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Prognostic value and clinicopathological significance of pre-and post-treatment systemic immune-inflammation index in colorectal cancer patients: a meta-analysis

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Abstract

Background In recent years, the association between systemic immune-inflammation index (SII) and the prognosis of patients with colorectal cancer (CRC) has remained a topic of considerable debate. To address this, the present study was carried out to investigate the prognostic significance of SII in CRC.

Methods Databases including PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science were scrutinized up to March 27, 2024. The relationship between pre- and post-treatment SII levels and the prognosis of CRC was evaluated. Following literature screening, quality assessment, and extraction of outcome measures, a meta-analysis was conducted using Stata. Publication bias was assessed by funnel plots and Egger's test.

Results A total of 27 studies were included in the analysis. Pooled results demonstrated that a high SII level was associated with poor overall survival (OS, HR = 1.78, 95% CI = 1.40–2.26), progression-free survival (PFS, HR = 1.80, 95% CI = 1.26–2.56), disease-free survival (DFS, HR = 1.91, 95% CI = 1.43–2.56), and recurrence-free survival (RFS, HR = 3.29, 95% CI = 1.58–6.88). Notably, the association between pre-treatment SII and OS, PFS, and DFS was stronger than that observed for post-treatment SII, indicating that treatment may attenuate the predictive valueof SII for survival outcomes. Additionally, elevated SII was correlated with poor tumor differentiation, tumor location in the rectum, and larger tumor size ≥ 5 cm.

Conclusion Our meta-analysis suggested that a high SII is a predictor of poor prognosis in CRC patients. High SII levels were strongly correlated with inferior OS, PFS, DFS, and RFS. The relationship between SII and survival outcomes was attenuated post-treatment compared to pre-treatment. Additionally, elevated SII was correlated with clinicopathological factors in CRC patients. These findings suggest that SII can serve as an independent prognostic indicator for CRC.

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Keywords Colorectal cancer, Meta-analysis, Systemic immune-inflammation index, Prognosis, Risk factors

Introduction

Colorectal cancer (CRC) is a prevalent malignancy and ranks among the leading causes of cancer-related death globally [1]. In 2022, it was estimated that there would be more than 1.9 million new cases of CRC (including anal cancer) and 904,000 deaths, accounting for nearly one-tenth of all cancer cases and deaths worldwide. Overall, CRC ranks third in terms of morbidity and second in terms of mortality [2]. Despite advancements in treatment methods, the prognosis of CRC has not significantly improved. Integrating effective biomarkers into treatment strategies has the potential to notably enhance the prognosis of patients with CRC [3]. Many prognostic and predictive biomarkers, such as RAS mutation status, BRAF mutation, and microsatellite instability, have been employed for early prediction and prognostic assessment in CRC. However, these biomarkers often require invasive testing and dependence on specialized laboratory equipment [4]. Thus, there is a pressing need to identify easily accessible adjunctive biomarkers to assist clinicians in implementing personalized treatments and enhancing patient prognosis.

Evidence has suggested that chronic inflammation is extensively involved in the occurrence and progression of CRC [5]. Systemic inflammatory responses are associated with the prognosis of various cancers, including gastric, esophageal, colorectal, liver, pancreatic, breast, and bladder cancers [6–8]. Systemic inflammation is considered a key component of the tumor immune microenvironment, which plays a critical role in the development and progression of many solid tumors [9, 10] Several studies have demonstrated that inflammation-based prognostic biomarkers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), prognostic nutritional index (PNI), and Glasgow prognostic score (GPS), can offer valuable survival information for patients with CRC [11–13]. Multiple studies have indicated that the SII is associated with the prognosis of malignant tumors [14]. SII is a promising inflammation-based biomarker, primarily calculated from lymphocyte, neutrophil, and platelet counts, and can be easily measured from venous blood samples, making it more convenientto obtain than other biomarkers [12, 15]. SII (formula: SII = Neutrophil Count × Platelet Count/Lymphocyte Count) offers a more comprehensive reflection of the immune environment in patients with CRC compared to NLR and PLR. Chen et al. found that the SII is a superior factor in predicting OS, PFS, and DFS compared to the PLR and NLR, which can demonstrate greater immunological effects [12].

To our knowledge, two meta-analyses have analyzed the relationship between SII and OS and PFS in CRC patients [4, 16]. In detail, Dong et al. and Li et al. conducted meta-analyses of 12 studies involving a total of 3919 patients with CRC. Their analyses revealed that higher pre-treatment SII is associated with poorer OS and PFS in patients with CRC, suggesting that SII may serve as a determinant in the determination of clinical treatment regimens for these patients. However, as clinical data continues to evolve, in recent years, an increasing number of studies have investigatedthe relationship between CRC and SII, not only in terms of OS and PFS but also with many other prognostic factors, including the recurrence of CRC patients and DFS. For example, in a retrospective study by Zhang et al. involving a total of 188 CRC patients, it was concluded that SII could effectively predict 1-year, 2-year, and 3-year DFS after surgery and could independently predict postoperative recurrence in CRC patients [12]. In a retrospective study by Chen et al. involving 206 CRC patients, it was found that the change in the SII (ΔSII) is an independent prognostic factor for CRC patients undergoing radical resection. In the future, ΔSII may be used as an important reference indicator to guide personalized treatment [17]. In a study by Sato et al. covering 86 patients with obstructive colorectal cancer (OCRC) at stages I to III, it was noted that lower preoperative PLR, SII, and PIV values were independently associated with poorer RFS [18]. Based on the above findings, the present studywas carried out to utilize recent publications to update the analysis, comprehensively review and summarize all available data, and assess the correlation between SII and OS, PFS, DFS, or RFS in CRC patients, alongside its connection with clinicopathological parameters.

In recent years, meta-analyses have been extensively utilized to assess the prognostic role of the SII in various cancers. Numerous related studies have shown that elevated preoperative SII is significantly associated with a worse prognosis in a range of solid tumors. However, current research on the specific prognostic value of SII in CRC patients remains limited. Existing meta-analyses predominantly focus on the prognostic significance of preoperative SII, with insufficient exploration of the impact of dynamic postoperative SII changes on patient outcomes. To address these limitations, this study was carried out to bridge the research gap by integrating the latest data to comprehensively evaluate the prognostic value of both preoperative and postoperative SII in CRC patients.

Methods

Study design

This study was conducted following the guidelines from PRISMA [19], ensuring transparent and comprehensive reporting of methods and results. Additionally, the study has been registered with PROSPERO (ID: CRD42024535199). As this study entails meta-analysis and systematic review of previously published research, ethical approval was deemed unnecessary.

Inclusion/exclusion criteria

The inclusion criteria were: [1] Patients of all age groups and geographic locations with pathologically confirmed colon cancer, rectal cancer, or metastatic intestinal cancer; [2] Prognostic predictors included SII; [3] The report confirmed the relationship between SII and the prognosis of CRC patients, such as OS, PFS, DFS, or other prognostic factors; [4] The study reports are limited to those published in English.

The exclusion criteria were: [1] Patients with cancers other than CRC or those with metastases to the colon from other cancers; [2] Previous meta-analyses/reviews, animal studies, descriptive studies, case reports, or conference abstracts; [3] Studies without clear prognostic predictors, including the relationship between OS, PFS, or DFS and SII; [4] Data results that are unclear or insufficient information for data analysis; [5] Newcastle-Ottawa Scale (NOS) score less than 5 [20]; [6]Studies with preoperative exclusion or emergency reduction for patients with serious infections.

Search strategy

Until March 28, 2024, two researchers (T.Y.T. and Q.L) independently performed comprehensive searches in PubMed, Embase, the CENTRAL, and Web of Science, without imposing restrictions on literature type, publication date, or publication status. MeSH and free textterms were employed for keyword searches, encompassing all known spellings of "colorectal cancer" and "systemic immune-inflammation index" to ensure comprehensive coverage of the literature. The full search strategy is presented in Additional file 1.

Literature screening

Based on the inclusion and exclusion criteria defined above, two researchers (T.Y.T. and Q.L.) independently conducted the literature screening. Initially, all potentially relevant studies were imported into EndNote 20, and duplicates were subsequently eliminated using both automatic and manual methods. Subsequently, studies that did not meet the inclusion criteria were excluded based on the examination of titles and abstracts. Following this, the full texts underwent further review and screening. Any discrepancies were resolved through discussion or mediation with a third researcher (W.C). Moreover, references of related articles were manually scrutinized to ensure no relevant studies were overlooked.

Data extraction and assessment of quality

The extracted information encompassed: [1] Basic details such as title, first author's name, authors' country, and year of publication; [2] Characteristics of the study design and subjects, including age, mean age, gender ratio, sample size, histological type, tumor TNM stage, SII cut-off value, treatment method, time of SII measurement, survival endpoints, and hazard ratio (HR) with corresponding 95% confidence interval (CI). OS and PFS/DFS served as the primary and secondary endpoints of this meta-analysis, respectively.

Assessment of quality

The methodological quality of the included studies was evaluated using the NOS. Scores on the NOS ranged from 0 to 9, with a score above 7 considered indicative of high quality in this study. In evaluating cohort selection, scoring criteria encompassed the representativeness of the cohort, selection of the non-exposed cohort from the same population, and accuracy of treatment records. Regarding comparability, scrutiny focused on whether exposed and non-exposed cohorts were selected and analyzed based on the most critical factors. For outcome assessment, criteria included independence, blinding, reliance on reliable records, sufficient follow-up time, and complete follow-up of all study subjects.

Data synthesis and statistical analysis

Summarized HRs and corresponding 95% CIs were employed to estimate the association between SII and OS, PFS, DFS, and RFS in CRC patients. Stata 16 was utilized to statistically assess heterogeneity among the included studies. If I^2 exceeded 50% or p was less than 0.05 (indicating significant heterogeneity among studies), a random-effects model would be employed. Otherwise, a fixed-effects model would be applied. Subgroup analyses were conducted based on country, age, mean age, sample size, treatment method, tumor type, SII cut-off value, TNM stage, NOS score, and time of SII measurement to identify sources of heterogeneity. To further investigate the relationship between SII and clinicopathological characteristics in CRC patients, Odds ratio (OR) and corresponding 95% CIs were calculated. OR served as the effect size for the association between SII and clinicopathological factors, expressed alongside 95% CIs. Sensitivity analysis was conducted to pinpoint the source of heterogeneity, while Egger's test was employed to examine potential publication bias. All statistical analyses were performed using Stata 16.0 (Stata Corporation,

College Station, TX). A *p*-value less than 0.05 (two-sided) was deemed statistically significant.

Results

Search results

The characteristics and specific process of study inclusion and exclusion are detailed in Fig. 1 Initially, a total of 223 relevant studies were identified from the aforementioned four databases. Following automated duplication removal of 37 studies and manual elimination of 38 studies, 6 studies (comprising meta-analyses, reviews, guidelines, and conference abstracts) were excluded. Subsequently, the full texts of the remaining 142 studies were assessed for credibility, leading to the exclusion of 115 articles based on predetermined criteria. These criteria included study subjects not being CRC patients, absence of pertinent data on SII and prognostic indicators, studies involving cancers metastatic to the intestine from other sites, insignificant findings, illogical cohort study designs, and unavailability of full-text data. Ultimately, 27 articles were deemed suitable and included.

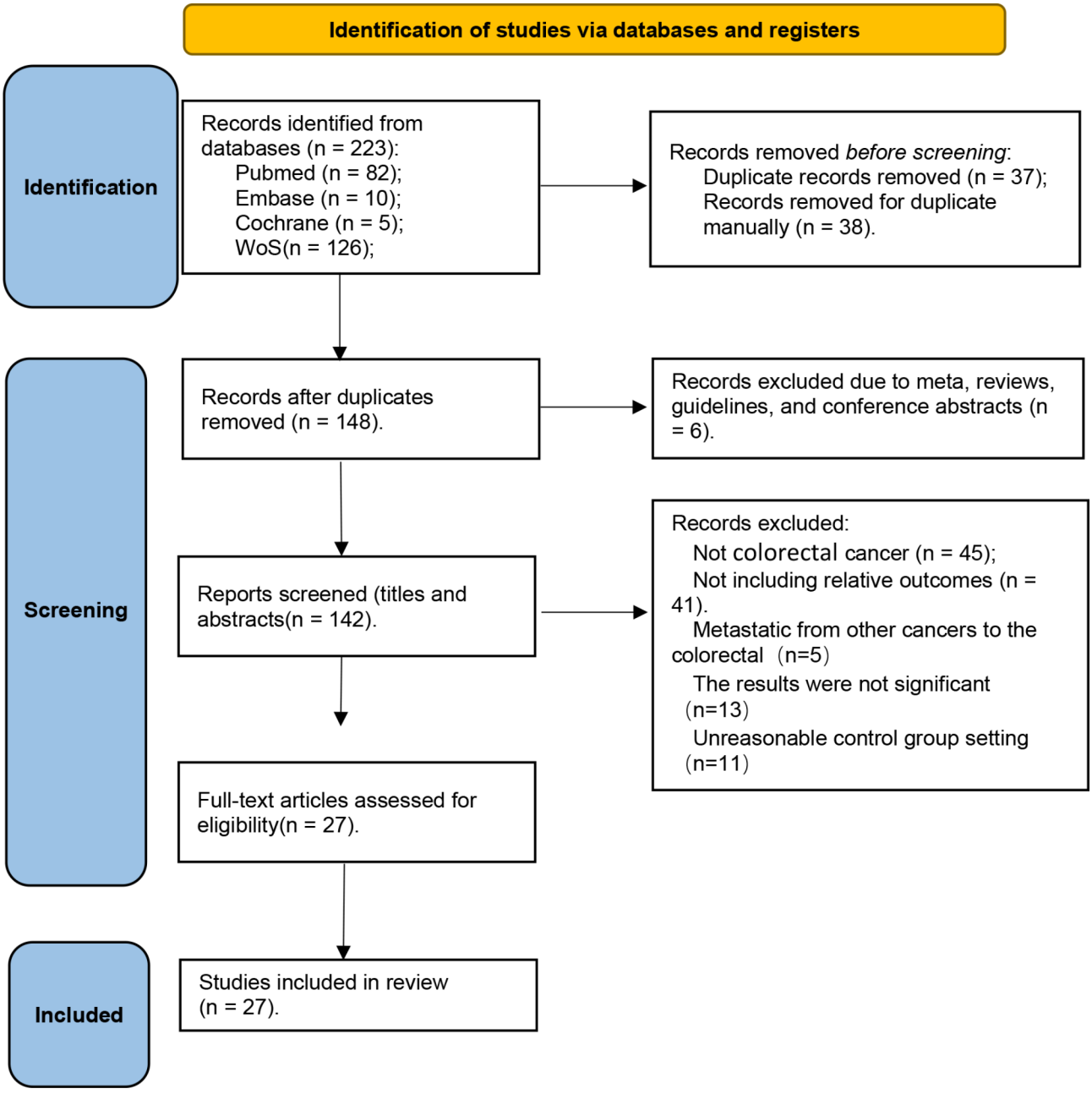

Fig. 1 Identification of studies via databases and registers

Characteristics of the studies included

Among the included studies, 19 studies were conducted in China [12, 18, 21–37], 4 in Japan [18, 38–40], 3 in Italy [28, 41, 42], and 1 in the USA [43]. Of these, 18 studies included patients with primary CRC [12, 18, 21, 22, 26–28, 30–39, 44], while 9 studies focused on recurrent CRC [23–25, 29, 40–43, 45]. Among the studies, 22 analyzed the relationship between SII and OS [12, 18, 22–30, 32–34, 36, 37, 39–45], 11 analyzed the relationship between SII and PFS [12, 23, 25, 34–37, 41–43, 45], 8 analyzed the relationship between SII and DFS [21, 22, 26, 27, 30, 33, 42, 44], and 3 analyzed the relationship between SII and RFS [18, 29, 38]. The sample sizes of the 27 studies ranged from 41 to 1383 individuals, with a median age range of 45–68 years. Among the 27 studies, 26 were retrospective cohort studies [12, 18, 21–40, 42–45], and 1 was a prospective cohort study [41]. The main characteristics of the 27 studies included in our study are presented in Table 1. The NOS scores of the 27 studies ranged from 6 to 9, with scores exceeding 7 indicative of high quality. Reasons for lower quality included inadequate and imprecise surgical records, non-independent or non-blinded outcome assessment, inadequate follow-up duration, incomplete follow-up, and absence of analysis concerning lost follow-up subjects.

Impact of SII on OS in CRC patients

The prognostic analysis of SII and OS was conducted on 8347 patients across 22 studies [12, 18, 22–30, 32–34, 36, 37, 39–45]. The data exhibited significant heterogeneity ($I^2 = 92.0\%$, $p < 0.000$; Fig. 2), thus a random-effects model was employed. The results indicated a significant association between SII and OS, with higher SII showing approximately twice the risk compared to lower SII (HR = 1.78, 95% CI = 1.40–2.26, $p < 0.001$; Fig. 2; Table 2). Subgroup analyses were conducted from the following aspects: region, age, mean age, sample size, TNM stage, treatment method, tumor type, SII cutoff value, NOS score, and time of SII measurement. Regardless of each subgroup, poor OS was always significantly associated with high SII (Table 2). For TNM stages I–III, the hazard ratio of high SII compared to low SII was 2.4 times (HR = 2.40, 95% CI = 1.38–4.18, $p = 0.002$) (Table 2), while in stage IV, the hazard ratio of high SII compared to low SII was 1.43 times (HR = 1.43, 95% CI = 1.21–1.69, $p = 0.000$) (Table 2), indicating that tumor TNM staging is a factor affecting the relationship between SII and OS. In the group with SII < 550, the hazard ratio of high SII occurrence was about 2 times higher than that of low SII (HR = 1.94, 95% CI = 1.34–2.820, $p = 0.000$) (Table 2). In the group with SII ≥ 550, the hazard ratio of high SII occurrence was 1.66 times higher than that of low SII (HR = 1.66, 95% CI = 1.31–2.11, $p = 0.000$) (Table 2). This also indicated that the determination of the SII cut-off value is one of the factors affecting the relationship between SII and OS. Besides, both pre-treatment and post-treatment SII are associated with OS. The correlation between pre-treatment SII and OS (HR = 1.83, 95% CI = 1.42–2.34, $p = 0.000$) (Table 2) was stronger than that of post-treatment SII (HR = 1.59, 95% CI = 1.10–2.30, $p = 0.014$) (Table 2). Furthermore, in subgroup analysis, we found that heterogeneity remained high in some subgroups ($I^2 > 50\%$, $p < 0.05$). (Table 2).

Impact of SII on PFS in CRC patients

Prognostic analysis of SII and PFS was conducted on 3996 patients across 11 articles [12, 23, 25, 34–37, 41–43, 45]. The data exhibited significant heterogeneity, thus a random-effects model was applied ($I^2 = 96.1\%$, $p < 0.001$) (Fig. 3). The analysis also indicated a significant correlation between high SII and poor PFS, with high SII showing approximately double the risk compared to low SII in PFS (HR = 1.80, 95% CI = 1.26–2.56, $p = 0.001$) (Fig. 3; Table 2). Subgroup analyses were conducted from the following aspects: region, age, mean age, sample size, TNM stage, treatment method, tumor type, SII cutoff value, and time of SII measurement. Poor PFS was always significantly associated with high SII in all subgroups (Table 2). In the subgroup analysis by region, the hazard ratio of high SII compared to low SII in China was 2.30 times (HR = 2.30, 95% CI = 1.95–2.78, $p = 0.000$) (Table 2). In Italy, the risk of high SII compared to low SII was 1.36 times higher (HR = 1.36, 95% CI = 0.81–2.29, $p = 0.241$) (Table 2), indicating that region is one of the factors influencing the relationship between SII and PFS. In the group with SII < 550, the hazard ratio of high SII occurrence was 2.26 times higher than that of low SII (HR = 2.26, 95% CI = 1.77–2.89, $p = 0.000$) (Table 2). In the group with SII ≥ 550, the hazard ratio of high SII occurrence was 1.44 times higher than that of low SII (HR = 1.44, 95% CI = 0.92–2.25, $p = 0.108$) (Table 2). This also indicated that the determination of the SII cut-off value is one of the factors affecting the relationship between SII and PFS. Moreover, in terms of treatment methods, the hazard ratio of high SII compared to low SII in the neoadjuvant chemotherapy group was 2.50 times higher (HR = 2.50, 95% CI = 1.39–4.50, $p = 0.002$) (Table 2). In the chemotherapy plus targeted therapy group, the hazard ratio of high SII to low SII was 1.58 times (HR = 1.58, 95% CI = 1.08–2.31, $p = 0.017$) (Table 2), also indicating that different treatment methods are factors influencing the relationship between SII and PFS. Irrespective of pre- or post-treatment status, SII exhibited a significant correlation with PFS ($p < 0.05$). Notably, the association between pre-treatment SII and PFS (HR = 1.89, 95% CI = 1.38–2.60, $p = 0.000$) (Table 2) appeared stronger than that observed with post-treatment SII (HR = 1.62, 95% CI = 1.02–2.57, $p = 0.041$) (Table 2). Moreover,

Table 1 Main characteristics of studies included

Author	Year	Country	Tumor type	Study time	Study design	Sample size	Sex M/F	Age, years Median (range)
Huang	2020	China	Primary	2013–2017	retrospective	1279	763/516	NA
Jiang	2019	China	metastatic	2010–2017	retrospective	102	72/30	NA
Passardi	2016	Italy	metastatic	-	Prospective	289	174/115	65.5
Xie	2018	China	metastatic	2009–2014	retrospective	240	157/83	59
Yang	2017	China	metastatic	2009–2015	retrospective	95	58/37	56
Yatabe	2020	Japan	Primary	2010–2014	retrospective	733	463/270	66
Yu	2024	China	Primary	2010–2018	retrospective	238	139/99	58.5
Zhang	2020	China	Primary	2011–2015	retrospective	472	313/159	56.29
Zhang	2019	China	Primary	2010–2013	retrospective	224	127/97	67
Gardini	2020	Italy	metastatic	2007 – 1012	retrospective	131	78/53	67
Chen	2017	China	Primary	1994–2010	retrospective	1383	788/595	NA
Deng	2021	China	metastatic	2006–2016	retrospective	283	187/96	57
Ding	2024	China	Primary	2015–2020	retrospective	198	138/60	NA
Miyamoto	2023	Japan	metastatic	2005–2019	retrospective	272	141/131	63
Passardi	2023	Italy	metastatic	-	retrospective	182	60/122	68
Peng	2023	China	Primary	2010–2017	retrospective	722	430/292	NA
Xiang	2023	China	Primary	2013–2017	retrospective	236	143/93	45
Xie	2020	China	Primary	2012–2014	retrospective	662	408/254	NA
Yang	2019	China	Primary	2009–2015	retrospective	220	133/87	57
Young	2023	USA	metastatic	2014–2019	retrospective	41	21/20	61.4
Zhang	2022	China	Primary	2013–2016	retrospective	585	348/237	62
Zhang	2023	China	Primary	2013–2018	retrospective	188	177/71	67
Zhou	2018	China	Primary	2007–2015	retrospective	516	331/185	51.5
Yang	2018	China	Primary	-	retrospective	98	59/39	53
Wang	2019	China	Primary	2002–2016	retrospective	452	289/163	57
Nakamoto	2023	Japan	Primary	2012–2017	retrospective	118	72/46	70
Sato	2022	Japan	metastatic	2013–2020	retrospective	86	50/36	71

Author	TNM Stage	Treatment	Optimal cut-off value for SII	Truncated value selection method	Duration of follow-up/month	Survival analysis	NOS score
Huang	I~III	surgery	-	ROC curve analysis	6(36–69)	OS DFS	8
Jiang	IV	chemotherapy + targeted therapy	660.55	ROC curve analysis	33.2(2.6–94.5)	OS PFS	7
Passardi	I~IV	chemotherapy + targeted therapy	730.00	Median	-	OS PFS	9
Xie	0~IV	surgery	649.45	Median	26.7(1.1–92.4)	OS	8
Yang	IV	chemotherapy + targeted therapy	460.66	Median	40.0(12.0–72.0)	OS PFS	7
Yatabe	I~IV	surgery	736.775	Median	3(3–72)	OS	8
Yu	T1-4,N0-+	neoadjuvant	-	ROC curve analysis	-	OS PFS	9
Zhang	0 ~ IV	neoadjuvant	797.6. 2.3	ROC curve analysis	3(12–36)	OS DFS	8
Zhang	I~IV	surgery	642.20	Median	48.0	OS	8
Gardini	I~IV	chemotherapy + targeted therapy	6068.00	Median	-	OS PFS	8
Chen	I~IV	surgery	340.00	ROC curve analysis	-	OS PFS	6
Deng	T1-4,N0-2	surgery	0.0135	ROC curve analysis	3(12–72)	OS	9
Ding	T2-4,N+	neoadjuvant	707.65	ROC curve analysis	-	OS DFS	8
Miyamoto	-	chemotherapy + targeted therapy	640.00	Median	-	OS	8
Passardi	-	chemotherapy + targeted therapy	730.00	Median	-	OS PFS	8
Peng	I~III	surgery	637.60	X-tile	3(3–24)	DFS	8
Xiang	T1-4,N0-2	surgery	637.60	Survminer	-	OS	8
Xie	I-IV	surgery	534.94	X-tile	28.0	OS DFS	8
Yang	0~IV	chemotherapy + targeted therapy	530.00	ROC curve analysis	23.9(12.0–87.0)	OS PFS	7
Young	I~III	transarterial radioembolization	660.55	Youden's index	3(3–60)	OS PFS	8
Zhang	I-III	surgery	354.18	ROC curve analysis	3(1–60)	PFS	8
Zhang	I-III	surgery	514.13	ROC curve analysis	4(3–60)	DFS	8

Table 1 (continued)

Author	TNM Stage	Treatment	Optimal cut-off value for SII	Truncated value selection method	Duration of follow-up/month	Survival analysis	NOS score
Zhou	I~IV	surgery	568.69	ROC curve analysis	21.7(2.1-118.7)	OS PFS	8
Yang	T1-4	neoadjuvant	437.72	Median	37,7	OS PFS	7
Wang	IV	surgery	517	X-tile	28.0	OS DFS	8
Nakamoto	0-III	surgery	598	ROC curve analysis	19.5(3–60)	RFS	8
Sato	I-III	surgery	597	ROC curve analysis	35	RFS	8

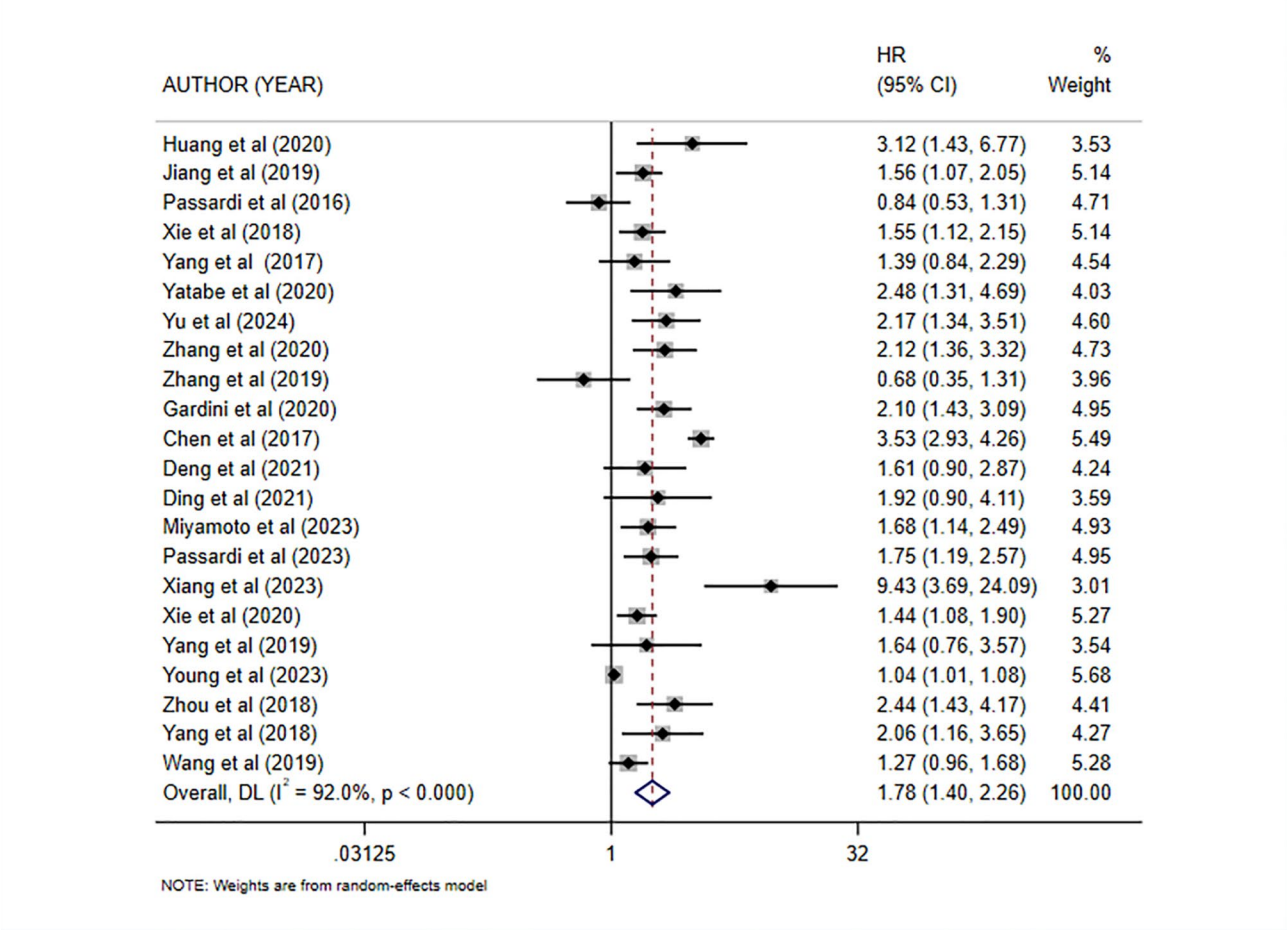

Fig. 2 Forest Plot of the Association Between SII and OS in Patients with CRC

concerning heterogeneity, the sources influencing the relationship between SII and PFS included region and age, while tumor TNM stage, sample size, SII cut-off value, treatment method, and time of SII measurement did not contribute to heterogeneity.

Impact of SII on DFS in CRC patients

Prognostic analysis of SII and DFS was conducted on 487 patients across 8 articles [17, 18, 21, 23, 25, 27, 33, 38]. The data exhibited significant heterogeneity, thus a random-effects model was applied ($I^2 = 71.4\%$, $p < 0.000$) (Fig. 4). A significant correlation between high SII and poor DFS was also observed. In terms of DFS, high SII showed nearly twice the hazard ratio compared to low SII (HR = 1.91, 95% CI = 1.43–2.56, $p = 0.000$) (Fig. 4; Table 2). Subgroup analyses were conducted and poor DFS was always significantly associated with high SII in all subgroups depending on the following aspects: age, mean age, sample size, TNM stage, treatment method, SII cutoff value, and time of SII measurement. (Table 2). Regarding the time of SII measurement, our findings indicated that pre-treatment SII is significantly correlated with DFS ($p = 0.000$), whereas post-treatment SII showed no significant correlation with DFS ($p = 0.181$). Furthermore, our analysis revealed that age, treatment method,

Table 2 Synthesized HR and 95% CI for subgroup analysis of SII and OS, PFS, DFS in patients with CRC

Variables	No. of the studies	No. of patients	Effects model	HR	95% CI	*p*	Heterogeneity	
							I^2, %	*p*
OS								
Total	22	8347	Random	1.78	1.40–2.26	0.000	92.0	< 0.000
Geographical region								
China	16	6699	Random	1.90	1.48–2.44	0.000	81.5	< 0.000
Italy	3	602	Random	1.47	0.88–2.48	0.143	79.6	0.007
Japan	2	1005	Random	1.87	1.33–2.64	0.000	4.5	0.306
USA	1	41	Random	1.04	1.01–1.08	0.022	0.0	< 0.000
Age								
≥ 60	6	1584	Random	1.47	1.04–2.09	0.003	86.2	< 0.000
< 60	10	2850	Random	1.92	1.50–2.46	0.000	59.3	0.009
Treatment								
surgery	10	6009	Random	2.03	1.40–2.94	0.000	88.1	< 0.000
chemotherapy + targeted therapy	6	1071	Random	1.53	1.21–1.93	0.000	50.8	0.071
neoadjuvant	4	1006	Random	2.10	1.61–2.74	0.000	0.0	0.995
Adjuvant chemoradiotherapy	1	220	Random	1.64	0.76–3.57	0.210	0.0	< 0.000
TNM stage								
I–III	5	2658	Random	2.40	1.38–4.18	0.002	75.7	0.002
I–IV	7	3375	Random	1.80	1.11–2.91	0.016	88.4	< 0.000
IV	4	889	Random	1.43	1.21–1.69	0.000	0.0	0.754
Sample size								
≥ 200	15	7500	Random	1.87	1.41–2.47	0.000	84.8	< 0.000
< 200	7	847	Random	1.59	1.17–2.14	0.003	82.3	< 0.000
Cut-off value of SII								
< 550	8	3285	Random	1.94	1.34–2.80	0.000	84.0	< 0.000
⩾550	14	5062	Random	1.66	1.31–2.11	0.000	85.4	< 0.000
Tumor type	13	6712	Random	2.09	1.54–2.85	0.000	83.2	< 0.000
Primary	9	1635	Random	1.44	1.14–1.81	0.002	79.9	< 0.000
Metastatic								
NOS score								
⩾7	21	6964	Random	1.67	1.39–2.02	0.000	82.7	< 0.000
< 7	1	1383	Random	3.35	2.92–4.26	0.000	0.0	< 0.000
SII at different treatment periods								
Pretreatment	17	6777	Random	1.83	1.42–2.34	0.000	82.3	< 0.000
Posttreatment	5	1570	Random	1.59	1.10–2.30	0.014	85.9	< 0.000
PFS								
Total	11	3996	Random	1.80	1.26–2.56	0.001	96.1	< 0.000
Geographical region								
China	7	3353	Random	2.33	1.95–2.78	0.000	47.2	0.078
Italy	3	602	Random	1.36	0.81–2.29	0.241	83.3	0.003
USA	1	41	Random	1.03	0.99–1.07	0.136	0.0	< 0.000
Age								
≥ 60	4	939	Random	1.61	1.04–2.51	0.033	90.8	< 0.000
< 60	4	1283	Random	1.89	1.46–2.43	0.000	0.0	0.596
Tumor type	5	3156	Random	2.49	2.01–3.08	0.000	33.7	0.196
Primary	6	840	Random	1.46	0.98–2.17	0.063	94.8	< 0.000
Metastatic								
Treatment								
surgery	3	2484	Random	2.42	1.77–3.30	0.000	65.8	0.054
neoadjuvant	1	452	Random	2.50	1.39–4.50	0.002	100.0	< 0.000
chemotherapy + targeted therapy	5	799	Random	1.58	1.08–2.31	0.017	85.0	< 0.000
Adjuvant chemoradiotherapy	1	220	Random	2.33	1.08–5.02	0.030	100.0	< 0.000
TNM stage								
I–IV	5	2771	Random	2.03	1.48–2.78	0.000	87.2	< 0.000

Table 2 (continued)

Variables	No. of the studies	No. of patients	Effects model	HR	95% CI	*p*	Heterogeneity	
							I^2, %	*p*
IV	2	197	Random	2.03	1.36–3.02	0.001	64.0	0.096
Sample size								
≥ 200	5	2993	Random	1.87	1.12–3.12	0.016	89.8	< 0.000
< 200	6	1003	Random	1.73	1.13–2.65	0.011	95.1	< 0.000
Cut-off value of SII								
< 550	6	3251	Random	2.26	1.77–2.89	0.000	54.2	0.053
⩾550	5	745	Random	1.44	0.92–2.25	0.108	95.7	0.000
SII at different treatment periods								
Pretreatment	7	3088	Random	1.89	1.38–2.60	0.000	86.7	< 0.000
Posttreatment	4	908	Random	1.62	1.02–2.57	0.041	86.7	< 0.000
DFS								
Total	8	4141	Random	1.91	1.43–2.56	0.000	71.4	< 0.000
Age								
≥ 60	1	118	Random	1.71	1.03–2.85	0.040	0.0	0.000
< 60	3	1162	Random	1.72	1.12–2.63	0.007	75.9	0.016
Treatment								
surgery	5	3233	Random	1.95	1.26-3.00	0.002	79.3	< 0.000
neoadjuvant	3	908	Random	1.99	1.53–2.60	0.000	0.0	0.569
TNM stage								
I–III	3	2139	Random	1.85	1.07–3.19	0.028	69.3	0.039
II–III	2	356	Random	2.07	1.47–2.90	0.000	0.0	0.326
Sample size								
≥ 200	6	316	Random	2.05	1.40–2.99	0.000	79.4	< 0.000
< 200	2	3825	Random	1.69	1.18–2.43	0.005	0.0	0.958
Cut-off value of SII								
< 550	4	1530	Random	2.08	1.23–3.52	0.007	82.4	< 0.000
⩾550	4	2611	Random	1.80	1.24–2.62	0.002	58.7	0.064
SII at different treatment periods								
Pretreatment	6	2757	Random	1.84	1.36–2.50	0.000	64.0	0.016
Posttreatment	2	1384	Random	2.40	0.67–8.67	0.181	71.4	0.001

TNM stage, and sample size contributed to heterogeneity, while the SII cut-off value and time of SII measurement did not.

Impact of SII on RFS in CRC patients

The prognostic analysis of SII and RFS was conducted on 487 patients across 3 studies [18, 29, 38]. The data exhibited significant heterogeneity, thus a random-effects model was applied ($I^2 = 58.5\%$, $p = 0.090$) (Additional file 2). The results indicated a significant correlation between high SII and poor RFS. In terms of RFS, high SII showed 3 times the hazard ratio compared to low SII (HR = 3.29, 95% CI = 1.58–6.88, $p = 0.002$) (Additional file 2, Table 2).

Correlation of SII with clinicopathological prognosis in CRC patients

Sixteen studies involving 5541 patients [12, 18, 21, 23, 25, 29, 32–35, 37–39, 41, 42, 45]reported the association of SII with 8 clinicopathological characteristics. The characteristics included: gender (male vs. female), tumor differentiation (poor vs. moderate/well differentiated), tumor location (rectum vs. colon), distant metastasis (yes vs. no), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (1–2 vs. 0), age (older adults vs. middle-aged), and tumor size (≥ 5 cm vs. <5 cm). The synthesized results showed that CRC patients with poorly differentiated tumors (OR = 0.24, 95% CI = 0.10–0.59, $p = 0.002$), tumor location in the rectum (OR = 0.48, 95% CI = 0.31–0.73, $p = 0.001$), and tumor size ≥ 5 cm (OR = 0.52, 95% CI = 0.27–0.99, $p = 0.002$) exhibited relatively high SII. However, high SII is not significantly associated with gender (OR = 1.04, 95% CI = 0.80–1.35, $p = 0.768$), distant metastasis (OR = 0.68, 95% CI = 0.14–3.17, $p = 0.622$), ECOG PS (OR = 0.59, 95% CI = 0.26–1.31, $p = 0.195$), or age (OR = 0.76, 95% CI = 0.40–1.44, $p = 0.407$) (Table 3, forest plots are provided in Additional file 3).

Sensitivity analysis

Due to significant heterogeneity among the included studies, a sensitivity analysis was conducted on the correlation results between SII and OS, PFS, and DFS

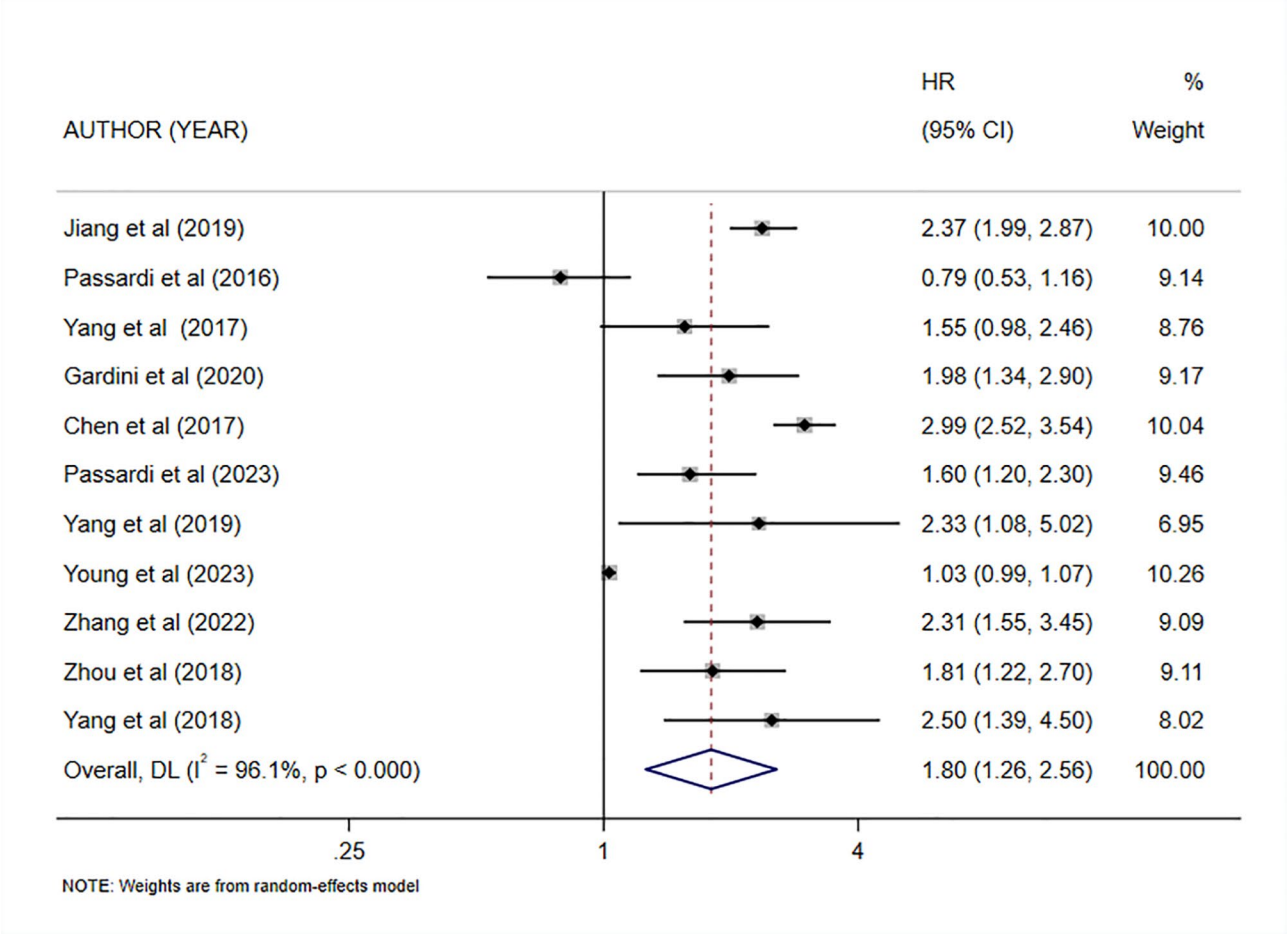

Fig. 3 Forest plot of the association between SII and PFS in patients with CRC

(provided in Additional file 4), by excluding individual datasets one at a time. The analysis concluded that the synthesized results were stable.

Meta-regression

Meta-regression analyses were performed to determine sources of heterogeneity and to explore the effects of SII and OS, PFS, DFS in Patients with CRC. No significant differences were found in age, area, sample size, treatment, tumor type, TNM stage, cut-off value of SII, or the selection time of the SII. Detailed results are shown in Additional file 5.

Publication bias

The *p*-values for Egger's test regarding OS, PFS, and DFS were 0.001, 0.029, and 0.002, respectively. Funnel plot analysis revealed significant publication bias. Egger's test results ($p < 0.05$) further suggested the presence of publication bias among the included studies. However, to evaluate the impact of publication bias on the main findings, a sensitivity analysis was subsequently performed. The publication bias did not affect the research results of OS, PFS, and DFS [OS: before trim and fill method: HR = 0.593, 95% CI = 0.359–0.826, *P* = 0.000, after trim and fill method: HR = 0.404, 95% CI = 0.200-0.608, *P* = 0.000; PFS: before trim and fill method: HR = 0.586, 95% CI = 0.230–0.941, *P* = 0.001, before trim and fill method: HR = 0.488, 95% CI = 0.195–0.782, *P* = 0.001; DFS: before trim and fill method: HR = 0.649, 95% CI = 0.359–0.940, *P* = 0.000, before trim and fill method: HR = 0.649, 95% CI = 0.359–0.940, *P* = 0.000]. The P values before and after trim and fill method were less than 0.05, with statistical significance. Hence, the pooled estimates were stable.

Discussion

This study included 27 studies encompassing a total of 10,779 CRC patients to evaluate the prognostic value of SII in this population. Significant results from various subgroups demonstrated that SII was strongly and consistently associated with OS, PFS, DFS, and RFS, with high SII levels significantly correlating with poorer outcomes for all these survival indicators. The predictive effect of SII on survival outcomes was reduced after

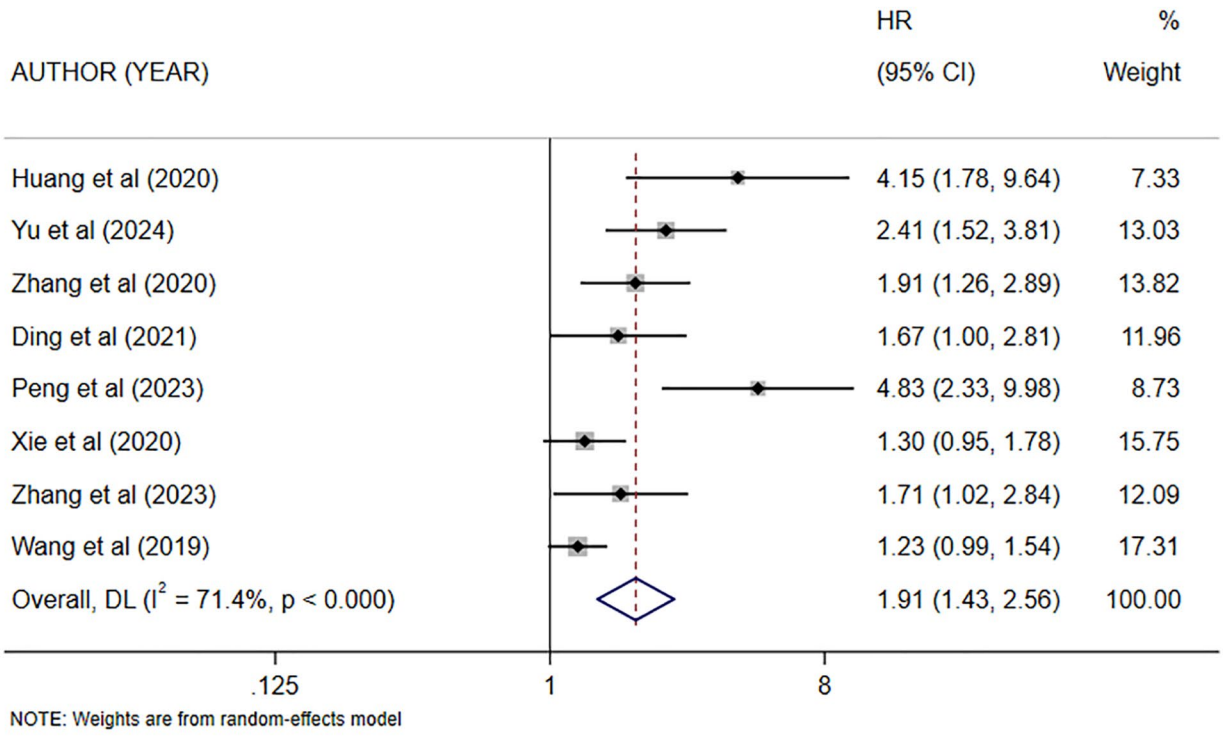

Fig. 4 Forest Plot of the Association Between SII and DFS in Patients with CRC

Table 3 Correlation between SII and Clinicopathological characteristics in patients with CRC

Characteristics	No. of studies	No. of patients	Effects model	OR	95% CI	*p*	Heterogeneity	
							I^2, %	*p*
Sex, male versus female	14	5171	Random	1.04	0.80–1.35	0.768	77.6	< 0.000
Tumor differentiation, poor versus moderate/well	7	2199	Random	0.48	0.31–0.77	0.002	90.4	< 0.000
Distant metastasis, yes versus no	3	980	Random	0.68	0.14–3.17	0.622	96.4	< 0.000
ECOG PS, 1–2 versus 0	6	1236	Random	0.59	0.26–1.31	0.195	91.5	< 0.000
Age, old group versus middle-aged group	9	3618	Random	0.76	0.40–1.44	0.407	96.4	< 0.000
Tumor size, ⩾5 cm versus < 5 cm	2	1533	Random	0.52	0.27–0.99	0.047	85.4	0.009
Tumor location, rectum versus colon	11	3047	Random	0.48	0.31–0.73	0.001	89.4	< 0.000

surgery compared to before surgery, likely due to changes in the postoperative inflammatory response and immune status.Moreover, high SII in CRC patients was associated with poorly differentiated tumors, tumor location in the rectum, and tumor size ≥ 5 cm.Although significant publication bias was identified during the assessment, sensitivity analysis indicated that its impact on the primary results was minimal, demonstrating the robustness of the study's main findings. However, we acknowledge that publication bias may influence certain secondary analysis results. Therefore, further high-quality studies are needed to validate these findings.

The SII, calculated using specific counts of peripheral lymphocytes, neutrophils, and platelets, reflects the interplay between immune and inflammatory responses within the tumor microenvironment. SII provides a more

precise and comprehensive assessment of immune and inflammatory activity, establishing it as a novel inflammatory biomarker. In recent years, SII has also been utilized in the prognostic prediction of various other solid tumors. For example, Salazar-Valdivia et al. concluded that SII could be used as a predictor of OS and PFS in patients with testicular cancer [46].Zhang et al. found that high SII values were an independent prognostic factor for low OS in patients with primary invasive bladder cancer [47]. Qiu et al. concluded that higher SII prior to treatment was significantly associated with poorer OS in patients with gastric cancer, as well as advanced tumor stage, positive lymph node metastasis, higher T-stage, and larger tumor size [48]. These findings suggested that SII could be used as an independent and effective prognostic biomarker for various cancers, enabling the stratification of cancer patients by risk. Our study results found that higher pre-treatment SII is associated with poorer OS and PFS in CRC patients, which are consistent with previous findings: Dong et al. and Li et al. collected data from 12 studies involving 3,919 CRC patients, demonstrating that, a high SII level indicates a poor prognosis and higher malignancy of the disease in CRC, suggesting that SII can serve as a determinant in the determination of clinical treatment regimens for these patients [4, 16]. Tumor cells can survive only by evading immune detection. Lymphocytes, integral to the immune system, primarily facilitate the lysis and apoptosis of target cells, exerting anti-tumor effects. Tumor-infiltrating lymphocytes recognize cancer cells through cytotoxic functions, inducing apoptotic cell demise andcontributing to the assault against micrometastases and residual tumor cells [49]. Neutrophils, in contrast, exhibit pro-tumor functions, and neutrophilia is associated with poor prognosis in cancer patients [50]. Tumor-associated N2 neutrophils, characterized by pro-tumor behaviors, can generate reactive nitrogen species (RNS) and reactive oxygen species (ROS), inducing genetic instability and DNA damage, and potentially instigating tumorigenesis [51, 52]. Platelets, a critical component of the tumor microenvironmentstroma, are reliable predictors of tumor prognosis [53]. Tumor cells activate platelets by secreting tissue factors and thrombin, which enable tumor cells to evade surveillance by natural killer (NK) cells [54]. Therefore, elevated platelet and neutrophil counts, along with decreased lymphocyte counts, indicate tumor growth towards infiltration, recurrence, or metastasis, and are associated with poor patient prognosis. The increase in SII is due to these cellular changes — elevated platelets and neutrophils, and reduced lymphocytes — signifying an unfavorable prognosis for patients. Although the effects of immunity and inflammation on tumors are not simply promotional or inhibitory, the balance of immune and inflammatory factors does affect the biological behaviors of tumors.

Recent studies have emphasized that personalized treatment, including surgery, chemotherapy, targeted therapy, and the latest immunotherapy, plays a crucial role in improving the prognosis of CRC patients. For example, Botrel et al. demonstrated that chemotherapy combined with bevacizumab improved response rates, progression-free survival, and overall survival in patients with metastatic CRC who had not previously received chemotherapy [55].Brenner et al. concluded that surgical techniques and adjuvant chemotherapy and/or radiotherapy increased the cure rate of patients after tumor resection and decreased the surgical mortality rate, which may improve survival in cancer patients [56]. Our study also found that the relationship between SII and prognostic survival of CRC patients was significantly attenuated after treatment. Although the relationship between SII and prognostic indicators varied across treatment modalities, SII remained a significant predictor of prognosis in CRC patients. This study suggested that SII can serve as a potential biomarker for evaluating the prognosis of CRC patients, though its application may be influenced by the patient's disease stage, treatment selection, and SII cutoff value. This enables more precise risk assessments and tailored treatment regimens, potentially enhancing survival rates and quality of life for patients with tumors. Co-infection status has been widely recognized as an important factor affecting the SII. Infection may significantly increase neutrophil counts and platelet counts while reducing lymphocyte counts, leading to elevated SII values. However, since some of the included studies did not clearly report co-infection status, the impact of this factor on the study results cannot be completely ruled out. Therefore, future studies should more clearly include or exclude co-infected patients to improve data reliability.

This study explored the sources of heterogeneity through subgroup analysis and meta-regression analysis. Although some subgroup analyses (such as by region and treatment method) effectively reduced heterogeneity, the heterogeneity of some subgroups was still high ($I^2 > 50\%$). Meta-regression analysis revealed that region and treatment method were key factors contributing to heterogeneity. This may be attributed to differences in medical conditions, treatment regimens, and measurement methods of the SII across regions. In addition, while the effects of sample size and SII cutoff values on heterogeneity are relatively small, their lack of standardization may still impact the interpretation of research findings. This study provides a preliminary discussion regarding the problem of heterogeneity but has not completely resolved the influence of high heterogeneity. Therefore, future studies should focus on further standardizing SII measurement methods, unifying the definition of cutoff values, and

adopting more consistent treatment regimens to reduce variability between studies.

The results of this study showed that elevated preoperative SII was significantly associated with poor prognosis in CRC patients. Unlike previous studies, this research further investigated the potential impact of postoperative changes in SII on patient prognosis. It was found that the predictive value of postoperative SII for survival outcomes was diminished. This suggests that the inflammatory response and immune status of postoperative patients may be complexly affected by treatment methods, thereby altering the prognostic relevance of SII. Moreover, through subgroup analysis, this study identified the moderating effects of region and treatment methods on the relationship between SII and prognosis, offering important insights and directions for future research.

Limitations

However, this study has several limitations. Given the retrospective nature of most included studies, heterogeneity may have arisen. Further prospective studies focusing on relevant patient populations are warranted, as variations in SII cutoff values and measurement methods among the included studies could lead to inconsistencies in SII levels and subsequent outcomes. A major limitation of this study is that there was significant heterogeneity among the included studies ($I^2 > 50\%$). Although subgroup analysis and meta-regression were used to explore potential sources of heterogeneity, some factors contributing to the heterogeneity could not be fully explained. This may be affected by differences in study design, patient characteristics, and data collection standards. Furthermore, the high level of heterogeneity may limit the generaliz ability of the findings. Therefore, it is recommended that future studies be conducted in broader regional and ethnic contexts to validate the results. One of the limitations of this study is that the coinfection status of all included patients was not fully controlled. Because infection may significantly affect SII values, future studies need to further refine the inclusion criteria and explicitly exclude coinfected patients or use them as confounding variables for correction analysis. Another major limitation of this study is that the included studies were mainly concentrated in East Asia, which may limit the generalize ability of the study results to other regions. This difference in geographical distribution may reflect differences in patient characteristics, medical practices, reference ranges of inflammatory indicators, and treatment regimens in different regions. Therefore, although this study revealed the potential application value of SII in East Asian CRC patients, further validation is required in studies involving diverse geographical and ethnic populations to enhance the universality and reliability of the conclusions. In addition, most of the included studies were retrospective studies or based on single-center data, which may lead to a low level of evidence. The absence of randomized designs and strict intervention controls in some studies could introduce selection bias and confounding factors, potentially affecting the robustness of the study conclusions. Therefore, future research should focus on conducting high-quality multicenter RCTs to validate the effectiveness of SII as a prognostic indicator for CRC patients.

Conclusion

In conclusion, this study reaffirms that high SII in CRC patients is associated with poorer OS, PFS, DFS, and RFS. The association between pre-treatment SII and OS, PFS, and DFS was stronger compared to post-treatment measures, indicating that treatment substantially attenuates the correlation between SII and survival outcomes in patients with CRC. Additionally, high SII in CRC patients is associated with poorly differentiated tumors, rectal tumor location, and tumor size ≥ 5 cm. These findings underscore the potential of SII as a prognostic biomarker for CRC patients.

Abbreviations

SII	Systemic immune-inflammation index
CRC	Colorectal cancer
PFS	Progression-free survival
DFS	Disease-free survival
RFS	Recurrence-free survival
CRC	Colorectal cancer
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
LMR	Lymphocyte-to-monocyte ratio
SIRI	Systemic inflammation response index
PNI	Prognostic nutritional index
GPS	Glasgow prognostic score
OCRC	Obstructive colorectal cancer
HR	Hazard ratio
CI	Confidence interval
OR	Odds ratio
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
NK	Natural killer

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03662-z.

Supplementary Material 1

Supplementary Material 2: Literature search strategy

Supplementary Material 3: Forest Plot of the Association Between SII and RFS in Patients with CRC

Supplementary Material 4: Forest Plot of correlation of SII with clinicopathological prognosis

Supplementary Material 5: Sensitivity analysis

Supplementary Material 6: Meta-regression Analysis for SII and OS, PFS, DFS in Patients with CRC

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Author contributions
All authors contributed to the study conception and design. Writing - original draft preparation: Y.T.; Writing - review and editing: Q.L.; Conceptualization: Y.T.; Methodology: Y.T. and B.H.; Formal analysis and investigation: Y.T. and B.H.; Funding acquisition: Y.T.; Resources: Q.L.; Supervision: W.C. and B.H. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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