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Inflammation and nutrition-based biomarkers in the prognosis of esophageal cancer: A systematic review and meta-analysis

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Abstract

Objectives: To compare the predictive value of inflammation and nutrition-based prognostic scores for patients with esophageal cancer.

Design: Systematic review and meta-analysis.

Data sources: PubMed, Web of Science and Cochrane Library databases were searched on 30 September 2020.

Eligibility criteria: We included case-control studies and cohort studies considering neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), c-reactive protein- to- albumin ratio (CAR), systemic inflammation index (SII), prognostic nutritional index (PNI), Glasgow Prognostic Score (GPS), and modified Glasgow Prognostic Score (mGPS) as prognostic scores for esophageal cancer patients.

Data extraction and synthesis: Two students independently extracted data and assessed the risk of bias. HR (95% CI), sensitivity, specificity, positive and negative likelihood ratios and area under the curve (AUC) together with 95% CI were used to estimate the diagnostic value.

Results: A total of 73 studies including 23308 patients were included in the analysis. We found that elevated NLR, PLR CAR, SII, GPS, mGPS and low LMR and PNI were associated with poor OS of esophageal cancer, high level of NLR, PLR and GPS were related to poor DFS, and high level of NLR and GPS were related to poor

CSS. The summarized AUC of CAR (0.72, 95% confidence interval: 0.68-0.75) and mGPS (0.75, 95% confidence interval: 0.71-0.78) surpassed any other indicators based on SROC curves.

Prospero registration number: CRD42020176587

Conclusions: NLR, PLR, LMR, PNI, SII, CAR, GPS, and mGPS, which are generally used as clinical indicators, have the moderate predictive ability in OS, DFS and CSS of esophageal cancer. The pretreatment level of CAR and mGPS showed an outstanding prediction value in 5-year OS for esophageal cancer in terms of SROC.

Keywords: Inflammation-Based Prognostic indicators; Nutrition-based Prognostic indicators; Esophageal cancer; Meta-analysis; Systematic review

Strengths and limitations of this study:

All stages of the study were conducted by two researchers independently and supervised by a third reviewer.

This study was the first time to comprehensively estimate the popular inflammatory and nutrition-related markers in OS, DFS and CSS of esophageal cancer. Moreover, this is the first systematic review to summarize the sensitivity and specificity and compare the AUC of these predictors in 5-year OS of EC.

The heterogeneity was relatively high. Study design and the different cutoff values of indicators were the primary sources of heterogeneity.

Due to few articles providing data of sensitivity and specificity for prediction the limited included literatures caused some subgroup analysis cannot be carried out.

Introduction

Globally, esophageal cancer is the world's 6th leading cause of cancer-related deaths and the 8th most common cancer. Pathologically, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) are the major histological types. EAC is mainly observed in industrialized countries and nearly half of cases occur in Northwest Europe and North America[1], while ESCC is more common in China, Central Asia, or South Africa[2]. Esophageal cancer is characterized by poor prognosis and high mortality[3]. Despite substantial efforts in diagnosis, accurate staging and advanced treatments[4, 5], esophageal cancer continues to be an ominous disease with poor survival[6]. Therefore, it is urgent to find better prognostic biomarkers to guide clinical treatment.

Increasing evidence indicates that systemic inflammatory response and nutritional status are involved in tumor development and considered to be important factors influencing the clinical prognosis. Main inflammation-based prognostic scores include a neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), c-reactive protein-to-albumin ratio (CAR), systemic inflammation index (SII), pretreatment albumin levels, and lymphocyte to monocyte ratio. Common nutrition-based prognostic scores are prognostic nutritional index (PNI) based on serum albumin and total lymphocyte count, Glasgow Prognostic Score (GPS) based on elevated C-reactive protein concentration and low levels of albumin, and modified Glasgow Prognostic Score (mGPS). Recently, accumulating literature have shown the prognostic values of these inflammation and nutrition-based prognostic markers, but with inconsistent findings[7]. Hence, it is meaningful to distinguish an accurate index of prognosis for patients with esophageal

cancer to guide individualized therapy and precision service.

In the current study, we performed a systematic review of relevant literature and applied the meta-analysis to explore the accuracy of inflammation and nutrition-based prognostic scores for patients with esophageal cancer.

Methods

Data sources and searches

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Two authors (Xu D and Jiang Y) independently searched PubMed, Web of Science and Cochrane Library Databases for eligible articles from the inception of the databases to September 30, 2020. Additionally, references in the eligible publications were also reviewed for potential studies. The language of articles was limited to English. The search terms are listed in Additional file S1. The detailed search strategy is illustrated in Fig. 1.

Selection criteria

Articles were included in this meta-analysis if they met the following criteria: 1) Patients were histopathologically confirmed to be primary esophageal cancer; 2) The prognostic indicators were measured before esophagectomy, chemotherapy or radiotherapy; 3) The hazard ratios (*HR*s) with their 95% confidence intervals (95% *CI*s) were reported in multivariate analysis. Studies were excluded if they were: (1) reviews, case reports, letters, or conference abstracts; (2) studies with insufficient data; or (3) duplicate publications.

Data extraction

For each study, the following information was extracted by two authors (Xu D and Jiang Y): the name of the first author, year of publication, country, study design, pathological type, number of patients, age, sex, end-point, follow-up time, cut-off selection, therapy, tumor stage, cut-off values, and *HR*s (95% *CI*s). We further collected the data of true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN) for 5-year overall survival (OS) directly provided in the paper or calculated by equivalent data (the number of people in the high-risk and low-risk groups according to cut-off values and the corresponding number of deaths and survivors). If only the AUC was reported in the paper, we contacted the corresponding author for original data. If we couldn't get a response, we only included the study in the first part of the analysis.

Quality assessment

Two reviewers (Tian D and Qiu B) independently assessed the methodological quality of the studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool[8]. Each item was judged as "yes", "no", or "unclear". Any signaling question that was answered "yes" indicated a low risk of bias, while "no" indicated a high risk of bias. If the answer was uncertain, the domain was judged as having an uncertain risk of bias.

Statistical analysis

The risk of bias was analyzed and plotted using Review Manager 5.3 (London, UK). The meta-analysis was performed using STATA 15.0 (Texas, USA). The strength of NLR, PLR, LMR, PNI, SII, CAR, GPS, mGPS in association with overall survival

(OS), cancer-specific survival (CSS) and disease-free survival (DFS) was measured by the combined *HR*s and their 95% *CI*s. Cochran's Q test and Higgins I-squared statistics were undertaken to assess the heterogeneity of studies. If $P \geq 0.10$ in the Q test or $I^2 < 50\%$, we used the fixed-effect model, otherwise we used the random-effect model. Publication bias was assessed by Begg and Egger test. The sensitivity analysis was utilized by omitting individual study one-by-one to assess the robustness of the results. All P-values were two-tailed and a P-value <0.05 was considered statistically significant.

The pooled sensitivity, specificity, AUC, and corresponding 95% *CI* were calculated by TP, FP, FN, and TN using a bivariate regression model. The threshold effects were calculated by testing Spearman correlation using Meta-DiSc (Madrid, Spain). If $I^2 \geq 50\%$ and *P*-value ≤ 0.05, the heterogeneity was significant due to the non-threshold effect, and then we used the meta-regression analysis to find the source of heterogeneity. The pooled positive likelihood ratio (P-LR), negative likelihood ratio (N-LR), and diagnostic odds ratio (DOR) were also calculated to better understand the performance of the prognostic index. Deek's funnel plot was used to detect publication bias. To evaluate the difference of AUC between biomarkers, we checked the overlap of 95% CIs. If not, we used the following *z*-test ($\frac{X_1 - X_2}{(SE_1^2 + SE_2^2)^{1/2}}$), where X_1 and X_2 represented the indicators, and SE_1 and SE_2 were the corresponding standard errors. If the *P*-value obtained from the z-test was less than p' (0.05/n, n was the number of comparisons), it was considered significantly different. The comparison for sensitivity, specificity, P-LR, N-LR, or DOR was also performed.

Results

Literature selection and study characteristics

The initial search identified 662 potentially relevant records. After removing duplicates and papers that did not meet the inclusion criteria, 73 studies with 23,308 subjects were remain for the systematic review (Additional file 2: Table S1). A flowchart demonstrating the process of study selection is illustrated in Fig. 1. Most studies were carried out in Asia (43 in China; 23 in Japan). The blood cell counts used to calculate NLR, PLR, LMR, and CAR were obtained before treatment. The baseline characteristics and treatment methods are presented in Additional file 2.

Risk-of-bias and quality assessments

Figures 2 illustrates the risk assessment of bias. A high risk of selection bias was observed in all studies. Nearly one-third of the studies had an unclear bias in study attrition. For detection bias, one study had an unclear bias and two studies had the risk of bias in measuring prognostic factors and outcomes, respectively. Six studies were judged as unclear performance bias.

3.3 Prognostic indicators in OS, DFS and CSS of esophageal cancer

As shown in Fig. 3 (A-H), factors significantly contributing to a short OS were a high level of NLR (*HR*: 1.43, 95% *CI*: 1.30–1.58, *P* <0.001; I^2 =61.7%, P_{het} <0.001), PLR (*HR*: 1.26, 95% *CI*: 1.18–1.35, *P* <0.001; I^2 =29.8%, P_{het} =0.108), CAR (*HR*: 1.84, 95% *CI*: 1.60–2.10, *P* <0.001; I^2 =41.8%, P_{het} =0.079), SII (*HR*: 1.46, 95% *CI*: 1.30–1.65, *P* <0.001; I^2=41.0%, P_{het}=0.118), GPS(*HR*: 2.35, 95% *CI*: 1.99–2.76, *P* <0.001; I^2 =36.5%, P_{het} =0.078), or mGPS (*HR*: 1.69, 95% *CI*: 1.49–1.92, *P* <0.001; I^2 =48.4%, P_{het} =0.022), and low level of LMR (*HR*: 1.37, 95% *CI*: 1.14–1.65, *P*

=0.001; I^2 =84.9%, P_{het} <0.001) and PNI (*HR*: 1.51 95% *CI*: 1.36–1.68, *P* <0.001; I^2 =45.8%, P_{het} =0.048).

Patients with an elevated NLR (*HR*: 1.21, 95% *CI*: 1.04–1.41, *P* =0.011; I^2 =43.4%, P_{het} =0.089) and GPS (*HR*: 1.74, 95% *CI*: 1.58–1.92, *P* <0.001; I^2 =45.7%, P_{het} =0.11) had a worse CSS (Fig.3 I-J) .

NLR (*HR*: 1.39, 95% *CI*: 1.10–1.75, *P* =0.005; I^2 =60.9%, P_{het} =0.018), PLR (*HR*: 1.30, 95% *CI*: 1.12–1.51, *P* <0.001; I^2 =33.0%, P_{het} =0.202), and GPS(*HR*: 2.44, 95% *CI*: 1.28–4.66, *P* <0.007; I^2 =57.5%, P_{het} =0.052) were negatively correlated with DFS. No significant association was found for LMR (*HR*: 1.03, 95% *CI*: 0.78–1.35, *P* =0.858; I^2 =82.2%, P_{het} <0.001) (Fig.3 K-N).

Subgroup analysis and meta-regression

Subgroup analysis and meta-regression were further conducted according to the cut-off value, sample size, follow-up time, sex, age, clinical stage, and region (Additional file 3). The heterogeneity of OS studies was relatively low except LMR (I^2 =84.9%) and NLR (I^2 =61.7%). The pooled *HR* was significantly different between studies with more or less than 280 patients, indicating that the sample size may be the source of heterogeneity for LMR. Similarly, we found the source of the heterogeneity for other indicators: the follow-up months may be the source of heterogeneity for PLR (*P*=0.004) and GPS (*P*=0.027), the sample size may be the source of heterogeneity for SII (*P*=0.047) and mGPS (*P*=0.014), and the sex ratio may be the source of heterogeneity for CAR (*P*=0.045). In DFS analysis, we found that cut-off value and region may be the source of high heterogeneity of LMR

(*P*=0.034) and NLR (*P*=0.018), respectively.

Publication bias

Begg's and Egger's tests were applied to estimate the publication bias. As shown in Additional file 3, no significant publication bias was observed.

Sensitivity analysis

We performed a sensitivity analysis by excluding one study each time. As shown in Additional file 6: Figure 1, the results were not substantially changed, showing the reliability and stability of current meta-analysis.

Pooled sensitivity, specificity, DOR, and AUC of indicators

We further extracted TP, FP, FN, and TN from each study (Additional file 2) to calculate the pooled accuracy of each indicator for a 5-year OS. There were 11 studies for NLR, 11 studies for PLR, 7 studies for LMR, 6 studies for CAR, 6 studies for SII, 7 studies for PNI, 6 studies for GPS and 5 studies for mGPS.

The Spearman correlation coefficient (*P*-value) for NLR, PLR, LMR, PNI, SII, CAR, GPS, and mGPS was 0.56 (0.07), 0.59 (0.06), 0.57 (0.18), 0.75 (0.05), 0.77 (0.07), 0.20 (0.70), 0.77 (0.07), and -0.10 (0.87), respectively, indicating no significant threshold effect.

Forest plots of sensitivity and specificity were shown in Fig. 4. SII had the highest pooled sensitivity (0.61, 95% *CI*: 0.48-0.73), while CAR (0.84, 95% *CI*: 0.71-0.91) had the highest pooled specificity. The I^2 of the sensitivity and specificity of these

prognostic indicators were relatively high (around 70%-90%) except GPS (sensitivity: 43.76%; specificity: 6.96%). We further conducted a subgroup analysis and meta-regression (Additional file 4). For SII, the sensitivity of studies with a cut-off level ≥410 ng/ml (0.47, 95% *CI*: 0.37–0.57) was significantly lower than the studies with a cut-off level <410 ng/ml (0.73, 95% *CI*: 0.66–0.81), while studies with a cut-off level ≥410 ng/ml (0.76 , 95% *CI*: 0.72–0.81) had a significantly higher specificity than studies with a cut-off level < 410 ng/ml (0.42, 95% *CI*: 0.38–0.47). Therefore the cut-off value may be the source of heterogeneity in both sensitivity and specificity of SII. Similarly, we found that sample size may be the source of sensitivity for mGPS (*P*<0.001), PLR (*P*=0.02), GPS (*P*=0.03), CAR (*P*=0.04), and LMR (*P*=0.04), and the source of heterogeneity in the specificity of NLR (*P*=0.03) and GPS (*P*<0.001). Additionally, the study area may be the source of heterogeneity in the specificity of mGPS (*P*=0.01). Also, age and clinical stage may be the source of heterogeneity in specificity for PLR (*P*<0.001) and PNI (*P*=0.01), respectively. However, we failed to find the source of heterogeneity for the sensitivity of NLR or PNI and the specificity of CAR or LMR.

Figure 5 shows the summarized ROC curves of eight indicators. We found that the scope of pooled AUC of CAR (0.72, 95% *CI*: 0.68-0.75) and mGPS (0.75, 95% *CI*: 0.71-0.78) surpassed other indicators except GPS (0.67, 95% *CI*: 0.63-0.71). We further compared CAR, mGPS, and GPS by *z* test. The pooled AUC of CAR or mGPS was larger than GPS (*P* =0.033; *P* =0.002), but there was no significant difference between CAR and mGPS (Additional file 7).

Only PNI (*P* =0.03) and mGPS (*P* =0.02) had a significant publication bias

(Additional file 5). The sensitivity analysis of combined DOR showed a robust finding (Additional file 6: Figure 2).

Discussion

In this meta-analysis, we summarized data from 73 studies and estimated the predictive ability of inflammation and nutrition-based indicators in esophageal cancer. In general, although these indicators have a high specificity, sensitivity is unsatisfactory. The pretreatment level of CAR and mGPS showed an outstanding prediction value for 5-year OS than other indicators.

Previous studies have systematically reviewed the role of NLR, PLR LMR, PNI and GPS in the prognosis of esophageal cancer, most of which focused on ESCC. Yang et al[9] investigated the relationship between NLR and esophageal cancer by summarizing six studies involving 1,633 patients. Sun et al[10] reviewed 26 studies to explore the NLR, PLR, and LMR in the OS, CSS, and EFS in ESCC. Li et al[11] reviewed nine observational studies and showed that a low PNI score was significantly correlated with a poor OS of esophageal cancer and recurrence-free survival of ESCC. Liu et al. collected eight observational studies and showed that high CAR was related to a worse OS. Although previous meta-analyses have reported the prognostic value of these indicators, this is the first study to comprehensively estimate the popular inflammatory and nutrition-related markers in OS, DFS, and CSS of esophageal cancer. Moreover, this is the first systematic review to summarize the sensitivity and specificity and compare the AUC of these predictors in the 5-year OS of esophageal cancer.

In this review, we observed that the AUC of CAR and mGPS was significantly higher as compared with NLR, PLR, SII, PNI, LMR, and GPS, indicating their predictive value in esophageal cancer. Previous researches have revealed that host inflammatory response or nutritional status plays a critical role in the development and progression of many cancers. CAR and mGPS are calculated based on the level of C-reactive protein (CRP) and albumin. CRP is a kind of acute reactive protein synthesized by liver cells or cancer cells[12], which can produce an attractive environment for tumor growth, induce DNA damage, promote angiogenesis, and favor neoplastic spread and metastasis[13]. Albumin reflects the malnutrition status of the host, triggers malignant transformation and tumor progression or even causes cachexia[14]. It was reported that the CAR had a better predictive performance for hepatocellular carcinoma and colorectal cancer than NLR, PLR or c-reactive protein alone[15]. Other studies demonstrated that mGPS was an independent marker of poor prognosis for patients with HCC and superior to NLR, PLR, and PNI[16].

Some limitations should be acknowledged. Firstly, the cut-off value of indicators varied between studies, which may affect the pooled analysis results and induce unavoidable potential heterogeneity and bias. Therefore, a standard and uniform cut-off value needs to be defined. Secondly, some factors, such as age, smoking, alcohol drinking, tumor stage, comorbidities, treatment method, and psychological factors, also affect the outcomes, which may cause potential confounding. Thirdly, publication bias was detected in studies on PNI and mGPS. Papers that failed to get published due to negative or null results could not be identified in our literature search and thus were not included in the meta-analysis. This may overestimate the prognostic effect of PNI and mGPS.

In conclusion, NLR, PLR, LMR, PNI, SII, CAR, GPS, and mGPS are commonly used as clinical indicators to predict OS, DFS, and CSS of esophageal cancer, but with unsatisfactory sensitivity. Pretreatment CAR and mGPS showed outstanding prognostic values in 5-year OS for patients with esophageal cancer. Future large prospective studies with rigorously designed methodologies are warranted to confirm our results.

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Authors 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.

Competing interests

The authors declare no competing financial interest.

Patient and public involvement

No patient involved.

Data sharing statement

All data generated or analyzed during this study are included in this published article.

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Figure legends

Fig. 1 Flow diagram of the search process.

Fig. 2 Risk of bias and applicability concerns.

Fig. 3 Forest plot of *HR* for 5-year OS, DFS, and CSS in patients with esophageal cancer.

(A) NLR-OS; (B) PLR-OS; (C) LMR-OS; (D) CAR-OS; (E) SII-OS; (F) PNI-OS; (G) GPS-OS; (H) mGPS-OS; (I) NLR-CSS; (J) GPS-CSS; (K) NLR-DFS; (L) PLR-DFS; (M) LMR-DFS; (N) GPS-DFS.

Fig. 4 Forest plot of sensitivity and specificity

(A) NLR; (B) PLR; (C) LMR; (D) CAR; (E) SII; (F) PNI; (G) GPS; (H) mGPS; Q: Cochran Q statistic.

Fig. 5 Summary receiver-operating characteristic (SROC) curves of 5-year OS.

(A) NLR; (B) PLR; (C) LMR; (D) CAR; (E) SII; (F) PNI; (G) GPS; (H) mGPS; AUC: area under curve

Additional files

Additional file 1. Searching strategy

Additional file 2. Characteristics of studies

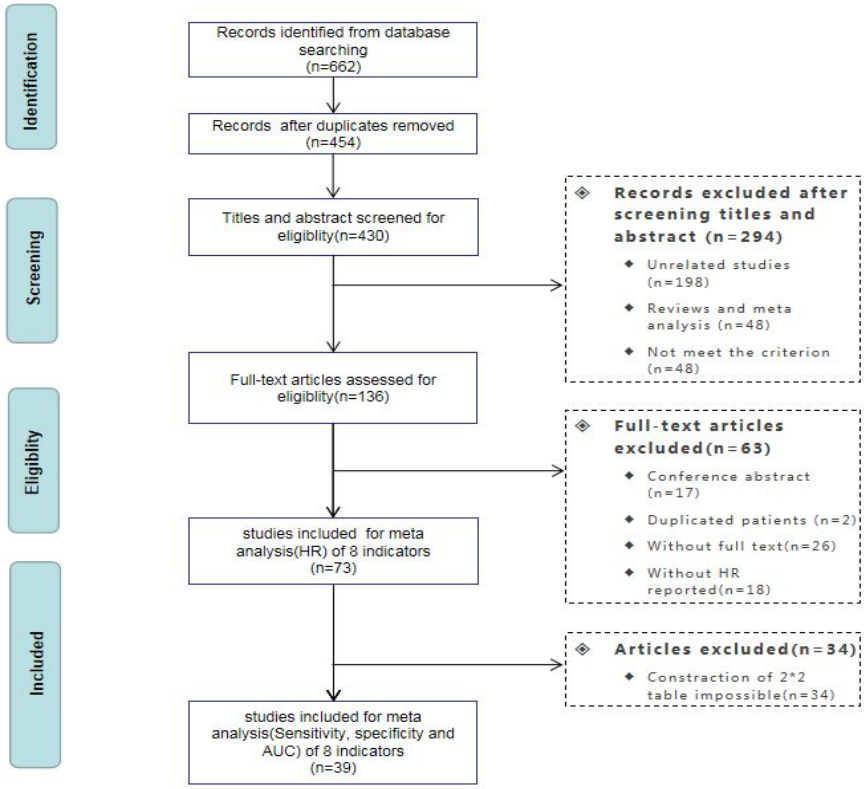
Additional file 3. Subgroup analysis (part 1)

Additional file 4. Subgroup analysis (part 2)

Additional file 5. Funnel plots

Additional file 6. Sensitivity analysis

Additional file 7. Comparisons



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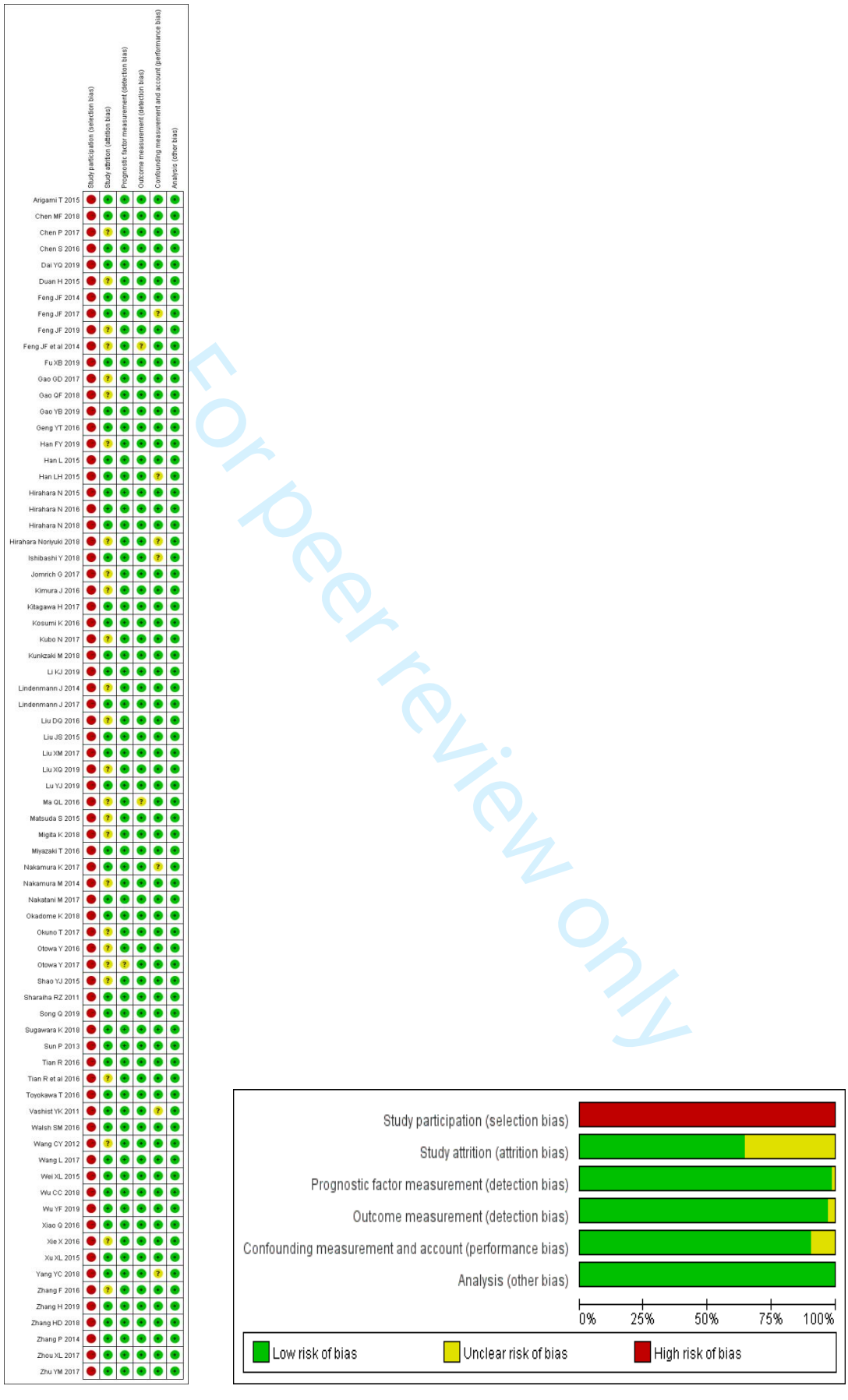
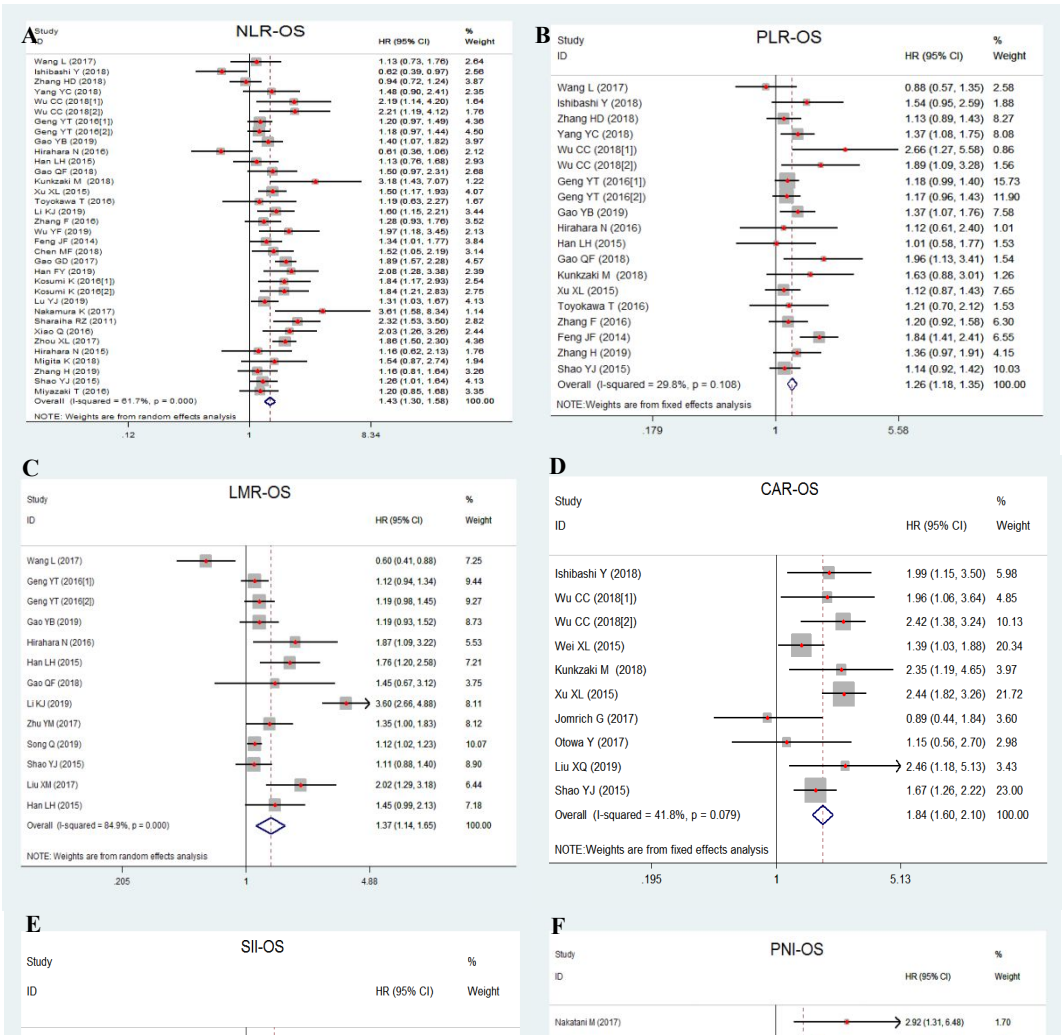


Fig. 2 Risk of bias and applicability concerns.



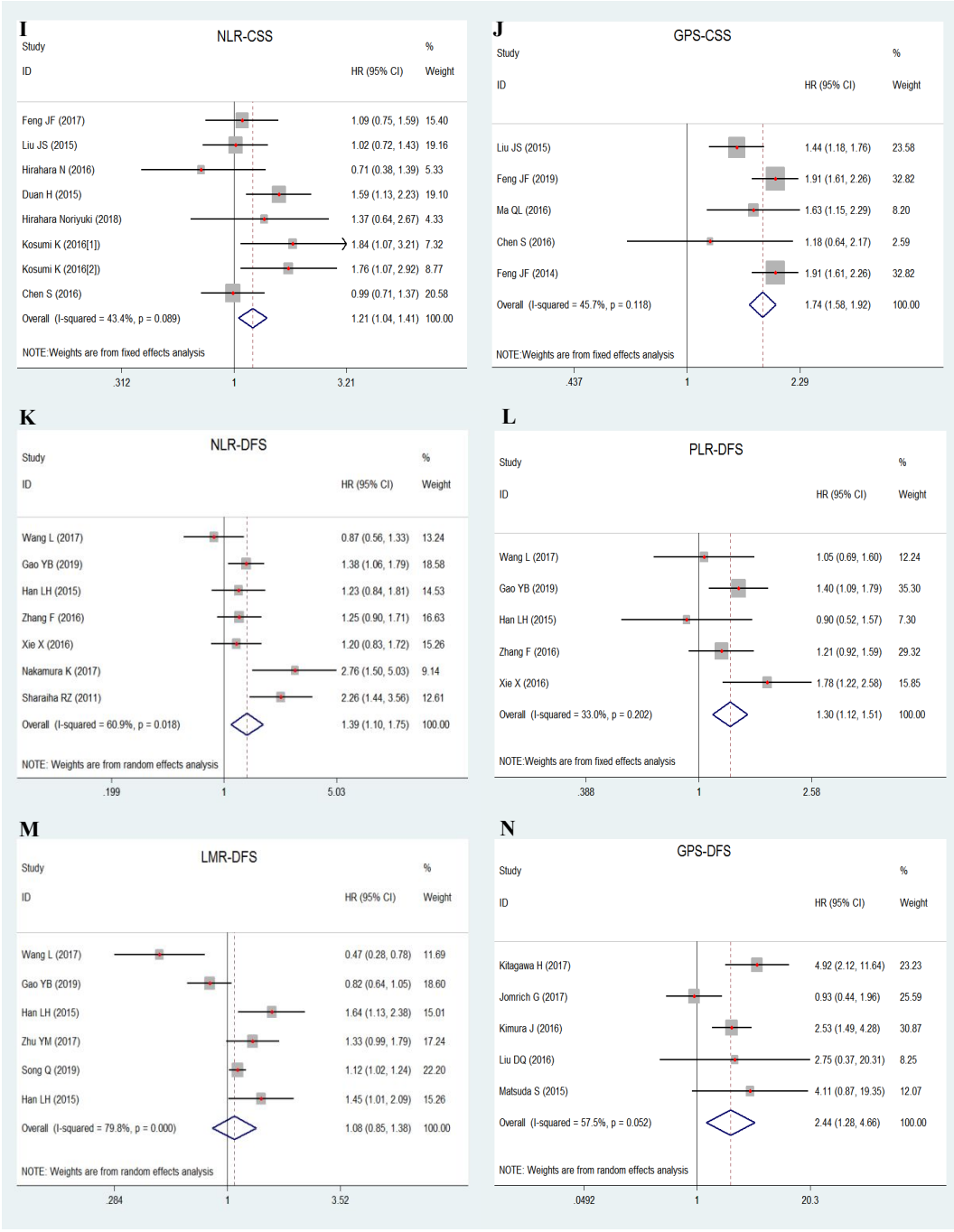


Fig. 3 Forest plot of *HR* of 5-year OS, DFS, and CSS in patients with esophageal cancer.

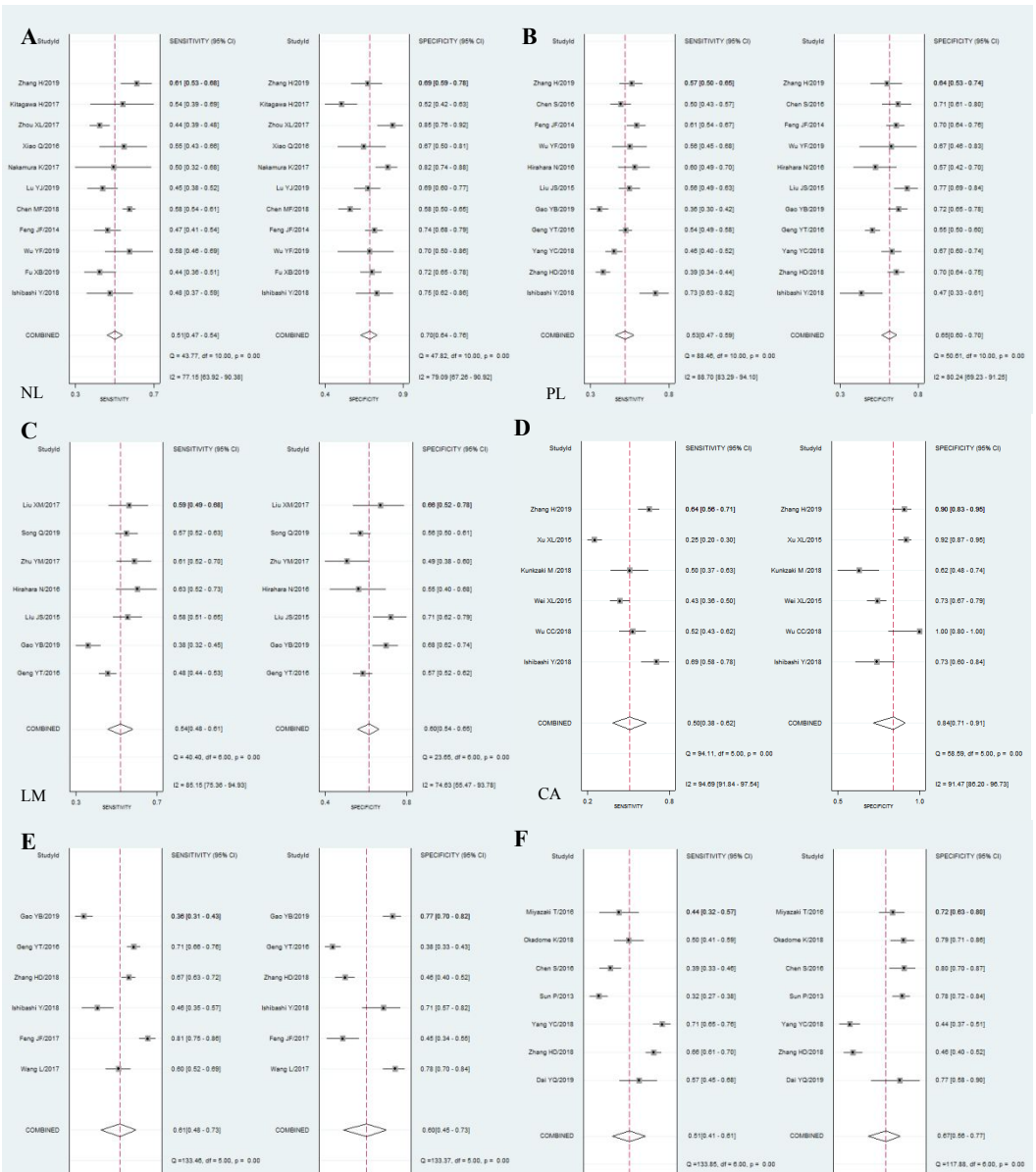


Fig. 4 Forest plot of sensitivity and specificity

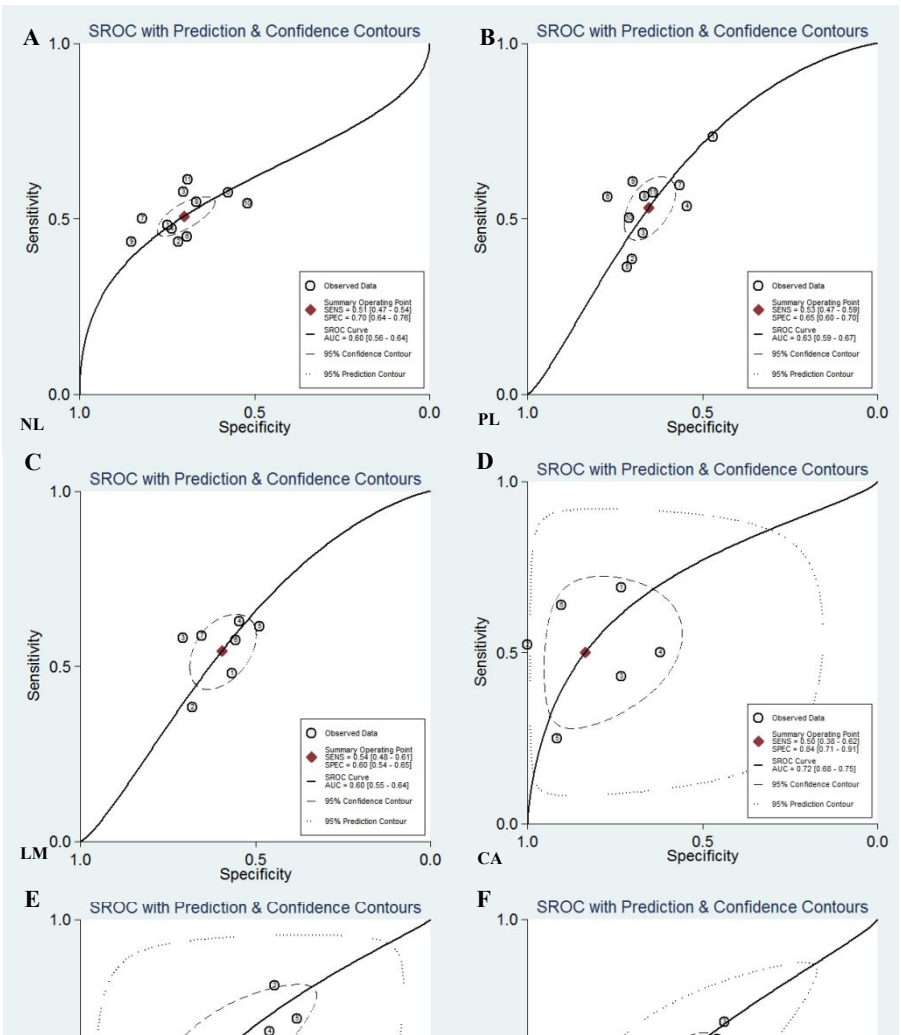


Fig.5 Summary receiver-operating characteristic (SROC) curves of 5-year OS.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6,7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8,19
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	21-24
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10,12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12,13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Searching strategy:

((((((((((NLR OR neutrophil to lymphocyte ratio) OR neutrophil-to-lymphocyte ratio) OR neutrophillymphocyte ratio) OR neutrophil lymphocyte ratio) OR (((((PLR OR platelet lymphocyte ratio) OR plateletlymphocyte ratio) OR platelet to lymphocyte ratio) OR platelet-to-lymphocyte ratio) OR platelet lymphocyte ratio)) OR (((((LMR OR lymphocyte monocyte ratio) OR lymphocytemonocyte ratio) OR lymphocyte to monocyte ratio) OR lymphocyte-to-monocyte ratio) OR lymphocyte monocyte ratio)) OR ((((SII OR Systemic Immune-Inflammation Index) OR Systemic Immune Inflammation Index) OR Systemic Inflammation Index) OR Systemic Immune-Inflammation Indices)) OR (PNI OR Prognostic nutritional index)) OR (((GPS OR Glasgow Outcome Scale) OR GOS) OR Glasgow Prognostic score)) OR (mGPS OR modified Glasgow Prognostic score)) AND ((((ESCC OR esophageal neoplasm) OR esophageal cancer) OR esophageal carcinoma) OR esophageal squamous cell carcinoma))

Table 1. The characteristics of the studies included.

Study	Ethnicity (country)	Sample size	Gender (M/F)	Age	Stage	NLR cutoff	PLR cutoff	LMR cutoff	PNI cutoff	SII cutoff	GPS cutoff	mGPS cutoff	CAR cutoff	Follow-up (months)	Treatment	Outcome	pathology	TP /FP /FN /TN (OS)
Wang L et al. (2017)[1]	China	280	233/47	64.071±7.412	0-IV	2	159	5.3	NR	560	NR	NR	NR	36	surgery	OS/DFS	SCC	SII:81 32 53 114
Feng JF et al. (2017)[2]	China	298	260/38	NR	I-III	5	150	NR	NR	410	NR	NR	NR	NR	surgery	CSS	SCC	SII:165 52 39 42
Nakatani M et al. (2017)[3]	Japan	66	56/10	64.7 ± 6.1	II-III	NR	NR	NR	45	NR	NR	NR	NR	31.9	surgery	OS/RFS	SCC	NR
Kubo N et al. (2017)[4]	Japan	202	162/40	63.73 ± 7.93	I-IV	NR	NR	NR	44	NR	NR	NR	NR	47.1	surgery	OS/RFS	SCC	NR
Hirahara N et al. (2018)[5]	Japan	169	150/19	PNI＜49.2：67.1±8.2 PNI≥49.2：65.4±8.0	Ia-IIIc	NR	NR	NR	49.2	NR	NR	NR	NR	NR	surgery	OS/CSS	SCC	NR
Dai YQ et al. (2019)[6]	China	106	79/27	<65:82; ≥65:24	T1-4/N0-1	2.1	104.1	3.45	48.15	305.6	NR	NR	NR	19(2–190)	CRT	OS	SCC	PNI: 43 7 33 23
Ishibashi Y et al. (2018)[7]	Japan	143	121/22	70.6 ± 8.4(43–90)	I-IV	3	135	NR	NR	650	NR	NR	0.085	NR	surgery	OS/CSS	SCC/ADC /Others	SII: 39 17 46 41 NLR: 42 14 45 42 PLR: 66 28 24 25 CAR: 60 15 27 41
Zhang HD et al. (2018)[8]	China	655	537/118	61(27–88)	0-III	1.87	140.08	NR	52.28	387.65	NR	NR	NR	36.0(3–144)	surgery	OS	SCC	PLR: 148 81 236 190 SII: 259 146 125 125 PNI: 264 137 138 116
Yang YC et al. (2018)[9]	China	515	418/97	61(33–92)	I-III	1.2	130	NR	57	NR	NR	NR	NR	35(2–106)	surgery	OS	SCC	PLR: 143 67 168 137 PNI: 217 117 90 91
Wu CC et al. (2018)[10]	China	126	122/4	58(37–80)	IIIa-IIIc	2.5	103	NR	NR	NR	NR	0/1,2	0.95	NR	mixed	OS	SCC	CAR: 57 1 52 17 mGPS: 77 2 34 15
Wei XL et al. (2015)[11]	China	423	341/82	58(24–88)	I-IV	1.835	163.8	NR	49.05	NR	NR	0,1,2	0.095	35.7(0.6–95.6)	surgery	OS	SCC	CAR: 90 57 119 157
Geng YT et al. (2016)[12]	China	916	696/220	60.0(37–84)	0-III	1.7	120	3.57	NR	307	NR	NR	NR	39(3–146)	surgery	OS	SCC	SII: 279 227 113 140 LMR: 239 181

																	258 238 PLR: 275 183 238 220
Gao YB et al. (2019)[13]	China	468	376/92	59.5(36–81)	I-III	2.27	117.05	5.26	NR	479.72	NR	NR	NR	49.1±32.6(3.2–114.5)	surgery	OS/DFS	SCC	SII: 93 50 162 163 PLR: 93 60 164 151 LMR: 96 69 155 148
Liu JS et al. (2015)[14]	China	326	283/43	59.2±7.9(38-80)	T1-4/N0-3	3.45	166	2.3	NR	NR	0/1,2	NR	NR	45	surgery	CSS	SCC	GPS: 108 31 95 92 PLR: 114 28 89 95 LMR: 112 36 81 87
Hirahara N et al. (2016)[15]	Japan	147	132/15	<70：46 ≥70：101	Ia-IIIc	1.6	147	4	NR	NR	NR	NR	NR	42(3-111)	surgery	OS/CSS	SCC	LMR: 59 24 35 29 PLR: 56 23 38 30
Han LH et al. (2015)[16]	China	218	177/41	60.5(32-84)	I-III	2.6	244	2.57	NR	NR	NR	NR	NR	38.6(3-71)	surgery	OS/DFS	SCC	NR
Gao QF et al. (2018)[17]	China	153	128/25	61.93±6.72	0-III	2.1	145.9	2.3	NR	NR	NR	NR	NR	NR	surgery	OS	SCC	NR
Kunkzaki M et al. (2018)[18]	Japan	116	98/18	66(44-83)	0-IV	5	150	NR	45	NR	0/1,2	0/1,2	0.042	NR	mixed	OS	SCC	CAR: 29 22 29 36
Xu XL et al. (2015)[19]	China	468	416/52	58	I-IIIc	2.4	147	NR	NR	NR	0/1/2	0/1/2	0.5	49.9(10.9–88.0)	surgery	OS	NR	CAR: 72 15 216 165
Toyokawa T et al. (2016)[20]	Japan	185	152/33	64(59–70)	I-IV	3.612	193	NR	NR	NR	0/1,2	NR	NR	81.5(IQR:45.8–112.3)	surgery	OS/RFS	SCC	NR
Li KJ et al. (2019)[21]	China	204	171/33	65.8(38-85)	T1-4/N0-2	2.64	NR	3.03	NR	NR	NR	NR	NR	11.5(2.1-77.4)	CRT	OS/RFS	SCC	NR
Fu XB et al. (2019)[22]	China	357	279/78	57(34-77)	I-IVa	2.27	NR	2.57	NR	SIS:0/1/2	NR	NR	NR	58(1–84)	surgery	OS	SCC	NLR: 77 50 100 128
Zhang F et al. (2016)[23]	China	468	376/92	60(36-81)	I-III	2.5	117.05	NR	NR	NR	NR	NR	NR	49.1±32.6(3.2-114.5)	surgery	OS/DFS	SCC	NR
Xie X et al. (2016)[24]	China	317	244/73	58.1±8.9(34–76)	I-III	2.1	103	NR	NR	NR	NR	NR	NR	46(36–62)	surgery	DSS	SCC	NR
Wu YF et al. (2019)[25]	China	105	98/7	57.69±8.6(38-81)	I-III	4.35	NR	NR	NR	NR	NR	NR	NR	19.5±14.1	CRT	OS/PFS	SCC	PLR: 44 9 34 18 NLR: 45 8 33 19
Feng JF et	China	483	411/72	59.1±8.0(34-80)	T1-4/N-+	3.5	150	NR	NR	NR	NR	NR	NR	NR	surgery	OS	SCC	NLR:115 63 129

al. (2014)[26]																		176 PLR: 148 72 96 167
Zhu YM et al. (2017)[27]	China	220	117/103	≤60/>60:124/96	T3N0M0	NR	NR	3.364	NR	NR	NR	NR	NR	DFS:40.0(34.2–45.8) OS:53.0(48.0–58.0)	mixed	OS/DFS	SCC	LMR: 81 45 51 43
Song Q et al. (2019)[28]	China	680	582/98	61(56-67)	Ia-IIIc	NR	NR	3.17	NR	NR	NR	NR	NR	NR	mixed	OS/DFS	SCC	LMR: 182 161 135 202
Chen MF et al. (2018)[29]	China	1168	1113/55	(<50/50-64/>64): 344/609/215	≤T2/T3-T4,N0/N+	3	NR	NR	NR	NR	NR	NR	NR	NR	mixed	OS/DFS	SCC	NLR: 567 77 419 105
Duan H et al. (2015)[30]	China	371	276/95	57.7±8.9	Ib-IIIc	3	NR	NR	NR	410	NR	NR	NR	66(49-76)	surgery	CSS/RFS	SCC	NR
Gao GD et al. (2017)[31]	China	1281	988/293	Survival/Dead(634/647) 57.7±8.9/60.2±27.7	0-IV	2.86	NR	NR	NR	NR	NR	NR	NR	NR	mixed	OS	SCC	NR
Han FY et al. (2019)[32]	China	354	267/87	<60/>=60:100/254	I-IV	1.88	NR	NR	NR	NR	NR	NR	NR	26(2-80)	surgery	OS/DFS	SCC/ADC /Others	NR
Hirahara Noriyuki et al. (2018)[33]	Japan	148	132/16	CONUT 0/1/2-3(48/37/11) 61.5±5.4/61.8±5.9/60.4±5.3	Ia-IIIc	3.5	NR	NR	NR	NR	NR	NR	NR	NR	surgery	CSS	SCC	NR
Kosumi K et al. (2016)[34]	Japan	313	248/35	<65/≥65(118/165)	0-IV	1.94	NR	NR	NR	NR	NR	NR	NR	33.6	surgery	OS/CSS	SCC	NR
Lu YJ et al. (2019)[35]	China	315	259/56	59(35-75)	I-IVa	3.18	NR	NR	NR	NR	NR	NR	NR	NR	surgery	OS	SCC	NLR: 87 37 107 84
Nakamura K et al. (2017)[36]	Japan	245	219/26	<65/≥65:110/135	T1a-b/N0-3	2.42	NR	NR	NR	NR	NR	NR	NR	37.2	surgery	OS/DFS	SCC/ADC /Others	NLR: 16 22 16 101
Sharaiha RZ et al. (2011)[37]	USA	295	237/58	62.8	I-IV	5	NR	NR	NR	NR	NR	NR	NR	31(13–61)	surgery	OS/DFS	SCC/ADC /Others	NR
Xiao Q et al. (2016)[38]	China	121	106/15	62(30–76)	I-III	1.77	NR	NR	NR	NR	NR	NR	NR	28.0(1–102)	surgery	OS/RFS	SCC	NLR: 45 13 37 26
Zhou XL et al. (2017)[39]	China	517	407/110	65(36–74)	II-IV	5	NR	NR	NR	NR	NR	NR	NR	17(2-76)	CRT	OS/PFS	SCC	NLR: 188 12 244 69
Arigami T et al. (2015)[40]	Japan	238	210/28	65(37–87)	I-III	3	NR	NR	NR	NR	NR	0/1,2	NR	26(1-182)	surgery	OS	SCC	mGPS: 44 26 54 114
Feng JF et al. (2019)[41]	China	493	420/73	59.1(34–80)	NR	NR	NR	NR	NR	NR	1-2 vs 0	NR	NR	45	surgery	CSS	SCC	NR
Lindenmann J et al.	Austria	174	148/26	61.1(22-81)	T0-4/N0-3	NR	NR	NR	NR	NR	1-2 vs 0	NR	NR	NR	mixed	AC/CSS	ADC/SCC	GPS: 33 6 41 25

(2017)[42]																		
Ma QL et al. (2016)[43]	China	725	539/186	58(32-80)	TNM I/II/III	NR	NR	NR	NR	NR	1-2 vs 0 不清楚	NR	NR	28	surgery	CSS	SCC	NR
Okuno T et al. (2017)[44]	Japan	142	119/12	62(37–75)	(UICC 5th) IIB/III/IVa/IVb	NR	NR	NR	NR	NR	1 vs 0 2 vs 0	NR	NR	NR	CRT	OS	SCC	NR
Sugawara K et al. (2018)[45]	Japan	47	32/15	63(47–81)	I/II/III/Iva/IVb	NR	NR	NR	NR	NR	1 vs 0 2 vs 0	NR	NR	26.5(4.4–97.9)	surgery	OS	SCC/ADC	GPS: 16 1 23 7
Vashist YK et al. (2011)[46]	Germany	495	391/104	63.2(34.5–85.2)	T1-4/N-+/M-+	NR	NR	NR	NR	NR	0 vs 1	NR	NR	NR	surgery	OS/CSS	ADC/SCC	GPS: 188 20 161 66
Hirahara N et al. (2015)[47]	Japan	141	97/12	NR	Ia-IIIc	2.5	NR	NR	NR	NR	1-2 vs 0	NR	NR	NR	surgery	OS	NR	GPS: 19 3 33 31
Kitagawa H et al. (2017)[48]	Japan	140	112/28	65(43–85)	I-IV	NR	NR	NR	NR	NR	1-2 vs 0	NR	NR	36.6	mixed	OS/DFS	SCC/ADC /others	NLR: 25 45 21 49
Jomrich G et al. (2017)[49]	Austria	449	225/58	63(31–88)	UICC stage:0-4	NR	NR	NR	NR	NR	1 vs 0 2 vs 0	1 vs 0 2 vs 0	0.95	63(35-95)	surgery	OS/DFS	SCC/ADC	NR
Kimura J et al. (2016)[50]	Japan	142	131/11	65.1(40–82)	III and IV	NR	NR	NR	NR	NR	1 vs 0 2 vs 0	1 vs 0 2 vs 0	NR	NR	CT+RT	PFS/DFS	SCC	NR
Chen P et al. (2017)[51]	China	163	134/29	57(31–79)	II/IV	NR	NR	NR	NR	NR	NR	0 vs 1 0 vs 2	NR	NR	radiotherapy	OS	SCC	NR
Otowa Y et al. (2016)[52]	Japan	100	88/12	68(44–82)	II/III	NR	NR	NR	NR	NR	NR	Pre-NAC 0 vs 1/2 Post-NAC 0 vs 1	NR	20.8(4.6–79.5)	surgery	OS	SCC	NR
Tian R et al. (2016)[53]	China	442	331/111	60.0(20.0-88.0)	I/II/III	NR	NR	NR	NR	NR	NR	1-2 vs 0	NR	DFS:35.6(24.3-46.9) OS:57.4(37.8-77.0)	surgery	OS/PFS	SCC	mGPS: 52 30 169 191
Walsh SM et al. (2016)[54]	Ireland	223	187/36	64(30–87)	I/II/III	NR	NR	NR	NR	NR	NR	1-2 vs 0	NR	21	surgery	OS/RFS	ADC	mGPS: 34 15 70 104
Zhang P et al. (2014)[55]	China	212	166/46	60.0(37-81)	I-II/ III/IV	NR	NR	NR	NR	NR	NR	0 vs 1 vs 2	NR	35.0(2-72)	radiotherapy	OS/PFS	SCC	mGPS: 103 19 59 31
Sun P et al. (2013)[56]	China	502	382/120	58.23±9.33	I–IV	NR	NR	NR	50	NR	NR	NR	NR	30	NR	OS	SCC	PNI: 92 47 194 169
Chen S al. (2016)[57]	China	308	268/40	NR	I–III	3.5	150	NR	45	NR	GPS1 vs	NR	NR	NR	Surgery		SCC	PNI: 83 19 129 74

											GPS0, GPS2 vs GPS0							GPS: 105 24 110 69 PLR:: 108 27 107 66
Okadome K et al. (2018)[58]	Japan	337	300/37	65.9	I–IV	NR	NR	NR	45	NR	NR	NR	NR	60	Surgery	OS/CSS	SCC/ADC /Others	PNI: 63 24 62 92
Migita K et al. (2018)[59]	Japan	137	76/16	NR	T1-T4/N0-N+	2.2	NR	NR	47	NR	NR	NR	NR	NR	mixed	OS	SCC	NR
Zhang H et al. (2019)[60]	China	266	172/94	67(48-87)	I–III	3.06	145.2	NR	NR	NR	NR	NR	0.13	NR	curative RT only or concurrent CRT	OS	SCC	NLR: 107 28 68 63 PLR: 100 33 74 59 CAR: 104 10 59 93
Otowa Y et al. (2017)[61]	Japan	149	129/20	66.9±8.3	II/III	NR	NR	NR	NR	NR	NR	NR	0.030	NR	Mixed	OS	SCC	NR
Liu XQ et al. (2019)[62]													0.15		radical radiotherapy	OS		NR
Shao YJ et al. (2015)[63]	China	916 primary:633 validation:283	primary :484/149 validation:211/72	Primary:60(37–83) Validation:61(38–84)	I–III	1.7	120	3.57	NR	NR	0/1/2	0/1/2	0.06/0.12	39(3-146.2)	Surgery	OS	SCC	NR
Liu DQ et al. (2016)[64]	China	260	217/43	59(39–83)	I-IV	NR	NR	NR	NR	NR	0/1/2	NR	NR	40.5 (2–91)	surgery	OS/DFS	SCC	NR
Wang CY et al. (2012)[65]	Taiwan, China	271	261/10	NR	I-IV	NR	NR	NR	NR	NR	0/1,2	NR	NR	30 (5–81)	mixed	OS	SCC/ADC	NR
Feng JF et al. (2014)[66]	China	493	420/73	59.1(34 to 80)	T1-4a/N-+	NR	NR	NR	NR	NR	2/0	NR	NR	45	surgery	NR	SCC	NR
Lindenmann J et al. (2014)[67]	Austria	214	181/33	67 ± 11.84(21–93)	III-IV	NR	NR	NR	NR	NR	0/1/2	NR	NR	NR	CT+RT	NR	SCC/ADC	NR
Matsuda S et al. (2015)[68]	Japan	199	180/19	62.9 ± 8.29	I-IV	NR	NR	NR	NR	NR	0/1/2	NR	NR	28.5	mixed	OS/DFS	SCC/ADC /Others	NR
Liu XM et al. (2017)[69]	China	162	127/35	63 (38–70)	II-III	NR	NR	4.02	NR	NR	NR	NR	NR	23.3 (8–43.7)	mixed	OS/PFS	SCC	LMR: 61 20 43 38
Tian R et al. (2016)[70]	China	260	193/67	59.0 (20.0-87.0)	I-III	NR	NR	NR	NR	NR	NR	0/1,2	NR	46.5	surgery	OS/DFS	SCC	NR
Nakamura M et al. (2014)[71]	Japan	168	135/33	67(47–85)	0-IV	NR	NR	NR	NR	NR	NR	0 vs 2	NR	39(5–99)	mixed	NR	SCC	NR

Han LH et al. (2015)[72]	China	206	165/41	60(32-84)	I-IV/T1-4/N0-3	NR	NR	2.9	45.5	NR	NR	NR	NR	39.5(3-71)	surgery	OS/DFS	SCC	NR
Miyazaki T et al. (2016)[73]	Japan	192	173/19	65.8(42-86)	I-IV/T1-4/N0-3/M0-1	3.49	NR	NR	47.7	NR	NR	NR	NR	26.5(1-108)	surgery	OS	NR	PNI: 31 34 39 88

Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; EC, esophageal carcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, c-reactive protein-to-albumin ratio; SII, systemic inflammation index; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative

Reference

[1] Wang L, Wang C, Wang JF, Huang XC, Cheng YF. A novel systemic immune-inflammation index predicts survival and quality of life of patients after curative resection for esophageal squamous cell carcinoma. Journal of Cancer Research and Clinical Oncology, 2017, 143(10):2077-2086.

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Table 1 Subgroup analysis and meta analysis of 8 indicators in OS, CSS, and DFS.

	OS					CSS					DFS				
	N	HR(95% CI), *P*	I2(%), *P*	Begg's P, Egger's P	P-reg	N	HR(95% CI), *P*	I2(%), *P*	Begg's P, Egger's P	P-reg	N	HR(95% CI), *P*	I2(%), *P*	Begg's P, Egger's P	P-reg
PNI															
Overall	11	1.51(1.36-1.68),<0.001	45.8, 0.048	0.036, 0.188											
Country															
China	4	1.45(1.27-1.64),<0.001	36.9, 0.190	0.497, 0.092	0.184										
Non-China	7	1.82(1.38-2.40),<0.001	51.4, 0.054	0.099, 0.006											
Sample size															
<255	7	1.69(1.19-2.40), 0.003	66.8, 0.006	0.099, 0.058	0.797										
≥255	4	1.52(1.34-1.72),<0.001	0.0, 0.949	0.174, 0.052											
Cut-off value															
<46	5	1.68(1.13-2.50), 0.010	59.5, 0.043	0.050, 0.432	0.774										
≥46	6	1.49(1.33-1.67),<0.001	39.9, 0.139	0.348, 0.288											
Treatment															
Surgery	7	1.46(1.20-1.78),<0.001	54.4, 0.041	0.752, 0.293	Ref										
Mixed	3	2.18(1.52-3.11),<0.001	0.0, 0.649	0.602, 0.448	0.139										
NR	1	1.50(1.16-1.93), NR	NR	NR	0.906										
Pathology															
SCC	9	1.56(1.39-1.76),<0.001	41.5, 0.091	0.061, 0.184	0.144										
Mixed	1	1.67(1.14-2.44), NR	NR	NR	0.231										
NR	1	1.09(0.80-1.49), NR	NR	NR	Ref										
Clinical stage															
0-III	5	1.62(1.41-1.86),<0.001	32.2, 0.207	0.050,<0.001	0.229										
0-IV	6	1.41(1.10-1.80), 0.006	52.4, 0.062	0.348, 0.687											
Follow-up															
<36	4	1.46(1.15-1.86), 0.002	53.4, 0.092	1.000, 0.523	0.962										
≥36	4	1.45(1.23-1.70),<0.001	46.1, 0.135	1.000, 0.801	Ref										
NR	3	2.26(1.63-3.14),<0.001	0.0, 0.988	0.602, 0.337	0.014										
Age															
<63.4	4	1.45(1.27-1.64),<0.001	36.9, 0.190	0.497, 0.092	Ref										
≥63.4	6	1.77(1.31-2.41),<0.001	55.0, 0.049	0.039, 0.016	0.270										
NR	1	2.21(1.28-3.82), NR	NR	NR	0.249										
Sex ratio															

<4.75	5	1.46(1.29-1.66),<0.001	25.1, 0.254	0.624, 0.545	0.253										
≥4.75	6	1.84(1.34-2.53),<0.001	59.1, 0.032	0.091, 0.011											
NLR															
Overall	34	1.43(1.30-1.58),<0.001	61.7,<0.001	0.113, 0.428		8	1.21(1.04-1.41), 0.011	43.4, 0.089	0.621, 0.695		7	1.39(1.10-1.75), 0.005	60.9, 0.018	0.453, 0.344	
Country															
China	23	1.43(1.30-1.57),<0.001	51.5, 0.002	0.107, 0.399	0.883	4	1.15(0.97-1.36), 0.117	38.8, 0.179	0.174, 0.971	0.436	5	1.22(1.05-1.42), 0.010	0.0, 0.514	0.050, 0.062	0.018
Non-China	11	1.45(1.06-1.98), 0.022	75.5,<0.001	0.484, 0.513		4	1.42(1.06-1.90), 0.020	49.8, 0.113	0.497, 0.376		2	2.43(1.69-3.49),<0.001	0.0, 0.604	NR	
Sample size															
<297	18	1.45(1.19-1.76),<0.001	65.6,<0.001	0.088, 0.192	0.965	2	0.95(0.59-1.54), 0.848	43.6, 0.183	NR	0.395	4	1.56(0.95-2.58), 0.080	78.9, 0.003	0.174, 0.316	0.553
≥297	15	1.42(1.27-1.58),<0.001	60.2, 0.001	0.347, 0.809	Ref	6	1.24(1.06-1.45), 0.006	47.5, 0.090	0.091, 0.138		3	1.29(1.08-1.54), 0.005	0.0, 0.799	0.117, 0.089	
NR	1	1.84(1.21-2.83), NR	NR	NR	0.466	NR	NR	NR	NR		NR	NR	NR	NR	
Cut-off value															
<2.5	16	1.38(1.20-1.58),<0.001	56.9, 0.003	0.072, 0.082	0.563	3	1.43(1.04-1.97), 0.030	66.5, 0.051	0.602, 0.268	0.493	4	1.34(0.94-1.91), 0.103	69.2, 0.021	1.000, 0.704	0.763
≥2.5	18	1.48(1.28-1.71),<0.001	62.5,<0.001	0.733, 0.623		5	1.16(0.98-1.37), 0.084	21.9, 0.275	0.142, 0.737		3	1.47(1.03-2.11), 0.034	61.8, 0.073	0.117, 0.377	
Treatment															
Surgery	24	1.32(1.19-1.48),<0.001	56.9,<0.001	0.215, 0.290	Ref	8	1.21(1.04-1.41), 0.010	43.4, 0.089	0.621, 0.695		7	1.39(1.10-1.75), 0.005	60.9, 0.018	0.453, 0.344	
CRT	3	1.79(1.51-2.13),<0.001	0.0, 0.704	0.602, 0.960	0.090	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mixed	7	1.73(1.51-1.99),<0.001	39.3, 0.130	0.176, 0.779	0.062	NR	NR	NR	NR		NR	NR	NR	NR	
Pathology															
SCC	27	1.42(1.28-1.57),<0.001	56.0,<0.001	0.084, 0.517	0.683	8	1.21(1.04-1.41), 0.011	43.4, 0.089	0.621, 0.695		5	1.22(1.05-1.42), 0.010	0.0, 0.514	0.050, 0.062	0.018
Mixed	4	1.75(0.84-3.66), 0.137	87.9,<0.001	1.000, 0.661	0.420	NR	NR	NR	NR	NR	2	2.43(1.69-3.49),<0.001	0.0, 0.604	NR	
NR	3	1.36(1.13-1.65), 0.002	0.0, 0.509	0.602, 0.452	Ref	NR	NR	NR	NR		NR	NR	NR	NR	
Clinical stage															
0-III	22	1.31(1.22-1.41),<0.001	43.0, 0.018	0.019, 0.039	0.262	6	1.12(0.96-1.32), 0.159	30.4, 0.207	0.573, 0.701	0.083	5	1.35(1.15-1.57),<0.001	36.4, 0.179	0.624, 0.229	0.963
0-IV	12	1.56(1.28-1.89),<0.001	71.1,<0.001	0.784, 0.600		2	1.80(1.24-2.60), 0.002	0.0, 0.907	0.317, NR		2	1.40(0.55-3.57), 0.486	89.0, 0.003	0.317, NR	
Follow-up															
<37	12	1.60(1.34-1.91),<0.001	60.5, 0.003	0.493, 0.485	0.079	2	1.80(1.24-2.60), 0.002	0.0, 0.907	0.317, NR	0.105	2	1.40(0.55-3.57), 0.486	89.0, 0.003	0.317, NR	0.963
≥37	10	1.26(1.15-1.38),<0.001	45.4, 0.058	0.531, 0.844	Ref	3	1.11(0.73-1.69), 0.623	67.1, 0.048	0.602, 0.534	0.740	5	1.35(1.15-1.57),<0.001	36.4, 0.179	0.624, 0.229	
NR	12	1.45(1.20-1.76),<0.001	64.8, 0.001	0.217, 0.832	0.307	3	1.06(0.84-1.34), 0.614	0.0, 0.712	0.117, 0.166	Ref	NR	NR	NR	NR	
Age															
<61.1	15	1.37(1.22-1.53),<0.001	53.9, 0.007	0.083, 0.446	Ref	3	1.28(1.02-1.61), 0.033	40.9, 0.184	0.602, 0.932		4	1.28(1.09-1.50), 0.003	0.0, 0.919	0.174, 0.075	Ref
≥61.1	11	1.45(1.16-1.82), 0.001	70.3,<0.001	0.697, 0.636	0.706	NR	NR	NR	NR	0.759	2	1.40(0.55-3.57), 0.486	89.0, 0.003	0.317, NR	0.775
NR	8	1.56(1.16-2.10), 0.003	62.9, 0.009	0.805, 0.875	0.461	5	1.20(0.88-1.62), 0.246	53.4, 0.072	1.000, 0.651		1	2.76(1.50-5.03), NR	NR	NR	0.152
Sex ratio															
<5.12	17	1.38(1.22-1.56),<0.001	62.3,<0.001	0.510, 0.856	0.458	7	1.14(0.96-1.34), 0.129	35.6, 0.157	0.453, 0.417	0.287	6	1.30(1.26-1.50),<0.001	48.4, 0.085	0.573, 0.960	0.123

≥5.12	17	1.52(1.27-1.81),<0.001	62.8,<0.001	0.021, 0.286		1	1.59(1.13-2.24), NR	NR	NR		1	2.76(1.50-5.03), NR	NR	NR	
PLR															
Overall	19	1.26(1.18-1.35),<0.001	29.8, 0.108	0.054, 0.108							5	1.30(1.12-1.51),<0.001	33.0, 0.202	0.142, 0.472	
Country															
China	15	1.26(1.17-1.35),<0.001	42.1, 0.043	0.125, 0.121	0.571						5	1.30(1.12-1.51),<0.001	33.0, 0.202	0.142, 0.472	NR
Non-China	4	1.40(1.07-1.83), 0.016	0.0, 0.854	1.000, 0.771							NR	NR	NR	NR	
Sample size															
<303	10	1.38(1.18-1.62),<0.001	25.5, 0.209	0.245, 0.157	0.341						2	0.99(0.71-1.39), 0.958	0.0, 0.682	0.602, 0.463	0.174
≥303	9	1.24(1.15-1.34),<0.001	33.7, 0.148	0.297, 0.206							3	1.39(1.18-1.64),<0.001	24.5, 0.266	NR	
Cut-off value															
<143	10	1.24(1.14-1.35),<0.001	11.7, 0.335	0.006, 0.001	0.567						3	1.39(1.18-1.64),<0.001	24.5, 0.266	NR	0.174
≥143	9	1.33(1.17-1.52),<0.001	44.7, 0.071	1.000, 0.858							2	0.99(0.71-1.39), 0.958	0.0, 0.682	0.602, 0.463	
Treatment															
Surgery	15	1.24(1.16-1.33),<0.001	24.2, 0.186	0.458, 0.553	0.079						5	1.30(1.12-1.51),<0.001	33.0, 0.202	0.142, 0.472	NR
Mixed	4	1.61(1.26-2.06),<0.001	1.6, 0.384	0.174, 0.086							NR	NR	NR	NR	
Pathology															
SCC	17	1.27(1.19-1.37),<0.001	33.2, 0.091	0.070, 0.122	0.432						5	1.30(1.12-1.51),<0.001	33.0, 0.202	0.142, 0.472	
Mixed	1	1.55(0.95-2.59), NR	NR	NR	0.356						NR	NR	NR	NR	NR
NR	1	1.12(0.87-1.43), NR	NR	NR	Ref						NR	NR	NR	NR	
Clinical stage															
0-III	15	1.27(1.18-1.36),<0.001	34.7, 0.091	0.033, 0.039	0.733						4	1.34(1.15-1.57),<0.001	37.6, 0.187	0.497, 0.709	0.461
0-IV	4	1.21(0.94-1.57), 0.139	24.5, 0.265	0.497, 0.205							1	1.05(0.69-1.60), NR	NR	NR	
Follow-up															
<39	4	1.17(1.01-1.36), 0.041	18.8, 0.296	0.497, 0.311	Ref						1	1.05(0.69-1.60), NR	NR	NR	0.461
≥39	8	1.19(1.09-1.30),<0.001	0.0, 0.974	0.458, 0.520	0.855						4	1.34(1.15-1.57),<0.001	37.6, 0.187	0.497, 0.709	
NR	7	1.71(1.46-2.02),<0.001	0.0, 0.682	0.293, 0.441	0.004						NR	NR	NR	NR	
Age															
<61.2	12	1.26(1.17-1.35),<0.001	41.5, 0.065	0.100, 0.097	Ref						4	1.34(1.15-1.57),<0.001	37.6, 0.187	0.497, 0.709	0.461
≥61.2	6	1.33(1.10-1.61), 0.003	21.9, 0.269	0.348, 0.470	0.698						1	1.05(0.69-1.60), NR	NR	NR	
NR	1	1.27(0.76-2.12), NR	NR	NR	0.994						NR	NR	NR	NR	
Sex ratio															
<4.55	8	1.22(1.12-1.33),<0.001	0.0, 0.863	1.000, 0.810	0.265						4	1.34(1.15-1.57),<0.001	37.6, 0.187	0.497, 0.709	0.461
≥4.55	11	1.41(1.17-1.69),<0.001	51.4, 0.024	0.102, 0.213							1	1.05(0.69-1.60), NR	NR	NR	
LMR															
Overall	13	1.37(1.14-1.65), 0.001	84.9,<0.001	0.028, 0.167							6	1.08(0.85-1.39), 0.522	79.8,<0.001	0.573, 0.838	

Country											
China	12	1.35(1.11-1.63), 0.002	85.7,<0.001	0.028, 0.229	0.525	6	1.08(0.85-1.39), 0.522	79.8,<0.001	0.573, 0.838	NR
Non-China	1	1.87(1.09-3.23), NR	NR	NR		NR	NR	NR	NR	
Sample size										
<280	7	1.86(1.36-2.55),<0.001	75.4,<0.001	0.881, 0.609	0.006	3	1.44(1.19-1.76),<0.001	0.0, 0.686	0.117, 0.290	0.085
≥280	6	1.09(0.97-1.22), 0.168	54.1, 0.053	0.348, 0.357		3	0.81(0.54-1.20), 0.296	87.0,<0.001	0.117, 0.013	
Cut-off value										
<3.57	6	1.65(1.11-2.47), 0.014	91.1,<0.001	0.851, 0.191	0.174	4	1.18(1.08-1.29),<0.001	49.5, 0.115	0.042, 0.025	0.034
≥3.57	7	1.17(0.97-1.42), 0.110	71.1, 0.002	0.293, 0.627		2	0.65(0.38-1.11), 0.116	73.7, 0.051	NR	
Treatment										
Surgery	9	1.20(1.02-1.41), 0.033	62.2, 0.007	0.144, 0.496	Ref	4	1.00(0.61-1.62), 0.984	86.3,<0.001	1.000, 0.995	
CCRT	1	3.60(2.66-4.88), NR	NR	NR	0.006	NR	NR	NR	NR	0.651
Mixed	3	1.36(1.01-1.83), 0.045	73.1, 0.024	0.117, 0.179	0.539	2	1.14(1.04-1.25), 0.005	12.4, 0.285	NR	
Pathology										
SCC	13	1.37(1.14-1.65), 0.001	84.9,<0.001	0.028, 0.167	NR	6	1.08(0.85-1.39), 0.522	79.8,<0.001	0.573, 0.838	NR
Mixed	NR	NR	NR	NR		NR	NR	NR	NR	
Clinical stage										
0-III	11	1.46(1.20-1.77),<0.001	84.7,<0.001	0.010, 0.055	0.176	4	1.15(0.92-1.45), 0.219	73.5, 0.010	0.174, 0.779	0.484
0-IV	2	0.93(0.39-2.21), 0.875	90.2, 0.001	0.317, NR		2	0.84(0.28-2.54), 0.754	92.2,<0.001	0.317, NR	
Follow-up										
<39	4	1.67(0.77-3.65), 0.198	94.3,<0.001	1.000, 0.505	0.429	2	0.89(0.26-3.02), 0.848	93.5,<0.001	0.317, NR	Ref
≥39	7	1.20(1.09-1.32),<0.001	0.0, 0.524	0.004, 0.002	0.891	3	1.15(0.79-1.66), 0.466	78.2, 0.010	0.117, 0.295	0.661
NR	2	1.12(1.02-1.23), 0.014	0.0, 0.515	0.317, NR	Ref	1	1.12(1.02-1.24), NR	NR	NR	0.767
Age										
<61.5	7	1.16(1.08-1.24),<0.001	12.9, 0.331	0.024, 0.044	Ref	4	1.17(0.92-1.50), 0.208	75.0, 0.007	0.174, 0.723	0.104
≥61.5	4	1.59(0.67-3.93), 0.312	94.3,<0.001	0.497, 0.692	0.373	1	0.47(0.28-0.78), NR	NR	NR	Ref
NR	2	1.46(1.12-1.90), 0.005	5.1, 0.305	0.317, NR	0.544	1	1.33(0.99-1.79), NR	NR	NR	0.119
Sex ratio										
<4.32	7	1.21(1.10-1.33),<0.001	21.5, 0.266	0.004, 0.005	0.575	3	1.15(0.79-1.66), 0466	78.2, 0.010	0.117, 0.295	0.708
≥4.32	6	1.50(0.91-2.46), 0.109	93.1,<0.001	0.851, 0.462		3	0.99(0.60-1.65), 0.969	87.1,<0.001	0.602, 0.808	
SII										
Overall	7	1.46(1.30-1.65),<0.001	41.0, 0.118	0.099, 0.113						
Country										
China	6	1.53(1.27-1.85),<0.001	50.5, 0.073	0.091, 0.082	0.890					
Non-China	1	1.65(0.74-3.96), NR	NR	NR						

Sample size														
<298	3	2.31(1.61-3.33),<0.001	0.0, 0.655	0.602, 0.400	0.047									
≥298	4	1.38(1.22-1.57),<0.001	0.0, 0.481	0.497, 0.490										
Cut-off value														
<410	3	1.31(1.11-1.54), 0.001	0.0, 0.372	0.117, 0.052	0.140									
≥410	4	1.67(1.40-1.99),<0.001	30.6, 0.229	0.497, 0.595										
Treatment														
Surgery	6	1.45(1.28-1.64),<0.001	45.0, 0.106	0.188, 0.204	0.428									
CRT	1	2.29(0.98-5.30), NR	NR	NR										
Pathology														
SCC	6	1.53(1.27-1.85),<0.001	50.5, 0.073	0.091, 0.082	0.890									
Mixed	1	1.65(0.74-3.96), NR	NR	NR										
Clinical stage														
0-III	5	1.40(1.23-1.59),<0.001	0.0, 0.435	0.327, 0.181	0.068									
0-IV	2	2.32(1.55-3.48),<0.001	0.0, 0.358	0.317, NR										
Follow-up														
<36	1	2.29(0.98-5.30), NR	NR	NR	0.469									
≥36	4	1.54(1.20-1.96), 0,001	66.6, 0.029	0.174, 0.098	0.908									
NR	2	1.46(1.08-1.98), 0.013	0.0, 0.771	0.317, NR	Ref									
Age														
<63.0	3	1.37(1.19-1.58),<0.001	16.6, 0.301	0.602, 0.607	Ref									
≥63.0	2	2.32(1.55-3.48),<0.001	0.0, 0.358	0.317, NR	0.084									
NR	2	1.53(1.13-2.06), 0.006	0.0, 0.319	0.317, NR	0.580									
Sex ratio														
<4.55	3	1.40(1.20-1.64),<0.001	46.1, 0.156	0.602, 0.475	0.646									
≥4.55	4	1.55(1.29-1.87),<0.001	48.0, 0.123	0.174, 0.468										
GPS														
Overall	15	2.35(1.99-2.76),<0.001	36.5, 0.078	0.729, 0.838		5	1.74(1.58-1.92),<0.001	45.7, 0.118	0.221, 0.271		5	2.44(1.28-4.67), 0.007	57.5, 0.052	1.000, 0.751	
Country														
China	4	2.23(1.57-3.17),<0.001	7.5, 0.356	0.497, 0.323	0.952	5	1.74(1.58-1.92),<0.001	45.7, 0.118	0.221, 0.271	NR	1	2.75(0.37-20.31), NR	NR	NR	0.931
Non-China	11	2.38(1.98-2.86),<0.001	46.5, 0.044	0.484, 0.699		NR	NR	NR	NR		4	2.43(1.17-5.06), 0.017	68.0, 0.025	0.497, 0.781	
Sample size														
<237	9	2.47(1.98-3.07),<0.001	48.5, 0.050	0.835, 0.944	0.653	NR	NR	NR	NR	NR	3	3.11(2.03-4.78),<0.001	0.0, 0.399	0.602, 0.499	0.108
≥237	6	2.21(1.73-2.82),<0.001	17.5, 0.300	0.851, 0.814		5	1.74(1.58-1.92),<0.001	45.7, 0.118	0.221, 0.271		2	1.06(0.53-2.14), 0.867	0.0, 0.320	NR	
Cut-off value														

1-2 VS 0	7	2.49(1.95-3.18),<0.001	39.0, 0.132	0.293, 0.232	0.821	3	1.69(1.49-1.90),<0.001	55.0, 0.108	0.602, 0.765	0.803	1	4.92(2.12-11.64), NR	NR	NR	0.303
2 VS 0	8	2.24(1.80-2.78),<0.001	40.6, 0.108	0.805, 0.553		2	1.84(1.56-2.17),<0.001	54.7, 0.137	NR		4	1.95(1.30-2.93), 0.001	47.5, 0.126	0.497, 0.866	
Treatment															
Surgery	8	2.16(1.73-2.70),<0.001	52.2, 0.041	0.621, 0.575	Ref	5	1.74(1.58-1.92),<0.001	45.7, 0.118	0.221, 0.271		2	1.06(0.53-2.14), 0.867	0.0, 0.320	0.317, NR	Ref
CRT	2	2.81(1.37-5.76), 0..005	76.1, 0.041	NR	0.449	NR	NR	NR	NR	NR	1	2.53(1.49-4.28), NR	NR	NR	0.192
Mixed	5	2.42(1.73-3.73),<0.001	0.0, 0.786	0.624, 0.364	0.730	NR	NR	NR	NR		2	4.72(2.24-9.95),<0.001	0.0, 0.843	NR	0.104
Pathology															
SCC	5	2.17(1.59-2.96),<0.001	40.6, 0.151	0.624, 0.620	0.706	5	1.74(1.58-1.92),<0.001	45.7, 0.118	0.221, 0.271		2	2.54(1.53-4.23),<0.001	0.0, 0.936	NR	0.945
Mixed	8	2.65(2.12-3.31),<0.001	44.3, 0.083	0.621, 0.847	0.342	NR	NR	NR	NR	NR	3	2.50(0.74-8.47), 0.141	78.1, 0.010	0.602, 0.680	
NR	2	1.89(1.31-2.74), 0.001	0.0, 0.786	NR	Ref	NR	NR	NR	NR		NR	NR	NR	NR	
Clinical stage															
0-III	4	2.16(1.63-2.85),<0.001	0.0, 0.511	0.174, 0.201	0.741	5	1.74(1.58-1.92),<0.001	45.7, 0.118	0.221,0.271	NR	NR	NR	NR	NR	NR
0-IV	11	2.45(2.00-3.00),<0.001	47.9, 0.038	0.938, 0.933		NR	NR	NR	NR		5	2.44(1.28-4.67), 0.007	57.5, 0.052	1.000, 0.751	
Follow-up															
<40	5	3.30(2.16-5.05),<0.001	16.0, 0.312	0.624, 0.701	0.027	1	1.63(1.16-2.29), NR	NR	NR	0.515	2	4.72(2.24-9.95),<0.001	0.0, 0.843	NR	0.104
≥40	4	1.56(1.11-2.20), 0.011	21.0, 0.284	0.497, 0.860	Ref	3	1.75(1.47-2.08),<0.001	64.0, 0.062	0.297, NR	0.384	2	1.06(0.53-2.14), 0.867	0.0, 0.320	0.317, NR	Ref
NR	6	2.51(2.04-3.08),<0.001	3.8, 0.392	0.851, 0.847	0.052	1	1.18(0.64-2.17), NR	NR	NR	Ref	1	2.53(1.49-4.28), NR	NR	NR	0.192
Age															
<62.1	5	2.15(1.66-2.78),<0.001	0.0, 0.490	0.050, 0.074	0.821	4	1.76(1.59-1.94),<0.001	48.1, 0.123	0.308, 0.542		1	2.75(0.37-20.31), NR	NR	NR	0.931
≥62.1	8	2.46(1.65-3.68),<0.001	59.6, 0.015	0.805, 0.690	0.632	NR	NR	NR	NR	0.337	4	2.43(1.17-5.06), 0.017	68.0, 0.025	0.497, 0.781	
NR	2	2.03(1.15-3.58), 0.014	0.0, 0.972	0.317, NR	Ref	1	1.18(0.64-2.17), NR	NR	NR		NR	NR	NR	NR	
Sex ratio															
<5.48	8	2.51(1.70-3.70),<0.001	51.9, 0.042	0.322, 0.602	0.690	1	1.63(1.16-2.29), NR	NR	NR	0.866	3	2.23(0.64-7.81), 0.211	76.3, 0.015	0.602, 0.826	0.724
≥5.48	7	2.25(1.80-2.82),<0.001	17.0, 0.300	0.881, 0.572		4	1.70(1.43-2.02),<0.001	58.4, 0.066	0.308, 0.368		2	2.66(1.62-4.37),<0.001	0.0, 0.560	0.317, NR	
mGPS															
Overall	14	1.69(1.49-1.92),<0.001	48.4, 0.022	0.702, 0.354											
Country															
China	8	1.90(1.47-2.46),<0.001	63.2, 0.008	0.083, 0.107	0.370										
Non-China	6	1.52(1.12-2.06), 0.007	10.9, 0.346	0.348, 0.795											
Sample size															
<212	6	2.50(1.91-3.28),<0.001	0.0, 0.652	0.348, 0.249	0.014										
≥212	8	1.52(1.31-1.75),<0.001	40.1, 0.111	0.805, 0.893											
Cut-off value															
1-2 VS 0	9	1.56(1.35-1.81),<0.001	4.7, 0.077	1.000, 0.736	0.092										
2 VS 0	5	2.23(1.70-2.92),<0.001	31.5, 0.212	0.624, 0.943											

Treatment					
Surgery	8	1.40(1.17-1.68),<0.001	31.2, 0.179	0.805, 0.577	Ref
RT	2	2.12(1.26-3.57), 0.005	73.3, 0.053	NR	0.138
Mixed	4	2.56(1.81-3.62),<0.001	0.0, 0.824	1.000, 0.888	0.030
Pathology					
SCC	11	1.88(1.48-2.40),<0.001	56.7, 0.010	0.815, 0.222	0.383
AD	1	1.24(0.69-2.22), NR	NR	NR	0.932
Mixed	1	1.17(0.53-2.60), NR	NR	NR	Ref
NR	1	1.82(1.17-2.83), NR	NR	NR	0.502
Clinical stage					
0-III	9	1.64(1.26-2.13),<0.001	50.9, 0.038	0.532, 0.227	0.314
0-IV	5	1.89(1.56-2.28),<0.001	38.7, 0.163	1.000, 0.475	
Follow-up					
<39	4	1.56(1.28-1.91),<0.001	0.0, 0.533	0.497, 0.066	Ref
≥39	6	1.64(1.18-2.26), 0.003	54.2, 0.053	0.188, 0.166	0.714
NR	4	2.66(1.98-3.59),<0.001	0.0, 0.783	0.497, 0.550	0.026
Age					
<61.7	8	1.90(1.47-2.46),<0.001	63.2, 0.008	0.083, 0.107	0.370
≥61.7	6	1.52(1.12-2.06), 0.007	10.9, 0.346	0.348, 0.795	
Sex ratio					
<4.91	7	1.77(1.32-2.38),<0.001	64.0, 0.011	0.652, 0.409	0.930
≥4.91	7	1.81(1.44-2.29),<0.001	25.4, 0.235	0.652, 0.680	
CAR					
Overall	10	1.84(1.60-2.10),<0.001	41.8, 0.079	0.531, 0.809	
Country					
China	5	1.90(1.50-2.41),<0.001	55.1, 0.063	1.000, 0.692	0.415
Non-China	4	1.58(1.13-2.20), 0.008	40.9, 0.166	0.497, 0.377	Ref
NR	1	2.46(1.18-5.13), NR	NR	NR	0.360
Sample size					
<283	5	2.06(1.59-2.66),<0.001	0.0, 0.585	0.142, 0.143	0.396
≥283	4	1.71(1.26-2.31), 0.001	65.4, 0.021	0.174, 0.411	Ref
NR	1	2.46(1.18-5.13), NR	NR	NR	0.406
Cut-off value					
<0.13	4	1.63(1.35-1.96),<0.001	0.0, 0.443	0.174, 0.185	0.490
≥0.13	5	2.19(1.78-2.69),<0.001	43.2, 0.133	0.142, 0.271	0.230

NR	1	1.15(0.56-2.70), NR	NR	NR	Ref
Treatment					
Surgery	4	1.79(1.28-2.50), 0.001	62.4, 0.047	0.497, 0.432	0.963
RT	1	2.46(1.18-5.13), NR	NR	NR	0.516
Mixed	5	1.71(1.39-2.11),＜0.001	36.8, 0.176	1.000, 0.632	Ref
Pathology					
SCC	6	1.70(1.44-2.01),＜0.001	21.2, 0.274	0.851, 0.586	0.535
Mixed	2	1.38(0.63-3.03), 0.427	67.2, 0.081	NR	Ref
NR	2	2.44(1.86-3.20),＜0.001	0.0, 0.981	NR	0.134
Clinical stage					
0-III	5	2.01(1.69-2.39),＜0.001	33.5, 0.198	0.624, 0.603	0.230
0-IV	4	1.50(1.19-1.90), 0.001	39.4, 0.175	1.000, 0.791	Ref
NR	1	2.46(1.18-5.13), NR	NR	NR	0.332
Follow-up					
<40	2	1.53(1.25-1.89),＜0.001	0.0, 0.390	0.317, NR	Ref
≥40	2	1.56(0.58-4.16), 0.377	84.7, 0.010	0.317, NR	0.405
NR	6	2.10(1.65-2.68), 0.001	0.0, 0.693	0.348, 0.261	0.213
Age					
<62.2	5	1.90(1.50-2.41),＜0.001	55.1, 0.063	1.000, 0.692	0.415
≥62.2	4	1.58(1.13-2.20), 0.008	40.9, 0.166	0.497, 0.377	Ref
NR	1	2.46(1.18-5.13), NR	NR	NR	0.360
Sex ratio					
<5.5	4	1.53(1.26-1.85),＜0.001	32.8, 0.216	0.497, 0.875	Ref
≥5.5	5	2.21(1.81-2.70),＜0.001	0.0, 0.471	0.014, 0.048	0.045
NR	1	2.46(1.18-5.13), NR	NR	NR	0.285

Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; EC, esophageal carcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, c-reactive protein-to-albumin ratio; SII, systemic inflammation index; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; Ref, reference; P-reg, the P-value of meta regression; NR, not reported.

Table 1. Subgroup and meta regression of sensitivity and specificity of prognostic indicators.

Category	NO. of Trails	Sensitivity (95%)	I^2(%), *P*	P-reg	Specificity (95%)	I^2(%), *P*	P-reg
SII							
Overall	6	0.61(0.48-0.73)	96.2, <0.001		0.60(0.45-0.73)	96.3, <0.001	
Country							
China	5	0.64(0.52-0.76)	96.6, <0.001	0.42	0.57(0.42-0.72)	96.9, <0.001	0.41
Non-China	1	0.46(0.15-0.76)	NR		0.71(0.41-1.00)	NR	
Sample size							
≤298	3	0.65(0.48-0.81)	94.7, <0.001	0.43	0.67(0.49-0.85)	93.0, <0.001	0.28
>298	3	0.59(0.42-0.76)	97.7, <0.001		0.54(0.35-0.74)	97.7, <0.001	
Cut-off value							
≤410	3	0.73(0.66-0.81)	84.1, 0.002	<0.001	0.42(0.38-0.47)	54.7, 0.110	<0.001
>410	3	0.47(0.37-0.57)	90.2, <0.001		0.76(0.72-0.81)	0.0, 0.541	
Treatment							
Surgery	6	0.61(0.48-0.73)	96.2, <0.001	NR	0.60(0.45-0.73)	96.3, <0.001	NR
CRT	0	NR	NR		NR	NR	
Pathology							
SCC	5	0.64(0.52-0.76)	96.6, <0.001	0.42	0.57(0.42-0.72)	96.9, <0.001	0.41
Mixed	1	0.46(0.15-0.76)	NR		0.71(0.41-1.00)	NR	
Clinical stage							
0-III	5	0.61(0.47-0.74)	96.9, <0.001	0.88	0.54(0.40-0.68)	95.9, <0.001	0.10
0-IV	1	0.60(0.30-0.91)	NR		0.78(0.56-1.00)	NR	
Follow-up							
≤36	2	0.66(0.61-0.70)	53.0, 0.145	0.07	0.57(0.52-0.62)	97.6, <0.001	0.94
>36	2	0.57(0.54-0.61)	98.7, <0.001		0.52(0.48-0.56)	98.8, <0.001	
NR	2	0.71(0.65-0.76)	97.0, <0.001		0.55(0.46-0.63)	90.0, 0.002	
Age							
≤63.0	3	0.59(0.42-0.76)	97.7, <0.001	0.93	0.54(0.35-0.74)	97.7, <0.001	0.67
>63.0	2	0.55(0.48-0.62)	77.6, 0.035		0.76(0.70-0.82)	17.4, 0.271	
NR	1	NR	NR		NR	NR	
Sex ratio							
≤4.55	3	0.59(0.42-0.76)	97.7, <0.001	0.93	0.54(0.35-0.74)	97.7, <0.001	0.67
>4.55	3	0.65(0.48-0.81)	94.7, <0.001		0.67(0.49-0.85)	93.0, <0.001	
PNI							
Overall	7	0.51(0.41-0.61)	95.6, <0.001		0.67(0.56-0.77)	95.0, <0.001	
Country							
China	5	0.52(0.40-0.64)	97.0, <0.001	0.82	0.63(0.51-0.76)	95.8, <0.001	0.09
Non-China	2	0.48(0.29-0.68)	0.0, 0.412		0.76(0.60-0.91)	40.1, 0.196	
Sample size							
≤255	2	0.51(0.31-0.71)	54.7, 0.137	0.99	0.72(0.53-0.91)	0.0, 0.612	0.30
>255	5	0.51(0.39-0.63)	97.0, <0.001		0.66(0.53-0.79)	96.4, <0.001	
Cut-off value							
≤46	2	0.44(0.26-0.62)	75.3, 0.044	0.51	0.80(0.67-0.93)	0.0, 0.963	0.01

>46	5	0.53(0.42-0.65)	96.5, <0.001		0.62(0.50-0.73)	95.4, <0.001	
Treatment							
Surgery	5	0.54(0.44-0.65)	94.2, <0.001	0.30	0.65(0.52-0.78)	95.3, <0.001	0.22
Mixed	1	NR	NR		NR	NR	
NR	1	NR	NR		NR	NR	
Pathology							
SCC	5	0.52(0.40-0.64)	97.0, <0.001	0.82	0.63(0.51-0.76)	95.8, <0.001	0.09
Mixed	2	0.48(0.29-0.68)	0.0, 0.412		0.76(0.60-0.91)	40.1, 0.196	
Clinical stage							
0-III	4	0.58(0.47-0.68)	94.8, <0.001	0.17	0.60(0.47-0.73)	93.7, <0.001	0.01
0-IV	3	0.41(0.29-0.53)	84.8, 0.001		0.76(0.65-0.87)	5.0, 0.349	
Follow-up							
≤36	5	0.48(0.36-0.60)	96.1, <0.001	0.64	0.69(0.57-0.82)	94.3, <0.001	0.30
>36	2	0.57(0.39-0.75)	89.2, 0.002		0.62(0.42-0.83)	97.4, <0.001	
Age							
≤63.4	3	0.51(0.35-0.67)	98.2, <0.001	0.88	0.75(0.62-0.88)	97.1, <0.001	0.99
>63.4	2	0.48(0.41-0.55)	0.0, 0.412		0.76(0.70-0.81)	40.1, 0.196	
NR	2	0.44(0.38-0.50)	85.4, 0.009		0.79(0.71-0.86)	0.0, 0.737	
Sex ratio							
≤4.75	4	0.56(0.44-0.68)	97.2, <0.001	0.43	0.59(0.47-0.71)	96.0, <0.001	0.75
>4.75	3	0.45(0.31-0.59)	50.8, 0.131		0.77(0.67-0.88)	11.6, 0.323	
NLR							
Overall	11	0.51(0.47-0.54)	77.1, <0.001		0.70(0.64-0.76)	79.1, <0.001	
Country							
China	8	0.51(0.47-0.55)	83.8, <0.001	0.98	0.70(0.64-0.77)	71.5, 0.001	0.04
Non-China	3	0.50(0.41-0.60)	0.0, 0.800		0.71(0.60-0.81)	91.4, <0.001	
Sample size							
≤297	6	0.56(0.50-0.61)	0.0, 0.462	0.14	0.70(0.62-0.78)	78.8, <0.001	0.03
>297	5	0.48(0.43-0.53)	88.5, <0.001		0.72(0.64-0.79)	83.6, <0.001	
Cut-off value							
≤2.5	3	0.47(0.42-0.53)	33.5, 0.223	0.76	0.75(0.70-0.80)	65.6, 0.055	0.06
>2.5	7	0.51(0.46-0.55)	84.2, <0.001		0.71(0.64-0.78)	75.8, <0.001	
NR	1	NR	NR		NR	NR	
Treatment							
Surgery	7	0.48(0.43-0.52)	0.0, 0.619	0.31	0.71(0.63-0.78)	75.8, <0.001	0.05
Mixed	4	0.53(0.48-0.58)	89.3, <0.001		0.71(0.61-0.81)	85.8, 0.001	
Pathology							
SCC	8	0.51(0.47-0.55)	83.8, <0.001	0.98	0.70(0.64-0.77)	71.5, 0.001	0.04
Mixed	3	0.50(0.41-0.60)	0.0, 0.800		0.71(0.60-0.81)	91.4, <0.001	
Clinical stage							
0-III	6	0.54(0.50-0.58)	55.0, 0.049	0.14	0.70(0.62-0.78)	78.8, <0.001	0.02
0-IV	5	0.46(0.42-0.50)	0.0, 0.642		0.71(0.63-0.79)	83.6, <0.001	
Follow-up							
≤37	4	0.47(0.44-0.51)	65.3, 0.034	NR	0.68(0.61-0.73)	86.9, <0.001	NR

>37	2	0.44(0.38-0.52)	0.0, 0.497		0.76(0.71-0.81)	76.6, 0.039	
NR	5	0.54(0.52-0.57)	80.7, <0.001		0.68(0.65-0.72)	70.5, 0.009	
Age							
≤61.1	4	0.47(0.43-0.51)	37.4, 0.187	0.92	0.72(0.68-0.76)	0.0, 0.861	0.07
>61.1	6	0.53(0.47-0.59)	70.9, 0.004		0.73(0.66-0.80)	84.6, <0.001	
NR	1	NR	NR		NR	NR	
Sex ratio							
≤5.12	5	0.50(0.44-0.55)	78.3, 0.001	0.91	0.70(0.62-0.78)	83.1, <0.001	0.03
>5.12	6	0.51(0.46-0.56)	53.3, 0.058		0.71(0.63-0.78)	79.3, <0.001	
CAR							
Overall	6	0.50(0.38-0.62)	94.8, <0.001		0.84(0.71-0.91)	89.2, <0.001	
Country							
China	4	0.45(0.32-0.59)	95.9, <0.001	0.31	0.87(0.81-0.94)	90.1, <0.001	0.64
Non-China	2	0.60(0.41-0.80)	81.0, 0.022		0.68(0.51-0.85)	38.4, 0.203	
Sample size							
≤283	4	0.60(0.51-0.69)	66.7, 0.029	0.04	0.82(0.70-0.94)	86.7, <0.001	0.61
>283	2	0.33(0.23-0.43)	94.4, <0.001		0.85(0.71-0.98)	95.7, <0.001	
Cut-off value							
≤0.13	4	0.56(0.44-0.68)	87.9, <0.001	0.28	0.77(0.67-0.86)	85.4, <0.001	0.46
>0.13	2	0.37(0.21-0.53)	96.1, <0.001		0.94(0.88-1.00)	0.0, 0.665	
Treatment							
Surgery	2	0.45(0.24-0.66)	98.2, <0.001	0.71	0.85(0.72-0.98)	91.2, 0.001	0.66
Mixed	4	0.53(0.38-0.67)	81.3, 0.001		0.81(0.69-0.93)	87.8, <0.001	
Pathology							
SCC	4	0.53(0.38-0.67)	81.3, 0.001	0.65	0.81(0.69-0.93)	87.8, <0.001	0.25
Mixed	2	0.45(0.24-0.66)	98.2, <0.001		0.85(0.72-0.98)	91.2, 0.001	
Clinical stage							
0-III	3	0.46(0.29-0.63)	97.2, <0.001	0.62	0.91(0.88-0.95)	0.0, 0.814	0.22
0-IV	3	0.54(0.37-0.71)	88.1, <0.001		0.71(0.66-0.76)	29.6, 0.242	
Follow-up							
≤40	1	NR	NR	NR	NR	NR	NR
>40	1	NR	NR		NR	NR	
NR	4	0.60(0.55-0.65)	66.7, 0.029		0.80(0.74-0.85)	86.7, <0.001	
Age							
≤62.2	3	0.39(0.28-0.50)	93.8, <0.001	0.08	0.87(0.77-0.97)	92.3, <0.001	0.08
>62.2	3	0.62(0.50-0.74)	63.3, 0.066		0.78(0.63-0.92)	89.5, <0.001	
Sex ratio							
≤5.5	4	0.56(0.44-0.68)	87.9, <0.001	0.28	0.77(0.67-0.86)	85.4, <0.001	0.46
>5.5	2	0.37(0.21-0.53)	96.1, <0.001		0.94(0.88-1.00)	0.0, 0.665	
PLR							
Overall	11	0.53(0.47-0.59)	88.6, <0.001		0.65(0.60-0.70)	78.9, <0.001	
Country							
China	9	0.50(0.45-0.56)	87.5, <0.001	0.02	0.68(0.64-0.72)	78.8, <0.001	0.64
Non-China	2	0.67(0.55-0.78)	74.5, 0.048		0.52(0.39-0.64)	0.0, 0.331	

Sample size							
≤303	4	0.62(0.54-0.70)	61.2, 0.052	0.02	0.58(0.49-0.68)	37.6, 0.186	0.44
>303	7	0.49(0.43-0.54)	89.5, <0.001		0.68(0.64-0.73)	84.0, <0.001	
Cut-off value							
≤143	5	0.48(0.41-0.56)	93.1, <0.001	0.54	0.62(0.55-0.69)	87.4, <0.001	0.16
>143	5	0.57(0.53-0.60)	28.3, 0.233		0.70(0.66-0.73)	55.1, 0.064	
NR	1	NR	NR		NR	NR	
Treatment							
Surgery	9	0.52(0.46-0.59)	90.4, <0.001	0.44	0.66(0.60-0.71)	83.1, <0.001	0.20
Mixed	2	0.57(0.43-0.71)	0.0, 0.875		0.65(0.52-0.79)	0.0, 0.808	
Pathology							
SCC	10	0.51(0.46-0.56)	86.7, <0.001	0.01	0.67(0.63-0.71)	77.4, <0.001	0.31
Mixed	1	0.73(0.59-0.88)	NR		0.47(0.29-0.65)	NR	
Clinical stage							
0-III	10	0.51(0.46-0.56)	86.7, <0.001	0.01	0.67(0.63-0.71)	77.4, <0.001	0.31
0-IV	1	0.73(0.59-0.88)	NR		0.47(0.29-0.65)	NR	
Follow-up							
≤39	4	0.47(0.45-0.50)	86.9, <0.001	NR	0.62(0.59-0.66)	84.7, <0.001	NR
>39	3	0.47(0.43-0.52)	92.0, <0.001		0.71(0.67-0.76)	73.0, 0.025	
NR	4	0.58(0.55-0.62)	80.1, 0.002		0.66(0.62-0.71)	71.9, 0.014	
Age							
≤61.2	7	0.49(0.43-0.56)	89.8, <0.001	0.58	0.68(0.63-0.73)	83.6, <0.001	<0.001
>61.2	3	0.62(0.57-0.67)	71.0, 0.032		0.58(0.50-0.65)	49.8, 0.137	
NR	1	NR	NR		NR	NR	
Sex ratio							
≤4.55	5	0.46(0.39-0.52)	90.0, <0.001	0.20	0.65(0.58-0.72)	84.5, <0.001	0.04
>4.55	6	0.60(0.53-0.66)	67.9, 0.008		0.67(0.60-0.74)	73.3, 0.002	
GPS							
Overall	6	0.48(0.43-0.54)	44.1, 0.111		0.79(0.72-0.85)	20.0, 0.282	
Country							
China	2	0.51(0.44-0.58)	0.0, 0.372	0.51	0.75(0.67-0.82)	0.0, 0.920	<0.001
Non-China	4	0.47(0.39-0.54)	62.6, 0.045		0.83(0.75-0.90)	23.9, 0.268	
Sample size							
≤237	3	0.41(0.34-0.49)	0.0, 0.663	0.03	0.86(0.78-0.94)	0.0, 0.464	<0.001
>237	3	0.52(0.49-0.56)	0.0, 0.486		0.75(0.70-0.80)	0.0, 0.918	
Cut-off value							
1-2 VS 0	3	0.47(0.39-0.54)	62.0, 0.072	0.51	0.81(0.73-0.89)	59.8, 0.083	<0.001
2 VS 0	3	0.50(0.44-0.57)	35.4, 0.213		0.77(0.69-0.85)	0.0, 0.651	
Treatment							
Surgery	6	0.48(0.43-0.54)	44.1, 0.111	NR	0.79(0.72-0.85)	20.0, 0.282	NR
Mixed	0	NR	NR		NR	NR	
Pathology							
SCC	2	0.51(0.46-0.56)	0.0, 0.372	0.94	0.75(0.68-0.80)	0.0, 0.920	0.01
Mixed	3	0.48(0.40-0.55)	48.8, 0.142		0.79(0.71-0.86)	0.0, 0.714	

NR	1	NR	NR		NR	NR	
Clinical stage							
0-III	4	0.47(0.41-0.54)	43.1, 0.153	0.78	0.79(0.72-0.86)	47.3, 0.127	0.05
0-IV	2	0.51(0.42-0.60)	56.9, 0.128		0.80(0.69-0.91)	0.0, 0.458	
Follow-up							
≤40	1	NR	NR	NR	NR	NR	NR
>40	1	NR	NR		NR	NR	
NR	4	0.50(0.46-0.54)	56.5, 0.076		0.78(0.73-0.83)	41.7, 0.161	
Age							
≤62.1	1	NR	NR		NR	NR	
>62.1	3	0.51(0.47-0.56)	48.8, 0.142	0.65	0.78(0.70-0.85)	0.0, 0.714	0.01
NR	2	0.47(0.37-0.57)	61.2, 0.108		0.81(0.72-0.90)	79.6, 0.027	
Sex ratio							
≤5.48	2	0.51(0.42-0.60)	56.9, 0.128	0.78	0.80(0.69-0.91)	0.0, 0.458	0.05
>5.48	4	0.47(0.41-0.54)	43.1, 0.153		0.79(0.72-0.86)	47.3, 0.127	
LMR							
Overall	7	0.54(0.48-0.61)	84.9, <0.001		0.60(0.54-0.65)	73.5, 0.001	
Country							
China	6	0.53(0.47-0.59)	85.8, <0.001	0.20	0.60(0.55-0.66)	77.4, 0.001	0.94
Non-China	1	0.63(0.47-0.79)	NR		0.55(0.37-0.72)	NR	
Sample size							
≤280	3	0.61(0.53-0.69)	0.0, 0.832	0.04	0.56(0.47-0.65)	49.7, 0.137	0.61
>280	4	0.50(0.44-0.56)	88.8, <0.001		0.62(0.56-0.68)	82.3, 0.001	
Cut-off value							
≤3.57	4	0.56(0.48-0.64)	76.3, 0.006	0.40	0.58(0.52-0.64)	75.8, 0.006	0.38
>3.57	3	0.52(0.42-0.62)	91.2, <0.001		0.63(0.55-0.72)	40.0, 0.189	
Treatment							
Surgery	4	0.51(0.44-0.58)	88.2, <0.001	0.11	0.63(0.57-0.69)	78.0, 0.003	0.53
Mixed	3	0.59(0.51-0.67)	0.0, 0.740		0.56(0.48-0.63)	49.6, 0.137	
Pathology							
SCC	7	0.54(0.48-0.61)	84.9, <0.001	NR	0.60(0.54-0.65)	73.5, 0.001	NR
Mixed	0	NR	NR		NR	NR	
Clinical stage							
0-III	7	0.54(0.48-0.61)	84.9, <0.001	NR	0.60(0.54-0.65)	73.5, 0.001	NR
0-IV	0	NR	NR		NR	NR	
Follow-up							
≤39	2	0.52(0.41-0.64)	74.1, 0.050	0.93	0.59(0.48-0.69)	38.1, 0.204	0.34
>39	4	0.52(0.48-0.56)	90.3, <0.001		0.64(0.59-0.68)	79.3, 0.002	
NR	1	NR	NR		NR	NR	
Age							
≤61.5	4	0.50(0.44-0.56)	88.8, <0.001	0.68	0.62(0.56-0.68)	82.3, 0.001	0.06
>61.5	2	0.61(0.53-0.67)	0.0, 0.554		0.60(0.51-0.70)	26.0, 0.245	
NR	1	NR	NR		NR	NR	
Sex ratio							

≤4.32	4	0.50(0.43-0.57)	87.4, <0.001	0.74	0.59(0.51-0.66)	77.3, 0.004	0.29
>4.32	3	0.59(0.51-0.67)	0.0, 0.643		0.60(0.51-0.68)	78.6, 0.009	
mGPS							
Overall	5	0.46(0.30-0.62)	96.0, <0.001		0.80(0.72-0.86)	76.2, 0.002	
Country							
China	3	0.51(0.31-0.71)	97.8, <0.001	0.44	0.76(0.65-0.87)	86.4, 0.001	0.01
Non-China	2	0.39(0.15-0.62)	68.5, 0.075		0.84(0.76-0.93)	42.6, 0.187	
Sample size							
≤212	2	0.66(0.56-0.76)	0.0, 0.320	0.00	0.68(0.57-0.80)	78.3, 0.032	0.43
>212	3	0.32(0.24-0.41)	86.2, 0.001		0.85(0.82-0.89)	10.1, 0.329	
Cut-off value							
1-2 VS 0	4	0.42(0.26-0.58)	95.6, <0.001	0.31	0.84(0.80-0.89)	0.0, 0.503	<0.001
2 VS 0	1	0.64(0.34-0.94)	NR		0.62(0.47-0.77)	NR	
Treatment							
Surgery	3	0.32(0.24-0.41)	86.2, 0.001	0.00	0.85(0.82-0.89)	10.1, 0.329	0.43
Mixed	2	0.66(0.56-0.76)	0.0, 0.320		0.68(0.57-0.80)	78.3, 0.032	
Pathology							
SCC	4	0.50(0.32-0.67)	96.8, <0.001	0.37	0.78(0.70-0.86)	79.6, 0.002	0.01
Mixed	1	0.33(0.02-0.63)	NR		0.87(0.78-0.97)	NR	
Clinical stage							
0-III	4	0.42(0.26-0.58)	95.6, <0.001	0.28	0.84(0.80-0.89)	0.0, 0.503	0.75
0-IV	1	0.64(0.34-0.94)	NR		0.62(0.47-0.77)	NR	
Follow-up							
≤39	3	0.47(0.25-0.68)	92.3, <0.001	0.99	0.79(0.71-0.88)	84.9, 0.001	0.15
>39	1	NR	NR		NR	NR	
NR	1	NR	NR		NR	NR	
Age							
≤61.7	3	0.51(0.31-0.71)	97.8, <0.001	0.59	0.76(0.65-0.87)	86.4, 0.001	0.38
>61.7	2	0.39(0.15-0.62)	68.5, 0.075		0.84(0.76-0.93)	42.6, 0.187	
Sex ratio							
≤4.91	2	0.42(0.17-0.67)	98.4, <0.001	0.67	0.77(0.64-0.90)	93.0, <0.001	0.35
>4.91	3	0.49(0.28-0.70)	93.5, <0.001		0.82(0.73-0.91)	0.0, 0.376	

Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; EC, esophageal carcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, c-reactive protein-to-albumin ratio; SII, systemic inflammation index; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; Ref, reference; P-reg, the P-value of meta regression; NR, not reported.

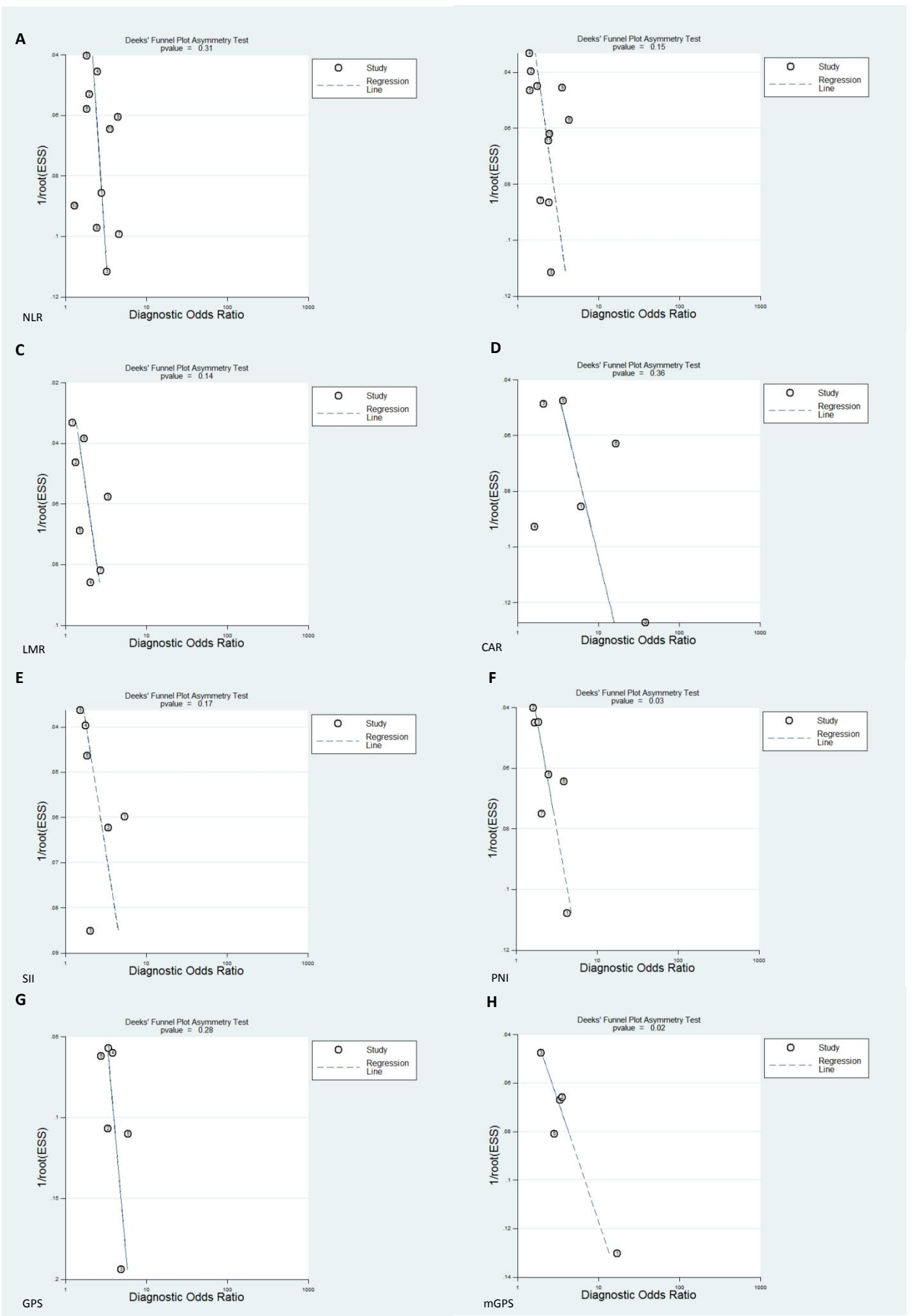
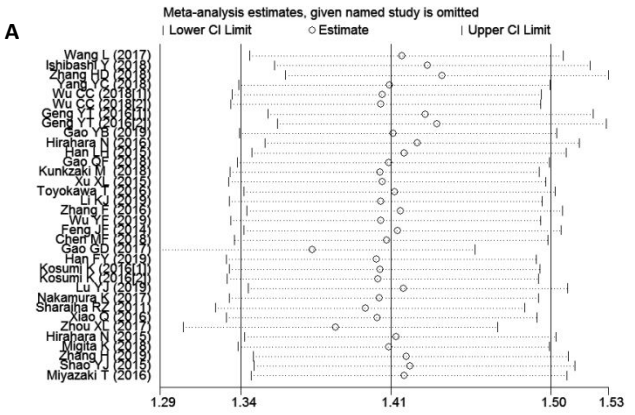
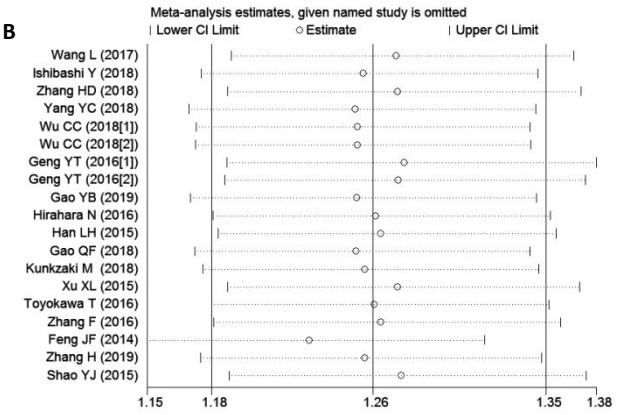
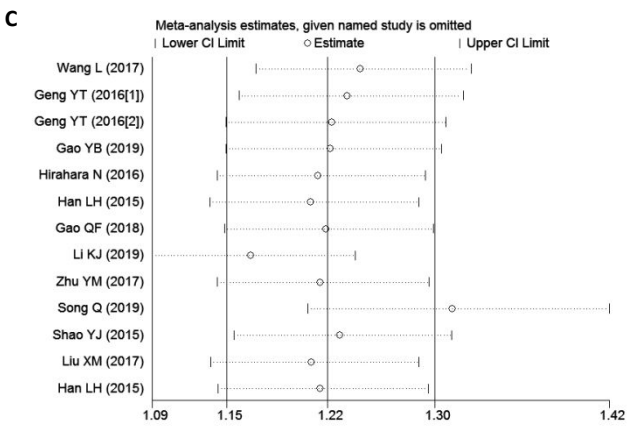
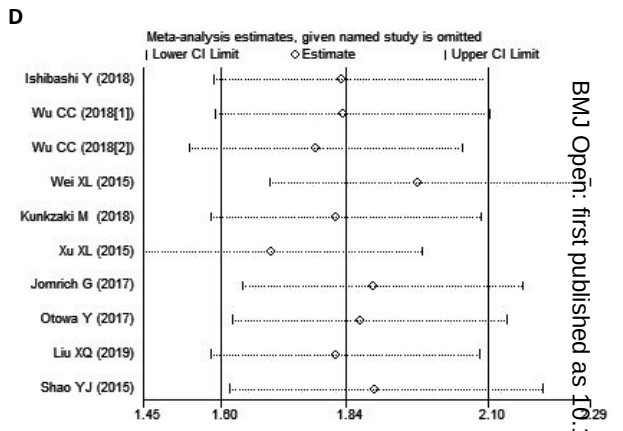


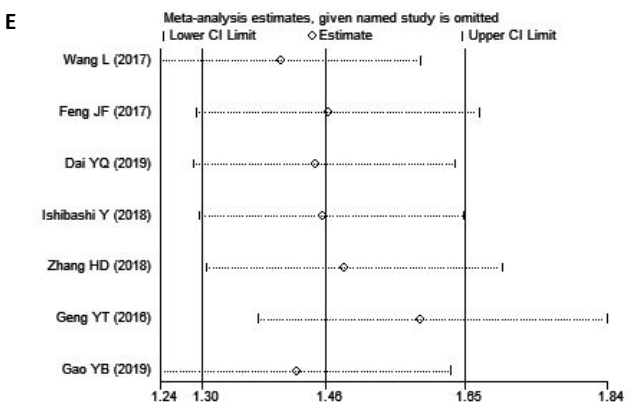
Figure 1. Deek's Funnel evaluating publication bias of DOR of 8 indicators. (A) NLR; (B) PLR; (C) LMR; (D) CAR; (E) SII; (F) PNI; (G) GPS; (H) mGPS.

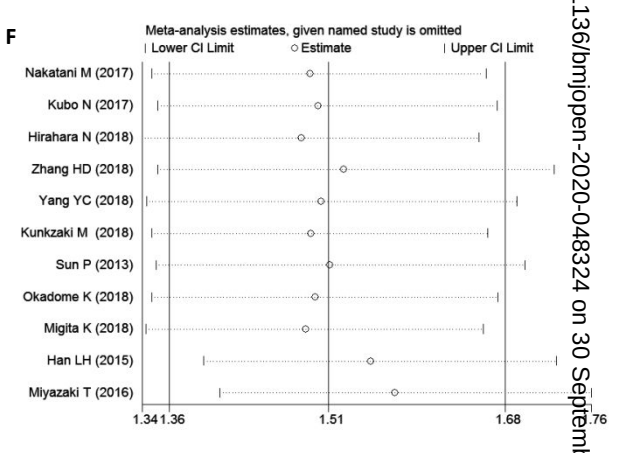


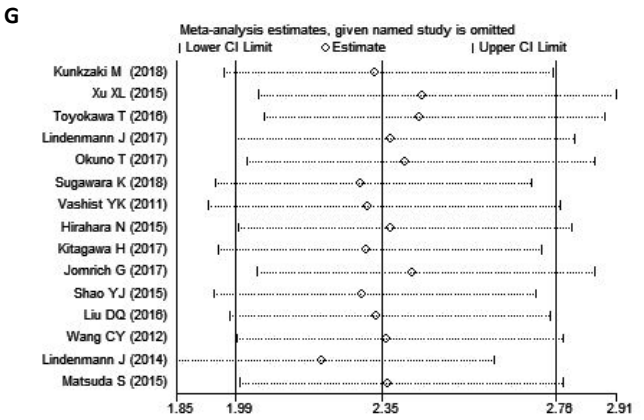


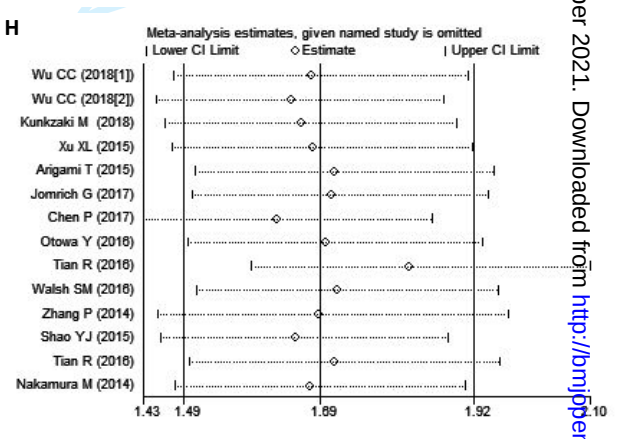












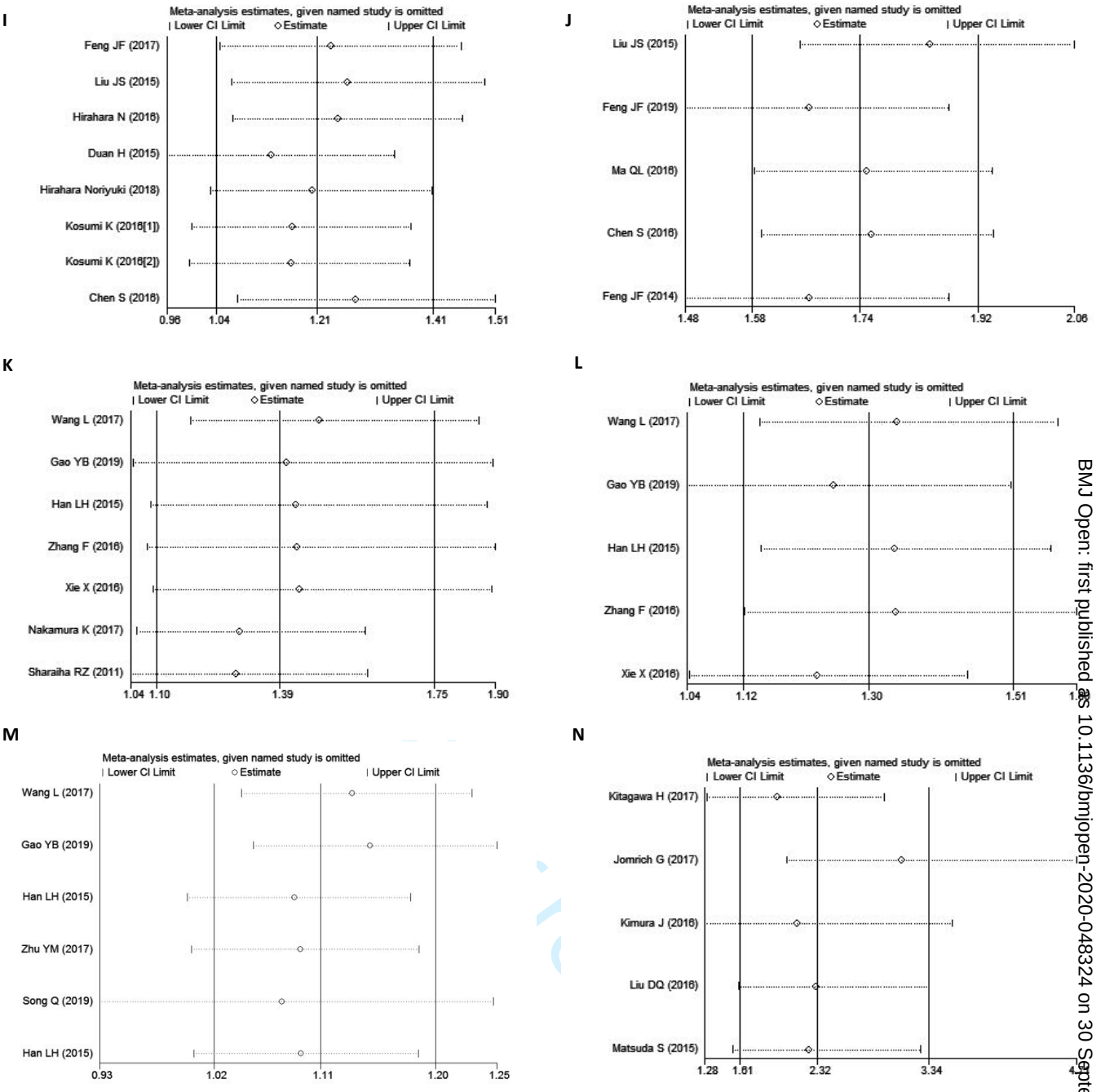


Figure 1. Sensitivity analyses of HR for 8 indicators in OS, CSS and DFS.

(A) NLR-OS; (B) PLR-OS; (C) LMR-OS; (D) CAR-OS; (E) SII-OS; (F) PNI-OS; (G) GPS-OS; (H) mGPS-OS; (I) NLR-CSS; (J) GPS-CSS; (K) NLR-DFS; (L) PLR-DFS; (M) LMR-DFS; (N) GPS-DFS.

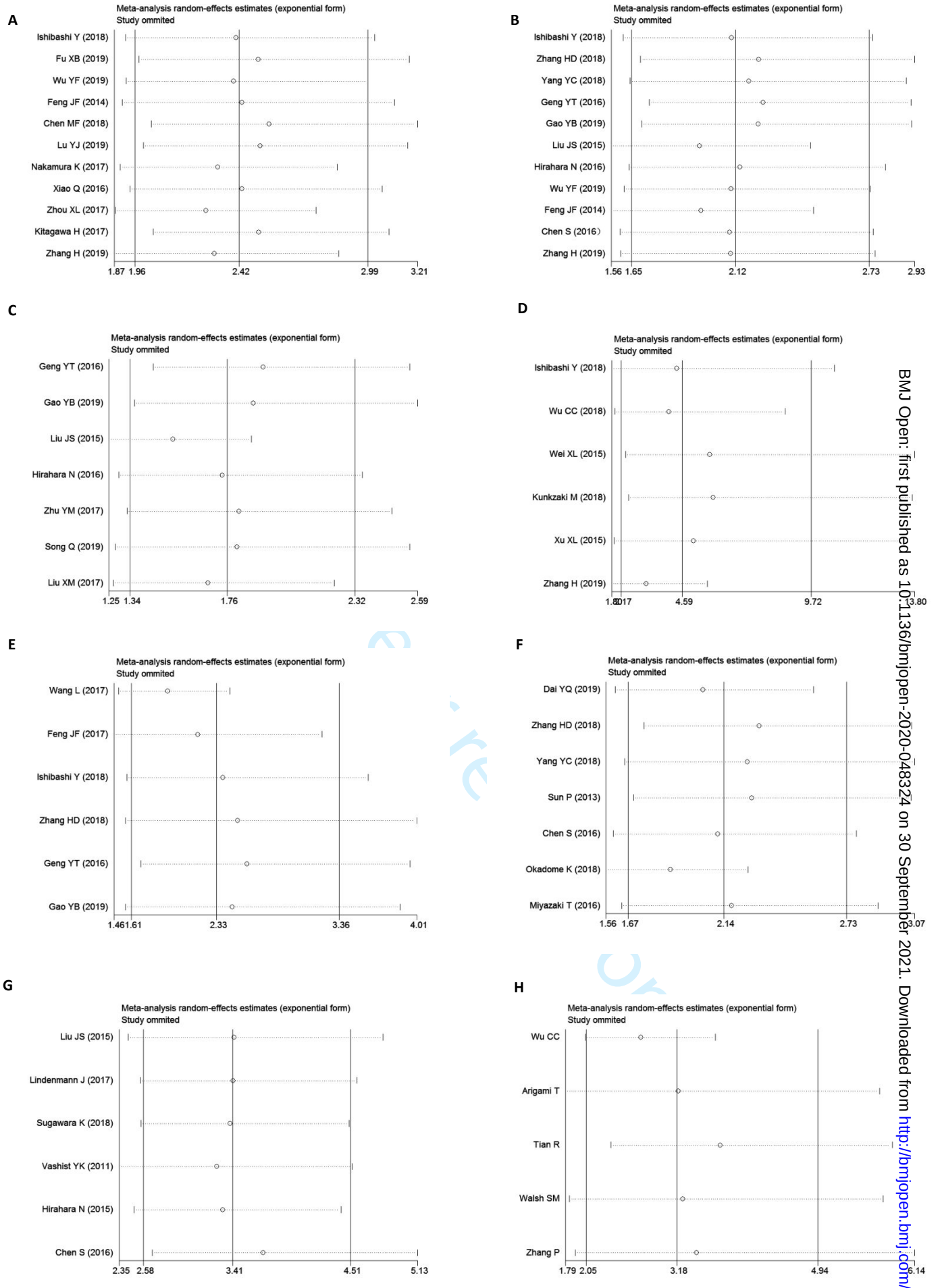


Figure 2. Sensitivity analyses of DOR for 8 indicators in 5-year OS of EC.
(A) NLR; (B) PLR; (C) LMR; (D) CAR; (E) SII; (F) PNI; (G) GPS; (H) mGPS;

Category	Sensitivity	P	Specificity	p	P-LR	p	N-LR	p	DOR	p	AUC
NLR	0.51 [0.47, 0.54]	NA	0.70 [0.64, 0.76]	NA	1.7 [1.5, 2.0]	NA	0.70 [0.66, 0.74]	NA	2.42 [1.96, 2.99]	NA	0.60 [0.56 - 0.64]
PLR	0.53 [0.47, 0.59]	NA	0.65 [0.60, 0.70]	NA	1.5 [1.3, 1.8]	NA	0.72 [0.64, 0.80]	NA	2.12 [1.65, 2.73]	NA	0.63 [0.59 - 0.67]
LMR	0.54 [0.48, 0.61]	NA	0.60 [0.54, 0.65]	NA	1.3 [1.2, 1.6]	NA	0.76 [0.67, 0.87]	NA	1.76 [1.34, 2.32]	NA	0.60 [0.55 - 0.64]
SII	0.61 [0.48, 0.73]	NA	0.60 [0.45, 0.73]	NA	1.5 [1.2, 1.9]	NA	0.65 [0.53, 0.79]	NA	2.33 [1.61, 3.36]	NA	0.64 [0.60 - 0.68]
PNI	0.51 [0.41, 0.61]	NA	0.67 [0.56, 0.77]	NA	1.6 [1.3, 1.9]	NA	0.73 [0.66, 0.81]	NA	2.14 [1.67, 2.73]	NA	0.61 [0.57 - 0.66]
CAR	0.50 [0.38, 0.62]	NA	0.84 [0.71, 0.91]	NA	3.0 [1.7, 5.6]	NA	0.60 [0.46, 0.77]	NA	4.59 [2.17, 9.72]	NA	0.72 [0.68 - 0.75]
GPS	0.48 [0.43, 0.54]	NA	0.79 [0.72, 0.85]	NA	2.3 [1.8, 3.0]	NA	0.65 [0.59, 0.72]	NA	3.41 [2.58, 4.51]	NA	0.67 [0.63 - 0.71]
mGPS	0.46 [0.30, 0.62]	NA	0.80 [0.72, 0.86]	NA	2.3 [1.8, 2.9]	NA	0.68 [0.53, 0.86]	NA	3.18 [2.05, 4.94]	NA	0.75 [0.71 - 0.78]
CAR vs GPS	50% vs 48%	＞0.05	84% vs 79%	＞0.05	3.0 vs 2.3	＞0.05	0.60 vs 0.65	＞0.05	4.59 vs 3.41	＞0.05	**0.72 vs 0.67**
mGPS vs GPS	46% vs 48%	＞0.05	80% vs 79%	＞0.05	2.3 vs 2.3	＞0.05	0.68 vs 0.65	＞0.05	3.18 vs 3.41	＞0.05	**0.75 vs 0.67**
CAR vs mGPS	50% vs 46%	＞0.05	84% vs 80%	＞0.05	3.0 vs 2.3	＞0.05	0.60 vs 0.68	＞0.05	4.59 vs 3.18	＞0.05	0.72 vs 0.75

Table 1. Pair-wise comparisons between modalities for sensitivity, specificity, P-LR, N-LR, DOR and AUC. P-DR, The pooled positive likelihood ratio; N-DR, negative likelihood ratio, DOR, diagnostic odds ratio.

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Inflammation and nutrition-based biomarkers in the prognosis of esophageal cancer: A systematic review and meta-analysis

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Abstract

Background

Accumulating literature has shown the predictive values of inflammation and nutrition-based biomarkers in the prognosis of esophageal cancer but with inconsistent findings.

Method

We performed a meta-analysis to systematically evaluate the predictive value of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), c-reactive protein- to- albumin ratio (CAR), systemic inflammation index (SII), prognostic nutritional index (PNI), Glasgow Prognostic Score (GPS) and modified Glasgow Prognostic Score (mGPS) in esophageal cancer. The outcome indicators include the overall survival (OS), disease-free survival (DFS), and cancer-specificity survival (CSS). We applied pooled hazard ratio (HR), sensitivity, specificity, positive likelihood ratio (P-LR), negative likelihood ratio (N-LR), diagnostic odds ratio (DOR), and area under the curve (AUC) together with 95% confidence interval (CI) to estimate the predictive accuracy.

Results

A total of 72 studies, including 22260 patients, were included in the meta-analysis. Elevated NLR, PLR CAR, SII, GPS, mGPS, and decreased LMR and PNI were associated with poor OS of esophageal cancer. A high level of NLR, PLR, and GPS was related to poor DFS. A high level of NLR and GPS was related to poor CSS. The summarized AUC of CAR (0.72, 95% CI: 0.68-0.75) and mGPS (0.75, 95% CI: 0.71-0.78) surpassed any other indicators.

Conclusions

Clinical indicators such as NLR, PLR, LMR, PNI, SII, CAR, GPS, and mGPS have the moderate predictive ability in OS, DFS, and CSS of esophageal cancer. The pretreatment level of CAR and mGPS showed an outstanding prediction value in 5-year OS for esophageal cancer.

Keywords: inflammation; nutrition; prognosis; esophageal cancer; meta-analysis; systematic review

Strengths and limitations of this study

Strengths

We used internationally recognized critical assessment tools to assess the quality of individual studies.

The pooled results were stable due to the large sample size.

The prognostic performance of biomarkers for esophageal cancer was systematically compared for the first time.

Limitations

Different cut-off values may result in heterogeneity and bias.

Heterogeneity was not fully explained.

1. Backgrounds

Globally, esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer death[1]. In 2020, there were 570,000 new cases of esophageal cancer and about 500,000 deaths worldwide[2]. Pathologically, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) are the major histological type. Esophageal adenocarcinoma (EAC) is mainly observed in industrialized countries, and nearly half of cases occur in Northwest Europe and North America, while esophageal squamous cell carcinoma (ESCC) is more common in China, Central Asia, or South Africa. Despite substantial efforts in diagnosis, accurate staging, and advanced treatments, the five-year survival rate remains unfavorable with frequent metastasis and recurrence[3]. The pathological tumor-node-metastasis (TNM) stage is the gold standard for predicting oncological outcomes after surgery[4]. However, with the diversification of treatment methods and the complexity of prognostic factors, prognosis prediction tends to be unsatisfactory. Therefore, it is urgent to find better prognostic biomarkers to guide clinical treatment and appropriate follow-up.

Increasing evidence indicates that systemic inflammatory response and nutritional status are involved in tumor development and influence the clinical prognosis. Principal inflammation-based prognostic scores[5-7] include a neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), c-reactive protein-to-albumin ratio (CAR), systemic inflammation index (SII), pretreatment albumin levels, and lymphocyte to monocyte ratio. Typical nutrition-based prognostic scores[8, 9] are prognostic nutritional index (PNI) based on serum albumin and total lymphocyte count, Glasgow Prognostic Score (GPS) based on elevated C-reactive protein concentration and low

levels of albumin, and modified Glasgow Prognostic Score (mGPS), a modified version of GPS. Recently, accumulating literature has shown the prognostic values of these inflammation and nutrition-based prognostic markers in esophageal cancer, but with inconsistent findings. Hence, it is meaningful to distinguish an accurate prognosis index for patients with esophageal cancer to guide individualized therapy and precision service.

In the current study, we performed a systematic review of relevant literature. We applied the meta-analysis to explore the accuracy of inflammation and nutrition-based prognostic scores for patients with esophageal cancer.

2. Materials and methods

2.1 Literature search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Two students (Jiang Y and Xu D) independently searched PubMed, Web of Science, and Cochrane Library Databases for eligible articles from the inception of databases to March 2020. Additionally, references in the eligible publications were also reviewed for potential studies. The language was limited to English. The search terms are listed in Additional file 1. The detailed search procedure is illustrated in Figure. 1.

2.2 The definition of outcome

Overall survival (OS) was defined as the time from the beginning of treatment to the death due to all causes or last follow-up. Cancer-specific survival (CSS) was defined as the time from the beginning of therapy to the time of cancer-related death.

Disease-free survival (DFS) was defined as the time from the start of treatment to the cancer recurrence or the occurrence of the second primary malignancy[10].

2.3 Selection criteria

Articles were included if they met the following criteria: 1) patients were histo-pathologically confirmed to be primary esophageal cancer; 2) prognostic indicators were measured before esophagectomy, chemotherapy, or radiotherapy; 3) hazard ratios (HRs) with 95% confidence intervals (CIs) were reported in multivariate analysis. Studies were excluded if they were: (1) reviews, case reports, letters, or conference abstracts; (2) studies with insufficient data; or (3) duplicate publications.

2.4 Data extraction

For each study, the following information was extracted by two students (Jiang Y and Xu D): the name of the first author, year of publication, country, study design, pathological type, number of patients, age, sex, end-point, follow-up time, cut-off selection, therapy, tumor stage, cut-off values, and HRs (95% CIs). We further collected the data of true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) for 5-year OS directly provided in the paper or calculated by comparable data (the number of people in the high-risk and low-risk groups according to cut-off values and the corresponding number of deaths and survivors). If only the area under the curve (AUC) was reported, we contacted the corresponding author for original data. If we couldn't get a response, we only included this study in the first part of the analysis.

2.5 Quality assessment

Two reviewers (Song H and Qiu B) independently assessed the methodological

quality of the studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool[11]. Each item was judged as "yes", "no", or "unclear". Any signaling question answered "yes" indicated a low risk of bias, while "no" showed a high risk of bias. If the answer was uncertain, the domain was judged as having an uncertain risk of bias.

2.6 Statistical analysis

The risk of bias was analyzed and plotted using Review Manager 5.3 (London, UK). The meta-analysis was performed using STATA 15.0 (Texas, USA). The strength of NLR, PLR, LMR, PNI, SII, CAR, GPS, mGPS in association with OS, CSS, and DFS was measured by the combined HRs and their 95% CIs. Cochran's Q test and Higgins I-squared statistics were undertaken to assess the heterogeneity of studies. If $P \geq 0.10$ in the Q test or $I^2 < 50\%$, we used the fixed-effect model; otherwise, we used the random-effect model. Publication bias was assessed by Begg and Egger test. The sensitivity analysis was utilized by omitting individual study one-by-one to evaluate the robustness of the results. All *P*-values were two-tailed, and a *P*-value <0.05 was considered statistically significant.

The pooled sensitivity, specificity, AUC, and corresponding 95% CI were calculated by TP, FP, FN, and TN using a bivariate regression model. The threshold effects were calculated by testing the Spearman correlation using Meta-DiSc (Madrid, Spain)[12]. If $I^2 \geq 50\%$ and *P*-value ≤ 0.05, the heterogeneity was significant due to the non-threshold effect, and then we used the meta-regression analysis to find the source of heterogeneity. The pooled positive likelihood ratio (P-LR), negative likelihood ratio (N-LR), and diagnostic odds ratio (DOR) were also calculated to understand the performance of the prognostic index better. Deek's funnel plot was used to detect

publication bias. To evaluate the difference of AUC between biomarkers, we checked the overlap of 95% CIs. If not, we used the following *z*-test $[(X_1\text{-}X_2)/(SE_1^2+SE_2^2)^{1/2}]$, where X_1 and X_2 represented the indicators, and SE_1 and SE_2 were the corresponding standard errors[13]. It was considered significantly different if the P-value obtained from the z-test was less than P' (0.05/n, n was the number of comparisons). The comparison for sensitivity, specificity, P-LR, N-LR, or DOR was also performed.

3. Results

3.1. Literature selection and study characteristics

The initial search identified 662 potentially relevant records. After removing duplicates and papers that did not meet the inclusion criteria, 72 studies with 22,260 subjects were remain for the systematic review (Additional file 2: Table 1). A flowchart demonstrating the process of study selection is illustrated in Figure. 1. Most studies were carried out in Asia (42 in China; 23 in Japan). Before treatment, the blood cell counts used to calculate NLR, PLR, LMR, and CAR were obtained. The baseline characteristics and treatment methods are presented in Additional file 2.

3.2 Risk-of-bias and quality assessments

Figure. 2 illustrates the risk assessment of bias. A high risk of selection bias was observed in all studies. Nearly one-third of the studies had an unclear bias in study attrition. One study had an unclear bias for detection bias, and two studies had the risk of bias in measuring prognostic factors and outcomes, respectively. Six studies were judged as having an unclear performance bias.

3.3 Prognostic indicators in OS, DFS, and CSS of esophageal cancer

As shown in Figure. 3 (A-H), factors significantly contributing to a short OS were a high level of NLR (HR: 1.43, 95% CI: 1.30–1.58, P <0.001; I^2 =61.7%, P_{het} <0.001), PLR (HR: 1.26, 95% CI: 1.18–1.35, P <0.001; I^2 =29.8%, P_{het} =0.108), CAR (HR: 1.84, 95% CI: 1.60–2.10, P <0.001; I^2 =41.8%, P_{het} =0.079), SII (HR: 1.46, 95% CI: 1.30–1.65, P <0.001; I^2=41.0%, P_{het}=0.118), GPS(HR: 2.35, 95% CI: 1.99–2.76, P <0.001; I^2 =36.5%, P_{het} =0.078), or mGPS (HR: 1.69, 95% CI: 1.49–1.92, P <0.001; I^2 =48.4%, P_{het} =0.022), and low level of LMR (HR: 1.37, 95% CI: 1.14–1.65, P =0.001; I^2 =84.9%, P_{het} <0.001) and PNI (HR: 1.51 95% CI: 1.36–1.68, P <0.001; I^2 =45.8%, P_{het} =0.048).

Patients with an elevated NLR (HR: 1.21, 95% CI: 1.04–1.41, P =0.011; I^2 =43.4%, P_{het} =0.089) and GPS (HR: 1.64, 95% CI: 1.33–1.94, P <0.001; I^2 =45.5%, P_{het} =0.119) had a worse CSS (Figure. 3 I-J) .

NLR (HR: 1.39, 95% CI: 1.10–1.75, P =0.005; I^2 =60.9%, P_{het} =0.018), PLR (HR: 1.30, 95% CI: 1.12–1.51, P <0.001; I^2 =33.0%, P_{het} =0.202), and GPS(HR: 2.44, 95% CI: 1.28–4.66, P <0.007; I^2 =57.5%, P_{het} =0.052) were negatively correlated with DFS. No significant association was found for LMR (HR: 1.03, 95% CI: 0.78–1.35, P =0.858; I^2 =82.2%, P_{het} <0.001) (Figure. 3 K-N).

3.4 Subgroup analysis and meta-regression

Subgroup analysis and meta-regression were further conducted according to the cut-off value, sample size, follow-up time, sex, age, clinical stage, and region (Additional file 3). The heterogeneity of OS studies was relatively low except LMR (I^2 =84.9%) and NLR (I^2 =61.7%). The pooled HR was significantly different between studies with more or less than 280 patients, indicating that the sample size may be the

source of heterogeneity for LMR. Similarly, we found the source of heterogeneity for other indicators. The follow-up time may be the source of heterogeneity for PLR (*P*=0.004) and GPS (*P*=0.027). The sample size may be the source of heterogeneity for SII (*P*=0.047) and mGPS (*P*=0.014). The sex ratio may be the source of heterogeneity for CAR (*P*=0.045). In DFS analysis, we found that cut-off value and region may be the source of high heterogeneity of LMR (*P*=0.034) and NLR (*P*=0.018), respectively.

3.5 Publication bias

Begg's and Egger's tests were applied to estimate the publication bias. As shown in Additional file 3, no significant publication bias was observed.

3.6 Sensitivity analysis

We performed a sensitivity analysis by excluding one study each time. As shown in Additional file 4, the results were not substantially changed, demonstrating the reliability and stability of the current meta-analysis.

3.7 Pooled sensitivity, specificity, DOR, and AUC of indicators

We further extracted TP, FP, FN, and TN from each study (Additional file 2) to calculate the pooled accuracy of each indicator for a 5-year OS. There were 11 studies for NLR, 11 studies for PLR, 7 studies for LMR, 6 studies for CAR, 6 studies for SII, 7 studies for PNI, 6 studies for GPS, and 5 studies for mGPS.

3.7.1 Threshold effect

The Spearman correlation coefficient (*P*-value) for NLR, PLR, LMR, PNI, SII, CAR, GPS, and mGPS was 0.56 (0.07), 0.59 (0.06), 0.57 (0.18), 0.75 (0.05), 0.77 (0.07),

0.20 (0.70), 0.77 (0.07), and -0.10 (0.87), respectively, indicating no significant threshold effect.

3.7.2 Forest plot and subgroup analysis

Forest plots of sensitivity and specificity were shown in Figure. 4. SII had the highest pooled sensitivity (0.61, 95% CI: 0.48-0.73), while CAR (0.84, 95% CI: 0.71-0.91) had the highest pooled specificity. The I^2 of the sensitivity and specificity of these prognostic indicators were relatively high (around 70%-90%) except GPS (sensitivity: 43.76%; specificity: 6.96%). We further conducted a subgroup analysis and meta-regression (Additional file 5). For SII, the sensitivity of studies with a cut-off level ≥410 ng/ml (0.47, 95% CI: 0.37–0.57) was significantly lower than the studies with a cut-off level <410 ng/ml (0.73, 95% CI: 0.66–0.81), while studies with a cut-off level ≥410 ng/ml (0.76 , 95% CI: 0.72–0.81) had a significantly higher specificity than studies with a cut-off level < 410 ng/ml (0.42, 95% CI: 0.38–0.47). Therefore the cut-off value may be the source of heterogeneity in both sensitivity and specificity of SII. Similarly, we found that sample size may be the source of sensitivity for mGPS (P<0.001), PLR (P=0.02), GPS (P=0.03), CAR (P=0.04), and LMR (P=0.04), and the source of heterogeneity in the specificity of NLR (P=0.03) and GPS (P<0.001). Additionally, the study area may be the source of heterogeneity in the specificity of mGPS (P=0.01). Also, age and clinical stage may be the source of heterogeneity in specificity for PLR (P<0.001) and PNI (P=0.01), respectively. However, we failed to find the source of heterogeneity for the sensitivity of NLR or PNI and the specificity of CAR or LMR.

3.7.3 Comparison of AUC

Figure. 5 shows the summarized ROC curves of eight indicators. We found that the

scope of pooled AUC of CAR (0.72, 95% CI: 0.68-0.75) and mGPS (0.75, 95% CI: 0.71-0.78) surpassed other indicators except GPS (0.67, 95% CI: 0.63-0.71). We further compared CAR, mGPS, and GPS by *z* test. The pooled AUC of CAR or mGPS was larger than GPS (*P* =0.033; *P* =0.002), but there was no significant difference between CAR and mGPS (Additional file 6).

3.7.4 Publication bias and sensitivity analysis

Only PNI (*P* =0.03) and mGPS (*P* =0.02) had a significant publication bias (Additional file 7). The sensitivity analysis of combined DOR showed a robust finding (Additional file 4: Figure. 2).

Discussion

In this meta-analysis, we summarized data from 72 studies and estimated the predictive ability of inflammation and nutrition-based indicators in esophageal cancer. In general, these indicators showed an excellent ability to predict the OS, DFS, and CSS of patients with esophageal cancer. The pretreatment level of CAR and mGPS showed an outstanding prediction value for 5-year OS than other indicators.

Inflammation plays an essential role in the development and progression of various malignant tumors[14]. In addition, nutritional status is closely related to carcinogenesis, cancer growth, tumor progression, and tumor prognosis[15]. The peripheral blood cell analysis is a good choice for establishing a prognostic prediction model based on inflammatory and nutrition-related indicators due to its convenience, repeatability, and low cost[16]. Previous studies have systematically reviewed the role of some inflammation and nutrition-based indicators in the prognosis of esophageal cancer,

most of which focused on ESCC. Yang et al. [17] investigated the relationship between NLR and esophageal cancer by summarizing six studies involving 1,633 patients. Sun et al. [5] reviewed 26 studies to explore the NLR, PLR, and LMR in the OS, CSS, and DFS in ESCC. Li et al. [18] reviewed nine observational studies and showed that a low PNI score was significantly correlated with a poor OS of esophageal cancer and recurrence-free survival of ESCC. Liu et al. collected eight observational studies and showed that high CAR was related to a worse OS[19]. Although previous meta-analyses have reported the prognostic value of these indicators, this is the first study to comprehensively estimate the popular inflammatory and nutrition-related markers in OS, DFS, and CSS of esophageal cancer. Moreover, this is the first systematic review to summarize the sensitivity and specificity and compare the AUC of these predictors in the 5-year OS of esophageal cancer.

In this review, we observed that the AUC of CAR and mGPS was significantly higher than NLR, PLR, SII, PNI, LMR, and GPS, indicating their outstanding predictive value in esophageal cancer. CAR and mGPS are calculated based on the level of C-reactive protein (CRP) and albumin. CRP is a kind of acute reactive protein synthesized by liver cells or cancer cells, which can produce an attractive environment for tumor growth, induce DNA damage, promote angiogenesis, and favor neoplastic spread and metastasis, revealing levels of inflammation in the body[20, 21]. Albumin reflects the malnutrition status of the host, triggers malignant transformation and tumor progression, or even causes cachexia[22]. Combining the two indicators can reveal a patient's inflammatory status and nutritional status, which can effectively predict prognosis. These may explain the prominent prognostic role of CAR and mGPS. Additionally, some prospective studies have revealed the better predictive power of CAR and mGPS in other types of cancer. For example, it was

reported that the CAR had a better predictive performance for hepatocellular carcinoma and colorectal cancer than NLR, PLR, or c-reactive protein alone[23]. Other studies demonstrated that mGPS was an independent marker of poor prognosis for patients with SCC and superior to NLR, PLR, and PNI[9].

Although the TNM staging system is well known as a predictive clinical parameter in terms of guiding treatment and clinical prognosis, the survival outcomes for esophageal cancer patients with the same TNM stage still vary widely[4]. In addition, many patients with esophageal cancer cannot undergo surgery to obtain pathological identification for various reasons. Thus their prognosis cannot be obtained. Moreover, multiple factors influence the prognosis of patients with esophageal cancer, such as neoadjuvant therapy, psychological factors, and behavior and eating habits, which will change the postoperative pathological stage of the tumor and thus affect the evaluation of disease progression[24-26]. Therefore, pathological diagnosis is not sufficient to accurately predict the prognosis of patients with esophageal cancer. More readily available objective indicators with high specificity and sensitivity are needed to predict the prognosis of cancer patients. Our results of this meta-analysis will help clinicians and patients to select appropriate indicators for prognosis prediction. In this way, patients can be classified, and appropriate treatment strategies and postoperative management methods can be selected, providing policymakers with ideas. Taken mGPS as an example, esophageal cancer patients with a score of 2 may have a high risk of prognosis, which may provide an effective way for clinicians to select high-risk patients with worse prognosis or severe adverse events before treatment and further timely adjust individualized treatment regimens and enhance postoperative rehabilitation. In addition, policymakers should develop policies to strengthen community guidance and management of such high-risk postoperative patients.

Malnutrition is closely related to carcinogenesis, cancer growth, tumor progression, and tumor prognosis[27]. The Global Leadership Initiative on Malnutrition (GLIM) standards integrate current best evidence and expert opinion on malnutrition to promote the prevention, identification, and treatment of malnutrition in cancer patients[28]. Inflammation is one of the etiological criteria in GLIM classification, and studies have demonstrated that the changes of GPS score, C-reactive protein, and albumin are highly consistent with the GLIM criteria in identifying malnutrition in patients[29]. Similar to this study, our findings confirm the value of mGPS and CAR in predicting the prognosis of esophageal cancer. GLIM criteria are reevaluated every 3-5 years based on new research. Our results may provide a basis for the optimization of GLIM criteria. Additionally, previous studies have reported that the combination of PNI and GLIM criteria has significant advantages in predicting the incidence and survival rate of perioperative malnutrition[30]. Our results show that the prognostic indicators we studied have high specificity but unsatisfactory sensitivity. More well-designed studies are needed to develop joint indicators to improve the sensitivity and specificity of prediction.

Some limitations should be acknowledged. Firstly, some heterogeneity was not fully explained. This may be due to the fact that some factors that may affect survival were not included, such as living behavior and eating habits, comorbidities, Neoadjuvant therapy, and psychological factors[10, 24]. Secondly, the cut-off value of indicators varied between studies, affecting the pooled analysis results and induce unavoidable potential heterogeneity and bias. Therefore, a standard and uniform cut-off value need to be defined. Thirdly, publication bias was detected in studies on PNI and mGPS. Papers that failed to get published due to negative or null results could not be

identified in our literature search and thus were not included in the meta-analysis. This may overestimate the prognostic effect of PNI and mGPS. Therefore, more well-designed prospective studies with large samples are needed to verify our findings.

Conclusion,

NLR, PLR, LMR, PNI, SII, CAR, GPS, and mGPS are commonly used as clinical indicators to predict OS, DFS, and CSS of esophageal cancer, but with unsatisfactory sensitivity. Pretreatment CAR and mGPS showed outstanding prognostic values in 5-year OS for patients with esophageal cancer. Future extensive prospective studies with rigorously designed methodologies are warranted to confirm our results.

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Authors contributions

Jiang Y and Xu D were mainly responsible for data collection, analysis, drafting, and revision. Wang J participated in the topic design, work plan, and paper revision. Song H and Qiu B helped complete the data collection. Tian D, Ji Y, and Li Z were involved in the data analysis and paper revision. Jiang Y, Xu D, and Song H

contributed equally to this paper. All authors finally approved the version to be published and agreed to be accountable for all aspects of the work.

Competing interests

The authors declare no competing financial interest.

Patient and public involvement

No patient was involved.

Data sharing statement

All data generated or analyzed during this study are included in this published article.

Ethics approval statement

All data were downloaded from the public database and followed the data access policies. This study was exempted from ethical review by the ethics committee of Nanjing Medical University. This study did not involve individual information, so there was no requirement for informed consent.

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Figure legends

Figure. 1 Flow diagram of the search process.

Figure. 2 Risk of bias and applicability concerns.

Figure. 3 Forest plot of HR for 5-year OS, DFS, and CSS in patients with esophageal cancer.

(A) NLR-OS; (B) PLR-OS; (C) LMR-OS; (D) CAR-OS; (E) SII-OS; (F) PNI-OS; (G) GPS-OS; (H) mGPS-OS; (I) NLR-CSS; (J) GPS-CSS; (K) NLR-DFS; (L) PLR-DFS; (M) LMR-DFS; (N) GPS-DFS.

Figure. 4 Forest plot of sensitivity and specificity

(A) NLR; (B) PLR; (C) LMR; (D) CAR; (E) SII; (F) PNI; (G) GPS; (H) mGPS; Q: Cochran Q statistic.

Figure. 5 Summary receiver-operating characteristic (SROC) curves of 5-year OS.

(A) NLR; (B) PLR; (C) LMR; (D) CAR; (E) SII; (F) PNI; (G) GPS; (H) mGPS; AUC: area under curve

Additional files

Additional file 1. Searching strategy

Additional file 2. Characteristics of studies

Additional file 3. Subgroup analysis (part 1)

Additional file 4. Subgroup analysis (part 2)

Additional file 5. Funnel plots

Additional file 6. Sensitivity analysis

Additional file 7. Comparisons

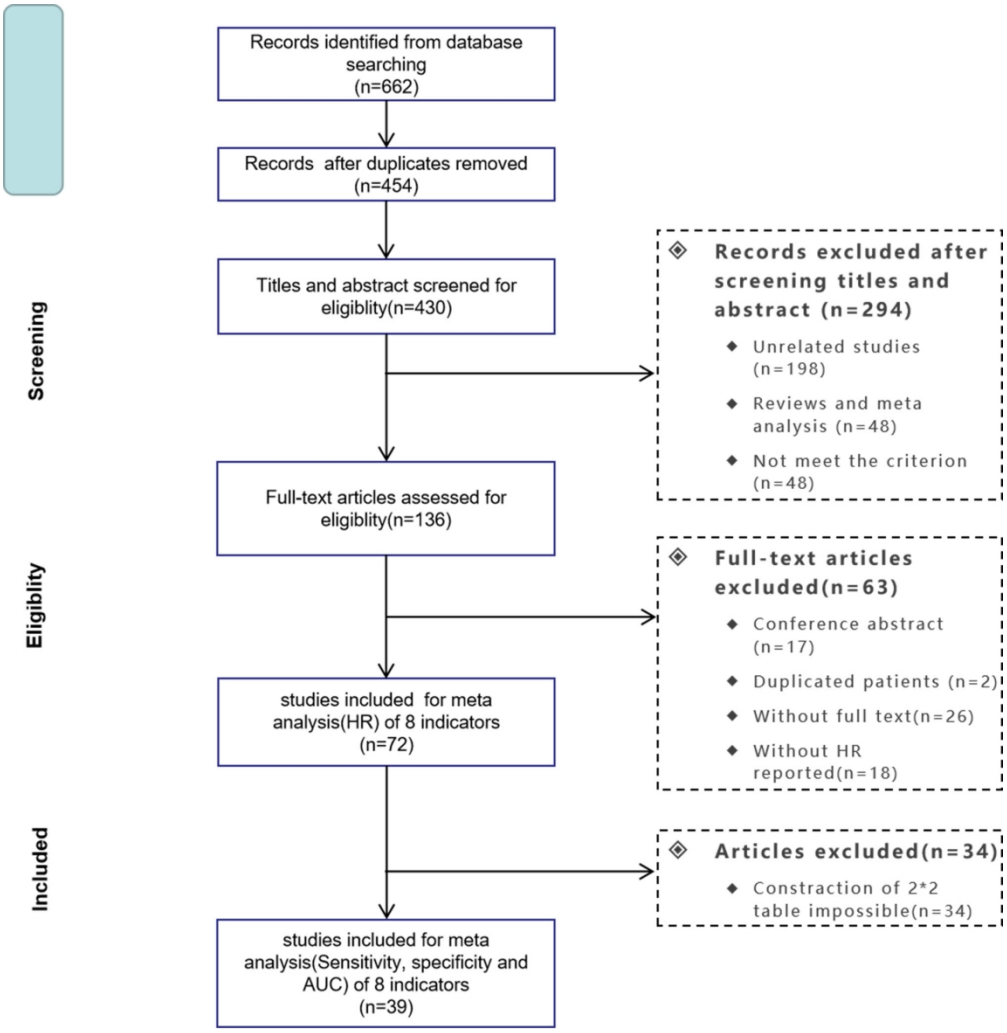

Fig. 1 Flow diagram of the search process.

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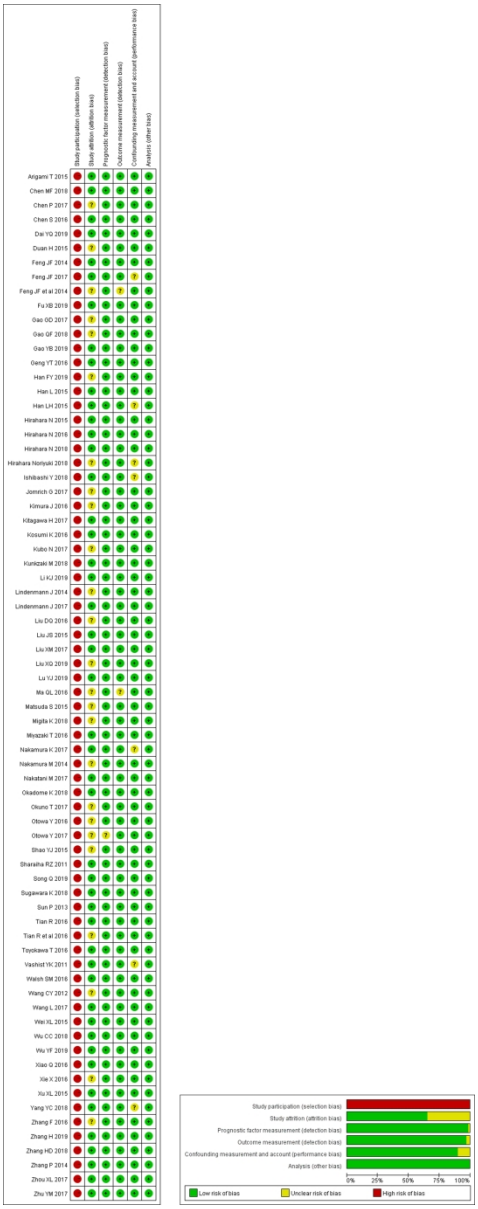

Fig. 2 Risk of bias and applicability concerns.

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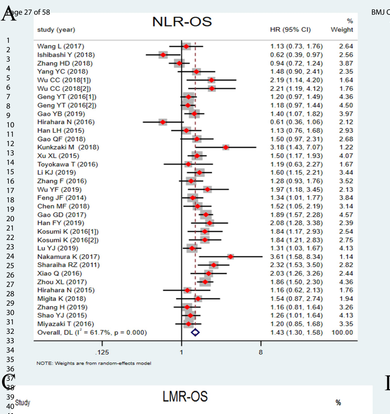

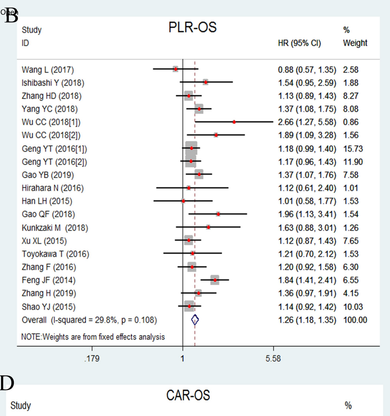

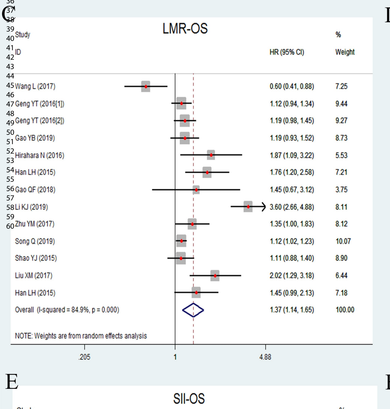

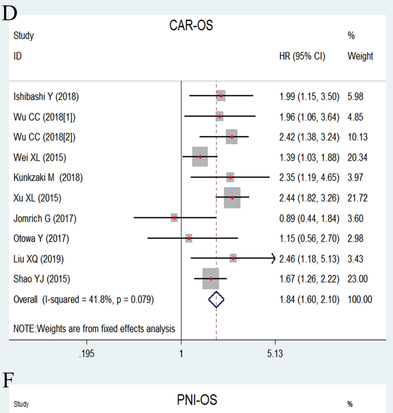

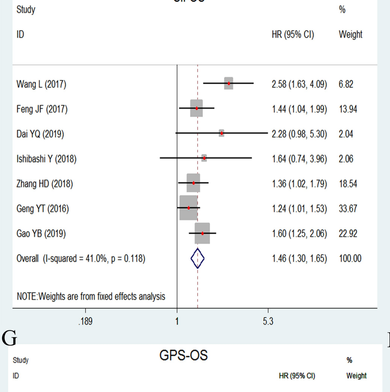

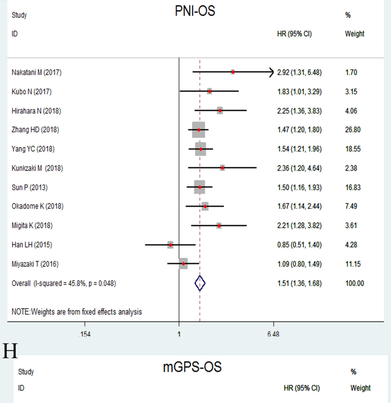

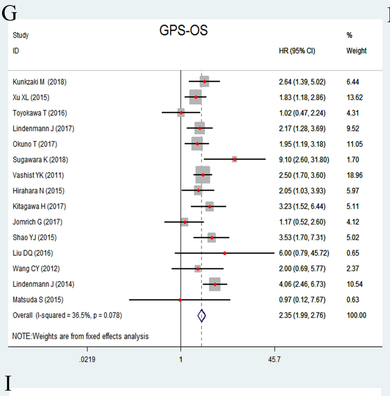

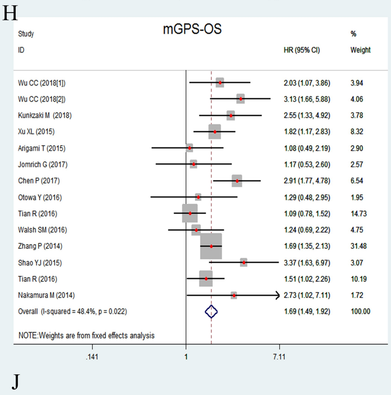

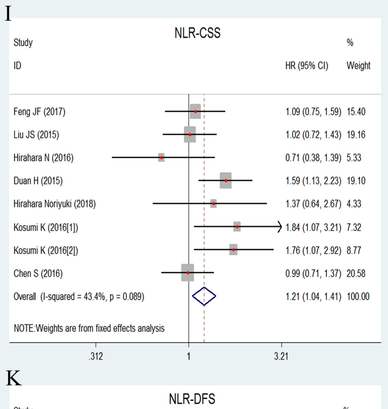

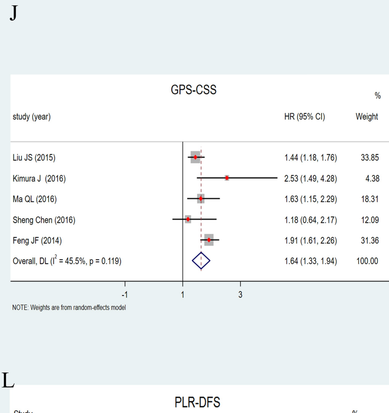

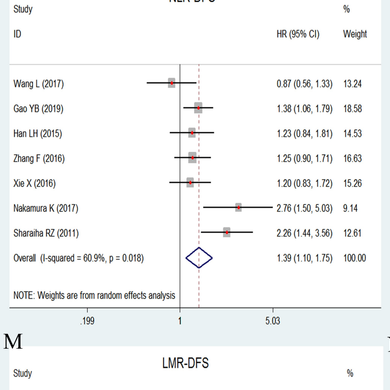

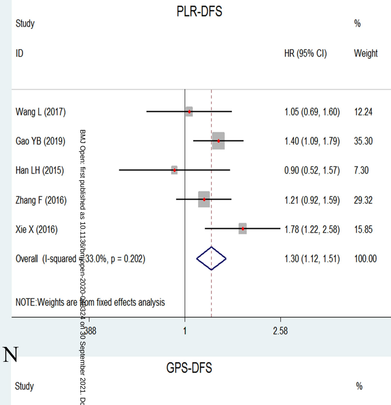

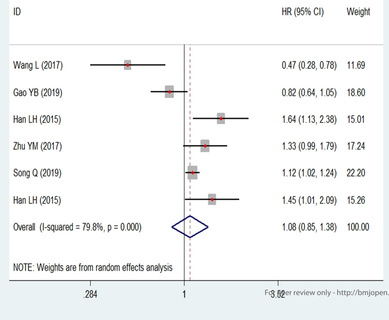

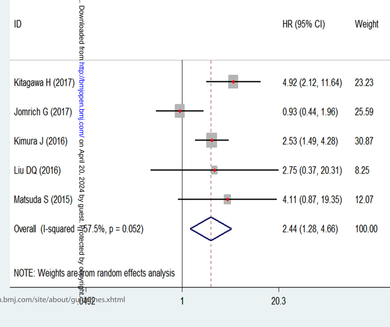

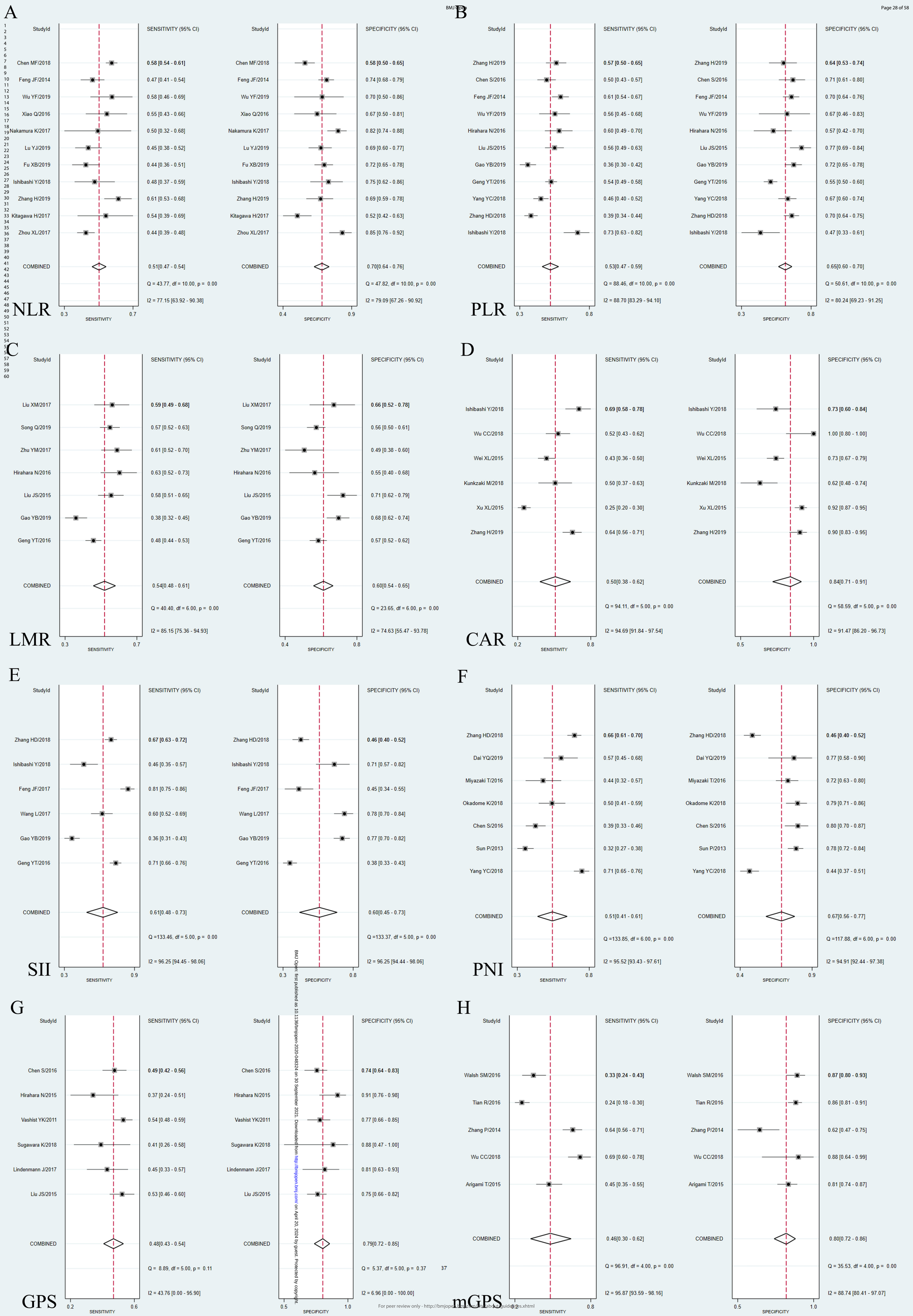

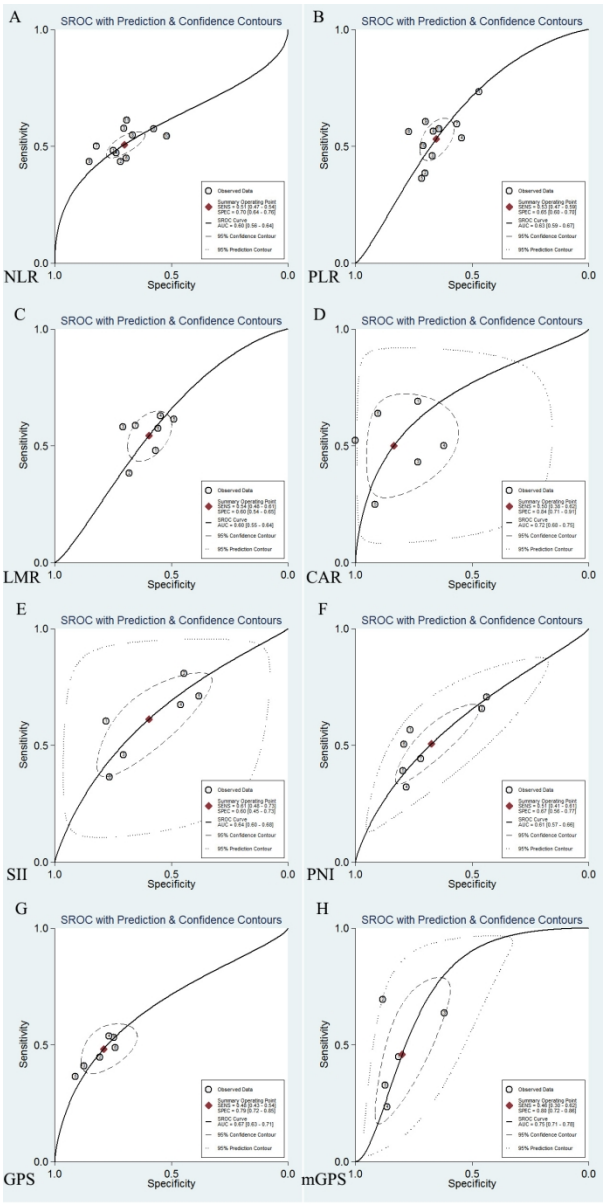

Fig. 5 Summary receiver-operating characteristic (SROC) curves of 5-year OS. (A) NLR; (B) PLR; (C) LMR; (D) CAR; (E) SII; (F) PNI; (G) GPS; (H) mGPS; AUC: area under curve

439x879mm (72 x 72 DPI)

Searching strategy:

((((((((((NLR OR neutrophil to lymphocyte ratio) OR neutrophil-to-lymphocyte ratio) OR neutrophillymphocyte ratio) OR neutrophil lymphocyte ratio) OR (((((PLR OR platelet lymphocyte ratio) OR plateletlymphocyte ratio) OR platelet to lymphocyte ratio) OR platelet-to-lymphocyte ratio) OR platelet lymphocyte ratio)) OR (((((LMR OR lymphocyte monocyte ratio) OR lymphocytemonocyte ratio) OR lymphocyte to monocyte ratio) OR lymphocyte-to-monocyte ratio) OR lymphocyte monocyte ratio)) OR ((((SII OR Systemic Immune-Inflammation Index) OR Systemic Immune Inflammation Index) OR Systemic Inflammation Index) OR Systemic Immune-Inflammation Indices)) OR (PNI OR Prognostic nutritional index)) OR (((GPS OR Glasgow Outcome Scale) OR GOS) OR Glasgow Prognostic score)) OR (mGPS OR modified Glasgow Prognostic score)) AND ((((ESCC OR esophageal neoplasm) OR esophageal cancer) OR esophageal carcinoma) OR esophageal squamous cell carcinoma))

Table 1. The characteristics of the studies included.

Study	Ethnicity (country)	Sample size	Gender (M/F)	Age	Stage	NLR cutoff	PLR cutoff	LMR cutoff	PNI cutoff	SII cutoff	GPS cutoff	mGPS cutoff	CAR cutoff	Follow-up (months)	Treatment	Outcome	pathology	TP /FP /FN /TN (OS)
Wang L et al. (2017)[1]	China	280	233/47	64.071±7.412	0-IV	2	159	5.3	NR	560	NR	NR	NR	36	surgery	OS/DFS	SCC	SII:81 32 53 114
Feng JF et al. (2017)[2]	China	298	260/38	NR	I-III	5	150	NR	NR	410	NR	NR	NR	NR	surgery	CSS	SCC	SII:165 52 39 42
Nakatani M et al. (2017)[3]	Japan	66	56/10	64.7 ± 6.1	II-III	NR	NR	NR	45	NR	NR	NR	NR	31.9	surgery	OS/RFS	SCC	NR
Kubo N et al. (2017)[4]	Japan	202	162/40	63.73 ± 7.93	I-IV	NR	NR	NR	44	NR	NR	NR	NR	47.1	surgery	OS/RFS	SCC	NR
Hirahara N et al. (2018)[5]	Japan	169	150/19	PNI＜49.2：67.1±8.2 PNI≥49.2：65.4±8.0	Ia-IIIc	NR	NR	NR	49.2	NR	NR	NR	NR	NR	surgery	OS/CSS	SCC	NR
Dai YQ et al. (2019)[6]	China	106	79/27	<65:82; ≥65:24	T1-4/N0-1	2.1	104.1	3.45	48.15	305.6	NR	NR	NR	19(2–190)	CRT	OS	SCC	PNI: 43 7 33 23
Ishibashi Y et al. (2018)[7]	Japan	143	121/22	70.6 ± 8.4(43–90)	I-IV	3	135	NR	NR	650	NR	NR	0.085	NR	surgery	OS/CSS	SCC/ADC /Others	SII: 39 17 46 41 NLR: 42 14 45 42 PLR: 66 28 24 25 CAR: 60 15 27 41
Zhang HD et al. (2018)[8]	China	655	537/118	61(27–88)	0-III	1.87	140.08	NR	52.28	387.65	NR	NR	NR	36.0(3–144)	surgery	OS	SCC	PLR: 148 81 236 190 SII: 259 146 125 125 PNI: 264 137 138 116
Yang YC et al. (2018)[9]	China	515	418/97	61(33–92)	I-III	1.2	130	NR	57	NR	NR	NR	NR	35(2–106)	surgery	OS	SCC	PLR: 143 67 168 137 PNI: 217 117 90 91
Wu CC et al. (2018)[10]	China	126	122/4	58(37–80)	IIIa-IIIc	2.5	103	NR	NR	NR	NR	0/1,2	0.95	NR	mixed	OS	SCC	CAR: 57 1 52 17 mGPS: 77 2 34 15
Wei XL et al. (2015)[11]	China	423	341/82	58(24–88)	I-IV	1.835	163.8	NR	49.05	NR	NR	0,1,2	0.095	35.7(0.6–95.6)	surgery	OS	SCC	CAR: 90 57 119 157
Geng YT et al. (2016)[12]	China	916	696/220	60.0(37–84)	0-III	1.7	120	3.57	NR	307	NR	NR	NR	39(3–146)	surgery	OS	SCC	SII: 279 227 113 140 LMR: 239 181

																	258 238 PLR: 275 183 238 220
Gao YB et al. (2019)[13]	China	468	376/92	59.5(36–81)	I-III	2.27	117.0	5.26	NR	479.72	NR	NR	NR	49.1±32.6(3.2–114.5)	surgery	OS/DFS	SCC	SII: 93 50 162 163 PLR: 93 60 164 151 LMR: 96 69 155 148
Liu JS et al. (2015)[14]	China	326	283/43	59.2±7.9(38-80)	T1-4/N0-3	3.45	166	2.3	NR	NR	0/1,2	NR	NR	45	surgery	CSS	SCC	GPS: 108 31 95 92 PLR: 114 28 89 95 LMR: 112 36 81 87
Hirahara N et al. (2016)[15]	Japan	147	132/15	<70：46 ≥70：101	Ia-IIIc	1.6	147	4	NR	NR	NR	NR	NR	42(3-111)	surgery	OS/CSS	SCC	LMR: 59 24 35 29 PLR: 56 23 38 30
Han LH et al. (2015)[16]	China	218	177/41	60.5(32-84)	I-III	2.6	244	2.57	NR	NR	NR	NR	NR	38.6(3-71)	surgery	OS/DFS	SCC	NR
Gao QF et al. (2018)[17]	China	153	128/25	61.93±6.72	0-III	2.1	145.9	2.3	NR	NR	NR	NR	NR	NR	surgery	OS	SCC	NR
Kunkzaki M et al. (2018)[18]	Japan	116	98/18	66(44-83)	0-IV	5	150	NR	45	NR	0/1,2	0/1,2	0.042	NR	mixed	OS	SCC	CAR: 29 22 29 36
Xu XL et al. (2015)[19]	China	468	416/52	58	I-IIIc	2.4	147	NR	NR	NR	0/1/2	0/1/2	0.5	49.9(10.9–88.0)	surgery	OS	NR	CAR: 72 15 216 165
Toyokawa T et al. (2016)[20]	Japan	185	152/33	64(59–70)	I-IV	3.612	193	NR	NR	NR	0/1,2	NR	NR	81.5(IQR:45.8–112.3)	surgery	OS/RFS	SCC	NR
Li KJ et al. (2019)[21]	China	204	171/33	65.8(38-85)	T1-4/N0-2	2.64	NR	3.03	NR	NR	NR	NR	NR	11.5(2.1-77.4)	CRT	OS/RFS	SCC	NR
Fu XB et al. (2019)[22]	China	357	279/78	57(34-77)	I-IVa	2.27	NR	2.57	NR	SIS:0/1/2	NR	NR	NR	58(1–84)	surgery	OS	SCC	NLR: 77 50 100 128
Zhang F et al. (2016)[23]	China	468	376/92	60(36-81)	I-III	2.5	117.0	NR	NR	NR	NR	NR	NR	49.1±32.6(3.2-114.5)	surgery	OS/DFS	SCC	NR
Xie X et al. (2016)[24]	China	317	244/73	58.1±8.9(34–76)	I-III	2.1	103	NR	NR	NR	NR	NR	NR	46(36–62)	surgery	DSS	SCC	NR
Wu YF et al. (2019)[25]	China	105	98/7	57.69±8.6(38-81)	I-III	4.35	NR	NR	NR	NR	NR	NR	NR	19.5±14.1	CRT	OS/PFS	SCC	PLR: 44 9 34 18 NLR: 45 8 33 19
Feng JF et	China	483	411/72	59.1±8.0(34-80)	T1-4/N-+	3.5	150	NR	NR	NR	NR	NR	NR	NR	surgery	OS	SCC	NLR:115 63 129

al. (2014)[26]																		176 PLR: 148 72 96 167
Zhu YM et al. (2017)[27]	China	220	117/103	≤60/>60:124/96	T3N0M0	NR	NR	3.364	NR	NR	NR	NR	NR	DFS:40.0(34.2–45.8) OS:53.0(48.0–58.0)	mixed	OS/DFS	SCC	LMR: 81 45 51 43
Song Q et al. (2019)[28]	China	680	582/98	61(56-67)	Ia-IIIc	NR	NR	3.17	NR	NR	NR	NR	NR	NR	mixed	OS/DFS	SCC	LMR: 182 161 135 202
Chen MF et al. (2018)[29]	China	1168	1113/55	(<50/50-64/>64): 344/609/215	≤T2/T3-T4,N0/N+	3	NR	NR	NR	NR	NR	NR	NR	NR	mixed	OS/DFS	SCC	NLR: 567 77 419 105
Duan H et al. (2015)[30]	China	371	276/95	57.7±8.9	Ib-IIIc	3	NR	NR	NR	410	NR	NR	NR	66(49-76)	surgery	CSS/RFS	SCC	NR
Gao GD et al. (2017)[31]	China	1281	988/293	Survival/Dead(634/647) 57.7±8.9/60.2±27.7	0-IV	2.86	NR	NR	NR	NR	NR	NR	NR	NR	mixed	OS	SCC	NR
Han FY et al. (2019)[32]	China	354	267/87	<60/>=60:100/254	I-IV	1.88	NR	NR	NR	NR	NR	NR	NR	26(2-80)	surgery	OS/DFS	SCC/ADC /Others	NR
Hirahara Noriyuki et al. (2018)[33]	Japan	148	132/16	CONUT 0/1/2-3(48/37/11) 61.5±5.4/61.8±5.9/60.4±5.3	Ia-IIIc	3.5	NR	NR	NR	NR	NR	NR	NR	NR	surgery	CSS	SCC	NR
Kosumi K et al. (2016)[34]	Japan	313	248/35	<65/≥65(118/165)	0-IV	1.94	NR	NR	NR	NR	NR	NR	NR	33.6	surgery	OS/CSS	SCC	NR
Lu YJ et al. (2019)[35]	China	315	259/56	59(35-75)	I-IVa	3.18	NR	NR	NR	NR	NR	NR	NR	NR	surgery	OS	SCC	NLR: 87 37 107 84
Nakamura K et al. (2017)[36]	Japan	245	219/26	<65/≥65:110/135	T1a-b/N0-3	2.42	NR	NR	NR	NR	NR	NR	NR	37.2	surgery	OS/DFS	SCC/ADC /Others	NLR: 16 22 16 101
Sharaiha RZ et al. (2011)[37]	USA	295	237/58	62.8	I-IV	5	NR	NR	NR	NR	NR	NR	NR	31(13–61)	surgery	OS/DFS	SCC/ADC /Others	NR
Xiao Q et al. (2016)[38]	China	121	106/15	62(30–76)	I-III	1.77	NR	NR	NR	NR	NR	NR	NR	28.0(1–102)	surgery	OS/RFS	SCC	NLR: 45 13 37 26
Zhou XL et al. (2017)[39]	China	517	407/110	65(36–74)	II-IV	5	NR	NR	NR	NR	NR	NR	NR	17(2-76)	CRT	OS/PFS	SCC	NLR: 188 12 244 69
Arigami T et al. (2015)[40]	Japan	238	210/28	65(37–87)	I-III	3	NR	NR	NR	NR	NR	0/1,2	NR	26(1-182)	surgery	OS	SCC	mGPS: 44 26 54 114
Lindenmann J et al. (2017)[41]	Austria	174	148/26	61.1(22-81)	T0-4/N0-3	NR	NR	NR	NR	NR	1-2 vs 0	NR	NR	NR	mixed	AC/CSS	ADC/SCC	GPS: 33 6 41 25
Ma QL et	China	725	539/186	58(32-80)	TNM I/II/III	NR	NR	NR	NR	NR	1-2 vs	NR	NR	28	surgery	CSS	SCC	NR

al. (2016)[42]											0							
Okuno T et al. (2017)[43]	Japan	142	119/12	62(37–75)	(UICC 5th) IIB/III/IVa/IVb	NR	NR	NR	NR	NR	1 vs 0 2 vs 0	NR	NR	NR	CRT	OS	SCC	NR
Sugawara K et al. (2018)[44]	Japan	47	32/15	63(47–81)	I/II/III/Iva/IVb	NR	NR	NR	NR	NR	1 vs 0 2 vs 0	NR	NR	26.5(4.4–97.9)	surgery	OS	SCC/ADC	GPS: 16 1 23 7
Vashist YK et al. (2011)[45]	Germany	495	391/104	63.2(34.5–85.2)	T1-4/N-+/M-+	NR	NR	NR	NR	NR	0 vs 1	NR	NR	NR	surgery	OS/CSS	ADC/SCC	GPS: 188 20 161 66
Hirahara N et al. (2015)[46]	Japan	141	97/12	NR	Ia-IIIc	2.5	NR	NR	NR	NR	1-2 vs 0	NR	NR	NR	surgery	OS	NR	GPS: 19 3 33 31
Kitagawa H et al. (2017)[47]	Japan	140	112/28	65(43–85)	I-IV	NR	NR	NR	NR	NR	1-2 vs 0	NR	NR	36.6	mixed	OS/DFS	SCC/ADC /others	NLR: 25 45 21 49
Jomrich G et al. (2017)[48]	Austria	449	225/58	63(31–88)	UICC stage:0-4	NR	NR	NR	NR	NR	1 vs 0 2 vs 0	1 vs 0 2 vs 0	0.95	63(35-95)	surgery	OS/DFS	SCC/ADC	NR
Kimura J et al. (2016)[49]	Japan	142	131/11	65.1(40–82)	III and IV	NR	NR	NR	NR	NR	1 vs 0 2 vs 0	1 vs 0 2 vs 0	NR	NR	CT+RT	PFS/DFS/ CSS	SCC	NR
Chen P et al. (2017)[50]	China	163	134/29	57(31–79)	II/IV	NR	NR	NR	NR	NR	NR 0 vs 2	0 vs 1	NR	NR	radiotherapy	OS	SCC	NR
Otowa Y et al. (2016)[51]	Japan	100	88/12	68(44–82)	II/III	NR	NR	NR	NR	NR	NR Pre-NAC 0 vs 1/2 Post-NAC 0 vs 1	NR	NR	20.8(4.6–79.5)	surgery	OS	SCC	NR
Tian R et al. (2016)[52]	China	442	331/111	60.0(20.0-88.0)	I/II/III	NR	NR	NR	NR	NR	NR	1-2 vs 0	NR	DFS:35.6(24.3-46.9) OS:57.4(37.8-77.0)	surgery	OS/PFS	SCC	mGPS: 52 30 169 191
Walsh SM et al. (2016)[53]	Ireland	223	187/36	64(30–87)	I/II/III	NR	NR	NR	NR	NR	NR	1-2 vs 0	NR	21	surgery	OS/RFS	ADC	mGPS: 34 15 70 104
Zhang P et al. (2014)[54]	China	212	166/46	60.0(37-81)	I-II/ III/IV	NR	NR	NR	NR	NR	NR	0 vs 1 vs 2	NR	35.0(2-72)	radiotherapy	OS/PFS	SCC	mGPS: 103 19 59 31
Sun P et al. (2013)[55]	China	502	382/120	58.23±9.33	I–IV	NR	NR	NR	50	NR	NR	NR	NR	30	NR	OS	SCC	PNI: 92 47 194 169
Chen S al. (2016)[56]	China	308	268/40	NR	I–III	3.5	150	NR	45	NR	GPS1 vs GPS0, GPS2 vs	NR	NR	NR	Surgery		SCC	PNI: 83 19 129 74 GPS: 105 24 110 69 PLR:: 108 27

											GPS0							107 66
Okadome K et al. (2018)[57]	Japan	337	300/37	65.9	I–IV	NR	NR	NR	45	NR	NR	NR	NR	60	Surgery	OS/CSS	SCC/ADC /Others	PNI: 63 24 62 92
Migita K et al. (2018)[58]	Japan	137	76/16	NR	T1-T4/N0-N+	2.2	NR	NR	47	NR	NR	NR	NR	NR	mixed	OS	SCC	NR
Zhang H et al. (2019)[59]	China	266	172/94	67(48-87)	I–III	3.06	145.24	NR	NR	NR	NR	NR	0.13	NR	curative RT only or concurrent CRT	OS	SCC	NLR: 107 28 68 63 PLR: 100 33 74 59 CAR: 104 10 59 93
Otowa Y et al. (2017)[60]	Japan	149	129/20	66.9±8.3	II/III	NR	NR	NR	NR	NR	NR	NR	0.030	NR	Mixed	OS	SCC	NR
Liu XQ et al. (2019)[61]													0.15		radical radiotherapy	OS		NR
Shao YJ et al. (2015)[62]	China	916 primary:633 validation:283	primary :484/149 validation:211/72	Primary:60(37–83) Validation:61(38–84)	I–III	1.7	120	3.57	NR	NR	0/1/2	0/1/2	0.06/0.12	39(3-146.2)	Surgery	OS	SCC	NR
Liu DQ et al. (2016)[63]	China	260	217/43	59(39–83)	I-IV	NR	NR	NR	NR	NR	0/1/2	NR	NR	40.5 (2–91)	surgery	OS/DFS	SCC	NR
Wang CY et al. (2012)[64]	Taiwan, China	271	261/10	NR	I-IV	NR	NR	NR	NR	NR	0/1,2	NR	NR	30 (5–81)	mixed	OS	SCC/ADC	NR
Feng JF et al. (2014)[65]	China	493	420/73	59.1(34 to 80)	T1-4a/N-+	NR	NR	NR	NR	NR	2/0	NR	NR	45	surgery	NR	SCC	NR
Lindenmann J et al. (2014)[66]	Austria	214	181/33	67 ± 11.84(21–93)	III-IV	NR	NR	NR	NR	NR	0/1/2	NR	NR	NR	CT+RT	NR	SCC/ADC	NR
Matsuda S et al. (2015)[67]	Japan	199	180/19	62.9 ± 8.29	I-IV	NR	NR	NR	NR	NR	0/1/2	NR	NR	28.5	mixed	OS/DFS	SCC/ADC /Others	NR
Liu XM et al. (2017)[68]	China	162	127/35	63 (38–70)	II-III	NR	NR	4.02	NR	NR	NR	NR	NR	23.3 (8–43.7)	mixed	OS/PFS	SCC	LMR: 61 20 43 38
Tian R et al. (2016)[69]	China	260	193/67	59.0 (20.0-87.0)	I-III	NR	NR	NR	NR	NR	NR	0/1,2	NR	46.5	surgery	OS/DFS	SCC	NR
Nakamura M et al. (2014)[70]	Japan	168	135/33	67(47–85)	0-IV	NR	NR	NR	NR	NR	NR	0 vs 2	NR	39(5–99)	mixed	NR	SCC	NR
Han LH et al. (2015)[71]	China	206	165/41	60(32-84)	I-IV/T1-4/N0-3	NR	NR	2.9	45.5	NR	NR	NR	NR	39.5(3-71)	surgery	OS/DFS	SCC	NR
Miyazaki T et al.	Japan	192	173/19	65.8(42-86)	I-IV/T1-4/N0-3/M0-1	3.49	NR	NR	47.7	NR	NR	NR	NR	26.5(1-108)	surgery	OS	NR	PNI: 31 34 39 88

(2016)[72]	

Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; EC, esophageal carcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, c-reactive protein-to-albumin ratio; SII, systemic inflammation index; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative

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Table 1. Subgroup analysis and meta analysis of 8 indicators in OS, CSS, and DFS.

	OS					CSS					DFS				
	N	HR(95% CI), *P*	I^2(%), *P*	Begg's *P*, Egger's *P*	*P*-reg	N	HR(95% CI), *P*	I^2(%), *P*	Begg's *P*, Egger's *P*	*P*-reg	N	HR(95% CI), *P*	I^2(%), *P*	Begg's *P*, Egger's *P*	*P*-reg
PNI															
Overall	11	1.51(1.36-1.68),<0.001	45.8, 0.048	0.036, 0.188											
Country															
China	4	1.45(1.27-1.64),<0.001	36.9, 0.190	0.497, 0.092	0.184										
Non-China	7	1.82(1.38-2.40),<0.001	51.4, 0.054	0.099, 0.006											
Sample size															
<255	7	1.69(1.19-2.40), 0.003	66.8, 0.006	0.099, 0.058	0.797										
≥255	4	1.52(1.34-1.72),<0.001	0.0, 0.949	0.174, 0.052											
Cut-off value															
<46	5	1.68(1.13-2.50), 0.010	59.5, 0.043	0.050, 0.432	0.774										
≥46	6	1.49(1.33-1.67),<0.001	39.9, 0.139	0.348, 0.288											
Treatment															
Surgery	7	1.46(1.20-1.78),<0.001	54.4, 0.041	0.752, 0.293	Ref										
Mixed	3	2.18(1.52-3.11),<0.001	0.0, 0.649	0.602, 0.448	0.139										
NR	1	1.50(1.16-1.93), NR	NR	NR	0.906										
Pathology															
SCC	9	1.56(1.39-1.76),<0.001	41.5, 0.091	0.061, 0.184	0.144										
Mixed	1	1.67(1.14-2.44), NR	NR	NR	0.231										
NR	1	1.09(0.80-1.49), NR	NR	NR	Ref										
Clinical stage															
0-III	5	1.62(1.41-1.86),<0.001	32.2, 0.207	0.050,<0.001	0.229										
0-IV	6	1.41(1.10-1.80), 0.006	52.4, 0.062	0.348, 0.687											
Follow-up															
<36	4	1.46(1.15-1.86), 0.002	53.4, 0.092	1.000, 0.523	0.962										
≥36	4	1.45(1.23-1.70),<0.001	46.1, 0.135	1.000, 0.801	Ref										
NR	3	2.26(1.63-3.14),<0.001	0.0, 0.988	0.602, 0.337	0.014										
Age															
<63.4	4	1.45(1.27-1.64),<0.001	36.9, 0.190	0.497, 0.092	Ref										
≥63.4	6	1.77(1.31-2.41),<0.001	55.0, 0.049	0.039, 0.016	0.270										
NR	1	2.21(1.28-3.82), NR	NR	NR	0.249										
Sex ratio															

<4.75	5	1.46(1.29-1.66),<0.001	25.1, 0.254	0.624, 0.545	0.253										
≥4.75	6	1.84(1.34-2.53),<0.001	59.1, 0.032	0.091, 0.011											
NLR															
Overall	34	1.43(1.30-1.58),<0.001	61.7,<0.001	0.113, 0.428		8	1.21(1.04-1.41), 0.011	43.4, 0.089	0.621, 0.695		7	1.39(1.10-1.75), 0.005	60.9, 0.018	0.453, 0.344	
Country															
China	23	1.43(1.30-1.57),<0.001	51.5, 0.002	0.107, 0.399	0.883	4	1.15(0.97-1.36), 0.117	38.8, 0.179	0.174, 0.971	0.436	5	1.22(1.05-1.42), 0.010	0.0, 0.514	0.050, 0.062	0.018
Non-China	11	1.45(1.06-1.98), 0.022	75.5,<0.001	0.484, 0.513		4	1.42(1.06-1.90), 0.020	49.8, 0.113	0.497, 0.376		2	2.43(1.69-3.49),<0.001	0.0, 0.604	NR	
Sample size															
<297	18	1.45(1.19-1.76),<0.001	65.6,<0.001	0.088, 0.192	0.965	2	0.95(0.59-1.54), 0.848	43.6, 0.183	NR	0.395	4	1.56(0.95-2.58), 0.080	78.9, 0.003	0.174, 0.316	0.553
≥297	15	1.42(1.27-1.58),<0.001	60.2, 0.001	0.347, 0.809	Ref	6	1.24(1.06-1.45), 0.006	47.5, 0.090	0.091, 0.138		3	1.29(1.08-1.54), 0.005	0.0, 0.799	0.117, 0.089	
NR	1	1.84(1.21-2.83), NR	NR	NR	0.466	NR	NR	NR	NR		NR	NR	NR	NR	
Cut-off value															
<2.5	16	1.38(1.20-1.58),<0.001	56.9, 0.003	0.072, 0.082	0.563	3	1.43(1.04-1.97), 0.030	66.5, 0.051	0.602, 0.268	0.493	4	1.34(0.94-1.91), 0.103	69.2, 0.021	1.000, 0.704	0.763
≥2.5	18	1.48(1.28-1.71),<0.001	62.5,<0.001	0.733, 0.623		5	1.16(0.98-1.37), 0.084	21.9, 0.275	0.142, 0.737		3	1.47(1.03-2.11), 0.034	61.8, 0.073	0.117, 0.377	
Treatment															
Surgery	24	1.32(1.19-1.48),<0.001	56.9,<0.001	0.215, 0.290	Ref	8	1.21(1.04-1.41), 0.010	43.4, 0.089	0.621, 0.695		7	1.39(1.10-1.75), 0.005	60.9, 0.018	0.453, 0.344	
CRT	3	1.79(1.51-2.13),<0.001	0.0, 0.704	0.602, 0.960	0.090	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mixed	7	1.73(1.51-1.99),<0.001	39.3, 0.130	0.176, 0.779	0.062	NR	NR	NR	NR		NR	NR	NR	NR	
Pathology															
SCC	27	1.42(1.28-1.57),<0.001	56.0,<0.001	0.084, 0.517	0.683	8	1.21(1.04-1.41), 0.011	43.4, 0.089	0.621, 0.695		5	1.22(1.05-1.42), 0.010	0.0, 0.514	0.050, 0.062	0.018
Mixed	4	1.75(0.84-3.66), 0.137	87.9,<0.001	1.000, 0.661	0.420	NR	NR	NR	NR	NR	2	2.43(1.69-3.49),<0.001	0.0, 0.604	NR	
NR	3	1.36(1.13-1.65), 0.002	0.0, 0.509	0.602, 0.452	Ref	NR	NR	NR	NR		NR	NR	NR	NR	
Clinical stage															
0-III	22	1.31(1.22-1.41),<0.001	43.0, 0.018	0.019, 0.039	0.262	6	1.12(0.96-1.32), 0.159	30.4, 0.207	0.573, 0.701	0.083	5	1.35(1.15-1.57),<0.001	36.4, 0.179	0.624, 0.229	0.963
0-IV	12	1.56(1.28-1.89),<0.001	71.1,<0.001	0.784, 0.600		2	1.80(1.24-2.60), 0.002	0.0, 0.907	0.317, NR		2	1.40(0.55-3.57), 0.486	89.0, 0.003	0.317, NR	
Follow-up															
<37	12	1.60(1.34-1.91),<0.001	60.5, 0.003	0.493, 0.485	0.079	2	1.80(1.24-2.60), 0.002	0.0, 0.907	0.317, NR	0.105	2	1.40(0.55-3.57), 0.486	89.0, 0.003	0.317, NR	0.963
≥37	10	1.26(1.15-1.38),<0.001	45.4, 0.058	0.531, 0.844	Ref	3	1.11(0.73-1.69), 0.623	67.1, 0.048	0.602, 0.534	0.740	5	1.35(1.15-1.57),<0.001	36.4, 0.179	0.624, 0.229	
NR	12	1.45(1.20-1.76),<0.001	64.8, 0.001	0.217, 0.832	0.307	3	1.06(0.84-1.34), 0.614	0.0, 0.712	0.117, 0.166	Ref	NR	NR	NR	NR	
Age															
<61.1	15	1.37(1.22-1.53),<0.001	53.9, 0.007	0.083, 0.446	Ref	3	1.28(1.02-1.61), 0.033	40.9, 0.184	0.602, 0.932		4	1.28(1.09-1.50), 0.003	0.0, 0.919	0.174, 0.075	Ref
≥61.1	11	1.45(1.16-1.82), 0.001	70.3,<0.001	0.697, 0.636	0.706	NR	NR	NR	NR	0.759	2	1.40(0.55-3.57), 0.486	89.0, 0.003	0.317, NR	0.775
NR	8	1.56(1.16-2.10), 0.003	62.9, 0.009	0.805, 0.875	0.461	5	1.20(0.88-1.62), 0.246	53.4, 0.072	1.000, 0.651		1	2.76(1.50-5.03), NR	NR	NR	0.152
Sex ratio															
<5.12	17	1.38(1.22-1.56),<0.001	62.3,<0.001	0.510, 0.856	0.458	7	1.14(0.96-1.34), 0.129	35.6, 0.157	0.453, 0.417	0.287	6	1.30(1.26-1.50),<0.001	48.4, 0.085	0.573, 0.960	0.123

≥5.12	17	1.52(1.27-1.81),<0.001	62.8,<0.001	0.021, 0.286		1	1.59(1.13-2.24), NR	NR	NR		1	2.76(1.50-5.03), NR	NR	NR	
PLR															
Overall	19	1.26(1.18-1.35),<0.001	29.8, 0.108	0.054, 0.108							5	1.30(1.12-1.51),<0.001	33.0, 0.202	0.142, 0.472	
Country															
China	15	1.26(1.17-1.35),<0.001	42.1, 0.043	0.125, 0.121	0.571						5	1.30(1.12-1.51),<0.001	33.0, 0.202	0.142, 0.472	NR
Non-China	4	1.40(1.07-1.83), 0.016	0.0, 0.854	1.000, 0.771							NR	NR	NR	NR	
Sample size															
<303	10	1.38(1.18-1.62),<0.001	25.5, 0.209	0.245, 0.157	0.341						2	0.99(0.71-1.39), 0.958	0.0, 0.682	0.602, 0.463	0.174
≥303	9	1.24(1.15-1.34),<0.001	33.7, 0.148	0.297, 0.206							3	1.39(1.18-1.64),<0.001	24.5, 0.266	NR	
Cut-off value															
<143	10	1.24(1.14-1.35),<0.001	11.7, 0.335	0.006, 0.001	0.567						3	1.39(1.18-1.64),<0.001	24.5, 0.266	NR	0.174
≥143	9	1.33(1.17-1.52),<0.001	44.7, 0.071	1.000, 0.858							2	0.99(0.71-1.39), 0.958	0.0, 0.682	0.602, 0.463	
Treatment															
Surgery	15	1.24(1.16-1.33),<0.001	24.2, 0.186	0.458, 0.553	0.079						5	1.30(1.12-1.51),<0.001	33.0, 0.202	0.142, 0.472	NR
Mixed	4	1.61(1.26-2.06),<0.001	1.6, 0.384	0.174, 0.086							NR	NR	NR	NR	
Pathology															
SCC	17	1.27(1.19-1.37),<0.001	33.2, 0.091	0.070, 0.122	0.432						5	1.30(1.12-1.51),<0.001	33.0, 0.202	0.142, 0.472	
Mixed	1	1.55(0.95-2.59), NR	NR	NR	0.356						NR	NR	NR	NR	NR
NR	1	1.12(0.87-1.43), NR	NR	NR	Ref						NR	NR	NR	NR	
Clinical stage															
0-III	15	1.27(1.18-1.36),<0.001	34.7, 0.091	0.033, 0.039	0.733						4	1.34(1.15-1.57),<0.001	37.6, 0.187	0.497, 0.709	0.461
0-IV	4	1.21(0.94-1.57), 0.139	24.5, 0.265	0.497, 0.205							1	1.05(0.69-1.60), NR	NR	NR	
Follow-up															
<39	4	1.17(1.01-1.36), 0.041	18.8, 0.296	0.497, 0.311	Ref						1	1.05(0.69-1.60), NR	NR	NR	0.461
≥39	8	1.19(1.09-1.30),<0.001	0.0, 0.974	0.458, 0.520	0.855						4	1.34(1.15-1.57),<0.001	37.6, 0.187	0.497, 0.709	
NR	7	1.71(1.46-2.02),<0.001	0.0, 0.682	0.293, 0.441	0.004						NR	NR	NR	NR	
Age															
<61.2	12	1.26(1.17-1.35),<0.001	41.5, 0.065	0.100, 0.097	Ref						4	1.34(1.15-1.57),<0.001	37.6, 0.187	0.497, 0.709	0.461
≥61.2	6	1.33(1.10-1.61), 0.003	21.9, 0.269	0.348, 0.470	0.698						1	1.05(0.69-1.60), NR	NR	NR	
NR	1	1.27(0.76-2.12), NR	NR	NR	0.994						NR	NR	NR	NR	
Sex ratio															
<4.55	8	1.22(1.12-1.33),<0.001	0.0, 0.863	1.000, 0.810	0.265						4	1.34(1.15-1.57),<0.001	37.6, 0.187	0.497, 0.709	0.461
≥4.55	11	1.41(1.17-1.69),<0.001	51.4, 0.024	0.102, 0.213							1	1.05(0.69-1.60), NR	NR	NR	
LMR															
Overall	13	1.37(1.14-1.65), 0.001	84.9,<0.001	0.028, 0.167							6	1.08(0.85-1.39), 0.522	79.8,<0.001	0.573, 0.838	

Country											
China	12	1.35(1.11-1.63), 0.002	85.7,<0.001	0.028, 0.229	0.525	6	1.08(0.85-1.39), 0.522	79.8,<0.001	0.573, 0.838	NR
Non-China	1	1.87(1.09-3.23), NR	NR	NR		NR	NR	NR	NR	
Sample size										
<280	7	1.86(1.36-2.55),<0.001	75.4,<0.001	0.881, 0.609	0.006	3	1.44(1.19-1.76),<0.001	0.0, 0.686	0.117, 0.290	0.085
≥280	6	1.09(0.97-1.22), 0.168	54.1, 0.053	0.348, 0.357		3	0.81(0.54-1.20), 0.296	87.0,<0.001	0.117, 0.013	
Cut-off value										
<3.57	6	1.65(1.11-2.47), 0.014	91.1,<0.001	0.851, 0.191	0.174	4	1.18(1.08-1.29),<0.001	49.5, 0.115	0.042, 0.025	0.034
≥3.57	7	1.17(0.97-1.42), 0.110	71.1, 0.002	0.293, 0.627		2	0.65(0.38-1.11), 0.116	73.7, 0.051	NR	
Treatment										
Surgery	9	1.20(1.02-1.41), 0.033	62.2, 0.007	0.144, 0.496	Ref	4	1.00(0.61-1.62), 0.984	86.3,<0.001	1.000, 0.995	
CCRT	1	3.60(2.66-4.88), NR	NR	NR	0.006	NR	NR	NR	NR	0.651
Mixed	3	1.36(1.01-1.83), 0.045	73.1, 0.024	0.117, 0.179	0.539	2	1.14(1.04-1.25), 0.005	12.4, 0.285	NR	
Pathology										
SCC	13	1.37(1.14-1.65), 0.001	84.9,<0.001	0.028, 0.167	NR	6	1.08(0.85-1.39), 0.522	79.8,<0.001	0.573, 0.838	NR
Mixed	NR	NR	NR	NR		NR	NR	NR	NR	
Clinical stage										
0-III	11	1.46(1.20-1.77),<0.001	84.7,<0.001	0.010, 0.055	0.176	4	1.15(0.92-1.45), 0.219	73.5, 0.010	0.174, 0.779	0.484
0-IV	2	0.93(0.39-2.21), 0.875	90.2, 0.001	0.317, NR		2	0.84(0.28-2.54), 0.754	92.2,<0.001	0.317, NR	
Follow-up										
<39	4	1.67(0.77-3.65), 0.198	94.3,<0.001	1.000, 0.505	0.429	2	0.89(0.26-3.02), 0.848	93.5,<0.001	0.317, NR	Ref
≥39	7	1.20(1.09-1.32),<0.001	0.0, 0.524	0.004, 0.002	0.891	3	1.15(0.79-1.66), 0.466	78.2, 0.010	0.117, 0.295	0.661
NR	2	1.12(1.02-1.23), 0.014	0.0, 0.515	0.317, NR	Ref	1	1.12(1.02-1.24), NR	NR	NR	0.767
Age										
<61.5	7	1.16(1.08-1.24),<0.001	12.9, 0.331	0.024, 0.044	Ref	4	1.17(0.92-1.50), 0.208	75.0, 0.007	0.174, 0.723	0.104
≥61.5	4	1.59(0.67-3.93), 0.312	94.3,<0.001	0.497, 0.692	0.373	1	0.47(0.28-0.78), NR	NR	NR	Ref
NR	2	1.46(1.12-1.90), 0.005	5.1, 0.305	0.317, NR	0.544	1	1.33(0.99-1.79), NR	NR	NR	0.119
Sex ratio										
<4.32	7	1.21(1.10-1.33),<0.001	21.5, 0.266	0.004, 0.005	0.575	3	1.15(0.79-1.66), 0466	78.2, 0.010	0.117, 0.295	0.708
≥4.32	6	1.50(0.91-2.46), 0.109	93.1,<0.001	0.851, 0.462		3	0.99(0.60-1.65), 0.969	87.1,<0.001	0.602, 0.808	
SII										
Overall	7	1.46(1.30-1.65),<0.001	41.0, 0.118	0.099, 0.113						
Country										
China	6	1.53(1.27-1.85),<0.001	50.5, 0.073	0.091, 0.082	0.890					
Non-China	1	1.65(0.74-3.96), NR	NR	NR						

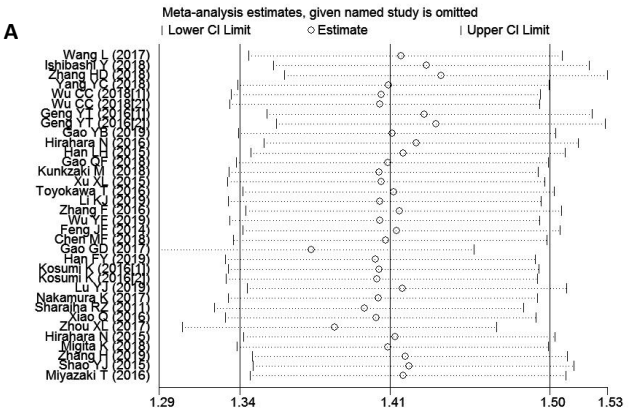
Sample size															
<298	3	2.31(1.61-3.33),<0.001	0.0, 0.655	0.602, 0.400	0.047										
≥298	4	1.38(1.22-1.57),<0.001	0.0, 0.481	0.497, 0.490											
Cut-off value															
<410	3	1.31(1.11-1.54), 0.001	0.0, 0.372	0.117, 0.052	0.140										
≥410	4	1.67(1.40-1.99),<0.001	30.6, 0.229	0.497, 0.595											
Treatment															
Surgery	6	1.45(1.28-1.64),<0.001	45.0, 0.106	0.188, 0.204	0.428										
CRT	1	2.29(0.98-5.30), NR	NR	NR											
Pathology															
SCC	6	1.53(1.27-1.85),<0.001	50.5, 0.073	0.091, 0.082	0.890										
Mixed	1	1.65(0.74-3.96), NR	NR	NR											
Clinical stage															
0-III	5	1.40(1.23-1.59),<0.001	0.0, 0.435	0.327, 0.181	0.068										
0-IV	2	2.32(1.55-3.48),<0.001	0.0, 0.358	0.317, NR											
Follow-up															
<36	1	2.29(0.98-5.30), NR	NR	NR	0.469										
≥36	4	1.54(1.20-1.96), 0,001	66.6, 0.029	0.174, 0.098	0.908										
NR	2	1.46(1.08-1.98), 0.013	0.0, 0.771	0.317, NR	Ref										
Age															
<63.0	3	1.37(1.19-1.58),<0.001	16.6, 0.301	0.602, 0.607	Ref										
≥63.0	2	2.32(1.55-3.48),<0.001	0.0, 0.358	0.317, NR	0.084										
NR	2	1.53(1.13-2.06), 0.006	0.0, 0.319	0.317, NR	0.580										
Sex ratio															
<4.55	3	1.40(1.20-1.64),<0.001	46.1, 0.156	0.602, 0.475	0.646										
≥4.55	4	1.55(1.29-1.87),<0.001	48.0, 0.123	0.174, 0.468											
GPS															
Overall	15	2.35(1.99-2.76),<0.001	36.5, 0.078	0.729, 0.838		5	1.64(1.33-1.94),<0.001	45.5, 0.119	0.624, 0.905		5	2.44(1.28-4.67), 0.007	57.5, 0.052	1.000, 0.751	
Country															
China	4	2.23(1.57-3.17),<0.001	7.5, 0.356	0.497, 0.323	0.952	4	1.66(1.48-1.87),<0.001	47.4, 0.812	0.734, 0432	0.246	1	2.75(0.37-20.31), NR	NR	NR	0.931
Non-China	11	2.38(1.98-2.86),<0.001	46.5, 0.044	0.484, 0.699		1	2.53(1.49-4.28), NR	NR	NR		4	2.43(1.17-5.06), 0.017	68.0, 0.025	0.497, 0.781	
Sample size															
<237	9	2.47(1.98-3.07),<0.001	48.5, 0.050	0.835, 0.944	0.653	1	2.53(1.49-4.28), NR	NR	NR	0.246	3	3.11(2.03-4.78),<0.001	0.0, 0.399	0.602, 0.499	0.108
≥237	6	2.21(1.73-2.82),<0.001	17.5, 0.300	0.851, 0.814		4	1.66(1.48-1.87),<0.001	47.4, 0.812	0.734, 0432		2	1.06(0.53-2.14), 0.867	0.0, 0.320	NR	
Cut-off value															

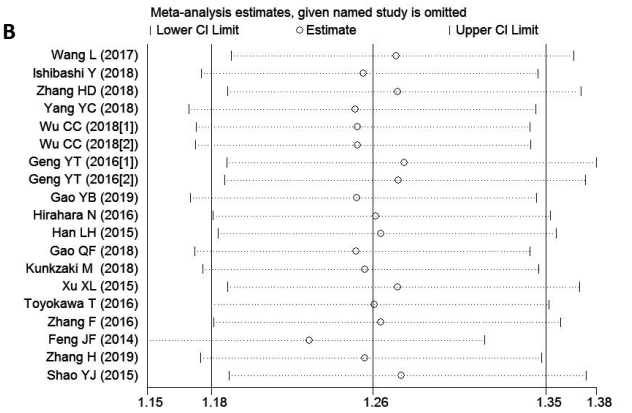
1-2 VS 0	7	2.49(1.95-3.18),<0.001	39.0, 0.132	0.293, 0.232	0.821	2	1.48(1.25-1.77),<0.001	0.0, 0.801	NR	0.169	1	4.92(2.12-11.64), NR	NR	NR	0.303
2 VS 0	8	2.24(1.80-2.78),<0.001	40.6, 0.108	0.805, 0.553		3	1.89(1.62-2.22),<0.001	42.5, 0.829	1.000, 0.861		4	1.95(1.30-2.93), 0.001	47.5, 0.126	0.497, 0.866	
Treatment															
Surgery	8	2.16(1.73-2.70),<0.001	52.2, 0.041	0.621, 0.575	Ref	5	1.64(1.33-1.94),<0.001	45.5, 0.119	0.624, 0.905	NR	2	1.06(0.53-2.14), 0.867	0.0, 0.320	0.317, NR	Ref
CRT	2	2.81(1.37-5.76), 0..005	76.1, 0.041	NR	0.449	NR	NR	NR	NR		1	2.53(1.49-4.28), NR	NR	NR	0.192
Mixed	5	2.42(1.73-3.73),<0.001	0.0, 0.786	0.624, 0.364	0.730	NR	NR	NR	NR		2	4.72(2.24-9.95),<0.001	0.0, 0.843	NR	0.104
Pathology															
SCC	5	2.17(1.59-2.96),<0.001	40.6, 0.151	0.624, 0.620	0.706	5	1.64(1.33-1.94),<0.001	45.5, 0.119	0.624, 0.905		2	2.54(1.53-4.23),<0.001	0.0, 0.936	NR	0.945
Mixed	8	2.65(2.12-3.31),<0.001	44.3, 0.083	0.621, 0.847	0.342	NR	NR	NR	NR	NR	3	2.50(0.74-8.47), 0.141	78.1, 0.010	0.602, 0.680	
NR	2	1.89(1.31-2.74), 0.001	0.0, 0.786	NR	Ref	NR	NR	NR	NR		NR	NR	NR	NR	
Clinical stage															
0-III	4	2.16(1.63-2.85),<0.001	0.0, 0.511	0.174, 0.201	0.741	4	1.66(1.48-1.87),<0.001	47.4, 0.812	0.734, 0432	0.246	NR	NR	NR	NR	NR
0-IV	11	2.45(2.00-3.00),<0.001	47.9, 0.038	0.938, 0.933		1	2.53(1.49-4.28), NR	NR	NR		5	2.44(1.28-4.67), 0.007	57.5, 0.052	1.000, 0.751	
Follow-up															
<40	5	3.30(2.16-5.05),<0.001	16.0, 0.312	0.624, 0.701	0.027	1	1.63(1.16-2.29), NR	NR	NR	0.567	2	4.72(2.24-9.95),<0.001	0.0, 0.843	NR	0.104
≥40	4	1.56(1.11-2.20), 0.011	21.0, 0.284	0.497, 0.860	Ref	3	1.73(1.53-1.97),<0.001	69.2, 0.889	1.000, 0.731	0.416	2	1.06(0.53-2.14), 0.867	0.0, 0.320	0.317, NR	Ref
NR	6	2.51(2.04-3.08),<0.001	3.8, 0.392	0.851, 0.847	0.052	1	1.18(0.64-2.17), NR	NR	NR	Ref	1	2.53(1.49-4.28), NR	NR	NR	0.192
Age															
<62.1	5	2.15(1.66-2.78),<0.001	0.0, 0.490	0.050, 0.074	0.821	4	1.72(1.53-1.94),<0.001	54.6, 0.831	1.000, 0.720		1	2.75(0.37-20.31), NR	NR	NR	0.931
≥62.1	8	2.46(1.65-3.68),<0.001	59.6, 0.015	0.805, 0.690	0.632	NR	NR	NR	NR	0.369	4	2.43(1.17-5.06), 0.017	68.0, 0.025	0.497, 0.781	
NR	2	2.03(1.15-3.58), 0.014	0.0, 0.972	0.317, NR	Ref	1	1.18(0.64-2.17), NR	NR	NR		NR	NR	NR	NR	
Sex ratio															
<5.48	8	2.51(1.70-3.70),<0.001	51.9, 0.042	0.322, 0.602	0.690	1	1.63(1.16-2.29), NR	NR	NR	0.893	3	2.23(0.64-7.81), 0.211	76.3, 0.015	0.602, 0.826	0.724
≥5.48	7	2.25(1.80-2.82),<0.001	17.0, 0.300	0.881, 0.572		4	1.71(1.51-1.93),<0.001	62.3, 0.852	0.734, 0.954		2	2.66(1.62-4.37),<0.001	0.0, 0.560	0.317, NR	
mGPS															
Overall	14	1.69(1.49-1.92),<0.001	48.4, 0.022	0.702, 0.354											
Country															
China	8	1.90(1.47-2.46),<0.001	63.2, 0.008	0.083, 0.107	0.370										
Non-China	6	1.52(1.12-2.06), 0.007	10.9, 0.346	0.348, 0.795											
Sample size															
<212	6	2.50(1.91-3.28),<0.001	0.0, 0.652	0.348, 0.249	0.014										
≥212	8	1.52(1.31-1.75),<0.001	40.1, 0.111	0.805, 0.893											
Cut-off value															
1-2 VS 0	9	1.56(1.35-1.81),<0.001	4.7, 0.077	1.000, 0.736	0.092										
2 VS 0	5	2.23(1.70-2.92),<0.001	31.5, 0.212	0.624, 0.943											

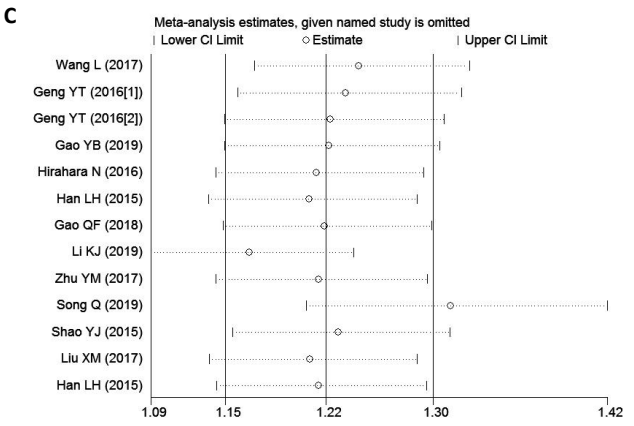
Treatment					
Surgery	8	1.40(1.17-1.68),<0.001	31.2, 0.179	0.805, 0.577	Ref
RT	2	2.12(1.26-3.57), 0.005	73.3, 0.053	NR	0.138
Mixed	4	2.56(1.81-3.62),<0.001	0.0, 0.824	1.000, 0.888	0.030
Pathology					
SCC	11	1.88(1.48-2.40),<0.001	56.7, 0.010	0.815, 0.222	0.383
AD	1	1.24(0.69-2.22), NR	NR	NR	0.932
Mixed	1	1.17(0.53-2.60), NR	NR	NR	Ref
NR	1	1.82(1.17-2.83), NR	NR	NR	0.502
Clinical stage					
0-III	9	1.64(1.26-2.13),<0.001	50.9, 0.038	0.532, 0.227	0.314
0-IV	5	1.89(1.56-2.28),<0.001	38.7, 0.163	1.000, 0.475	
Follow-up					
<39	4	1.56(1.28-1.91),<0.001	0.0, 0.533	0.497, 0.066	Ref
≥39	6	1.64(1.18-2.26), 0.003	54.2, 0.053	0.188, 0.166	0.714
NR	4	2.66(1.98-3.59),<0.001	0.0, 0.783	0.497, 0.550	0.026
Age					
<61.7	8	1.90(1.47-2.46),<0.001	63.2, 0.008	0.083, 0.107	0.370
≥61.7	6	1.52(1.12-2.06), 0.007	10.9, 0.346	0.348, 0.795	
Sex ratio					
<4.91	7	1.77(1.32-2.38),<0.001	64.0, 0.011	0.652, 0.409	0.930
≥4.91	7	1.81(1.44-2.29),<0.001	25.4, 0.235	0.652, 0.680	
CAR					
Overall	10	1.84(1.60-2.10),<0.001	41.8, 0.079	0.531, 0.809	
Country					
China	5	1.90(1.50-2.41),<0.001	55.1, 0.063	1.000, 0.692	0.415
Non-China	4	1.58(1.13-2.20), 0.008	40.9, 0.166	0.497, 0.377	Ref
NR	1	2.46(1.18-5.13), NR	NR	NR	0.360
Sample size					
<283	5	2.06(1.59-2.66),<0.001	0.0, 0.585	0.142, 0.143	0.396
≥283	4	1.71(1.26-2.31), 0.001	65.4, 0.021	0.174, 0.411	Ref
NR	1	2.46(1.18-5.13), NR	NR	NR	0.406
Cut-off value					
<0.13	4	1.63(1.35-1.96),<0.001	0.0, 0.443	0.174, 0.185	0.490
≥0.13	5	2.19(1.78-2.69),<0.001	43.2, 0.133	0.142, 0.271	0.230

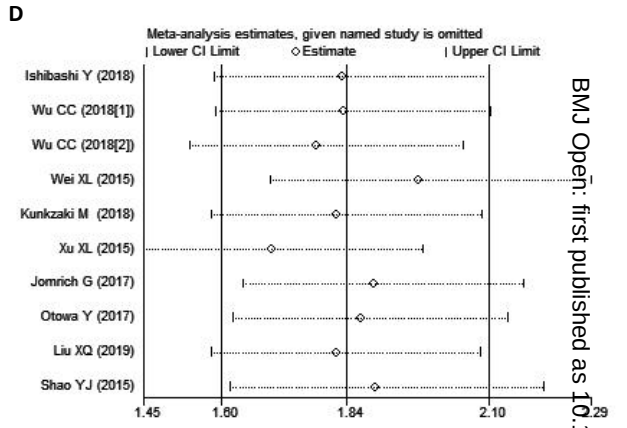
NR	1	1.15(0.56-2.70), NR	NR	NR	Ref
Treatment					
Surgery	4	1.79(1.28-2.50), 0.001	62.4, 0.047	0.497, 0.432	0.963
RT	1	2.46(1.18-5.13), NR	NR	NR	0.516
Mixed	5	1.71(1.39-2.11),<0.001	36.8, 0.176	1.000, 0.632	Ref
Pathology					
SCC	6	1.70(1.44-2.01),<0.001	21.2, 0.274	0.851, 0.586	0.535
Mixed	2	1.38(0.63-3.03), 0.427	67.2, 0.081	NR	Ref
NR	2	2.44(1.86-3.20),<0.001	0.0, 0.981	NR	0.134
Clinical stage					
0-III	5	2.01(1.69-2.39),<0.001	33.5, 0.198	0.624, 0.603	0.230
0-IV	4	1.50(1.19-1.90), 0.001	39.4, 0.175	1.000, 0.791	Ref
NR	1	2.46(1.18-5.13), NR	NR	NR	0.332
Follow-up					
<40	2	1.53(1.25-1.89),<0.001	0.0, 0.390	0.317, NR	Ref
≥40	2	1.56(0.58-4.16), 0.377	84.7, 0.010	0.317, NR	0.405
NR	6	2.10(1.65-2.68), 0.001	0.0, 0.693	0.348, 0.261	0.213
Age					
<62.2	5	1.90(1.50-2.41),<0.001	55.1, 0.063	1.000, 0.692	0.415
≥62.2	4	1.58(1.13-2.20), 0.008	40.9, 0.166	0.497, 0.377	Ref
NR	1	2.46(1.18-5.13), NR	NR	NR	0.360
Sex ratio					
<5.5	4	1.53(1.26-1.85),<0.001	32.8, 0.216	0.497, 0.875	Ref
≥5.5	5	2.21(1.81-2.70),<0.001	0.0, 0.471	0.014, 0.048	0.045
NR	1	2.46(1.18-5.13), NR	NR	NR	0.285

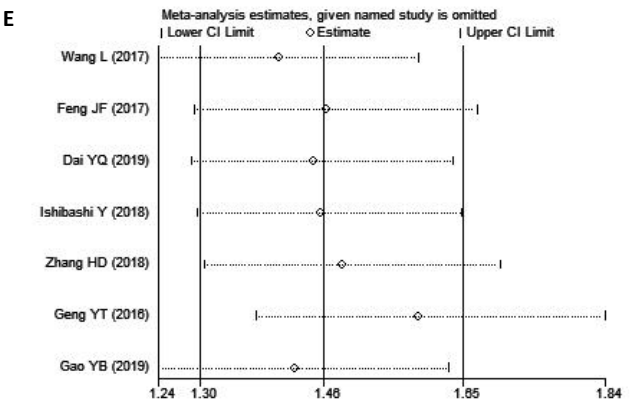
Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; EC, esophageal carcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, c-reactive protein-to-albumin ratio; SII, systemic inflammation index; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; Ref, reference; P-reg, the P-value of meta regression; NR, not reported.

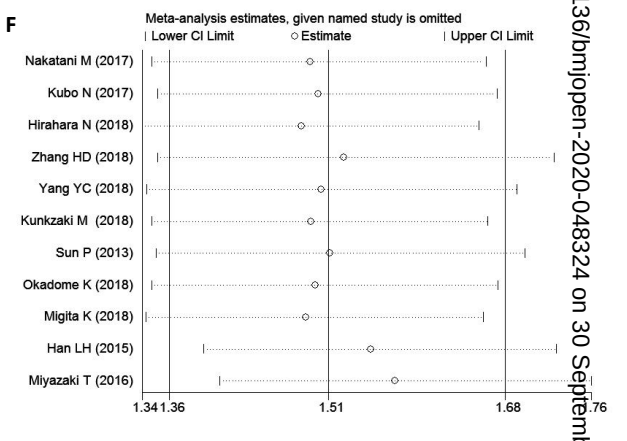


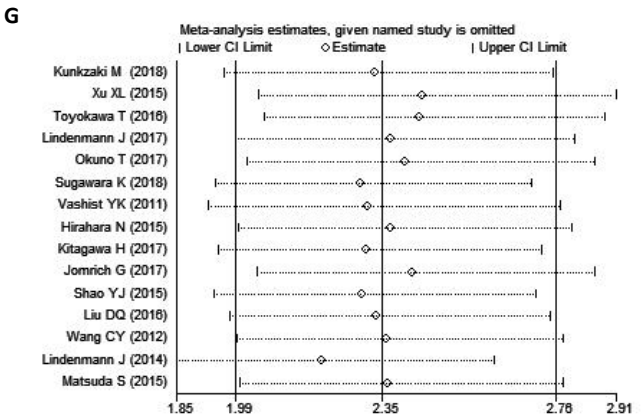


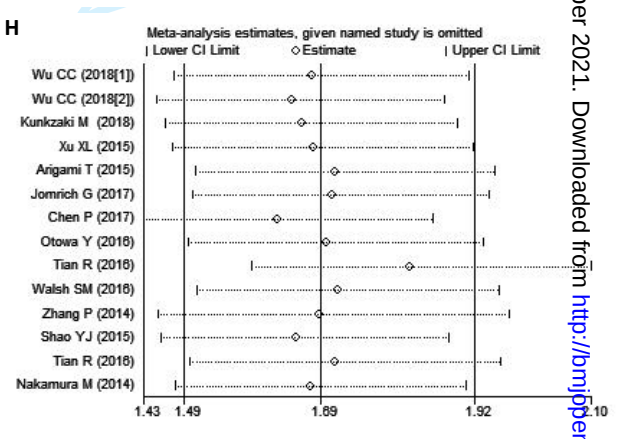












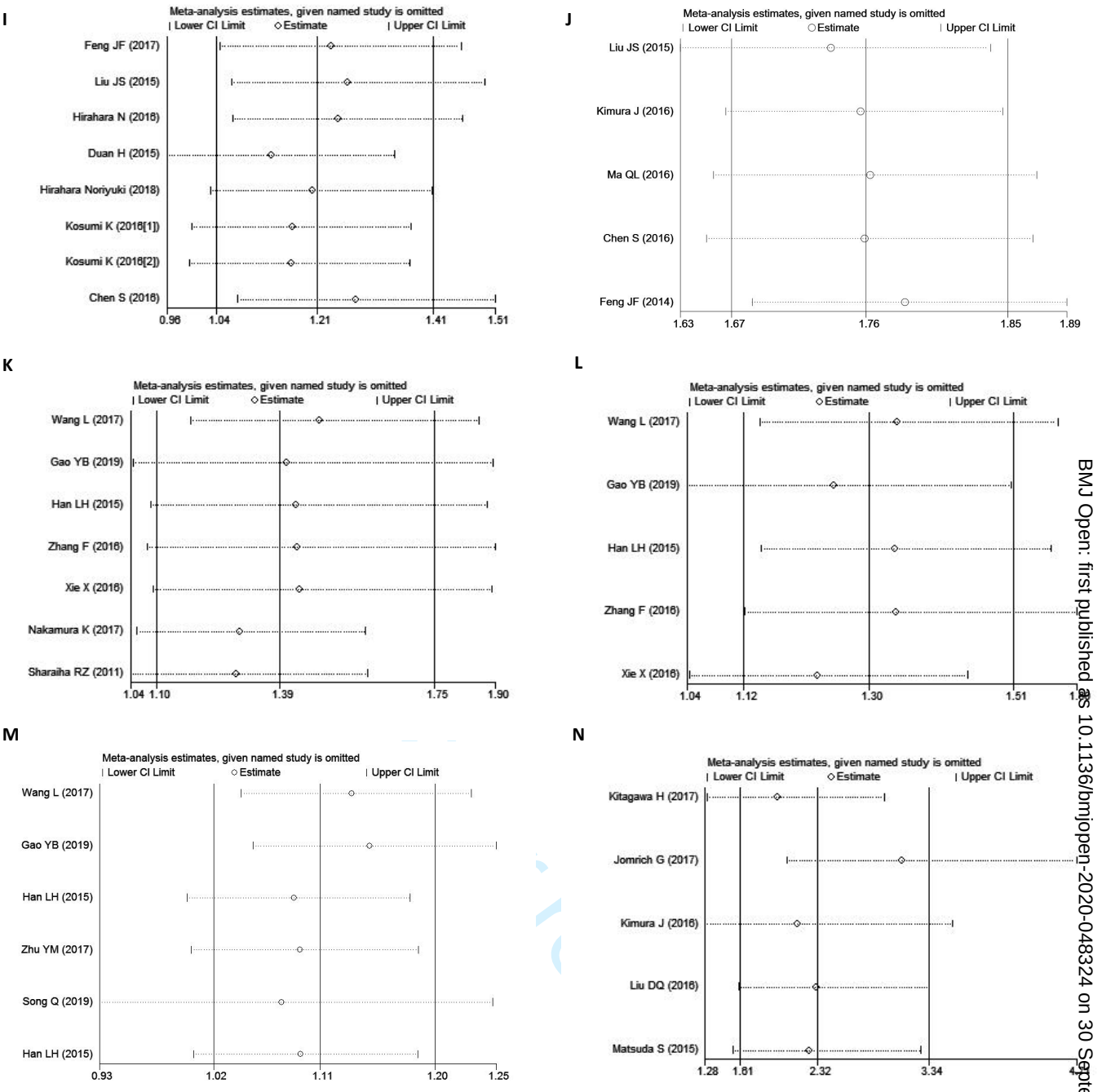


Figure 1. Sensitivity analyses of HR for 8 indicators in OS, CSS and DFS.
(A)NLR-OS; (B) PLR-OS; (C) LMR-OS; (D) CAR-OS; (E) SII-OS; (F) PNI-OS; (G) GPS-OS; (H) mGPS-OS; (I) NLR-CSS; (J) GPS-CSS; (K) NLR-DFS; (L) PLR-DFS; (M) LMR-DFS; (N) GPS-DFS.

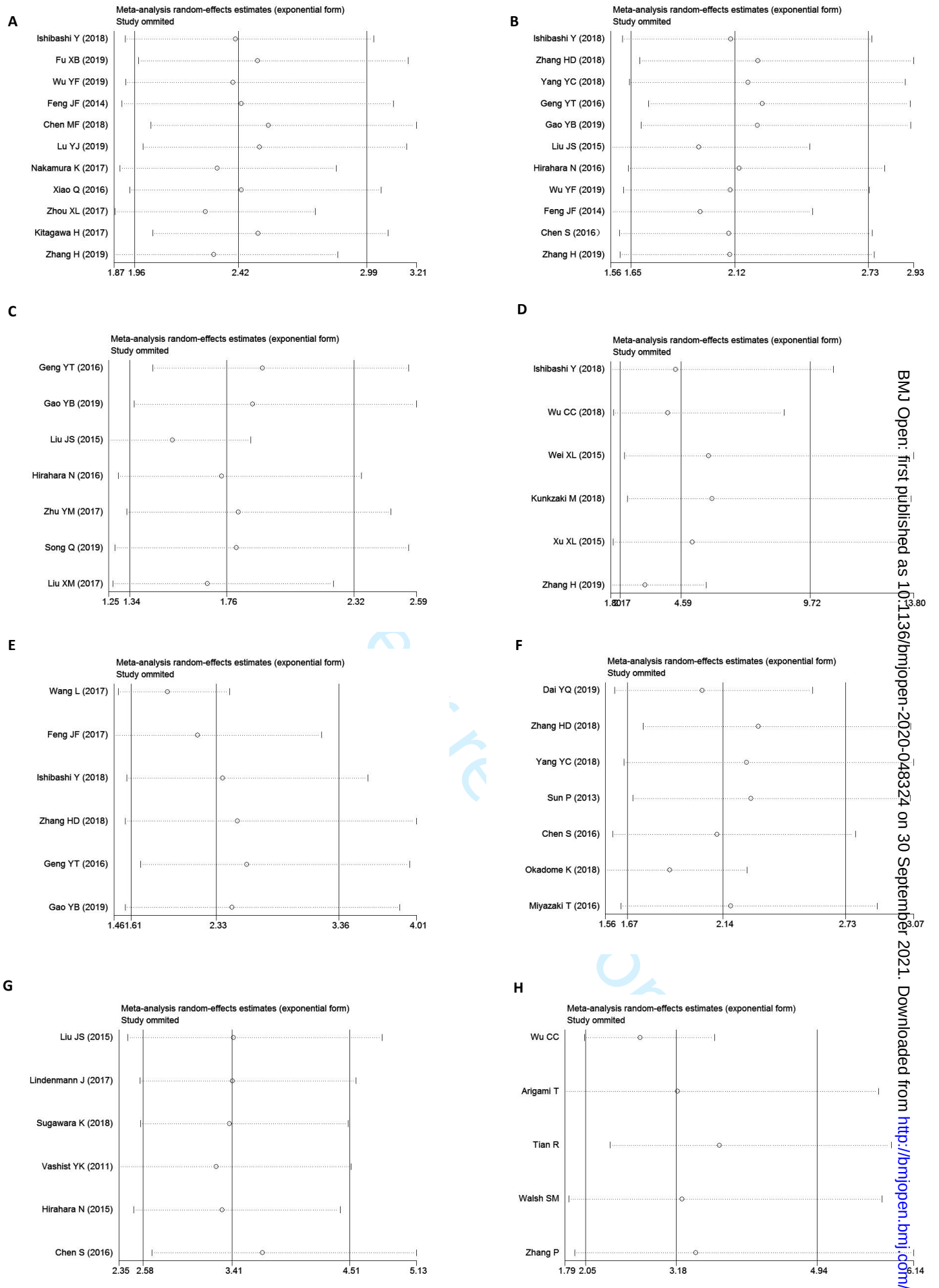


Figure 2. Sensitivity analyses of DOR for 8 indicators in 5-year OS of EC.
(A) NLR; (B) PLR; (C) LMR; (D) CAR; (E) SII; (F) PNI; (G) GPS; (H) mGPS;

Table 1. Subgroup and meta regression of sensitivity and specificity of prognostic indicators.

Category	NO. of Trails	Sensitivity (95%)	I^2(%), *P*	*P*-reg	Specificity (95%)	I^2(%), *P*	*P*-reg
SII							
Overall	6	0.61(0.48-0.73)	96.2, <0.001		0.60(0.45-0.73)	96.3, <0.001	
Country							
China	5	0.64(0.52-0.76)	96.6, <0.001	0.42	0.57(0.42-0.72)	96.9, <0.001	0.41
Non-China	1	0.46(0.15-0.76)	NR		0.71(0.41-1.00)	NR	
Sample size							
≤298	3	0.65(0.48-0.81)	94.7, <0.001	0.43	0.67(0.49-0.85)	93.0, <0.001	0.28
>298	3	0.59(0.42-0.76)	97.7, <0.001		0.54(0.35-0.74)	97.7, <0.001	
Cut-off value							
≤410	3	0.73(0.66-0.81)	84.1, 0.002	<0.001	0.42(0.38-0.47)	54.7, 0.110	<0.001
>410	3	0.47(0.37-0.57)	90.2, <0.001		0.76(0.72-0.81)	0.0, 0.541	
Treatment							
Surgery	6	0.61(0.48-0.73)	96.2, <0.001	NR	0.60(0.45-0.73)	96.3, <0.001	NR
CRT	0	NR	NR		NR	NR	
Pathology							
SCC	5	0.64(0.52-0.76)	96.6, <0.001	0.42	0.57(0.42-0.72)	96.9, <0.001	0.41
Mixed	1	0.46(0.15-0.76)	NR		0.71(0.41-1.00)	NR	
Clinical stage							
0-III	5	0.61(0.47-0.74)	96.9, <0.001	0.88	0.54(0.40-0.68)	95.9, <0.001	0.10
0-IV	1	0.60(0.30-0.91)	NR		0.78(0.56-1.00)	NR	
Follow-up							
≤36	2	0.66(0.61-0.70)	53.0, 0.145	0.07	0.57(0.52-0.62)	97.6, <0.001	0.94
>36	2	0.57(0.54-0.61)	98.7, <0.001		0.52(0.48-0.56)	98.8, <0.001	
NR	2	0.71(0.65-0.76)	97.0, <0.001		0.55(0.46-0.63)	90.0, 0.002	
Age							
≤63.0	3	0.59(0.42-0.76)	97.7, <0.001	0.93	0.54(0.35-0.74)	97.7, <0.001	0.67
>63.0	2	0.55(0.48-0.62)	77.6, 0.035		0.76(0.70-0.82)	17.4, 0.271	
NR	1	NR	NR		NR	NR	
Sex ratio							
≤4.55	3	0.59(0.42-0.76)	97.7, <0.001	0.93	0.54(0.35-0.74)	97.7, <0.001	0.67
>4.55	3	0.65(0.48-0.81)	94.7, <0.001		0.67(0.49-0.85)	93.0, <0.001	
PNI							
Overall	7	0.51(0.41-0.61)	95.6, <0.001		0.67(0.56-0.77)	95.0, <0.001	
Country							
China	5	0.52(0.40-0.64)	97.0, <0.001	0.82	0.63(0.51-0.76)	95.8, <0.001	0.09
Non-China	2	0.48(0.29-0.68)	0.0, 0.412		0.76(0.60-0.91)	40.1, 0.196	
Sample size							
≤255	2	0.51(0.31-0.71)	54.7, 0.137	0.99	0.72(0.53-0.91)	0.0, 0.612	0.30
>255	5	0.51(0.39-0.63)	97.0, <0.001		0.66(0.53-0.79)	96.4, <0.001	
Cut-off value							
≤46	2	0.44(0.26-0.62)	75.3, 0.044	0.51	0.80(0.67-0.93)	0.0, 0.963	0.01

>46	5	0.53(0.42-0.65)	96.5, <0.001		0.62(0.50-0.73)	95.4, <0.001	
Treatment							
Surgery	5	0.54(0.44-0.65)	94.2, <0.001	0.30	0.65(0.52-0.78)	95.3, <0.001	0.22
Mixed	1	NR	NR		NR	NR	
NR	1	NR	NR		NR	NR	
Pathology							
SCC	5	0.52(0.40-0.64)	97.0, <0.001	0.82	0.63(0.51-0.76)	95.8, <0.001	0.09
Mixed	2	0.48(0.29-0.68)	0.0, 0.412		0.76(0.60-0.91)	40.1, 0.196	
Clinical stage							
0-III	4	0.58(0.47-0.68)	94.8, <0.001	0.17	0.60(0.47-0.73)	93.7, <0.001	0.01
0-IV	3	0.41(0.29-0.53)	84.8, 0.001		0.76(0.65-0.87)	5.0, 0.349	
Follow-up							
≤36	5	0.48(0.36-0.60)	96.1, <0.001	0.64	0.69(0.57-0.82)	94.3, <0.001	0.30
>36	2	0.57(0.39-0.75)	89.2, 0.002		0.62(0.42-0.83)	97.4, <0.001	
Age							
≤63.4	3	0.51(0.35-0.67)	98.2, <0.001	0.88	0.75(0.62-0.88)	97.1, <0.001	0.99
>63.4	2	0.48(0.41-0.55)	0.0, 0.412		0.76(0.70-0.81)	40.1, 0.196	
NR	2	0.44(0.38-0.50)	85.4, 0.009		0.79(0.71-0.86)	0.0, 0.737	
Sex ratio							
≤4.75	4	0.56(0.44-0.68)	97.2, <0.001	0.43	0.59(0.47-0.71)	96.0, <0.001	0.75
>4.75	3	0.45(0.31-0.59)	50.8, 0.131		0.77(0.67-0.88)	11.6, 0.323	
NLR							
Overall	11	0.51(0.47-0.54)	77.1, <0.001		0.70(0.64-0.76)	79.1, <0.001	
Country							
China	8	0.51(0.47-0.55)	83.8, <0.001	0.98	0.70(0.64-0.77)	71.5, 0.001	0.04
Non-China	3	0.50(0.41-0.60)	0.0, 0.800		0.71(0.60-0.81)	91.4, <0.001	
Sample size							
≤297	6	0.56(0.50-0.61)	0.0, 0.462	0.14	0.70(0.62-0.78)	78.8, <0.001	0.03
>297	5	0.48(0.43-0.53)	88.5, <0.001		0.72(0.64-0.79)	83.6, <0.001	
Cut-off value							
≤2.5	3	0.47(0.42-0.53)	33.5, 0.223	0.76	0.75(0.70-0.80)	65.6, 0.055	0.06
>2.5	7	0.51(0.46-0.55)	84.2, <0.001		0.71(0.64-0.78)	75.8, <0.001	
NR	1	NR	NR		NR	NR	
Treatment							
Surgery	7	0.48(0.43-0.52)	0.0, 0.619	0.31	0.71(0.63-0.78)	75.8, <0.001	0.05
Mixed	4	0.53(0.48-0.58)	89.3, <0.001		0.71(0.61-0.81)	85.8, 0.001	
Pathology							
SCC	8	0.51(0.47-0.55)	83.8, <0.001	0.98	0.70(0.64-0.77)	71.5, 0.001	0.04
Mixed	3	0.50(0.41-0.60)	0.0, 0.800		0.71(0.60-0.81)	91.4, <0.001	
Clinical stage							
0-III	6	0.54(0.50-0.58)	55.0, 0.049	0.14	0.70(0.62-0.78)	78.8, <0.001	0.02
0-IV	5	0.46(0.42-0.50)	0.0, 0.642		0.71(0.63-0.79)	83.6, <0.001	
Follow-up							
≤37	4	0.47(0.44-0.51)	65.3, 0.034	NR	0.68(0.61-0.73)	86.9, <0.001	NR

>37	2	0.44(0.38-0.52)	0.0, 0.497		0.76(0.71-0.81)	76.6, 0.039	
NR	5	0.54(0.52-0.57)	80.7, <0.001		0.68(0.65-0.72)	70.5, 0.009	
Age							
≤61.1	4	0.47(0.43-0.51)	37.4, 0.187	0.92	0.72(0.68-0.76)	0.0, 0.861	0.07
>61.1	6	0.53(0.47-0.59)	70.9, 0.004		0.73(0.66-0.80)	84.6, <0.001	
NR	1	NR	NR		NR	NR	
Sex ratio							
≤5.12	5	0.50(0.44-0.55)	78.3, 0.001	0.91	0.70(0.62-0.78)	83.1, <0.001	0.03
>5.12	6	0.51(0.46-0.56)	53.3, 0.058		0.71(0.63-0.78)	79.3, <0.001	
CAR							
Overall	6	0.50(0.38-0.62)	94.8, <0.001		0.84(0.71-0.91)	89.2, <0.001	
Country							
China	4	0.45(0.32-0.59)	95.9, <0.001	0.31	0.87(0.81-0.94)	90.1, <0.001	0.64
Non-China	2	0.60(0.41-0.80)	81.0, 0.022		0.68(0.51-0.85)	38.4, 0.203	
Sample size							
≤283	4	0.60(0.51-0.69)	66.7, 0.029	0.04	0.82(0.70-0.94)	86.7, <0.001	0.61
>283	2	0.33(0.23-0.43)	94.4, <0.001		0.85(0.71-0.98)	95.7, <0.001	
Cut-off value							
≤0.13	4	0.56(0.44-0.68)	87.9, <0.001	0.28	0.77(0.67-0.86)	85.4, <0.001	0.46
>0.13	2	0.37(0.21-0.53)	96.1, <0.001		0.94(0.88-1.00)	0.0, 0.665	
Treatment							
Surgery	2	0.45(0.24-0.66)	98.2, <0.001	0.71	0.85(0.72-0.98)	91.2, 0.001	0.66
Mixed	4	0.53(0.38-0.67)	81.3, 0.001		0.81(0.69-0.93)	87.8, <0.001	
Pathology							
SCC	4	0.53(0.38-0.67)	81.3, 0.001	0.65	0.81(0.69-0.93)	87.8, <0.001	0.25
Mixed	2	0.45(0.24-0.66)	98.2, <0.001		0.85(0.72-0.98)	91.2, 0.001	
Clinical stage							
0-III	3	0.46(0.29-0.63)	97.2, <0.001	0.62	0.91(0.88-0.95)	0.0, 0.814	0.22
0-IV	3	0.54(0.37-0.71)	88.1, <0.001		0.71(0.66-0.76)	29.6, 0.242	
Follow-up							
≤40	1	NR	NR	NR	NR	NR	NR
>40	1	NR	NR		NR	NR	
NR	4	0.60(0.55-0.65)	66.7, 0.029		0.80(0.74-0.85)	86.7, <0.001	
Age							
≤62.2	3	0.39(0.28-0.50)	93.8, <0.001	0.08	0.87(0.77-0.97)	92.3, <0.001	0.08
>62.2	3	0.62(0.50-0.74)	63.3, 0.066		0.78(0.63-0.92)	89.5, <0.001	
Sex ratio							
≤5.5	4	0.56(0.44-0.68)	87.9, <0.001	0.28	0.77(0.67-0.86)	85.4, <0.001	0.46
>5.5	2	0.37(0.21-0.53)	96.1, <0.001		0.94(0.88-1.00)	0.0, 0.665	
PLR							
Overall	11	0.53(0.47-0.59)	88.6, <0.001		0.65(0.60-0.70)	78.9, <0.001	
Country							
China	9	0.50(0.45-0.56)	87.5, <0.001	0.02	0.68(0.64-0.72)	78.8, <0.001	0.64
Non-China	2	0.67(0.55-0.78)	74.5, 0.048		0.52(0.39-0.64)	0.0, 0.331	

Sample size							
≤303	4	0.62(0.54-0.70)	61.2, 0.052	0.02	0.58(0.49-0.68)	37.6, 0.186	0.44
>303	7	0.49(0.43-0.54)	89.5, <0.001		0.68(0.64-0.73)	84.0, <0.001	
Cut-off value							
≤143	5	0.48(0.41-0.56)	93.1, <0.001	0.54	0.62(0.55-0.69)	87.4, <0.001	0.16
>143	5	0.57(0.53-0.60)	28.3, 0.233		0.70(0.66-0.73)	55.1, 0.064	
NR	1	NR	NR		NR	NR	
Treatment							
Surgery	9	0.52(0.46-0.59)	90.4, <0.001	0.44	0.66(0.60-0.71)	83.1, <0.001	0.20
Mixed	2	0.57(0.43-0.71)	0.0, 0.875		0.65(0.52-0.79)	0.0, 0.808	
Pathology							
SCC	10	0.51(0.46-0.56)	86.7, <0.001	0.01	0.67(0.63-0.71)	77.4, <0.001	0.31
Mixed	1	0.73(0.59-0.88)	NR		0.47(0.29-0.65)	NR	
Clinical stage							
0-III	10	0.51(0.46-0.56)	86.7, <0.001	0.01	0.67(0.63-0.71)	77.4, <0.001	0.31
0-IV	1	0.73(0.59-0.88)	NR		0.47(0.29-0.65)	NR	
Follow-up							
≤39	4	0.47(0.45-0.50)	86.9, <0.001	NR	0.62(0.59-0.66)	84.7, <0.001	NR
>39	3	0.47(0.43-0.52)	92.0, <0.001		0.71(0.67-0.76)	73.0, 0.025	
NR	4	0.58(0.55-0.62)	80.1, 0.002		0.66(0.62-0.71)	71.9, 0.014	
Age							
≤61.2	7	0.49(0.43-0.56)	89.8, <0.001	0.58	0.68(0.63-0.73)	83.6, <0.001	<0.001
>61.2	3	0.62(0.57-0.67)	71.0, 0.032		0.58(0.50-0.65)	49.8, 0.137	
NR	1	NR	NR		NR	NR	
Sex ratio							
≤4.55	5	0.46(0.39-0.52)	90.0, <0.001	0.20	0.65(0.58-0.72)	84.5, <0.001	0.04
>4.55	6	0.60(0.53-0.66)	67.9, 0.008		0.67(0.60-0.74)	73.3, 0.002	
GPS							
Overall	6	0.48(0.43-0.54)	44.1, 0.111		0.79(0.72-0.85)	20.0, 0.282	
Country							
China	2	0.51(0.44-0.58)	0.0, 0.372	0.51	0.75(0.67-0.82)	0.0, 0.920	<0.001
Non-China	4	0.47(0.39-0.54)	62.6, 0.045		0.83(0.75-0.90)	23.9, 0.268	
Sample size							
≤237	3	0.41(0.34-0.49)	0.0, 0.663	0.03	0.86(0.78-0.94)	0.0, 0.464	<0.001
>237	3	0.52(0.49-0.56)	0.0, 0.486		0.75(0.70-0.80)	0.0, 0.918	
Cut-off value							
1-2 VS 0	3	0.47(0.39-0.54)	62.0, 0.072	0.51	0.81(0.73-0.89)	59.8, 0.083	<0.001
2 VS 0	3	0.50(0.44-0.57)	35.4, 0.213		0.77(0.69-0.85)	0.0, 0.651	
Treatment							
Surgery	6	0.48(0.43-0.54)	44.1, 0.111	NR	0.79(0.72-0.85)	20.0, 0.282	NR
Mixed	0	NR	NR		NR	NR	
Pathology							
SCC	2	0.51(0.46-0.56)	0.0, 0.372	0.94	0.75(0.68-0.80)	0.0, 0.920	0.01
Mixed	3	0.48(0.40-0.55)	48.8, 0.142		0.79(0.71-0.86)	0.0, 0.714	

NR	1	NR	NR		NR	NR	
Clinical stage							
0-III	4	0.47(0.41-0.54)	43.1, 0.153	0.78	0.79(0.72-0.86)	47.3, 0.127	0.05
0-IV	2	0.51(0.42-0.60)	56.9, 0.128		0.80(0.69-0.91)	0.0, 0.458	
Follow-up							
≤40	1	NR	NR	NR	NR	NR	NR
>40	1	NR	NR		NR	NR	
NR	4	0.50(0.46-0.54)	56.5, 0.076		0.78(0.73-0.83)	41.7, 0.161	
Age							
≤62.1	1	NR	NR		NR	NR	
>62.1	3	0.51(0.47-0.56)	48.8, 0.142	0.65	0.78(0.70-0.85)	0.0, 0.714	0.01
NR	2	0.47(0.37-0.57)	61.2, 0.108		0.81(0.72-0.90)	79.6, 0.027	
Sex ratio							
≤5.48	2	0.51(0.42-0.60)	56.9, 0.128	0.78	0.80(0.69-0.91)	0.0, 0.458	0.05
>5.48	4	0.47(0.41-0.54)	43.1, 0.153		0.79(0.72-0.86)	47.3, 0.127	
LMR							
Overall	7	0.54(0.48-0.61)	84.9, <0.001		0.60(0.54-0.65)	73.5, 0.001	
Country							
China	6	0.53(0.47-0.59)	85.8, <0.001	0.20	0.60(0.55-0.66)	77.4, 0.001	0.94
Non-China	1	0.63(0.47-0.79)	NR		0.55(0.37-0.72)	NR	
Sample size							
≤280	3	0.61(0.53-0.69)	0.0, 0.832	0.04	0.56(0.47-0.65)	49.7, 0.137	0.61
>280	4	0.50(0.44-0.56)	88.8, <0.001		0.62(0.56-0.68)	82.3, 0.001	
Cut-off value							
≤3.57	4	0.56(0.48-0.64)	76.3, 0.006	0.40	0.58(0.52-0.64)	75.8, 0.006	0.38
>3.57	3	0.52(0.42-0.62)	91.2, <0.001		0.63(0.55-0.72)	40.0, 0.189	
Treatment							
Surgery	4	0.51(0.44-0.58)	88.2, <0.001	0.11	0.63(0.57-0.69)	78.0, 0.003	0.53
Mixed	3	0.59(0.51-0.67)	0.0, 0.740		0.56(0.48-0.63)	49.6, 0.137	
Pathology							
SCC	7	0.54(0.48-0.61)	84.9, <0.001	NR	0.60(0.54-0.65)	73.5, 0.001	NR
Mixed	0	NR	NR		NR	NR	
Clinical stage							
0-III	7	0.54(0.48-0.61)	84.9, <0.001	NR	0.60(0.54-0.65)	73.5, 0.001	NR
0-IV	0	NR	NR		NR	NR	
Follow-up							
≤39	2	0.52(0.41-0.64)	74.1, 0.050	0.93	0.59(0.48-0.69)	38.1, 0.204	0.34
>39	4	0.52(0.48-0.56)	90.3, <0.001		0.64(0.59-0.68)	79.3, 0.002	
NR	1	NR	NR		NR	NR	
Age							
≤61.5	4	0.50(0.44-0.56)	88.8, <0.001	0.68	0.62(0.56-0.68)	82.3, 0.001	0.06
>61.5	2	0.61(0.53-0.67)	0.0, 0.554		0.60(0.51-0.70)	26.0, 0.245	
NR	1	NR	NR		NR	NR	
Sex ratio							

≤4.32	4	0.50(0.43-0.57)	87.4, <0.001	0.74	0.59(0.51-0.66)	77.3, 0.004	0.29
>4.32	3	0.59(0.51-0.67)	0.0, 0.643		0.60(0.51-0.68)	78.6, 0.009	
mGPS							
Overall	5	0.46(0.30-0.62)	96.0, <0.001		0.80(0.72-0.86)	76.2, 0.002	
Country							
China	3	0.51(0.31-0.71)	97.8, <0.001	0.44	0.76(0.65-0.87)	86.4, 0.001	0.01
Non-China	2	0.39(0.15-0.62)	68.5, 0.075		0.84(0.76-0.93)	42.6, 0.187	
Sample size							
≤212	2	0.66(0.56-0.76)	0.0, 0.320	0.00	0.68(0.57-0.80)	78.3, 0.032	0.43
>212	3	0.32(0.24-0.41)	86.2, 0.001		0.85(0.82-0.89)	10.1, 0.329	
Cut-off value							
1-2 VS 0	4	0.42(0.26-0.58)	95.6, <0.001	0.31	0.84(0.80-0.89)	0.0, 0.503	<0.001
2 VS 0	1	0.64(0.34-0.94)	NR		0.62(0.47-0.77)	NR	
Treatment							
Surgery	3	0.32(0.24-0.41)	86.2, 0.001	0.00	0.85(0.82-0.89)	10.1, 0.329	0.43
Mixed	2	0.66(0.56-0.76)	0.0, 0.320		0.68(0.57-0.80)	78.3, 0.032	
Pathology							
SCC	4	0.50(0.32-0.67)	96.8, <0.001	0.37	0.78(0.70-0.86)	79.6, 0.002	0.01
Mixed	1	0.33(0.02-0.63)	NR		0.87(0.78-0.97)	NR	
Clinical stage							
0-III	4	0.42(0.26-0.58)	95.6, <0.001	0.28	0.84(0.80-0.89)	0.0, 0.503	0.75
0-IV	1	0.64(0.34-0.94)	NR		0.62(0.47-0.77)	NR	
Follow-up							
≤39	3	0.47(0.25-0.68)	92.3, <0.001	0.99	0.79(0.71-0.88)	84.9, 0.001	0.15
>39	1	NR	NR		NR	NR	
NR	1	NR	NR		NR	NR	
Age							
≤61.7	3	0.51(0.31-0.71)	97.8, <0.001	0.59	0.76(0.65-0.87)	86.4, 0.001	0.38
>61.7	2	0.39(0.15-0.62)	68.5, 0.075		0.84(0.76-0.93)	42.6, 0.187	
Sex ratio							
≤4.91	2	0.42(0.17-0.67)	98.4, <0.001	0.67	0.77(0.64-0.90)	93.0, <0.001	0.35
>4.91	3	0.49(0.28-0.70)	93.5, <0.001		0.82(0.73-0.91)	0.0, 0.376	

Abbreviations: OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; EC, esophageal carcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, c-reactive protein-to-albumin ratio; SII, systemic inflammation index; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; Ref, reference; P-reg, the P-value of meta regression; NR, not reported.

Table 1. Pair-wise comparisons between modalities for sensitivity, specificity, P-LR, N-LR, DOR and AUC.

Category	Sensitivity	*P*	Specificity	*P*	P-LR	*P*	N-LR	*P*	DOR	*P*	AUC	*P*
NLR	0.51 [0.47, 0.54]	NA	0.70 [0.64, 0.76]	NA	1.7 [1.5, 2.0]	NA	0.70 [0.66, 0.74]	NA	2.42 [1.96, 2.99]	NA	0.60 [0.56 - 0.64]	NA
PLR	0.53 [0.47, 0.59]	NA	0.65 [0.60, 0.70]	NA	1.5 [1.3, 1.8]	NA	0.72 [0.64, 0.80]	NA	2.12 [1.65, 2.73]	NA	0.63 [0.59 - 0.67]	NA
LMR	0.54 [0.48, 0.61]	NA	0.60 [0.54, 0.65]	NA	1.3 [1.2, 1.6]	NA	0.76 [0.67, 0.87]	NA	1.76 [1.34, 2.32]	NA	0.60 [0.55 - 0.64]	NA
SII	0.61 [0.48, 0.73]	NA	0.60 [0.45, 0.73]	NA	1.5 [1.2, 1.9]	NA	0.65 [0.53, 0.79]	NA	2.33 [1.61, 3.36]	NA	0.64 [0.60 - 0.68]	NA
PNI	0.51 [0.41, 0.61]	NA	0.67 [0.56, 0.77]	NA	1.6 [1.3, 1.9]	NA	0.73 [0.66, 0.81]	NA	2.14 [1.67, 2.73]	NA	0.61 [0.57 - 0.66]	NA
CAR	0.50 [0.38, 0.62]	NA	0.84 [0.71, 0.91]	NA	3.0 [1.7, 5.6]	NA	0.60 [0.46, 0.77]	NA	4.59 [2.17, 9.72]	NA	0.72 [0.68 - 0.75]	NA
GPS	0.48 [0.43, 0.54]	NA	0.79 [0.72, 0.85]	NA	2.3 [1.8, 3.0]	NA	0.65 [0.59, 0.72]	NA	3.41 [2.58, 4.51]	NA	0.67 [0.63 - 0.71]	NA
mGPS	0.46 [0.30, 0.62]	NA	0.80 [0.72, 0.86]	NA	2.3 [1.8, 2.9]	NA	0.68 [0.53, 0.86]	NA	3.18 [2.05, 4.94]	NA	0.75 [0.71 - 0.78]	NA
CAR vs GPS	50% vs 48%	＞0.05	84% vs 79%	＞0.05	3.0 vs 2.3	＞0.05	0.60 vs 0.65	＞0.05	4.59 vs 3.41	＞0.05	**0.72 vs 0.67**	**0.0327**
mGPS vs GPS	6% vs 448%	＞0.05	80% vs 79%	＞0.05	2.3 vs 2.3	＞0.05	0.68 vs 0.65	＞0.05	3.18 vs 3.41	＞0.05	**0.75 vs 0.67**	**0.0016**
CAR vs mGPS	50% vs 46%	＞0.05	84% vs 80%	＞0.05	3.0 vs 2.3	＞0.05	0.60 vs 0.68	＞0.05	4.59 vs 3.18	＞0.05	0.72 vs 0.75	＞0.05

P-DR, The pooled positive likelihood ratio; N-DR, negative likelihood ratio, DOR, diagnostic odds ratio.

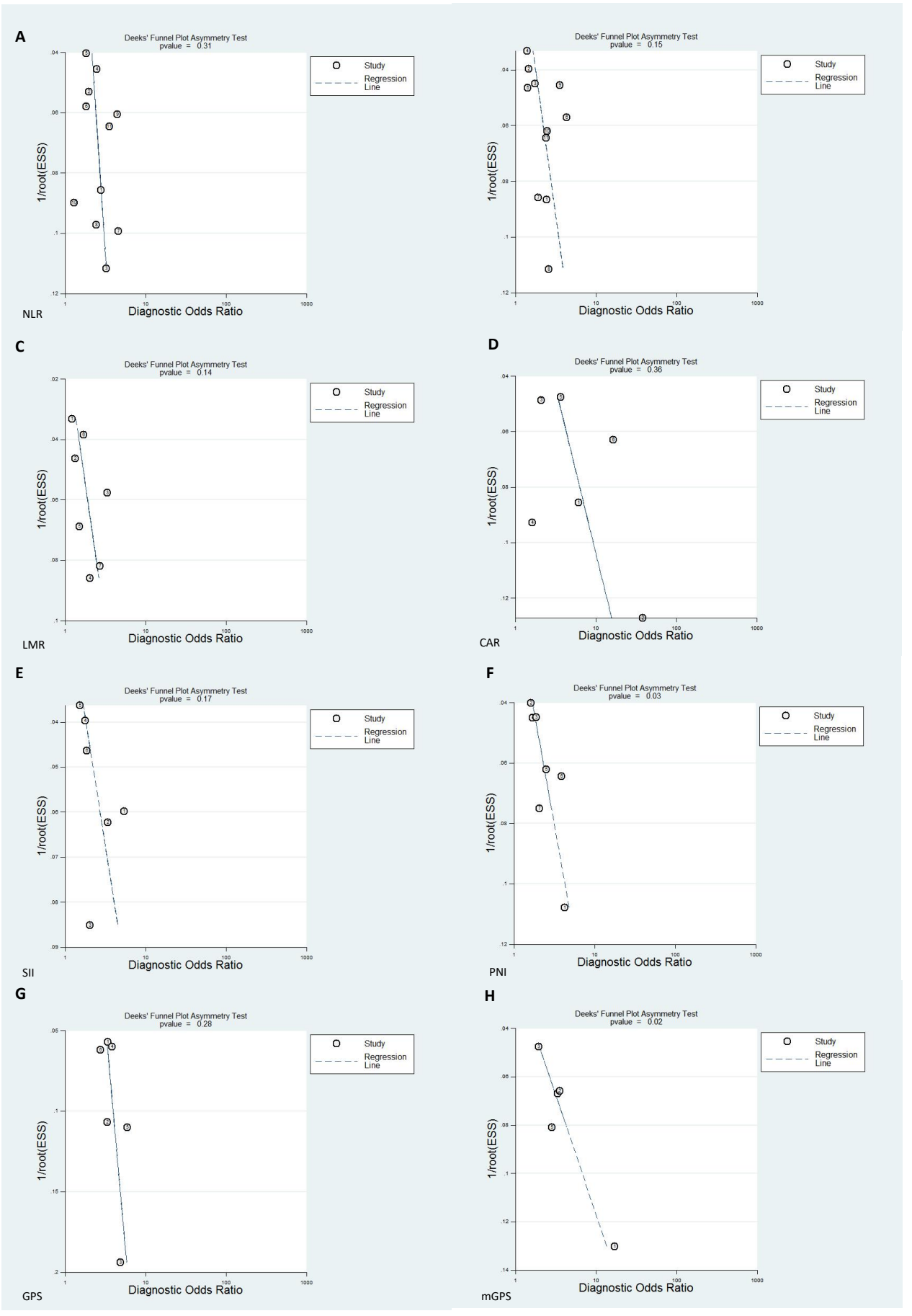


Figure 1. Deek's Funnel evaluating publication bias of DOR of 8 indicators. (A) NLR; (B) PLR; (C) LMR; (D) CAR; (E) SII; (F) PNI; (G) GPS; (H) mGPS.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5,6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5,7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7,8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7,8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7,8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7,8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	Supplementary 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 3,4,5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9,11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9,10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	10
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	10,12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	12
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12,13
	23b	Discuss any limitations of the evidence included in the review.	16
	23c	Discuss any limitations of the review processes used.	16
	23d	Discuss implications of the results for practice, policy, and future research.	14,15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	17
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	17
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	17
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16,17
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	17

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71