Prognostic and clinicopathological significance of systemic immune-inflammation index in colorectal cancer: a meta-analysis

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Abstract

Background: Previous studies on the systemic immune-inflammation index (SII), which is based on platelet, neutrophil and lymphocyte counts, as a prognostic marker in patients with colorectal cancer (CRC) yielded inconsistent results. The aim of this study was to evaluate the prognostic and clinicopathological role of SII in CRC via meta-analysis.

Methods: A comprehensive literature survey was performed on PubMed, Web of Science, Embase and the Cochrane Library databases to include studies published up to 6 April 2020. Pooled hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were computed to estimate the prognostic and clinicopathological value of SII in CRC.

Results: A total of 12 studies published between 2016 and 2019 were included in our meta-analysis. The combined analysis showed that high SII levels were significantly associated with worse overall survival (OS; HR = 1.61, 95% CI = 1.21–2.13, p < 0.001) and progression-free survival (HR = 1.74, 95% CI = 1.26–2.39, p = 0.001) in CRC. Moreover, elevated SII was also correlated with poor tumor differentiation (OR = 1.60, 95% CI = 1.27–2.02, p < 0.001), presence of distant metastasis (OR = 2.27, 95% CI = 1.10–4.67, p = 0.026), ECOG PS of 1–2 (OR = 1.98, 95% CI = 1.39–2.84, p < 0.001) and tumor size ≥5 cm (OR = 1.49, 95% CI = 1.18–1.88, p = 0.001). However, high SII was not significantly associated with sex, tumor location, lymph node metastasis, or age in patients with CRC.

Conclusion: Our meta-analysis indicated that high SII levels predicted poor prognosis in CRC. In addition, an elevated SII was also associated with clinical factors, implying higher malignancy of the disease.

Keywords: colorectal cancer, meta-analysis, prognosis, risk factors, systemic immune-inflammation index

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readily-accessible and cost-effective prognostic indexes are urgently needed to predict prognosis and to evaluate the therapeutic effectiveness in clinical practice for patients with CRC.

Previous evidence has shown that chronic inflammation is extensively involved in CRC development and progression. Tumor-associated systemic inflammatory responses involve inflammatory cells and a variety of inflammatory mediators. A number of studies have focused on peripheral inflammatory cells and calculated ratios as parameters reflecting the status of immune responses in cancer patients. These parameters include the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, C-reactive protein levels and systemic immune-inflammation index (SII). SII is defined as the platelet count × neutrophil count/lymphocyte count, and can be easily derived from daily laboratory tests. Many studies have investigated the prognostic role of SII in patients with CRC, yet the results were inconsistent. For example, SII was proposed as a significant prognostic factor in several studies whereas the correlation between SII and survival outcomes in CRC was not significant in other studies. Therefore, we comprehensively searched for relevant studies in the literature and carried out a quantitative meta-analysis to evaluate the potential of SII as a CRC biomarker.

Materials and methods

Search strategy

The current meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We thoroughly searched the PubMed, Web of Science, Embase and Cochrane Library databases for eligible studies published up until 6 April 2020. The following search phrases were used for literature retrieval: (colonic neoplasms OR colorectal neoplasms OR colon cancer OR rectal cancer OR rectal cancers OR rectal tumor OR colorectal cancer OR CRC OR colorectal tumor OR colorectal carcinoma) AND (systemic immune-inflammatory index OR SII OR systemic-immune-inflammation index OR systemic immune-inflammation index). The detailed search strategies for PubMed are shown in the Supplemental material online. We also manually examined the references of the included articles to identify potential inclusions. Since the data used in this study were extracted from previously published literature, no patient consent or ethical approval was necessary.

Inclusion and exclusion criteria

Studies were included, if (1) CRC diagnosis was histopathologically confirmed in patients, (2) hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of pretreatment SII with survival outcomes including overall survival (OS) and/or progression-free survival (PFS) were reported, or sufficient data were available to calculate them, or the association between SII and clinicopathological features of CRC was reported, (3) a definite cut-off value of pretreatment SII was determined and (4) full-text articles published in English. Following studies were excluded: (1) reviews, editorials, conference abstracts, letters and case reports, (2) duplicate publications, (3) basic research or animal studies and (4) studies without sufficient data.

Data extraction and quality assessment

Two investigators (MD and YS) independently extracted data from eligible studies. Any disagreements were resolved via discussion with a third investigator (XG). The following information was extracted: name of the first author, year of publication, country of origin, sample size, age of patients, sex distribution, study design, recruitment time, histological type, follow-up, tumor stage, treatment methods, cut-off values of SII, cut-off selection method, survival endpoints and HRs with corresponding 95% CIs. OS and PFS were the primary and secondary endpoints of this meta-analysis, respectively. We evaluated the methodological quality of the included studies using the Newcastle–Ottawa Scale (NOS). The NOS is based on patient selection, comparability and outcome of interest. NOS scores range from 0 to 9, and studies with scores higher than 6 are regarded high quality.

Statistical analysis

The pooled HRs and 95% CIs were calculated to estimate the association between SII and OS/ PFS in CRC. Statistical heterogeneity among studies was evaluated using Cochran’s Q test and Higgins P statistics. If $P > 50\%$ or $p < 0.10$ (indicating significant heterogeneity among studies), the data were combined using a random-effects model. Otherwise, a fixed-effects model
was applied. Subgroup analyses were performed based on geographical region, treatment, Tumor Node Metastasis (TNM) stage, sample size, cut-off value, cut-off selection method and NOS score to identify the sources of heterogeneity. ORs and 95% CIs were computed to assess the association between SII and clinicopathological characteristics of patients with CRC. OR, as the effect size for association between SII and clinicopathological factors, was expressed along with 95% CI. ORs >1 with 95% CIs that did not overlap with 1 suggested that a high SII increased the trend of that clinical factor, whereas ORs <1 with 95% CIs that did not overlap with 1 were indicators of the decreased trend of that clinical factor. Sensitivity analysis was also conducted to evaluate the effect of the individual study data on the HRs of OS and PFS. Potential publication bias was examined using Begg’s and Egger’s tests. All statistical calculations were performed using Stata version 12.0 (Stata Corporation, College Station, TX, USA). $p < 0.05$ (two-sided) was considered statistically significant.

Results

Search results and study characteristics

A total of 65 records were identified from database searches. Duplicate records were removed to yield 41 studies. After reviewing the titles and abstracts, a further 26 of them were excluded. Subsequently, 15 studies were evaluated by full-text reading, and five of them were discarded for the following reasons: four studies lacked necessary data and one study was a review article. Through an updated literature search, two more eligible studies \cite{16, 19} were identified. Finally, a total of 12 studies \cite{8–19} published between 2016 and 2019 were included in our meta-analysis. The literature search flowchart is shown in Figure 1. The 12 eligible studies recruited a total of 3919...
Table 1. Major features of included studies in this meta-analysis.

| Author  | Year | Country | Histology | Study period | Study design | Sample size | Age, years Median (range) | Sex M/F | TNM stage | Treatment | Cut-off value | Cut-off selection | Follow-up, months | Survival analysis | NOS score |
|---------|------|---------|-----------|--------------|--------------|-------------|---------------------------|---------|-----------|-----------|--------------|-----------------|-----------------|-----------------|-----------|
| Passardi 2016 | Italy | CRC | 2007–2012 | Prospective | 289 | 65.5 | 174/115 | I–IV | Chemotherapy+ targeted therapy | 730 | X-tile software | 36 [1–65] | OS, PFS | 9 |
| Chen 2017 | China | CRC | 1994–2010 | Retrospective | 1383 | NA | 788/595 | I–IV | Surgical resection | 340 | ROC analysis | NA | OS, PFS | 6 |
| Yang 2017 | China | CRC | 2009–2015 | Retrospective | 95 | 57 | 58/37 | IV | Chemotherapy+ targeted therapy | 460.66 | Median value | 40 [12–72] | OS, PFS | 7 |
| Tao 2018 | China | Colon cancer | 2011–2013 | Retrospective | 118 | 60 | 63/55 | I–IV | Surgical resection | 667.75 | Median value | 36 | OS | 8 |
| Xie 2018 | China | CRC | 2009–2014 | Retrospective | 240 | 59 [18–90] | 157/83 | IV | Surgical resection | 649.45 | Median value | 26.7 [1.1–92.4] | OS | 8 |
| Yang 2018 | China | CRC | 2010–2015 | Retrospective | 98 | 53 [26–83] | 59/39 | I–IV | Neoadjuvant chemoradiotherapy | 437.72 | Median value | 37 [16.2–93.3] | OS, PFS | 7 |
| Zhou 2018 | China | CRC | 2007–2015 | Retrospective | 516 | 16–87 | 331/185 | I–IV | Surgical resection | 568.69 | ROC analysis | 21.7 [2.1–118.7] | OS, PFS | 8 |
| Jiang 2019 | China | CRC | 2010–2017 | Retrospective | 102 | 28–75 | 72/30 | IV | Chemotherapy+ targeted therapy | 660.55 | ROC analysis | 33.2 [2.6–94.5] | OS, PFS | 7 |
| Lu 2019 | China | CRC | 2010–2017 | Retrospective | 182 | 53.5 [15–93] | 95/87 | I–II | Surgical resection | 1505 | ROC analysis | NA | NA | 7 |
| Wang 2019 | China | CRC | 2002–2016 | Retrospective | 452 | 57 | 289/163 | IV | Surgical resection | 517 | X-tile software | 28 | OS, PFS | 8 |
| Yang 2019 | China | CRC | 2009–2015 | Retrospective | 220 | 57 | 133/87 | III–IV | Adjuvant chemoradiotherapy | 534.94 | ROC analysis | 23.9 [12–87] | OS, PFS | 7 |
| Zhang 2019 | China | CRC | 2010–2013 | Retrospective | 224 | 67 [30–89] | 127/97 | I–IV | Surgical resection | 642.2 | Median value | 48 | OS | 8 |

CRC, colorectal cancer; F, female; M, male; NA, not available; NOS, Newcastle–Ottawa Scale; OS, overall survival; PFS, progression-free survival; ROC, receiver-operating characteristics curve
patients, with the number of patients in individual studies ranging from 95 to 1383. Eleven studies were conducted in China\(^9\)–\(^{19}\) and one in Italy.\(^8\) Eleven studies included patients with CRC,\(^8\)–\(^{10,12–19}\) and one study with colon cancer.\(^11\) Eleven studies investigated the relationship between SII and OS,\(^8\)–\(^{15,17–19}\) eight studies reported the association between SII and PFS,\(^8\)–\(^{10,13–18}\) and nine studies provided data on the correlation of SII and clinicopathological features in CRC.\(^8\)\(^{–13,15,16,18}\) The cut-off values ranged from 340 to 1505. Eleven studies were retrospective\(^9\)–\(^{19}\) and one study was a prospective trial.\(^8\) The main characteristics of the 12 included studies are summarized in Table 1. The NOS scores of all studies ranged from 6 to 9, which indicates high quality (NOS scores \(\geq 6\)).

**Prognostic impact of SII on OS in CRC patients**
Eleven studies\(^8\)–\(^{15,17–19}\) provided data from 3737 patients for the OS analysis. A random-effects model was applied due to the significant heterogeneity detected in these data ($P=83.1\%$, $p<0.001$, Figure 2 and Table 2). Pooled HR from eligible studies was found to be 1.61, with 95\% CI=1.21–2.13 and $p=0.001$ (Figure 2 and Table 2), indicating an association between high SII and poor OS in CRC. Subgroup analysis was also conducted based on the geographical region, treatment procedure, TNM stage, sample size, cut-off value, cut-off selection method and NOS score. High SII was found to be consistently correlated with worse OS irrespective of geographical region, sample size, cut-off value, cut-off selection method or NOS score (Table 2).

**Prognostic role of SII for PFS in CRC**
Data for PFS analysis were extracted from eight studies covering 3155 patients.\(^8\)–\(^{10,13–15,17,18}\) The combined data showed that an elevated SII indicated a worse PFS in CRC (HR=1.74, 95\% CI=1.26–2.39, $p=0.001$) (Figure 3 and Table 2). There was significant heterogeneity among the studies as well ($P=84.8\%$, $p<0.001$). Therefore, a random-effects model was adopted. High SII was again associated with poor PFS irrespective of TNM stage, cut-off value, cut-off selection and NOS score. Moreover, high SII also predicted poor PFS in Chinese patients (HR=1.87, 95\% CI=1.34–2.61, $p<0.001$), in patients receiving chemo- and targeted therapy (HR=1.31, 95\% CI=1.07–1.61, $p=0.010$) and in patients
### Table 2. Subgroup analysis of pooled HRs and 95% CIs between SII and OS and PFS in colorectal cancer.

| Variables                                             | No. of studies | No. of patients | Effects model | HR (95% CI) | p       | Heterogeneity |
|-------------------------------------------------------|----------------|-----------------|---------------|-------------|---------|---------------|
|                                                        |                |                 |               |             |         | I², %         | p           |
| **OS**                                                |                |                 |               |             |         |               |             |
| Total                                                 | 11             | 3737            | Random        | 1.61 [1.21–2.13] | 0.001   | 83.1          | <0.001      |
| Geographical region                                   |                |                 |               |             |         |               |             |
| China                                                 | 10             | 3448            | Random        | 1.63 [1.20–2.23] | 0.002   | 83.2          | <0.001      |
| Italy                                                 | 1              | 289             | –             | 1.37 [1.03–1.82] | 0.030   | –             | –           |
| Treatment                                             |                |                 |               |             |         |               |             |
| Surgical resection                                    | 6              | 2933            | Random        | 1.50 [0.93–2.42] | 0.097   | 90.0          | <0.001      |
| Chemotherapy + targeted therapy                       | 3              | 486             | Fixed         | 1.42 [1.14–1.76] | 0.002   | 0             | 0.873       |
| Neoadjuvant/adjuvant chemoradiotherapy                | 2              | 318             | Fixed         | 2.29 [1.66–3.17] | <0.001 | 0             | 0.655       |
| TNM stage                                             |                |                 |               |             |         |               |             |
| I–IV                                                  | 6              | 2628            | Random        | 1.61 [0.99–2.61] | 0.056   | 88.1          | <0.001      |
| III–IV                                                | 1              | 220             | –             | 2.41 [1.63–3.58] | <0.001 | –             | –           |
| IV                                                    | 4              | 889             | Fixed         | 1.38 [1.15–1.66] | <0.001 | 0             | 0.858       |
| Sample size                                           |                |                 |               |             |         |               |             |
| <230                                                  | 6              | 857             | Random        | 1.62 [1.16–2.27] | 0.005   | 58.4          | 0.034       |
| ⩾230                                                  | 5              | 2880            | Random        | 1.59 [1.02–2.50] | 0.042   | 91.3          | <0.001      |
| Cut-off value of SII                                  |                |                 |               |             |         |               |             |
| <550                                                  | 5              | 2248            | Random        | 1.96 [1.27–3.04] | 0.002   | 87.6          | <0.001      |
| ⩾550                                                  | 6              | 1489            | Fixed         | 1.37 [1.15–1.63] | <0.001 | 24.5          | 0.250       |
| Cut-off selection                                     |                |                 |               |             |         |               |             |
| X-tile software                                       | 2              | 741             | Fixed         | 1.32 [1.08–1.61] | 0.006   | 0             | 0.715       |
| ROC analysis                                          | 4              | 2221            | Random        | 2.04 [1.31–3.17] | 0.002   | 81.2          | 0.001       |
| Median analysis                                       | 5              | 775             | Fixed         | 1.45 [1.16–1.80] | 0.001   | 47.7          | 0.105       |
| NOS score                                             |                |                 |               |             |         |               |             |
| ⩽7                                                    | 6              | 2122            | Random        | 1.78 [1.17–2.71] | 0.007   | 83.4          | <0.001      |
| >7                                                    | 5              | 1615            | Fixed         | 1.37 [1.17–1.61] | <0.001 | 0             | 0.712       |
| **PFS**                                               |                |                 |               |             |         |               |             |
| Total                                                 | 8              | 3155            | Random        | 1.74 [1.26–2.39] | 0.001   | 84.8          | <0.001      |
Table 2. (Continued)

| Variables                                      | No. of studies | No. of patients | Effects model | HR (95% CI)   | p       | Heterogeneity |
|------------------------------------------------|----------------|-----------------|---------------|---------------|---------|---------------|
|                                                 |                |                 | p             |               |         |               |
| Geographical region                            |                |                 |               |               |         |               |
| China                                          | 7              | 2866            | Random        | 1.87 [1.34–2.61] | <0.001 | 81.6          | <0.001 |
| Italy                                          | 1              | 289             | –             | 1.16 [0.90–1.50] | 0.259  | –             | –      |
| Treatment                                      |                |                 |               |               |         |               |
| Surgical resection                             | 3              | 2351            | Random        | 1.80 [0.99–3.29] | 0.056  | 93.4          | <0.001 |
| Chemotherapy + targeted therapy                | 3              | 486             | Fixed         | 1.31 [1.07–1.61] | 0.010  | 13.9          | 0.313  |
| Neoadjuvant/adjuvant chemoradiotherapy         | 2              | 318             | Fixed         | 2.43 [1.53–3.88] | <0.001 | 0             | 0.888  |
| TNM stage                                      |                |                 |               |               |         |               |
| I–IV                                           | 4              | 2286            | Random        | 1.90 [1.13–3.21] | 0.016  | 89.9          | <0.001 |
| III–IV                                         | 1              | 220             | –             | 2.33 [1.08–5.02] | 0.030  | –             | –      |
| IV                                             | 2              | 649             | Fixed         | 1.34 [1.11–1.61] | 0.002  | 0             | 0.428  |
| Sample size                                    |                |                 |               |               |         |               |
| <230                                           | 4              | 515             | Fixed         | 1.85 [1.41–2.43] | <0.001 | 0             | 0.557  |
| ⩾230                                          | 4              | 2640            | Random        | 1.61 [0.98–2.64] | 0.061  | 93.2          | <0.001 |
| Cut-off value of SII                           |                |                 |               |               |         |               |
| <550                                           | 5              | 2248            | Random        | 1.94 [1.26–2.99] | 0.003  | 87.4          | <0.001 |
| ⩾550                                          | 3              | 907             | Fixed         | 1.31 [1.06–1.62] | 0.013  | 22.7          | 0.274  |
| Cut-off selection                              |                |                 |               |               |         |               |
| X-tile software                                | 2              | 741             | Fixed         | 1.20 [1.01–1.42] | 0.034  | 0             | 0.726  |
| ROC analysis                                   | 4              | 2221            | Fixed         | 2.49 [2.14–2.91] | <0.001 | 42.3          | 0.158  |
| Median value                                   | 2              | 193             | Fixed         | 1.86 [1.30–2.68] | 0.001  | 35.4          | 0.213  |
| NOS score                                      |                |                 |               |               |         |               |
| ⩽7                                            | 5              | 1898            | Fixed         | 2.43 [2.10–2.82] | <0.001 | 46.9          | 0.110  |
| >7                                             | 3              | 1257            | Fixed         | 1.23 [1.05–1.45] | 0.011  | 0             | 0.494  |

CI, confidence interval; HR, hazard ratio; NOS, Newcastle–Ottawa Scale; OS, overall survival; PFS, progression-free survival; ROC, receiver-operating characteristics curve; SII, systemic immune-inflammatory index; TNM, Tumor Node Metastasis.
receiving neoadjuvant chemoradiotherapy (HR = 2.43, 95% CI = 1.53–3.88, \( p < 0.001 \)) (Table 2).

**Correlation between SII and clinicopathological factors in CRC**

Nine studies comprising 2727 patients8–13,15,16,18 reported the connection between SII and eight clinicopathological features. The features were as follows: sex (male versus female), tumor differentiation (poor versus moderate/well-differentiated), tumor location (rectum versus colon), distant metastasis (yes versus no), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (1–2 versus 0), lymph node metastasis (yes versus no), age (years) (>60 versus \( \leq 60 \)) and tumor size (\( \geq 5 \) cm versus <5 cm) (Table 3 and Figure 4). The pooled results suggested that a high SII prior to treatment was associated with poor tumor differentiation (OR = 1.60, 95% CI = 1.27–2.02, \( p < 0.001 \)), presence of distant metastasis (OR = 2.27, 95% CI = 1.10–4.67, \( p = 0.026 \)), ECOG PS of 1–2 (OR = 1.98, 95% CI = 1.39–2.84, \( p < 0.001 \)) and tumor size \( \geq 5 \) cm (OR = 1.49, 95% CI = 1.18–1.88, \( p = 0.001 \)) (Table 3 and Figure 4). However, the association between high SII and sex (OR = 0.95, 95% CI = 0.80–1.13, \( p = 0.592 \)), tumor location (OR = 0.76, 95% CI = 0.58–1.03, \( p = 0.081 \)), lymph node metastasis (OR = 1.25, 95% CI = 0.65–2.41, \( p = 0.509 \)) or age (OR = 1.16, 95% CI = 0.95–1.43, \( p = 0.153 \)) was non-significant in patients with CRC (Table 3 and Figure 4).

**Sensitivity analysis**

We conducted a sensitivity analysis to assess the reliability of pooled HRs of OS and PFS. The overall HR estimates for OS and PFS (Figure 5) were not significantly altered upon sequentially omitting each study from the analysis. Thus, the reliability of the results of this meta-analysis was also confirmed by the sensitivity analysis.

**Publication bias**

Begg’s funnel and Egger’s tests were used to estimate potential publication bias. As illustrated in Figure 6, there was no significant bias in studies on SII with respect to OS (Begg’s \( p = 0.938 \),
Discussion

To the best of our knowledge, this study is the first meta-analysis exploring the prognostic and clinicopathological impact of SII in patients with CRC. As a novel prognostic parameter, SII can be easily calculated from routine complete blood count tests and reflects the overall status of the immune systems of cancer patients. Previous investigations on the prognostic value of SII in CRC yielded controversial results. For the current meta-analysis, we collected data from 12 studies with 3919 patients to clarify the role of SII in CRC prognosis. Significant prognostic efficiency in different subgroups suggests that high SII was a robust prognostic marker for long-term survival outcomes, including the OS and PFS. Moreover, high SII prior to treatment was related to poor tumor differentiation, presence of distant metastasis, ECOG PS of 1–2 and tumor size of ≥5 cm. Considering these clinical parameters related to the invasiveness and aggressiveness of malignant tumors, high SII could be a potential marker of disease progression and tumor recurrence possibility. The results of our comprehensive and aggregated analysis demonstrate the effectiveness of SII as an index for CRC prognosis.

The tumor microenvironment has recently attracted increasing attention in the field of cancer immunology. Various inflammatory cells and mediators are important components of the tumor microenvironment. SII is based on peripheral lymphocyte, neutrophil and platelet counts. A high SII corresponds to high platelet/neutrophil and (or) low lymphocyte counts. Therefore, an elevated SII indicates a highly-inflammatory tumor microenvironment with infiltrating immune cells. The presence of neutrophils in the peripheral blood is generally associated with poor prognosis in patients with cancer. Neutrophils can activate endothelial and parenchymal cells and thereby facilitate the metastasis of circulating tumor cells (CTCs). Neutrophils also mediate the proliferation and metastasis of cancer cells by secreting inflammatory mediators. Moreover, platelets may shield CTCs to protect them from antitumor immune responses, and therefore promote angiogenesis and metastasis of cancer cells. Platelets also release a variety of growth factors that enhance cancer cell proliferation in vitro. Lymphocytes, especially tumor-infiltrating lymphocytes, further

| Characteristics                              | No. of studies | No. of patients | Effects model | OR (95% CI)          | p     | Heterogeneity |
|----------------------------------------------|----------------|----------------|---------------|----------------------|-------|--------------|
|                                              |                |                |               |                      |       | p            |
| Sex, male versus female                     | 8              | 2529           | Fixed         | 0.95 (0.80–1.13)     | 0.592 | 12.4         | 0.333        |
| Tumor differentiation, poor versus moderate/well | 7              | 2427           | Fixed         | 1.60 (1.27–2.02)     | 0.001 | 32.0         | 0.184        |
| Tumor location, rectum versus colon          | 6              | 1166           | Fixed         | 0.76 (0.58–1.03)     | 0.081 | 1.0          | 0.409        |
| Distant metastasis, yes versus no            | 4              | 1990           | Random        | 2.27 (1.10–4.67)     | 0.026 | 84.5         | <0.001       |
| ECOG PS, 1–2 versus 0                        | 4              | 702            | Fixed         | 1.98 (1.39–2.84)     | 0.001 | 0            | 0.442        |
| Lymph node metastasis, yes versus no         | 3              | 1721           | Random        | 1.25 (0.65–2.41)     | 0.509 | 73.9         | 0.022        |
| Age, years, >60 versus ≤60                   | 3              | 1725           | Fixed         | 1.16 (0.95–1.43)     | 0.153 | 49.5         | 0.138        |
| Tumor size, ≥5 cm versus <5 cm               | 3              | 1721           | Fixed         | 1.49 (1.18–1.88)     | 0.001 | 7.4          | 0.340        |

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; OR, odds ratio
Figure 4. Forest plots of the relationship between systemic immune-inflammation index and clinical factors in colorectal cancer. (A) Sex (male versus female); (B) tumor differentiation (poor versus moderate/well); (C) tumor location (rectum versus colon); (D) distant metastasis (yes versus no); (E) Eastern Cooperative Oncology Group Performance Status (1–2 versus 0); (F) lymph node metastasis (yes versus no); (G) age (years) (>60 versus ≤60); (H) tumor size (≥5 cm versus <5 cm).
CI, confidence interval; OR, odds ratio
play a pivotal role in the host immune response to malignancy. Lymphocytes can induce cytotoxic cell death and inhibit tumor cell proliferation and migration. Therefore, SII may also reflect the activation of inflammatory and immune pathways in the host. In addition, the measurements required for the calculation of SII are inexpensive, easily-performed and reproducible, rendering SII a promising marker for CRC prognosis in clinical practice.

The prognostic role of SII in solid tumors has also been investigated in several meta-analyses previously. A meta-analysis focusing on the use of SII in multiple cancers showed that high SII was associated with poor OS.
data from 2786 lung cancer patients based on seven studies indicated that SII prior to treatment was a prognostic factor for OS.35 Another recent retrospective study showed that baseline SII could serve as an independent prognostic marker for patients with advanced pancreatic cancer.36 The SII was also suggested as a novel independent prognostic factor for predicting OS and PFS in patients with classical Hodgkin lymphoma.37 Here, we demonstrated the prognostic efficiency of SII with respect to OS and PFS in CRC, in line with the findings on other cancer types. In addition, we also demonstrated correlations between high SII and clinical parameters in CRC. Based on our findings and other relevant studies, SII may assist in the cancer prognosis and help develop clinical treatment strategies. For example, hepatocellular carcinoma patients with high SII prior to treatment may benefit more from neoadjuvant chemoradiotherapy, postoperative adjuvant chemoradiotherapy and other cancer-related therapies than patients with low SII.38 SII has also shown good prognostic efficiency in multiple cancers,33,34 which suggests that elevated SII may be a general feature in solid tumors. However, the prognostic value of SII for hematological and other types of cancer, such as gynecological tumors, remains to be investigated. Further investigations focusing on the prognostic impact of SII on diverse cancer types are needed to justify the application of SII in the clinical management of patients with cancer.

Although this study is the first meta-analysis on SII and CRC prognosis to date, there are also several limitations. First, most of the included studies were of retrospective design, which hindered controlling the selection criteria and led to heterogeneity among studies. Second, several HRs were extracted from univariate analyses, and may eventually overestimate effect sizes. Univariate analysis was performed without consideration of confounding factors. Third, SII cut-off values as well as determination methods are not uniform in the included studies, which could cause bias in the results.

In summary, this meta-analysis indicated that higher SII before treatment was correlated with poor OS and PFS in patients with CRC. In addition, high SII was associated with clinical factors implying higher malignancy of the disease. We conclude that SII may play an important role in improving clinical decision-making for CRC. However, larger-scale prospective studies are still needed to validate our results due to the limitations of this study.

Author contribution
MD, YS, JY, QZ, YL, DW, TM and XG collected and extracted the data and performed quality assessment; MD, YZ, YM, XG, and RF analyzed the data; MD, YS, XG and RF conceived, designed this study and wrote the paper. All authors reviewed the final manuscript. All authors read and approved the final manuscript.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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