCC	Surg	45	NR	CSS	316/121/56	R	8
Toyokawa et al[21]	2016	Japan	2000–2014	ROS	185	33/152	SCC	Surg	81.5	I-IV	OS	171/13/1	R	7
Xu et al[22]	2015	China	2000–2010	ROS	468	52/416	SCC	Surg	49.9	I-III	OS	336/101/31	R	6
Lindenmann et al[23]	2014	Austria	1999–2010	ROS	214	33/181	SCC/AC	CT+RT	NR	III-IV	OS	88/95/31	E	6
Ohira et al[24]	2015	Japan	2000–2013	ROS	91	17/74	SCC	Mixed	NR	T4	OS	40/37/14	R	6
Kobayashi et al[25]	2008	Japan	2000–2007	ROS	48	9/39	SCC	NCRT+Surg	NR	II-III	CSS	27/16/5	R	6
Matsuda et al[26]	2015	Japan	2004–2012	ROS	199	19/180	SCC/AC/Other	Surg (+NCT/NCRT)	28.5	I-IV	OS/DFS	180/17/2	R	7
Ma et al[27]	2016	China	2006–2010	ROS	725	186/539	SCC	Surg	28	I-III	OS	616/100/9	R	7
Jomrich et al[28]	2017	Austria	2003–2014	ROS	279	NR	SCC/AC	Mixed	NR	I-IV	OS/DFS	207/58/14	R	6
Tan et al[29]	2017	China	2008–2010	ROS	1135	247/888	SCC	Surg	NR	NR	OS	NR	R	7
Yu et al[30]	2018	China	2005–2012	ROS	160	55/105	SCC	Surg (+CT)	71.8	I	OS	74/86 (0/1–2)	R	8
Kunizaki et al[31]	2017	Japan	2007–2014	ROS	116	18/98	SCC	Mixed	36	I-IV	OS	93/23 (0/1–2)	R	6
Kitagawa et al[32]	2017	Japan	2005–2016	ROS	140	28/112	SCC/AC/Other	Mixed	36.6	I-IV	OS/CSS	123/15/2	R	7

Abbreviations: F, female; M, male; TNM, tumor-node-metastasis; GPS, Glasgow Prognostic Score; HR, hazard ratio; NOS, Newcastle-Ottawa Scale; ROS, retrospective observational study; RCT, randomized controlled trial; SCC, squamous cell carcinoma; AC, adenocarcinoma; Surg, Surgery; CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; NCT, neoadjuvant chemotherapy; NCRT, neoadjuvant chemoradiotherapy; CSS, cancer specific survival; OS, overall survival; DFS, disease free survival; R, reported; E, estimated; NR, not reported.

articles were published between 2008 and 2018 and NOS scores of the included studies ranged from 6 to 8 which indicated that these studies were of high quality.

Association of GPS with OS, DFS and CSS

There were 17, 4 and 5 studies which reported the correlation of GPS with OS, DFS and CSS. The results demonstrated a significant relationship between elevated GPS and poor OS (HR =2.12, 95% CI: 1.83–2.45, $P<0.001$) with low heterogeneity ($I^2=25.9\%$, $P=0.159$) (Figure 2) and poor CSS (HR =2.16, 95% CI: 1.56–2.98, $P<0.001$) with high heterogeneity ($I^2=73.2\%$, $P=0.005$) (Figure 3), but failed to show a significant correlation between GPS and DFS (HR =2.14, 95% CI: 1.00–4.61, $P=0.051$) with high heterogeneity ($I^2=60.9\%$, $P=0.053$) (Figure 4).

Subgroup analysis

Patients with elevated GPS had a significantly worse OS compared with those with GPS 0. Subgroup analyses based on the ethnicity, sample size, pathology type, source of GPS, treatment and NOS score were performed to further explain our findings and the results manifested that none of these factors affected the prognostic role of GPS on OS. Detailed information was presented in Table 2.

Sensitivity analysis

The influence of every single study on the combined HRs was evaluated by excluding each study individually from the meta-analysis. The results showed that the pooled HRs for OS were robust in our study. No significant deviation from the overall results was detected (Figure 5).

Publication bias

Begg's funnel plot and Egger's test were performed to evaluate the publication bias of included studies presenting the association of GPS with OS. The funnel plot was symmetric ($P=0.711$, Figure 6) and no substantial publication bias was detected in the Egger's test ($P=0.553$).

Discussion

The significant role of systemic inflammatory response in the genesis, development, and progression of malignancies has

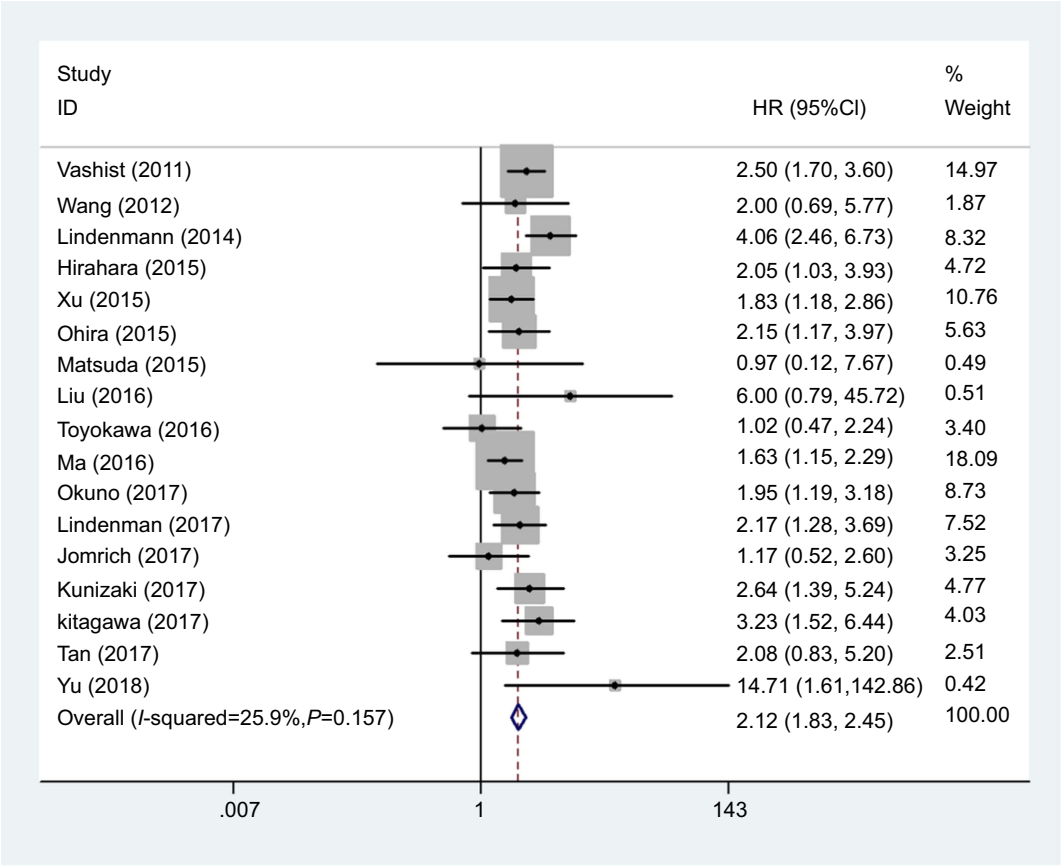


Figure 2 Forest plot of the association between GPS and overall survival.

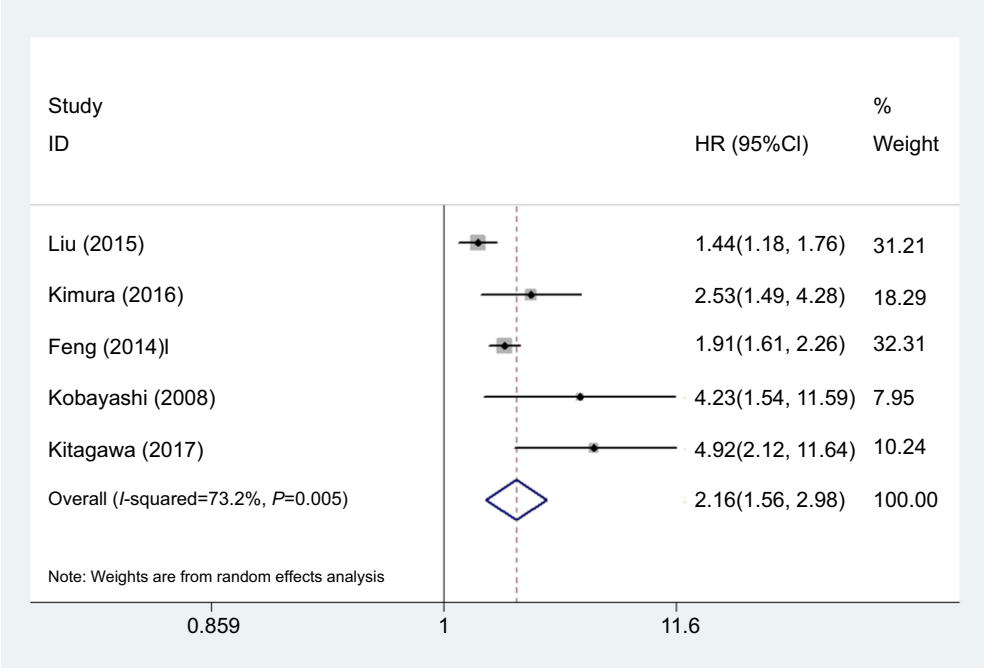


Figure 3 Forest plot of the association between GPS and cancer-specific survival.

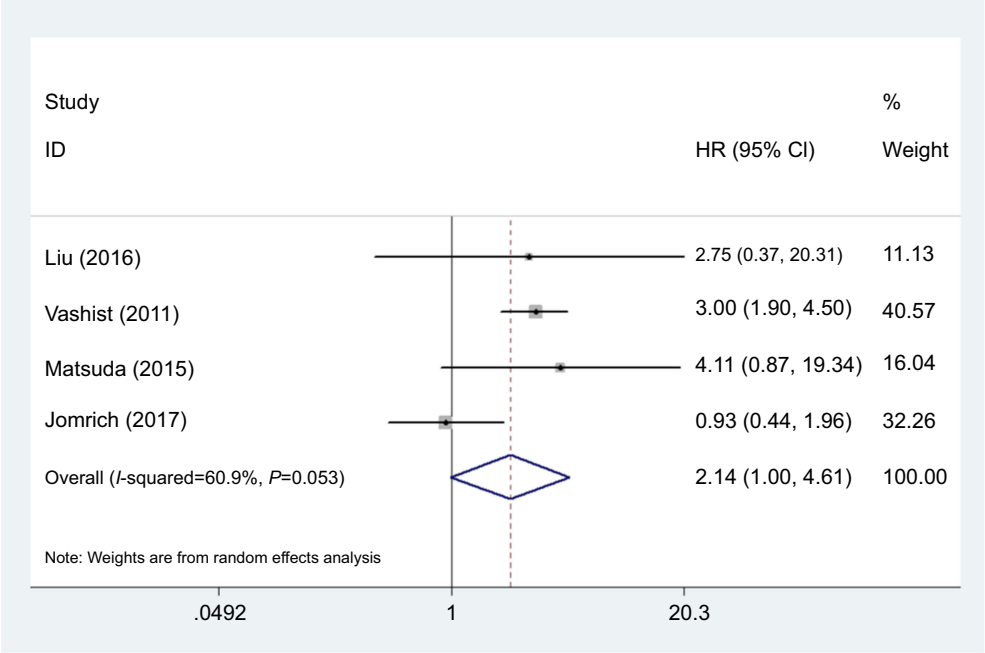


Figure 4 Forest plot of the association between GPS and disease-free survival.

been identified and verified.[2–7] GPS is an easily obtained inflammation-based score which combines serum CRP and albumin. During the past decade, increasing studies have investigated the prognostic role of GPS in several solid cancers like lung cancer, liver cancer, as well as esophageal cancer.[7,9,11] Most of the studies about esophageal cancer demonstrated that the elevated GPS was significantly associated with poor long-term survival.[16–32] However, the sample sizes of these studies were relatively small and the results were inconsistent with each other. Therefore, we designed the current research to further verify the prognostic value of GPS in esophageal cancer patients. Our meta-analysis,

Table 2 Summary of HRs for the overall and subgroup analyses of GPS and esophageal cancer

Analysis		No. of studies	HR (95% CI)	*P*-value	I^2 (%)
Overall survival		17	2.12 (1.83–2.45)	<0.001	25.9
Ethnic	China	6	1.84 (1.41–2.39)	<0.001	3.8
	Japan	7	2.06 (1.59–2.66)	<0.001	0.0
Sample size	Non-Asian	4	2.42 (1.61–3.65)	<0.001	58.6
	≥200	8	2.12 (1.76–2.55)	<0.001	46.2
	<200	9	2.12 (1.69–2.67)	<0.001	6.8
Pathology	SCC	10	1.87 (1.55–2.26)	<0.001	0.0
	SCC+AC+(Other)	7	2.54 (2.02–3.19)	<0.001	31.1
Source of GPS	GPS=2	7	2.30 (1.86–2.84)	<0.001	44.4
	GPS≥1	10	1.97 (1.62–2.41)	<0.001	7.8
Treatment	Surgery	10	1.95 (1.58–2.40)	<0.001	13.3
NOS	Chemoradiotherapy	2	2.81 (1.37–5.76)	0.005	76.1
	≥7	7	1.85 (1.45–2.35)	<0.001	34.1
	<7	10	2.29 (1.91–2.75)	<0.001	14.4
Cancer specific survival		5	2.16 (1.56–2.98)	<0.001	73.2
Disease-free survival		4	2.14 (1.00–4.61)	0.051	60.9

Abbreviations: HR, hazard ratio; GPS, CI, confidence interval; Glasgow Prognostic Score; SCC, squamous cell carcinoma; AC, adenocarcinoma; NOS, Newcastle-Ottawa Scale.

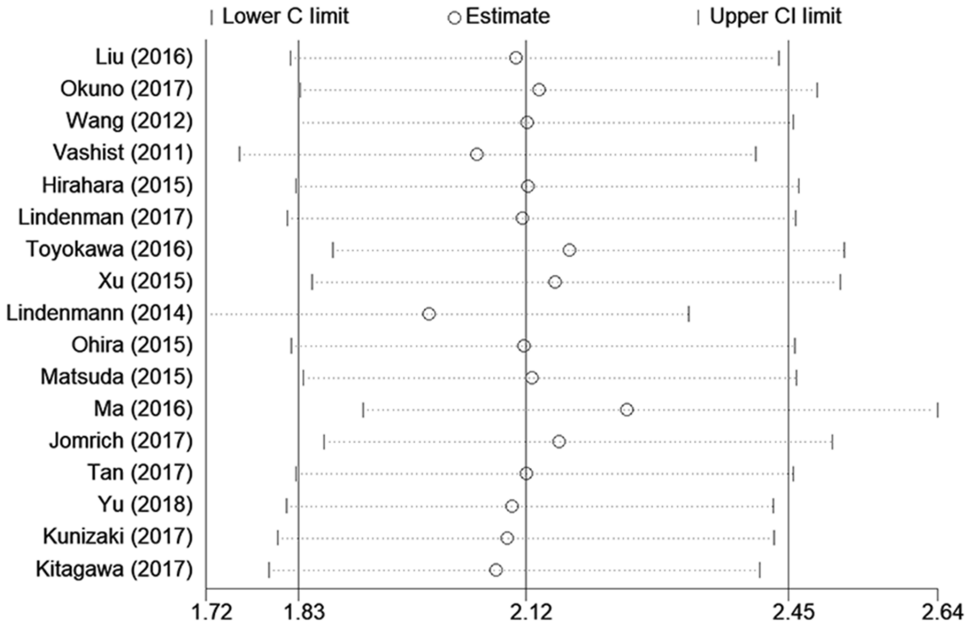


Figure 5 Sensitivity analysis of the association between GPS and overall survival.

including 21 studies, certified that the elevated GPS was associated with significantly poorer OS and CSS and the subgroup analyses based on the ethnicity, sample size, pathology, treatment and NOS score confirmed the strong connection between elevated GPS and worse OS in each subgroup.

As an acute phase protein, CRP has long been regarded as a marker of the inflammatory response, which is associated with cancer pathogenesis and progression.[33] CRP is a non-specific inflammatory factor and any disturbance such as neoadjuvant therapy could influence its level, so only studies in which GPS were obtained before any

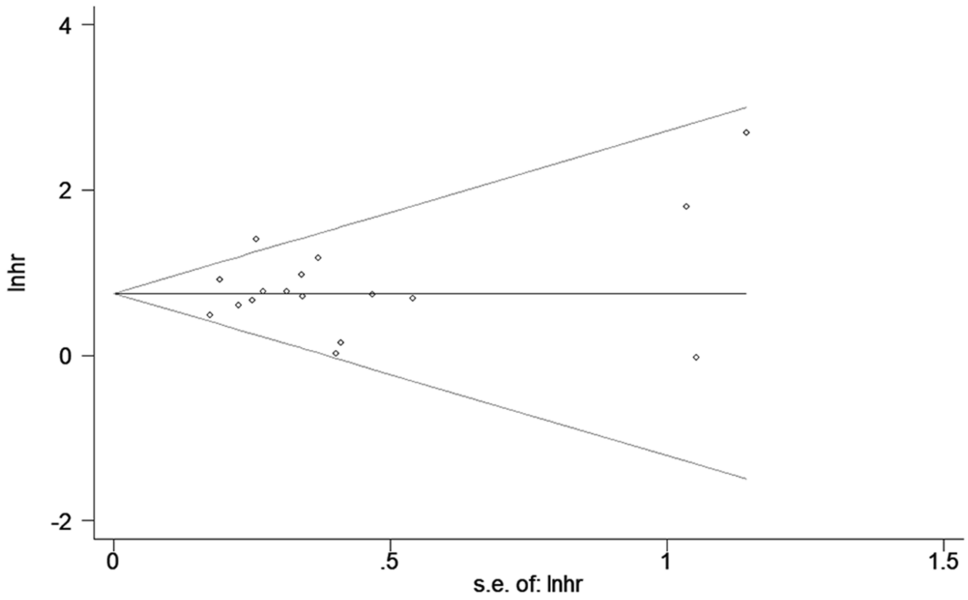


Figure 6 Begg's funnel plot of the association between GPS and overall survival.

treatment were included. A recently published meta-analysis concluded that elevated serum CRP levels were associated with poorer prognosis after pooling 5215 patients with nasopharyngeal carcinoma.[33]

Serum albumin is a factor not only reflecting the nutritional status, but also reflecting the inflammatory status which called the negative phase protein. Hypoalbuminemia could be commonly observed in cancer patients especially patients with gastric or esophageal cancer. Pretreatment hypoalbuminemia has been proved to be significantly associated with worse prognosis in several kinds of cancer.[34,35]

GPS is composed of CRP and serum albumin, which evaluates both the inflammatory response and nutritional status; and it has been proved to be a reliable factor in predicting survival of various kinds of cancers. Shim et al.[36] argued in their meta-analysis that higher GPS was significantly associated with tumor progression and predict poorer survival in patients with renal cell carcinoma after pooling 9 studies. Li et al.[37] demonstrated a significant relationship between elevated GPS and inferior OS in patients with hepatocellular carcinoma in their meta-analysis, and those patients with increased GPS tend to have shorter progression-free survival though it did not reach statistical significance. Dolan et al.[38] proved in another meta-analysis that GPS was significantly associated with OS and CSS of operable cancer including esophageal cancer. Our results were in consistence with previous meta-analyses, making the results credible.

According to our meta-analysis, GPS could serve as a promising prognostic biomarker of esophageal cancer in predicting prognosis. McMillan[39] reported that GPS may not only identify the risk of esophageal cancer but also provide a well-defined therapeutic target for future clinical treatment. Furthermore, we believed that patients with elevated pretreatment GPS should receive more active therapies like nonsteroidal anti-inflammatory drugs (NSAIDs) which were proved to have an apparent ability to reduce the risk of metastasis development in cancer patients by a recent meta-analysis.[40] This may illustrate the great clinical significance of our research. However, these recommendations or opinions still need to be confirmed in future studies.

There are some limitations in our meta-analysis. First of all, some baseline characteristics such as the treatment, TNM stage and follow-up duration varied between studies. These confounding factors might lead to heterogeneity. Secondly, almost all the included studies were retrospective, which was susceptible to some biases. More well-designed prospective studies are still needed to verify the prognostic value of GPS in esophageal cancer. Thirdly, the significant relationship between GPS and CSS was observed, but we failed to perform subgroup analysis to explore the source of high heterogeneity due to the shortage of related studies. Fourthly, the subgroup analysis based on the pathology type manifested the prognostic value of GPS in ESCC (HR =1.87, 95% CI: 1.55–2.26, $p<0.001$). However, we failed to explore the role of GPS

in predicting survival of EAC patients because none of the included studies provided the data of the association between GPS and prognosis of EAC.

In conclusion, our meta-analysis demonstrated that pretreatment GPS was significantly associated with OS and CSS and could be regarded as an ideal factor in predicting the prognosis of patients with esophageal cancer. Large prospective cohort studies are warranted to verify our findings.

Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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