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ORIGINAL RESEARCH

# Prognostic value of the Glasgow prognostic score in colorectal cancer: a meta-analysis of 9,839 patients

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**Purpose:** The aim of this study was to perform a systematic review and meta-analysis to evaluate the value of the Glasgow prognostic score (GPS) or modified Glasgow prognostic score (mGPS) in patients with colorectal cancer (CRC).

**Methods:** A comprehensive medical literature search was performed using the online databases PubMed, Embase, Web of Science, and the Cochrane Library. After extracting basic characteristics and prognostic data from the included studies, overall survival (OS) and cancer-specific survival (CSS) were pooled as primary outcomes. Subgroup analyses were performed according to therapeutic strategies, models, cutoff values, regions, tumor, node, metastasis stages, sample size, and ages.

**Results:** Forty-three independent cohorts from 41 studies with 9,839 CRC patients were included in the present study. Correlation between GPS or mGPS and OS was analyzed in 32 cohorts of 7,714 patients, and 23 independent cohorts of 5,375 patients focused on the correlation between GPS or mGPS and CSS. The overall outcomes showed that patients with elevated GPS or mGPS were associated with poor OS (HR: 2.20, 95% CI: 1.88–2.57, $P<0.001$). Elevated GPS or mGPS also resulted in worse CSS (HR: 1.86, 95% CI: 1.59–2.17, $P<0.001$). The results of the subgroup analyses confirmed the overall outcomes.

**Conclusion:** GPS or mGPS is an accurate prognostic predictor in patients with CRC. Patients with elevated pretreatment GPS or mGPS have a poor prognosis. Subgroup analyses confirmed the overall outcomes. Pretreatment GPS is a useful biomarker in the management of CRC.

**Keywords:** colorectal cancer, Glasgow prognostic score, modified Glasgow prognostic score, systematic review, meta-analysis

## Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies and the fourth leading cause of cancer-related mortality worldwide.[1,2] CRC accounts for ~10% of all newly diagnosed cancers each year.[3] Although diagnostic technologies and therapeutic strategies for CRC have markedly improved, the prognosis of patients remains poor, which is attributed to the high rate of tumor recurrence and metastasis.[2,4] The treatment strategies for CRC are based on the biological characteristics of the tumor and the systemic condition of patients. Surgery remains the optimal curative treatment for resectable cancer and the optional strategy for many patients with advanced cancer,[5] while chemotherapy, immunotherapeutic strategies, and targeted therapy are optional for unresectable cancers.[4,5] Therefore, an accurate prediction model which can predict the prognosis of CRC patients would be useful for the selection of therapeutic modalities.

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In previous studies, the tumor, node, metastasis (TNM) stage, which was proposed by the American Joint Committee on Cancer, was considered an effective system for predicting CRC recurrence and patient prognosis.[6,7] However, the TNM stage alone was demonstrated to be inadequate in evaluating prognostic outcomes as tumor progression may be determined by the tumor characteristics as well as systemic inflammation and nutritional status.[8,9] Recently, an increasing number of studies have focused on the prognostic role of inflammation biomarkers in predicting the prognosis of malignancies.[10–12] The Glasgow prognostic score (GPS), an inflammation-based model, has been shown to be an accurate predictor of prognosis in CRC patients in several studies.[13–17] This score is based on the combination of C-reactive protein (CRP) and serum albumin (ALB) levels. It was first reported by Forrest et al in 2003 for its prognostic value in non-small-cell lung cancer.[18] GPS was defined based on the presence of hypoalbuminemia (<35 g/L) and elevated CRP (>10 mg/L): if both were abnormal, the score was 2; if either was abnormal, the score was 1; if neither was abnormal, the score was 0.[19–21] Subsequently, more studies have evaluated the prognostic role of the GPS in a variety of cancers, such as pancreatic cancer, esophageal cancer, and hepatocellular carcinoma.[12,22,23] In addition, some centers applied the modified Glasgow Prognostic Score (mGPS) to evaluate the prognostic outcomes of CRC patients. mGPS is also calculated using CRP and ALB levels. Patients with CRP <10 mg/L were scored 0, those with CRP >10 mg/L were scored 1, and those with CRP >10 mg/L and ALB <35 g/L were scored 2.[20] However, the role of the GPS in CRC remains controversial. Ishizuka et al verified the accurate predictive value of GPS,[24] while other researchers showed no association between the GPS and the prognosis of CRC patients.[13,19,25,26]

In this study, we investigated the prognostic value of pretreatment GPS in CRC patients by searching available relevant studies and conducting a meta-analysis. We also investigated the predictive role of the GPS in patients in different subgroups by subgroup analysis.

# Methods

## Literature search strategy

A comprehensive medical literature search was performed in May 2018 using the online databases PubMed, Embase, Web of Science, and the Cochrane Library. Studies which focused on the association between GPS and the prognostic outcomes of CRC patients were retrieved. There were no restrictions on language, publication region, and type. Search terms were confined to the following free-text words and Medical Subject Headings: ((C-reactive protein) or (CRP) or (albumin) or (Glasgow prognostic score) or (GPS)) and ((colorectal) or (colon) or (rectum) or (rectal)) and ((cancer) or (cancers) or (tumor) or (tumors) or (carcinoma)). A backward search was also conducted using cross-references from the bibliographies of primary selected studies and relevant studies to ensure a comprehensive search. Two reviewers (Lu X and Guo WY) completed searching for titles and abstracts independently.

## Inclusion and exclusion criteria

Two reviewers (Lu X and Guo WY) selected eligible studies independently based on the prespecified inclusion and exclusion criteria. When there were disagreements, a final decision was made by a senior reviewer (Zhao WZ). Inclusion and exclusion criteria were established by all authors.

The inclusion criteria were as follows: 1) studies evaluating patients with CRC; 2) studies evaluating either GPS or mGPS in patients prior to treatment; and 3) studies with a clear presentation of the main outcomes including overall survival (OS) and cancer-specific survival (CSS).

The exclusion criteria were as follows: 1) studies not focusing on the prognosis of CRC patients; 2) studies without survival data; 3) studies not focusing on either pretreatment GPS or mGPS; 4) review articles/editorials; and 5) conference abstracts/case reports.

For duplicate publications by the same authors or departments, only the publications with most representative patient cohorts were included in this meta-analysis. If two or more independent sample sets such as training cohorts and validation cohorts were analyzed in the same study, the cohorts were analyzed independently. Moreover, if the researches were repetitive, only one was included. A flow diagram of study retrieval and selection is shown in Figure 1.

## Data management and statistical analyses

EndNote software (version X7, Thomson Reuters, USA) was used for sorting and preliminary screening. Data from the included studies were extracted by two authors (Xu W and Zhang XL) by reading the full text independently. Baseline information including the full list of authors, year of publication, regions of the research, research centers, sample size, follow-up period, TNM stages, and therapeutic strategies was summarized. The endpoints of OS and CSS were characterized by HRs with 95% CIs.

Data were extracted from tables or the text of the included studies. In some studies, the HRs and 95% CIs were not presented in the tables or text. These values were then computed from the Kaplan–Meier graph using the Engauge Digitizer

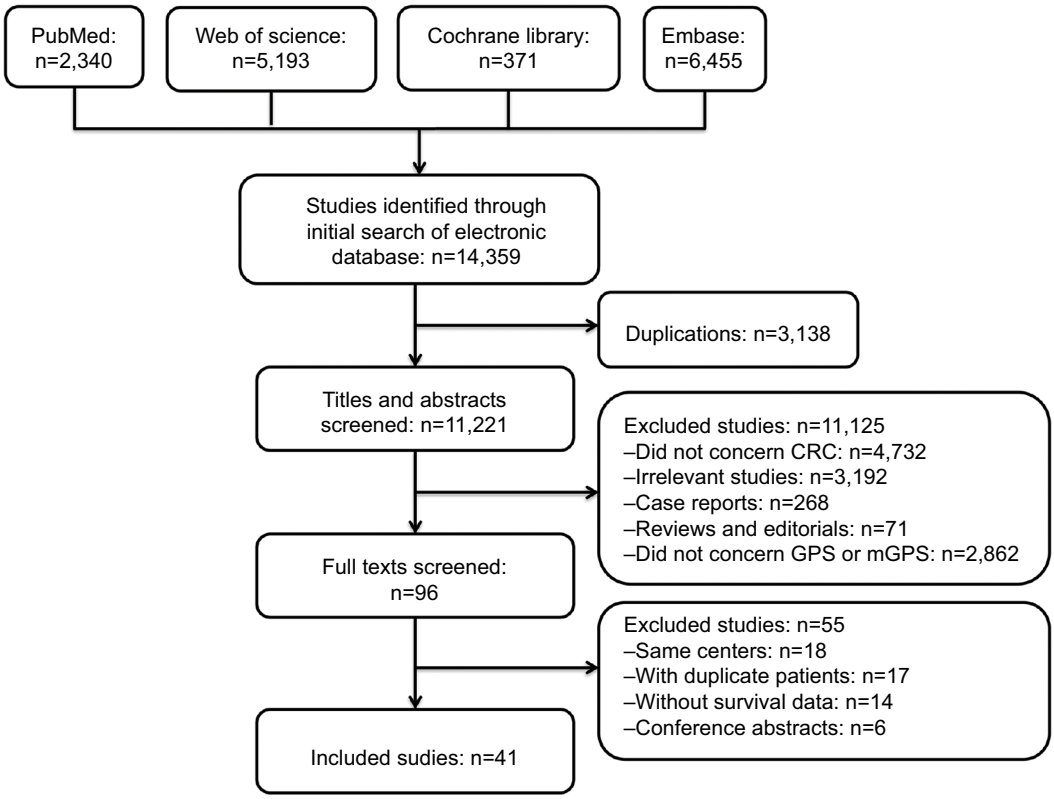



**Figure 1** Flow diagram showing study retrieval and selection process.
**Abbreviations:** CRC, colorectal cancer; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score.

software (version 4.1, M Mitchell, Engauge Digitizer, http://digitizer.sourceforge.net).[27,28] All data from the included studies were pooled using the Cochrane Collaboration's Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). A fixed effects model was used when there was no obvious heterogeneity ($I^2$=0); otherwise, a random effects model was used. Statistical heterogeneity among the studies was determined using the chi-squared test with a significance level of $P$=0.10, and heterogeneity was quantified using the $I^2$ statistic. A sensitivity analysis of OS was performed using Stata software (version 12.0; StataCorp LP, College Station, TX, USA).[29] Funnel plots were used to evaluate publication bias. Symmetry of the funnel plots was analyzed using Egger and Begg tests (Stata, version 12.0).

## Risk of bias assessment

All the included studies were critically assessed for methodological quality by two researchers independently (Lu X and Guo WY) by using the Quality In Prognosis Studies tool.[30] Each study was graded for the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The risk of bias for each domain is graded as low (−), moderate (±), or high (+).

## Subgroup analyses

Subgroup analyses were performed according to the models used to predict the prognostic outcomes of CRC patients as the scoring of the GPS and mGPS models was different. Subgroups were set according to therapeutic strategies, score cutoff values, sample size, region of publication, and TNM stages of patients in the included studies. The treatment modalities included surgical resection (SR) and chemotherapy. The cutoff value for sample size in the studies was a total of 300 patients. The region subgroups were defined as Asian countries and countries out of Asia taking into consideration the differences between the epidemiologic features and clinicopathological characteristics of CRC. Subgroups of TNM stages were divided into patients with advanced tumors of TNM stage IV and patients with TNM stage 0–III.

# Results

## Characteristics of the included studies

The comprehensive literature search identified a total of 14,359 studies from the above four databases. A flow diagram of study identification and selection is shown in Figure 1. Of these studies, 3,138 were duplicates. The titles and abstracts of the remaining 11,221 studies

were then screened. Among the 11,125 studies excluded, 4,732 were not related to CRC, 3,192 were irrelevant studies, 268 were case reports, 71 were reviews or editorials, and 2,862 did not evaluate GPS or mGPS. The full texts of the remaining 96 articles were carefully reviewed, 56 articles were excluded, and 41 articles were finally included in the present study. Of the 56 excluded studies, 18 studies were published by the same center, 18 included duplicate sample sets, 14 did not include survival outcomes, and six were conference abstracts. Two studies were published by the same author in the same year.[31] However, the patients enrolled in these studies received different treatment modalities (SR and chemotherapy). As a result, both studies were included in this meta-analysis. Two other studies were published by the same center[13,24] and both were included as independent cohorts due to their different endpoints. Patient cohorts in these studies were analyzed independently. Hence, 43 independent cohorts from 41 studies were included in this study.[13–17,19–21,24–26,31–59] The methodological quality of the included studies is summarized in Table S1.

The characteristics of the included studies are summarized in Table 1. A total of 9,839 patients were enrolled. Thirty-three independent cohorts of 8,006 CRC patients analyzed the correlation between GPS or mGPS and OS, and 26 independent cohorts of 7,616 patients focused on the correlation between GPS or mGPS and CSS. The overall outcomes showed that patients with elevated GPS or mGPS were associated with poor OS (HR: 2.20, 95% CI: 1.88–2.57, $P<0.001$). In addition, higher GPS or mGPS resulted in worse CSS (HR: 1.86, 95% CI: 1.59–2.17, $P<0.001$).

## Subgroup analysis

The results of the subgroup analyses are shown in Table 2. In the model subgroups, elevated GPS resulted in worse OS (HR: 2.08, 95% CI: 1.69–2.55, $P<0.001$) and CSS (HR: 2.38, 95% CI: 1.63–3.46, $P<0.001$). Patients in the mGPS subgroup with elevated mGPS were associated with a worse OS (HR: 2.23, 95% CI: 1.79–2.78, $P<0.001$) and CSS (HR: 1.73, 95% CI: 1.47–2.03, $P<0.001$) (Figure 2). Patients with increased GPS or mGPS who underwent SR had a poor OS (HR: 2.30, 95% CI: 1.90–2.79, $P<0.001$) and CSS (HR: 2.06, 95% CI: 1.67–2.53, $P<0.001$). The chemotherapy subgroup confirmed that elevated GPS or mGPS was associated with a worse OS (HR: 1.95, 95% CI: 1.46–2.62, $P<0.001$) and CSS (HR: 1.47, 95% CI: 1.24–1.74, $P<0.001$) (Figure 3). The pooled outcomes of studies which used 1 as the cutoff value demonstrated that

**Table 1** Characteristics of included studies

| Study | Year | Country | Design, center | Models | Endpoint | HRs | Sample size | Cutoff | Age (years) | Male (%) | TNM stages | Follow-up (months) | Therapies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adachi et al[20] | 2014 | Japan | Prospective, one center | mGPS | OS | Reported | 65 | 2 | 64 (17–38) | 59. 6 | I–IV | N/A | Resection |
| Chan et al[33] | 2017 | Australia | Retrospective, database | mGPS | OS | Reported | 386 | 1 | ≤70: 107; >70: 279 | 44 | I–III | 52 (27–92) | Resection |
| Choi et al[17] | 2014 | Korea | Retrospective, one center | GPS | CSS | Reported | 105 | 2 | 63 (32–86) | 60 | I–IV | 44 (2–81) | Resection |
| Dréanic et al[34] | 2013 | France | Retrospective, one center | GPS | OS and CSS | Reported | 49 | 1 | <65: 29; ≥65: 20 | 63 | IV | 35 (16.5–74.7) | Chemotherapy |
| Eren et al[35] | 2015 | Turkey | Retrospective, one center | GPS | CSS | Reported | 115 | 2 | 66 (32–91) | 56 | I–IV | 20 (7–41) | Resection |
| Furukawa et al[36] | 2011 | Japan | Retrospective, one center | GPS | OS | Reported | 40 | 2 | 66.1±9.6 | 75 | IV | N/A | Chemotherapy |
| Ghanim et al[37] | 2015 | Austria | Retrospective, one center | mGPS | OS | Reported | 52 | 1 | 62.7±11.4 | 53.8 | III, IV | N/A | Resection |
| Hong et al[38] | 2017 | China | Retrospective, one center | mGPS | CSS | Reported | 571 | 1 | 62.99±11.78 | 52 | I–III | Median: 42 | Resection |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ide et al[39] | 2017 | Japan | Retrospective, one center | mGPS | OS and CSS | Reported | 115 | 1 | 64 (33–83) | 71 | I–III | 65 (2–189) | Resection |
| Inoue et al[40] | 2013 | Japan | Retrospective, one center | mGPS | CSS | Reported | 163 | 1 | 64 (29–85) | 60 | IV | 621±145 days | Chemotherapy |
| Ishizuka et al[13] | 2012 | Japan | Retrospective, one center | GPS | CSS | Reported | 271 | 1 | 67.4±11.1 | 66.4 | 0–IV | 1,536±898 days | Resection |
| Ishizuka et al[24] | 2016 | Japan | Retrospective, one center | GPS | OS | Reported | 627 | 2 | 67.7±11.7 | 63.8 | 0–IV | 1,091±828 days | Resection |
| Kim et al[41] | 2017 | Korea | Retrospective, one center | mGPS | OS and CSS | Reported | 503 | 2 | 62 (18–88) | 63 | IV | Median: 17.6 | Chemotherapy |
| Kishiki et al[21] | 2013 | Japan | Retrospective, one center | mGPS | CSS | Reported | 79 | 2 | ≤70: 43; >70: 36 | 53.2 | IV | 32 (1–66) | Resection |
| Kobayashi et al[42] | 2010 | Japan | Retrospective, one center | GPS | OS | Reported | 63 | 1 | <70: 41; ≥70: 22 | 69.8 | IV | 38 (30.5–45.6) | Resection |
| Køstner et al[43] | 2016 | Sweden; Finland; Norway | Retrospective, multiple centers | GPS | OS | Reported | 492 | 1 | 65 (32–87) | 62.8 | IV | 50 (2.2–177.6) | Resection |
| Leitch et al[14] | 2007 | UK | Retrospective, one center | mGPS | OS and CSS | Reported | R: 149; U: 84 | 2 | R: <65: 48; 65–74: 52; >74: 49; U: <65: 34; 65–74: 27; >74: 23 | R: 54.4; U: 57.1 | R: I–III; U: IV | R: 48 (36–73); U: 12 (6–73) | Resection; chemotherapy |
| Lin et al[44] | 2015 | China | Retrospective, one center | GPS | OS | Reported | 99 | 2 | 62.6±10.7 | 35.4 | II | 60 | Resection |
| Maeda et al[45] | 2013 | Japan | Retrospective, one center | GPS | OS | Reported | 94 | 2 | <70: 62; ≥70: 32 | 54.3 | IV | Median: 30 | Resection |
| Maillet et al[46] | 2014 | France | Retrospective, one center | GPS | OS and CSS | Extracted from survival plots | 80 | 2 | 65 (36–83) | 56.3 | IV | 14 (1–58) | Chemotherapy |
| McSorley et al[47] | 2017 | UK | Retrospective, one center | mGPS | CSS | Reported | 70 | 1 | <65: 33; 65–74: 29; >74: 8 | 54.3 | I–III | 25 (8–78) | Resection |
| Moug et al[48] | 2010 | UK | Retrospective, two centers | mGPS | OS | Reported | 206 | 1 | 69.9±10.6 | 55.3 | I–III | 44.4 (1.2–81.6) | Resection |
| Nakagawa et al[49] | 2014 | Japan | Retrospective, one center | mGPS | CSS | Reported | 343 | 1 | 62.83±3.85 | 63.8 | IV | N/A | Resection |
| Ni et al[50] | 2016 | China | Retrospective, one center | GPS | OS | Reported | 148 | 1 | 60.2 (20–74) | 65.5 | IV | 12 (0.4–67) | Chemotherapy |
| Nozoe et al[15] | 2014 | Japan | Retrospective, one center | mGPS | OS | Reported | 272 | 2 | 70.4 (24–90) | 58.8 | I–IV | N/A | Resection |
| Okimoto et al[25] | 2017 | Japan | Retrospective, one center | GPS | OS and CSS | Reported | 134 | 1 | 63 (30–87) | 67 | IV | 43 (5–155) | Resection |

(*continued*)

**Table 1** (*continued*)

| Study | Year | Country | Design, center | Models | Endpoint | HRs | Sample size | Cutoff | Age (years) | Male (%) | TNM stages | Follow-up (months) | Therapies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Okugawa et al[51] | 2018 | Japan | Retrospective, two centers | mGPS | OS | Reported | T: 125; V: 545 | 2 | T: 72.7±11.9; V: 66.9±11.3 | T: 56.8; V: 58.9 | I–IV | N/A | Resection |
| Read et al[19] | 2006 | Australia | Retrospective, two centers | GPS | OS | Extracted from survival plots | 51 | 1 | 64 (40–79) | 58.8 | IV | Median: 29.8 | Chemotherapy |
| Sharma et al[52] | 2008 | Australia | Retrospective, multiple centers | GPS | OS | Extracted from survival plots | 52 | 2 | Median: 70.5 | 64 | IV | N/A | Chemotherapy |
| Shibutani et al (1)[31] | 2015 | Japan | Retrospective, one center | GPS | OS and CSS | Extracted from survival plots | 110 | 1 | 64 (27–86) | 57.3 | IV | N/A | Chemotherapy |
| Shibutani et al (2)[31] | 2015 | Japan | Retrospective, one center | GPS | OS | Reported | 254 | 1 | 66 (26–86) | 54.7 | II, III | N/A | Resection |
| Shimura et al[32] | 2017 | Japan | Retrospective, one center | mGPS | OS | Reported | 92 | 2 | 65 (31–90) | 61.9 | IV | 16.2 (0.2–110.4) | Resection |
| Sirniö et al[26] | 2018 | Finland | Prospective, one center | mGPS | OS and CSS | Reported | 271 | 1 | 69.5±11.6 | 50.9 | I–IV | Median: 64.3 | Resection |
| Son et al[53] | 2013 | Korea | Retrospective, one center | mGPS | OS | Reported | 624 | 2 | <60: 295; ≥60: 329 | 58.9 | I–III | 42 (1–66) | Resection |
| Song et al[54] | 2015 | Korea | Retrospective, one center | mGPS | OS | Reported | 177 | 1 | 52 (25–81) | 46.9 | IV | 3.1 (0.1–33.3) | Chemotherapy |
| Sugimoto et al[16] | 2012 | Japan | Retrospective, one center | GPS | CSS | Reported | 366 | 2 | ≤70: 240; >70: 126 | 57.1 | II–III | Median: 70.8 | Resection |
| Sun et al[55] | 2014 | China | Retrospective, one center | mGPS | OS and CSS | Reported | 255 | 1 | 59.47±12.63 | 52.9 | I–III | N/A | Resection |
| Toiyama et al[56] | 2011 | Japan | Retrospective, one center | mGPS | OS and CSS | Reported | 219 | 1 | 66 (29–91) | 62.1 | II, III | 56.9±63.8 | Resection |
| Tokunaga et al[57] | 2017 | Japan | Retrospective, one center | mGPS | OS and CSS | Reported | 468 | 1 | 68 (19–93) | 59.2 | I–III | 48.5 (2–124) | Resection |
| Watt et al[58] | 2016 | UK | Retrospective, one center | mGPS | OS and CSS | Reported | 813 | 1 | <65: 268; 65–74: 286; >74: 259 | 54.6 | 0–III | T: 116 (72–180); V: 31 (10–71) | Resection |
| Yamamoto et al[59] | 2012 | Japan | Retrospective, two centers | mGPS | CSS | Reported | 42 | 2 | <70: 12; ≥70: 30 | 61.9 | IV | Median: 424 days | Chemotherapy |

**Note:** Age and follow-up periods were expressed as mean ± SD or median (range).

**Abbreviations:** CSS, cancer-specific survival; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; N/A, not available; OS, overall survival; R, resectable; T, training; TNM, tumor, node, metastases; U, unresectable; V, validation.

**Table 2** Results of subgroup analyses of overall survival and cancer-specific survival

| Subgroups | Independent cohorts | Sample size | HR (95% CI) (H/L) | *P*-value | Study heterogeneity | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | $\chi^2$ | df | $I^2$ (%) | *P*-value |
| Overall survival | 32 | 7,714 | 2.20 (1.88, 2.57) | <0.00001 | 91.05 | 31 | 66 | <0.00001 |
| Models | | | | | | | | |
| GPS | 14 | 2,293 | 2.08 (1.69, 2.55) | <0.00001 | 19.95 | 13 | 35 | 0.10 |
| mGPS | 18 | 5,421 | 2.23 (1.79, 2.78) | <0.00001 | 70.68 | 17 | 76 | <0.00001 |
| Therapies | | | | | | | | |
| Resection | 23 | 6,504 | 2.30 (1.90, 2.79) | <0.00001 | 70.01 | 22 | 69 | <0.00001 |
| Chemotherapy | 9 | 1,210 | 1.95 (1.46, 2.62) | <0.00001 | 19.36 | 8 | 59 | 0.01 |
| Cutoff value | | | | | | | | |
| 1 | 18 | 4,263 | 1.85 (1.58, 2.16) | <0.00001 | 37.66 | 17 | 55 | 0.003 |
| 2 | 14 | 3,451 | 3.02 (2.21, 4.13) | <0.00001 | 39.04 | 13 | 67 | 0.0002 |
| Regions | | | | | | | | |
| Asia | 21 | 5,113 | 2.44 (1.98, 3.02) | <0.00001 | 56.26 | 20 | 64 | <0.0001 |
| Others | 11 | 2,601 | 1.79 (1.47, 2.18) | <0.00001 | 20.44 | 10 | 51 | 0.03 |
| Age, years | | | | | | | | |
| Mean/median <65 | 11 | 1,709 | 1.91 (1.50, 2.43) | <0.00001 | 21.98 | 10 | 55 | 0.02 |
| Mean/median ≥65 | 17 | 5,091 | 2.46 (1.93, 3.13) | <0.00001 | 67.21 | 16 | 76 | <0.00001 |
| Sample size | | | | | | | | |
| Sample <300 | 24 | 3,256 | 2.43 (1.97, 3.00) | <0.00001 | 60.13 | 23 | 62 | <0.0001 |
| Sample ≥300 | 8 | 4,458 | 1.86 (1.50, 2.31) | <0.00001 | 21.04 | 7 | 67 | 0.004 |
| TNM stages | | | | | | | | |
| 0–III | 12 | 3,588 | 1.95 (1.57, 2.42) | <0.00001 | 31.86 | 10 | 69 | 0.0004 |
| IV | 14 | 2,085 | 1.95 (1.56, 2.42) | <0.00001 | 26.46 | 13 | 51 | 0.01 |
| Cancer-specific survival | 23 | 5,375 | 1.86 (1.59, 2.17) | <0.00001 | 45.42 | 22 | 52 | 0.002 |
| Models | | | | | | | | |
| GPS | 8 | 1,230 | 2.38 (1.63, 3.46) | <0.00001 | 12.75 | 7 | 45 | 0.08 |
| mGPS | 15 | 4,145 | 1.73 (1.47, 2.03) | <0.00001 | 28.10 | 14 | 50 | 0.01 |
| Therapies | | | | | | | | |
| Resection | 16 | 4,344 | 2.06 (1.67, 2.53) | <0.00001 | 35.67 | 15 | 58 | 0.002 |
| Chemotherapy | 7 | 1,031 | 1.47 (1.24, 1.74) | <0.00001 | 6.06 | 6 | 1 | 0.42 |
| Cutoff value | | | | | | | | |
| 1 | 14 | 3,852 | 1.74 (1.48, 2.05) | <0.00001 | 21.26 | 13 | 39 | 0.07 |
| 2 | 9 | 1,523 | 2.34 (1.61, 3.40) | <0.00001 | 24.07 | 8 | 67 | 0.002 |
| Regions | | | | | | | | |
| Asia | 15 | 3,744 | 2.01 (1.65, 2.44) | <0.00001 | 27.86 | 14 | 50 | 0.01 |
| Others | 8 | 1,631 | 1.56 (1.24, 1.96) | <0.00001 | 10.65 | 7 | 34 | 0.15 |
| Age, years | | | | | | | | |
| Mean/median <65 | 9 | 2,299 | 1.83 (1.47, 2.27) | <0.00001 | 16.28 | 8 | 51 | 0.04 |
| Mean/median ≥65 | 10 | 2,512 | 1.73 (1.34, 2.24) | <0.00001 | 17.68 | 9 | 49 | 0.04 |
| Sample size | | | | | | | | |
| Sample <300 | 17 | 2,311 | 2.02 (1.64, 2.49) | <0.00001 | 27.01 | 16 | 41 | 0.04 |
| Sample ≥300 | 6 | 3,064 | 1.61 (1.32, 1.96) | <0.00001 | 10.35 | 5 | 52 | 0.07 |
| TNM stages | | | | | | | | |
| 0–III | 9 | 3,026 | 2.01 (1.57, 2.58) | <0.00001 | 19.29 | 8 | 59 | 0.01 |
| IV | 10 | 1,587 | 1.80 (1.43, 2.27) | <0.00001 | 15.76 | 9 | 43 | 0.07 |

**Abbreviations:** df, degrees of freedom; GPS, Glasgow prognostic score; H, high group; L, low group; mGPS, modified Glasgow prognostic score; TNM, tumor, node, metastases.

CRC patients with elevated GPS or mGPS had a worse OS (HR: 1.85, 95% CI: 1.58–2.16, *P*<0.001) and CSS (HR: 1.74, 95% CI: 1.48–2.05, *P*<0.001). Studies which used 2 as the cutoff value also demonstrated that elevated GPS resulted in poor OS (HR: 3.02, 95% CI: 2.21–4.13, *P*<0.001) and CSS (HR: 2.34, 95% CI: 1.61–3.40, *P*<0.001) (Figure 4). The pooled outcomes of 21 independent cohorts published in Asia showed that increased GPS or mGPS was associated with worse OS (HR: 2.44, 95% CI: 1.98–3.02, *P*<0.001) and CSS (HR: 2.01, 95% CI: 1.65–2.44, *P*<0.001) (Figure 5). The subgroup analysis based on geographical regions showed that Asian patients with increased GPS or mGPS level had a poor OS (HR: 2.44, 95% CI: 1.98–3.02, *P*<0.001) and CSS (HR: 2.01, 95% CI: 1.65–2.44, *P*<0.001)

(Figure 6). For elderly patients with a mean/median age >65 years, elevated GPS or mGPS was also associated with worse OS (HR: 2.46, 95% CI: 1.93–3.13, *P*<0.001) and CSS (HR: 1.73, 95% CI: 1.34–2.24, *P*<0.001) (Figure 7). The subgroup of patients with CRC TNM stage 0–III demonstrated the prognostic value of GPS or mGPS in predicting OS (HR: 2.13, 95% CI: 1.66–2.73, *P*<0.001) and CSS (HR: 2.01, 95% CI: 1.57–2.58, *P*<0.001) (Figure 8). The subgroup of patients with CRC TNM stage IV indicated that elevated GPS or mGPS was associated with poor OS (HR: 1.95, 95% CI: 1.56–2.42, *P*<0.001) and CSS (HR: 1.80, 95% CI: 1.43–2.27, *P*<0.001).

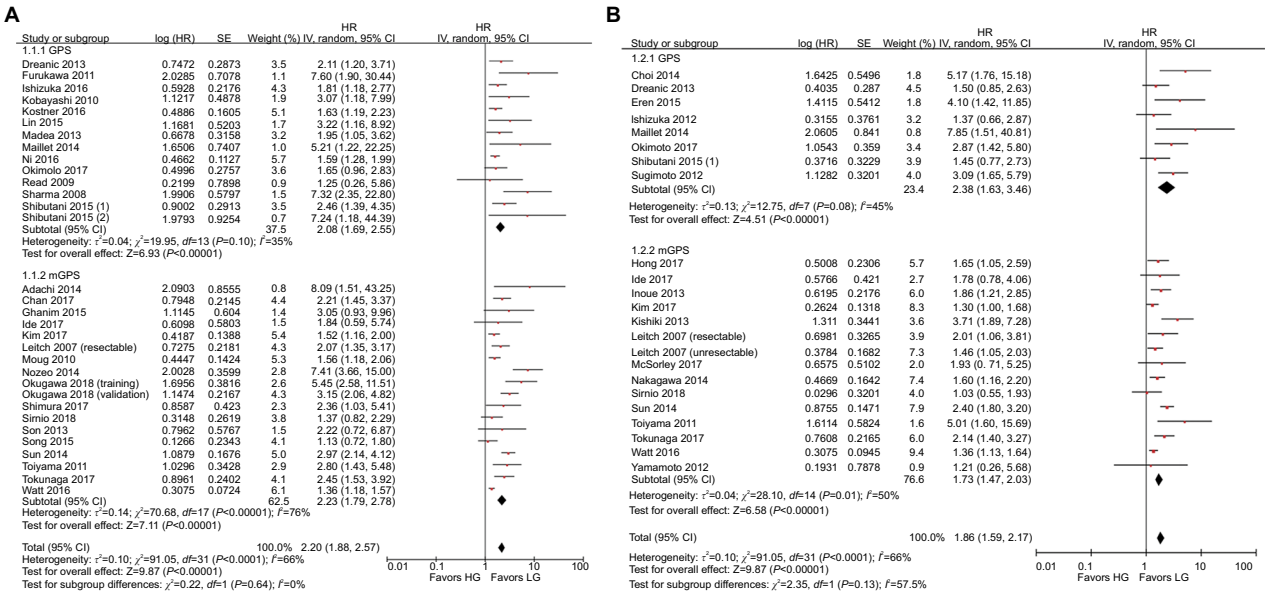



**Figure 2** Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to models.
**Note:** (**A**) Overall survival and (**B**) cancer-specific survival.
**Abbreviations:** CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

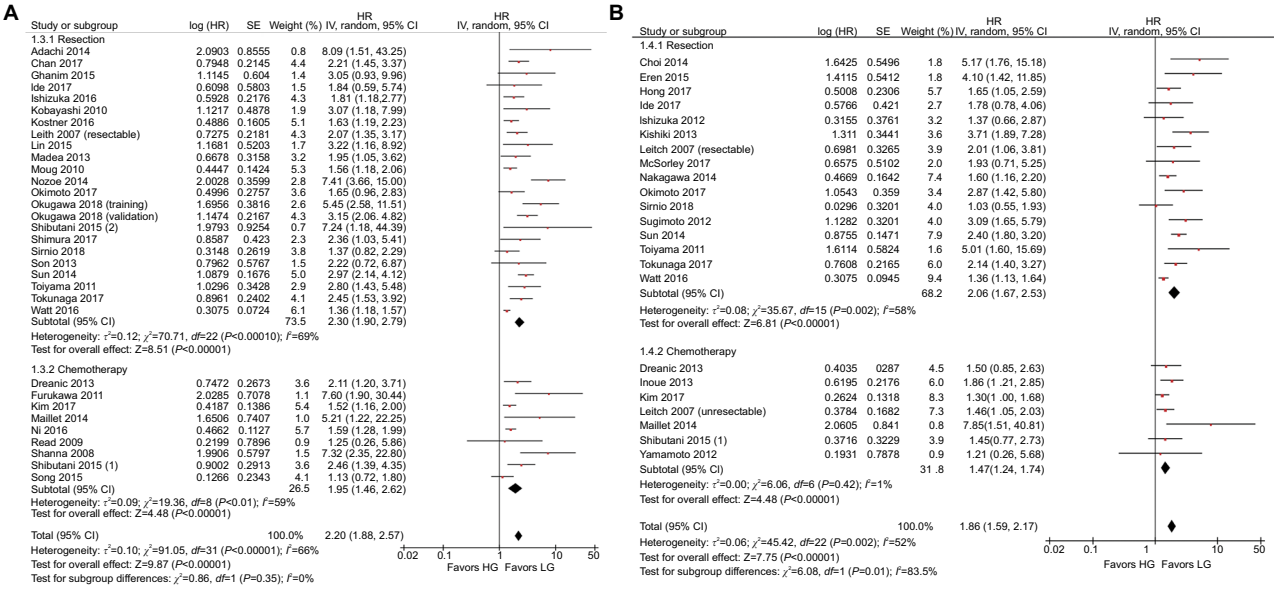



**Figure 3** Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to therapeutic strategies.
**Note:** (**A**) Overall survival and (**B**) cancer-specific survival.
**Abbreviations:** CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

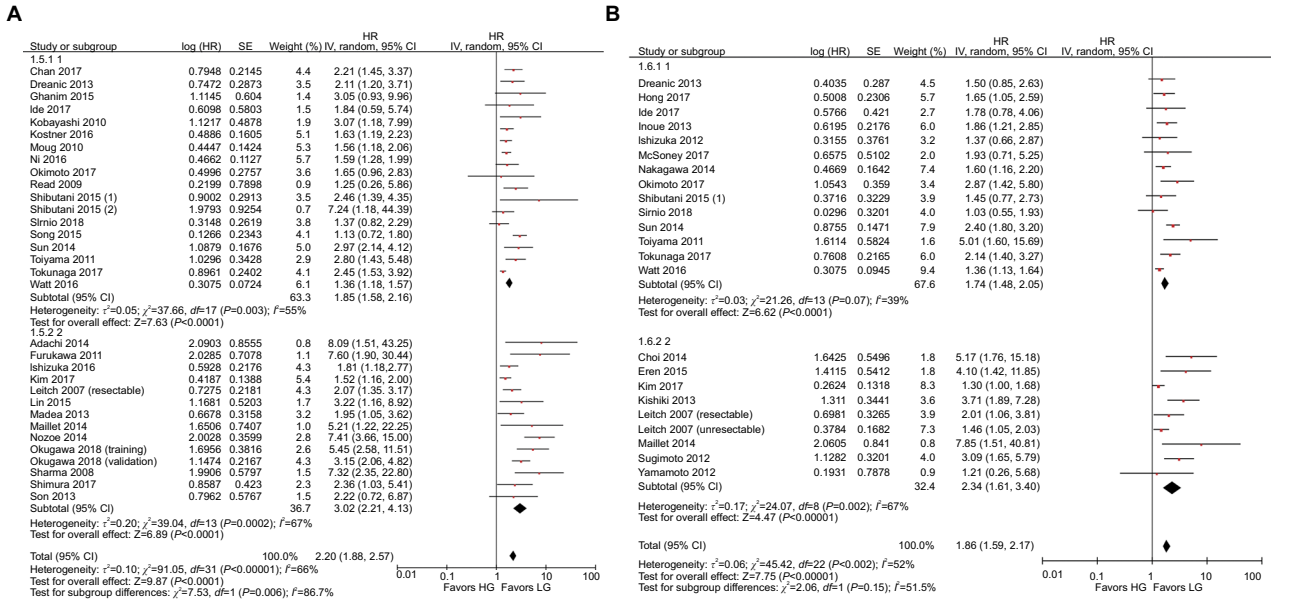



**Figure 4** Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to cutoff values.
**Note:** (**A**) Overall survival and (**B**) cancer-specific survival.
**Abbreviations:** CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

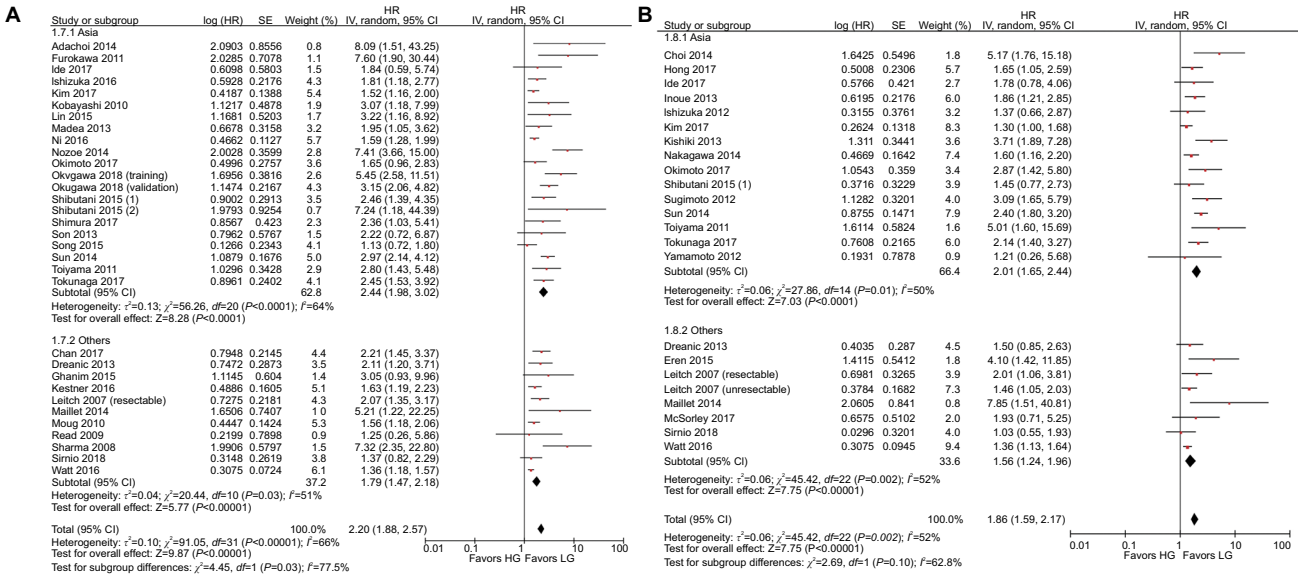



**Figure 5** Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to the region of publication.
**Note:** (**A**) Overall survival and (**B**) cancer-specific survival.
**Abbreviations:** CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

## Sensitivity analysis and publication bias

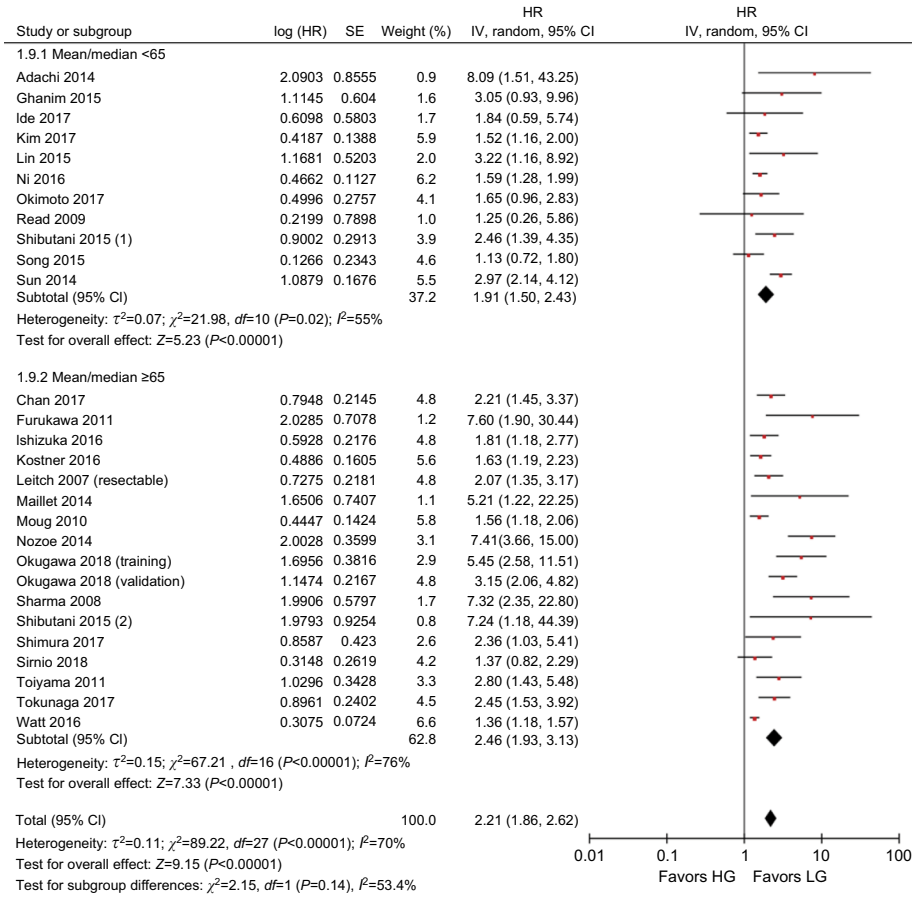
Sensitivity analysis was conducted by omitting the included studies in sequence to investigate the stability of HR for OS. The results showed that several studies deviated from the center line (Figure 9A).[15,51,52,55,58] After eliminating these studies, the pooled HRs did not alter significantly (Figure 9B).

The funnel plot showed publication bias in the included studies (Figure 9C). The studies were almost symmetrically distributed around the center line after removing the studies associated with publication bias (Figure 9D). In addition, statistical tests were carried out to evaluate dissymmetry of the funnel plot using Begg (z=1.86, $P$=0.132) and Egger (bias coefficient −0.905, standard error 0.405, $t$=1.91, $P$=0.070) tests.

## Discussion

CRC is one of the most common gastrointestinal malignancies and accounts for ~10% of all newly diagnosed

**A**




**B**

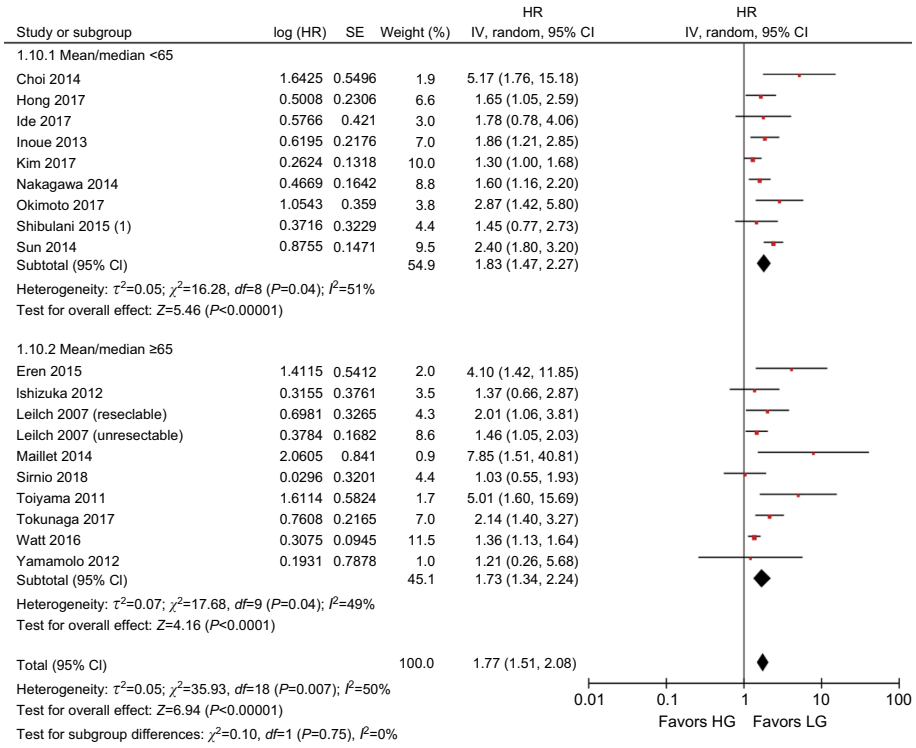



**Figure 6** Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to patient age.
**Note:** (**A**) Overall survival and (**B**) cancer-specific survival.
**Abbreviations:** CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

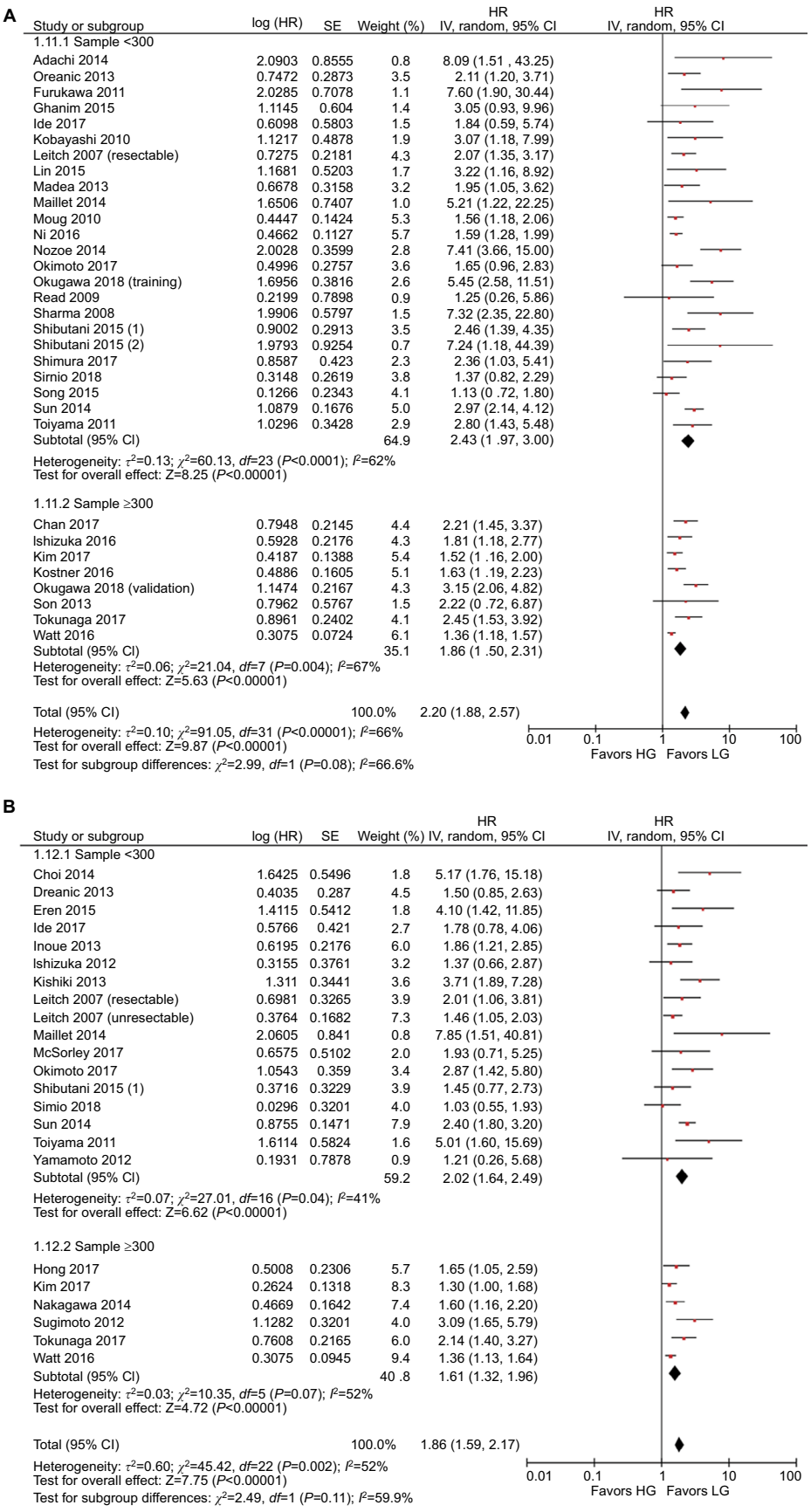



**Figure 7** Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to sample size.
**Note:** (**A**) Overall survival and (**B**) cancer-specific survival.
**Abbreviations:** CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error.

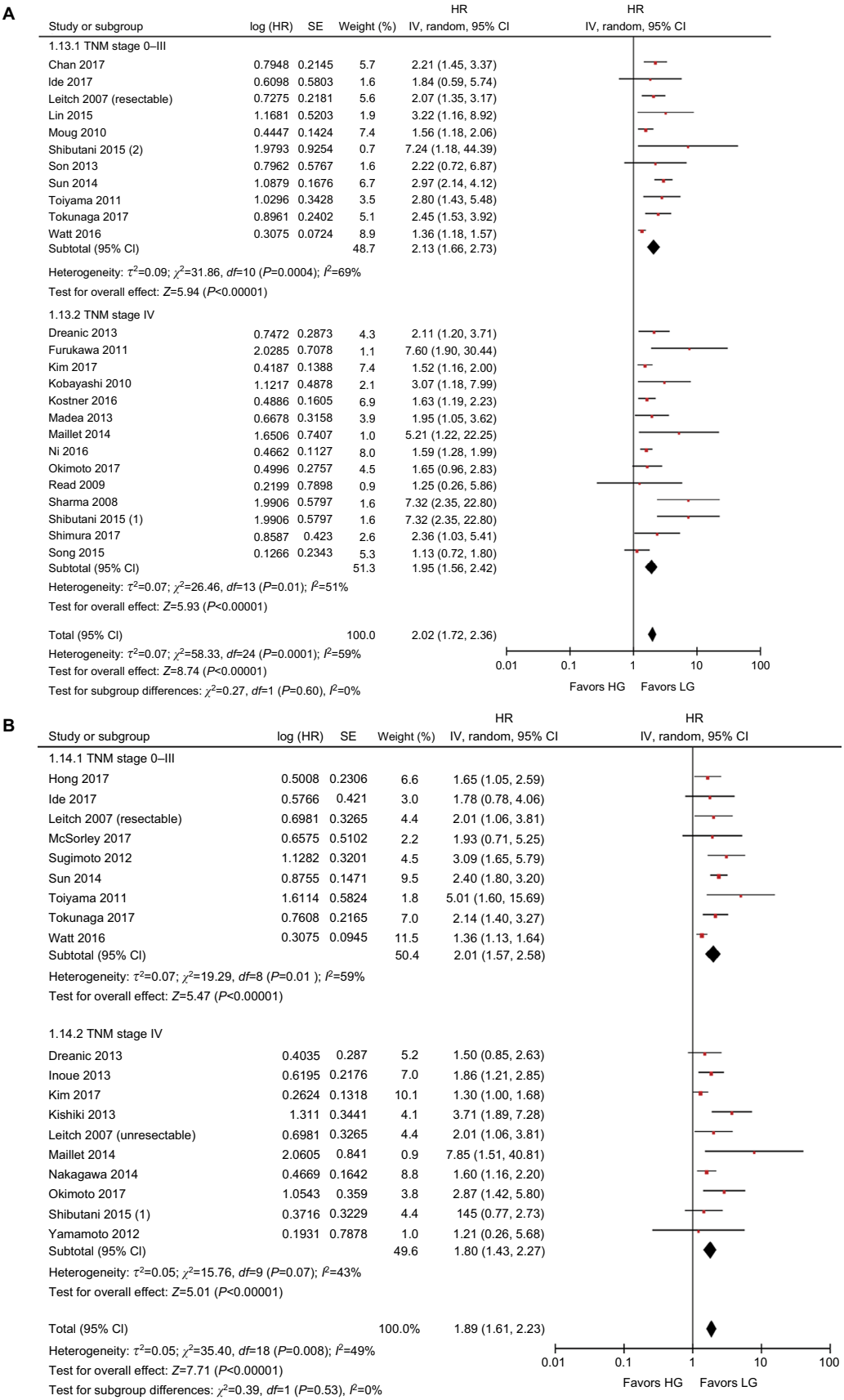



**Figure 8** Subgroup analysis showing correlation between GPS and prognosis of CRC patients according to TNM stages.
**Note:** (**A**) Overall survival and (**B**) cancer-specific survival.
**Abbreviations:** CRC, colorectal cancer; df, degrees of freedom; GPS, Glasgow prognostic score; LG, low group; HG, high group; SE, standard error; TNM, tumor, node, metastases.

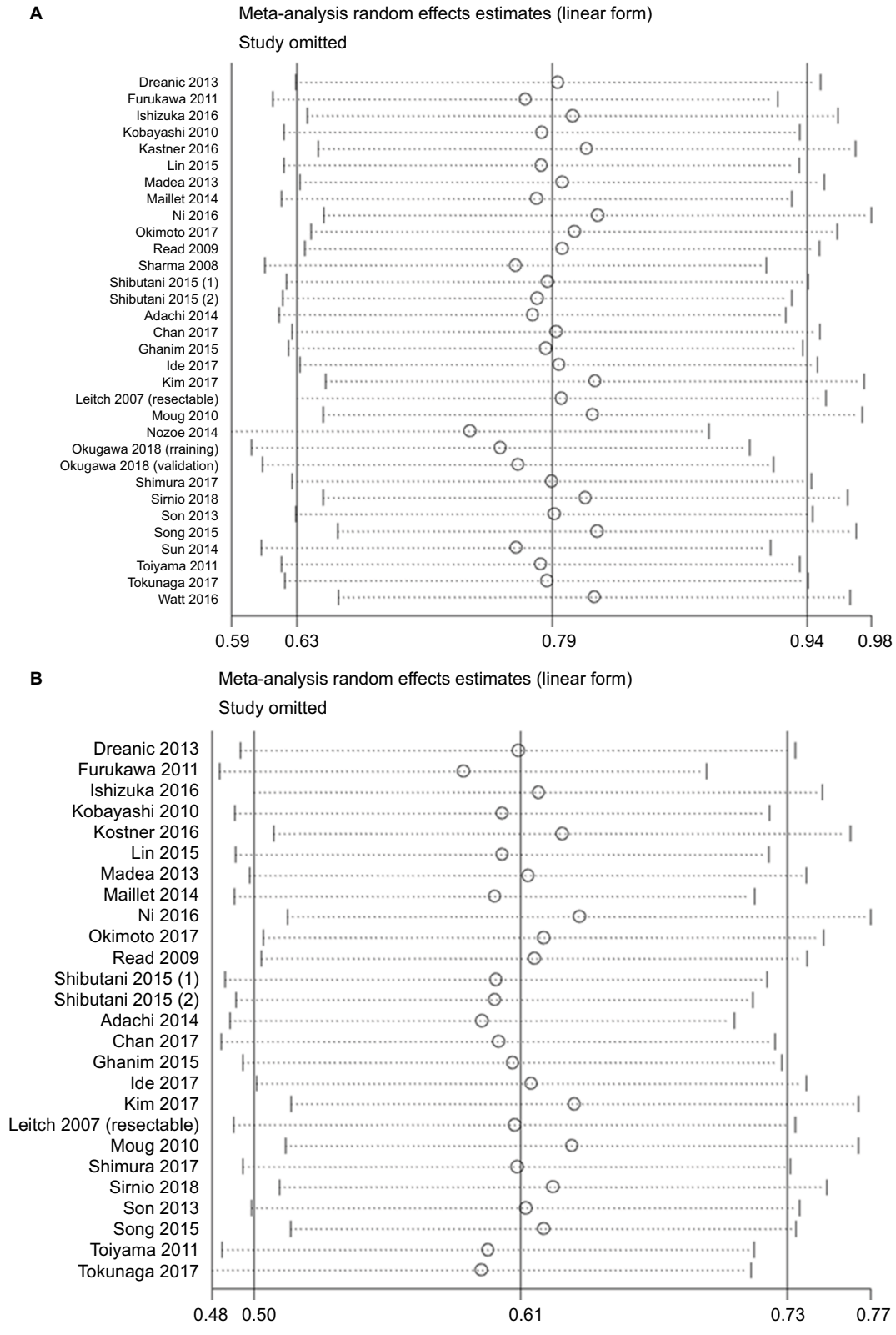



**Figure 9** (*Continued*)

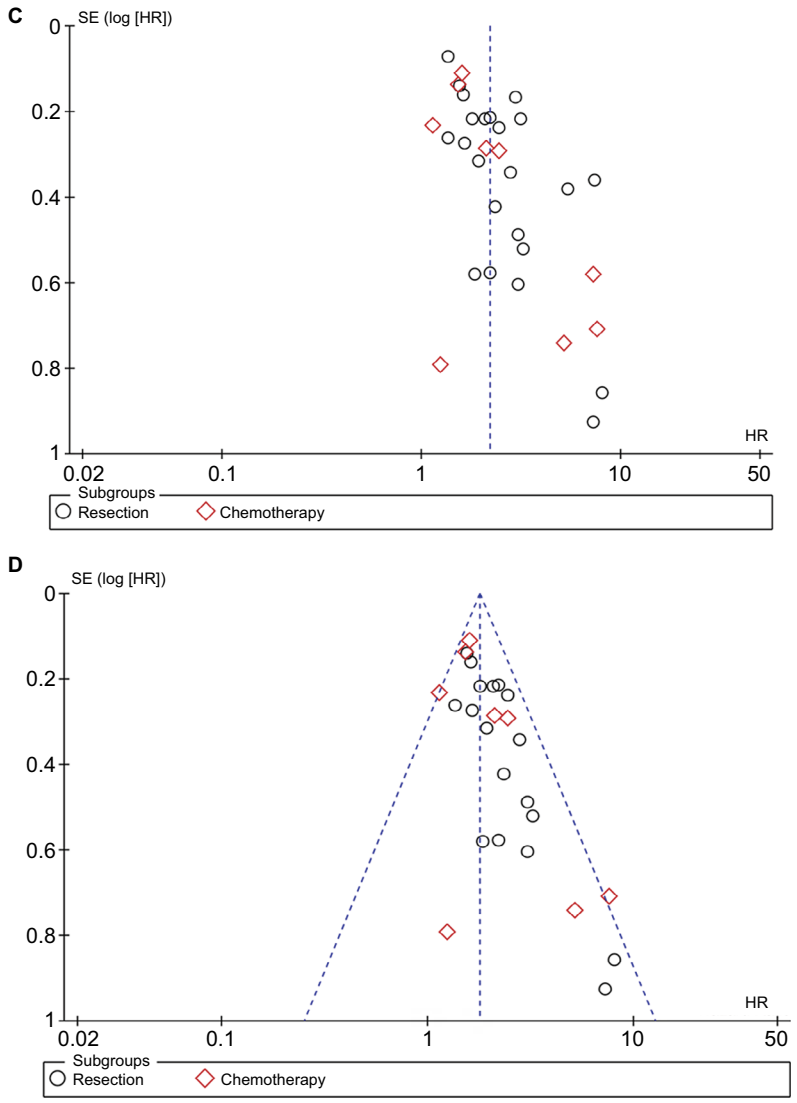



**Figure 9** Sensitivity analysis and funnel plot of OS of patients with CRC.
**Notes:** Sensitivity analysis for (**A**) overall patients focusing on OS and (**B**) patients after removing studies with potential publication bias. Funnel plot for (**C**) overall patients focusing on OS and (**D**) patients after removing studies with potential publication bias.
**Abbreviations:** CRC, colorectal cancer; OS, overall survival; SE, standard error.

cancers. The development of therapeutic strategies and improvements in posttreatment quality of life remains a challenge as various factors influence prognosis. An increasing number of prognostic models or indicators have been used to predict the prognosis of patients with CRC. Inflammation-related models including the neutrophil to lymphocyte, platelet to lymphocyte, CRP, and the systemic inflammatory index were developed and demonstrated to be prognostic predictors in recent years. The GPS model was also designed to assess the prognosis of CRC patients. The present study attempted to identify the predictive role of GPS and mGPS by performing a meta-analysis based on the pooled outcomes of research worldwide.

This study included pooled survival outcomes from 43 independent cohorts involving 9,839 CRC patients. The pooled outcomes showed that CRC patients with an increased level of pretreatment GPS or mGPS were associated with worse OS following SR or chemotherapy (HR: 2.20, 95% CI: 1.88–2.57, $P<0.001$). Moreover, elevated GPS or mGPS levels were also associated with poor CSS (HR: 1.86, 95% CI: 1.59–2.17, $P<0.001$). We also conducted subgroup analyses to reduce the heterogeneity. Subgroups were set according to models, therapeutic strategies, cutoff values, geographical regions, age, sample size, and TNM stages. The results of subgroup analyses confirmed the overall outcomes. By conducting the subgroup analyses, heterogeneity was reduced in the subgroups. Thus, the above-mentioned factors should be taken into consideration in future research.

CRC is one of the most common malignancies, and the prediction of prognosis is an important consideration in the

establishment of clinical treatment strategies. Recently, the prognostic role of inflammation factors in the management of CRC has been a focus of attention in surgeons.[60,61] GPS is a prognostic score for cancer patients which calculates prognosis based on the combination of CRP and ALB levels. A growing number of studies have demonstrated the potential predictive value of GPS or mGPS in CRC patients. However, other studies found no correlation between the GPS or mGPS and the survival outcomes of CRC patients. Therefore, it was necessary to perform this systematic review and meta-analysis to draw credible conclusions on the controversial role of GPS in CRC.

As therapeutic strategy was one of the most important factors that influenced the prognostic outcomes of CRC patients, further subgroup analysis was performed to assess the effect of GPS or mGPS in CRC patients according to treatment. The results were consistent with the overall outcomes. Patients with low GPS or mGPS before undergoing SR had a better prognosis and longer CSS. GPS or mGPS was divided into three categories and there was no agreed conclusion on the cutoff values. Thus, subgroup analysis based on cutoff values was performed. The pooled outcomes obtained confirmed the accurate prognostic role of GPS and mGPS using either of the cut-off values. Moreover, patient age was considered another factor that influenced the overall outcomes. Tominaga et al demonstrated that the GPS was not correlated with patient prognosis as all the enrolled patients were over 65 years.[62] We then conducted another subgroup analysis based on the mean/median patient age of 65 years as most of the patients included in this study were in the 65 years age group. In addition, 65 years was considered to be the dividing line between elderly and middle aged. Subgroup analyses of TNM stages, sample size, and publication regions were also carried out. The results of the subgroup analyses confirmed the overall outcomes and demonstrated the effective prognostic value of GPS or mGPS in predicting survival outcomes in CRC patients.

The results of the sensitivity analysis and funnel plot showed potential publication bias in several studies. After omitting these studies, the OS in the remaining studies was more symmetrically distributed. The reasons for this bias may be due to differences in the baseline characteristics of CRC patients and factors related to the study protocols. Moreover, the differences in detection methods and data storage may have resulted in heterogeneity. Although the random effects model reduced the effect of heterogeneity, the heterogeneity between studies was not abolished.

Two previous meta-analyses reported the prognostic value of GPS or mGPS in CRC patients.[63,64] Dolan et al examined the evidence for the role of several systemic inflammation-based prognostic scores in patients who underwent SR.[63] Only 12 studies with 4,739 CRC patients were included in the meta-analysis and no subgroup analyses were conducted. Liu et al performed a meta-analysis by pooling the outcomes of 25 retrospective studies.[64] The inclusion and exclusion criteria were not rigorous enough and several studies which focused on the prognostic value of GPS were not included. In their study, subgroup analyses were performed based on sample size, cutoff values, and geographical regions. However, they did not include therapeutic strategies, tumor clinical stages, and modifications of the GPS, which accounted for some of the heterogeneity. The present meta-analysis, to our knowledge, is the most comprehensive and included 41 studies. Furthermore, subgroup analyses were also performed.

GPS or mGPS is calculated based on serum CRP and ALB levels. CRP is an acute-phase protein produced in hepatocytes via activation of tumor necrosis factor-α and interleukin-6.[51] Several studies have reported that increased serum CRP levels were associated with poor outcomes in a variety of solid tumors.[65–67] In contrast, hypoalbuminemia is considered to be an indicator of malnutrition and cachexia. Two studies have shown that hypoalbuminemia was associated with poor outcomes in various cancers.[68,69] The GPS or mGPS enables better appreciation of systemic inflammation or malnutrition in CRC patients. This study pooled outcomes and then drew reliable conclusions with regard to the prognostic value of the GPS or mGPS. Based on these conclusions, the GPS or mGPS should be highlighted in the clinical management of CRC. For patients with elevated GPS or mGPS, a management protocol for systemic inflammatory response via the tumor–host interaction during the postoperative course is urgently needed to improve their prognosis.[51]

The present meta-analysis was performed based on the largest patient sample available to date. However, the study had several limitations. Firstly, most of the included studies were retrospectively designed. This increased the risk of bias due to inadequate random blinding and sequencing. Secondly, even though subgroup analyses were performed, heterogeneity still existed among subgroups. This may have been due to a variety of baseline characteristics and follow-up information. Furthermore, the overall outcomes might be overvalued due to unpublished studies which had negative data. Finally, all included studies were written in English, and this may have resulted in publication bias. These limitations should be taken into consideration in further studies to confirm our results.

Nevertheless, the present meta-analysis was conducted at an appropriate time based on sufficient studies with enough data to investigate the prognostic value of GPS or mGPS in CRC patients. A meta-analysis is a statistical inspection of scientific studies, and its level of evidence is considered to be superior to that of individual studies.[70] The results of this meta-analysis are encouraging although multiple strategies were used to identify relevant studies, with strict criteria used for study inclusion and evaluation. Subgroup analyses were performed to minimize heterogeneity due to different treatment modalities, cutoff values, regions, ages, and tumor stages. In addition, our study is the most comprehensive and up-to-date systematic review and meta-analysis which focused on the role of GPS or mGPS in predicting the prognosis of CRC.

## Conclusion

The present study indicated that pretreatment GPS or mGPS was an accurate prognostic predictor in patients with CRC. Patients with elevated pretreatment GPS or mGPS were associated with worse prognosis. Subgroup analyses confirmed the overall outcomes. Pretreatment GPS or mGPS should be identified as an important parameter in the management of CRC.

## Disclosure

The authors report no conflicts of interest in this work.

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# Supplementary material

**Table S1** Summary of risk of bias

| Study | Study participation | Study attrition | Prognostic factor measurement | Outcome measurement | Study confounding | Statistical analysis and reporting |
|---|---|---|---|---|---|---|
| Adachi et al[1] | – | – | ± | – | – | ± |
| Chan et al[2] | – | – | – | – | ± | ± |
| Choi et al[3] | – | – | ± | – | ± | – |
| Dréanic et al[4] | – | ± | – | ± | ± | – |
| Eren et al[5] | – | – | ± | – | ± | – |
| Furukawa et al[6] | ± | ± | – | – | – | – |
| Ghanim et al[7] | ± | ± | – | – | – | – |
| Hong et al[8] | – | – | – | – | ± | – |
| Ide et al[9] | – | – | ± | – | ± | – |
| Inoue et al[10] | – | – | – | – | ± | – |
| Ishizuka et al[11] | – | – | – | – | – | – |
| Ishizuka et al[12] | – | – | – | – | ± | ± |
| Kim et al[13] | – | – | – | – | ± | – |
| Kishiki et al[14] | – | – | – | – | ± | – |
| Kobayashi et al[15] | ± | – | – | – | ± | – |
| Køstner et al[16] | – | – | – | – | ± | – |
| Leitch et al[17] | – | – | – | – | – | ± |
| Lin et al[18] | ± | – | – | – | ± | ± |
| Maeda et al[19] | ± | – | – | – | ± | – |
| Maillet et al[20] | ± | – | – | – | ± | – |
| McSorley et al[21] | ± | – | – | – | – | ± |
| Moug et al[22] | – | – | – | ± | ± | ± |
| Nakagawa et al[23] | – | ± | – | – | ± | – |
| Ni et al[24] | – | – | ± | – | ± | – |
| Nozoe et al[25] | – | ± | – | – | ± | ± |
| Okimoto et al[26] | – | – | – | – | ± | – |
| Okugawa et al[27] | – | ± | – | – | – | – |
| Read et al[28] | ± | – | – | – | – | – |
| Sharma et al[29] | ± | ± | – | – | ± | – |
| Shibutani et al (1)[30] | – | ± | – | – | ± | – |
| Shibutani et al (2)[30] | – | – | – | – | ± | – |
| Shimura et al[31] | – | – | ± | – | – | – |
| Sirniö et al[32] | – | – | – | – | ± | – |
| Son et al[33] | – | – | – | – | ± | – |
| Song et al[34] | – | – | – | – | – | ± |
| Sugimoto et al[35] | ± | – | – | – | ± | – |
| Sun et al[36] | – | ± | – | – | ± | – |
| Toiyama et al[37] | – | – | – | – | – | ± |
| Tokunaga et al[38] | – | – | – | – | ± | – |
| Watt et al[39] | – | – | – | ± | ± | – |
| Yamamoto et al[40] | ± | – | – | – | ± | ± |

**Note:** The risk of bias for each domain is graded as low (–), moderate (±), or high (+).

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