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Prognostic role of the systemic immune-inflammation index and pan-immune inflammation value for outcomes of breast cancer: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This review examined the literature for evidence on the prognostic ability of systemic immune-inflammation index (SII) and pan-immune inflammation value (PIV) for predicting overall survival (OS) and disease-free survival (DFS) in breast cancer patients.

MATERIALS AND METHODS: PubMed, Embase, Scopus, and Web of Science were searched with Google Scholar for gray literature. All types of studies reporting the association between SII or PIV and OS or DFS of breast cancer were eligible.

RESULTS: 13 studies on SII and 4 studies on PIV were included. Meta-analysis showed that a high SII was a significant predictor of OS (HR: 1.97 95% CI: 1.54, 2.52 I^2=76%) and DFS (HR: 2.07 95% CI: 1.50, 2.86 I^2=79%) in breast cancer patients. These results did not change on sensitivity analysis and were more or less stable on multiple subgroup analyses. Pooled analysis showed that high PIV was also a significant predictor of poor OS (HR: 2.63 95% CI: 1.46, 4.74 I^2=71%) and DFS (HR: 1.64 95% CI: 1.23, 2.17 I^2=0%) in breast cancer patients.

CONCLUSIONS: High SII and PIV can predict poor OS and DFS in breast cancer patients. High heterogeneity and the observational nature of data are important limitations of the review. Further studies are needed specifically on PIV to increase the strength of the evidence.

Key Words:
Prognosis, Inflammation, Survival, Recurrence, Breast cancer.

Introduction

The most common female malignancy and the prime cause of female cancer-related death continue to be breast cancer[1]. The prevalence of this malignancy continues to grow across the globe, leading to a high number of patients and an escalating burden on the healthcare apparatus[2]. Research[3] is on the rise to understand the intricate pathophysiological process behind breast cancer, which has indeed led to refinements and breakthroughs in the treatment procedure, be it surgical, chemotherapy, radiation, or immunotherapy. Nevertheless, the diminished survival and chances of recurrence remain a matter of concern. Prognostication of women with poor overall survival (OS) and disease-free survival (DFS) is an area of continuous research with several clinical markers being used in the recent past, but their resource-intensive and expensive nature have been major limitations for clinical application[4]. The need for a practical, inexpensive, and reliable prognostic indicator that can help model the treatment plan for breast cancer patients cannot be underestimated.

Inflammation is now being recognized as a cause of cancer in several research studies[5,6]. It has been shown[6] that inflammatory mediators like the tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VERF), interleukin (IL)-6, TGF-β, and IL-10 play a role in the development and progression of various cancers. Macrophages, which essentially form the immune-inflammatory response of the body, have been implicated in the development and spread of colorectal cancer[7]. In this context, several hematological indices that represent the body's immune and inflammation status have been used to predict the prognosis of cancer, including breast cancer[8,9]. Nevertheless, the use of just two markers, like in the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, may limit the predictive power owing to complex interactions between various hematological cells and cancer prognosis. Therefore, newer indices like the systemic immune-inflammation index (SII), which is based on

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neutrophil, platelet, and lymphocyte counts, and the pan-immune-inflammation value (PIV) based on the neutrophil, platelet, monocyte, and lymphocyte counts have been developed with an aim that they could better demonstrate the immune and inflammatory state of the body and therefore predict prognosis cancer patients. These two indices have shown a good prognostic ability for various cancer subtypes[10-13], but data regarding breast cancer has been limited. We, therefore, aimed to review the available evidence on the prognostic ability of SII and PIV for breast cancer patients through a systematic review and meta-analysis.

Materials and Methods

Protocol Registration

The review protocol was registered on the PROSPERO database managed by the National Institute for Health Research, University of York, Center for Reviews and Dissemination, and was provided the registration number CRD42023475103. The manuscript was prepared according to PRISMA[14] guidelines.

Research Questions

The following questions were to be answered by this review:

1. Does the SII predict OS and DFS in breast cancer patients?
2. Does the PIV predict OS and DFS in breast cancer patients?

PECOS Inclusion Criteria

The following PECOS framework was generated for searching studies for inclusion:

Population: All types of breast cancer patients, irrespective of treatment.

Exposure: High SII or PIV.

Comparison: Low SII or PIV.

Outcomes: OS or DFS.

Study type: All types.

The cut-off for high and low SII/PIV scores was not predefined, and all values used by the studies were acceptable.

Exclusion Criteria

The following studies were excluded:

1. Studies not reporting on either OS or DFS.
2. Studies not reporting multivariable adjusted data.
3. Studies on general cancer patients and not reporting separate data for breast cancer.
4. Studies with overlapping or duplicate data (in such cases, the study with maximal sample size was included).

Search Methods

A detailed search was carried out by two reviewers separately on the online databases of PubMed, Embase, Scopus, and Web of Science. Gray literature was explored using the Google Scholar database. All articles published between the inception of the databases to 1st November 2023 were searched using the search strings: [“systemic immune-inflammation index” AND “breast cancer”] and [“pan-immune- inflammation value” AND “breast cancer”]. There was no restriction on the language of publication. All search results were examined first by their titles and abstracts to identify studies relevant to the review. The selected full texts were read by the two reviewers independently, and any disagreements were resolved by discussion. A manual search of the referenced studies among the included studies was also conducted.

Data Extraction

Two reviewers were involved in data extraction, which included the first author, publication year, study type, study location, type of breast cancer, the therapy used, sample size, median age, cancer stages included, the cut-off value of SII or PIV, the method to obtain cut-off value, median follow-up, and outcomes. In case of missing data, the corresponding author was contacted by email. Data for SII and PIV were tabulated separately. The outcomes analyzed for both indices were OS and DFS.

Risk of Bias Assessment

As all studies were observational, the quality of studies was examined by the Newcastle-Ottawa scale (NOS)[15]. It was done independently by two reviewers, and any disagreements were solved by a discussion with the third reviewer. The NOS awards stars for the selection of study population, comparability, and outcomes. These are given a maximum of four, two, and three points, respectively.

Statistical Analysis

The software “Review Manager” (RevMan, version 5.3; Nordic Cochrane Centre – Cochrane Collaboration, Copenhagen, Denmark; 2014) was used for the meta-analysis. Multivariable adjusted outcome ratios were combined by the generic inverse variance function of the meta-analysis software. Data was pooled as HR with 95% CI. The random-effects model was chosen. Heterogeneity was assessed using the I^2

statistic. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity. Publication bias was assessed by using funnel plots. We also conducted a sensitivity analysis for SII wherein individual studies were excluded one at a time and the effect size was recalculated for the remaining studies. Subgroup analyses were conducted for SII based on the type of breast cancer, treatment, cut-off value, and cut-off determination method. Additional analyses were not conducted for PIV due to limited data.

Results

Search Results

The number of studies at each stage of the search protocol is shown in Figure 1. In the end, 19 studies were analyzed by their full texts, two of which were excluded. A total of 13 studies[16-28] on SII and 4 studies[29-32] on PIV were included in the review.

Baseline Details

Details of SII studies are presented in Table I. The studies were published between 2019 and 2022. The number of patients ranged from 147 to 1,026, with a total sample size of 5,199 patients. Most studies[17-20,22,23,27] were on mixed breast cancer populations, while other[21,25] included only human epidermal growth factor receptor 2 (HER2), triple negative[24,28], and luminal breast cancer[16]. All except for one study[27], which included stage I-III patients. Treatment modality was mixed in most studies[17,19,21,23-26,28] except for a few[16,18,20,22,27], which included only non-surgical or surgical cases. The cut-off for SII was generated either by receiver operating characteristics (ROC) or median values. The cut-off was variable across studies ranging from 429.4 to 836. The median follow-up of studies was equal to or more than 2 years (where data was available). The NOS score of SII studies varied from 6 to 8.

The details of four PIV studies[29-32] are shown in Table II. Three studies[29,31,32] included mixed breast cancer, while one[30] was on HER2-positive breast cancer patients. The sample size of all PIV studies combined was 2,433. Studies included patients with different stages. In one study[31], therapy was mixed, while only chemotherapy or surgery was used in the remaining studies[29,30,32]. The cut-off of PIV ranged from 205 to 310.6 and was determined by either ROC, median value or maximally selected rank statistics. The NOS score of PIV studies also varied from 6 to 8.

Analysis

Meta-analysis showed that a high SII was a significant predictor of OS in breast cancer patients (HR: 1.97 95% CI: 1.54, 2.52 I^2=76%) (Figure 2). The results remained unchanged on sensitivity analysis. There was no evidence of publication bias (Figure 3). Similarly, SII was found to be a significant predictor of DFS in breast cancer patients (HR: 2.07 95% CI: 1.50, 2.86 I^2=79%) (Figure 4). No change in the outcome was observed on sensitivity analysis. There was no evidence of publication bias (Figure 5).

Subgroup analyses for SII are shown in Table III. For OS, the results remained unchanged on subgroup analyses based on the type of breast cancer, cut-off value, and cut-off determination method. For analysis based on treatment type, the result was significant only for the mixed group. For DFS, the results remained unchanged on subgroup analyses based on cut-off value and cut-off determination method but turned non-significant for HER2-positive type of breast cancer and only surgical or non-surgical treatment.

Pooled analysis of PIV studies showed that high PIV was a significant predictor of poor OS (HR: 2.63 95% CI: 1.46, 4.74 I^2=71%) and DFS (HR: 1.64 95% CI: 1.23, 2.17 I^2=0%) in breast cancer patients (Figure 6).

Discussion

To summarize, the current meta-analysis of 13 studies[16-28] on SII and 4 studies[29-32] on PIV demonstrated that both indices could independently predict outcomes of breast cancer. High SII and high PIV were associated with poor OS and DFS in such patients. Further, on subgroup analysis, the results for SII did not change depending upon the cut-off and cut-off determination method.

The SII value is generated by the following equation: "neutrophil count × platelet count/ lymphocyte count". Therefore, high SII reflects increased neutrophil and platelet counts and reduced lymphocyte counts. Such variations in neutrophil, platelet, and lymphocyte count in dual combinations have been shown[33,34] to predict outcomes of breast cancer. Studies[33,34] have demonstrated worse OS and DFS in breast cancer with a high neutrophil:lymphocyte ratio and platelet:lymphocyte ratio. Individually, these blood cells have either cancer-promotive or cancer-protective effects. In the case of neutrophils, the inflammatory cytokines they secrete, like IL-6,

Table I. Details of included studies on SII.

Study	Location	Molecular type	Sample size	Median Age	Stage	Treatment	Outcomes	Cut-off	Cut-off determination	Median follow-up (months)	NOS score
De Giorgi et al[27] 2019	Italy	Mixed	516	59	IV	Non-Surgical	OS	836	ROC analysis	24	8
Li et al[16] 2019	China	Luminal	161	58	I-III	Non-Surgical	DFS	518	ROC analysis	28.4	7
Liu et al[24] 2019	China	TNBC	160	NR	I-III	Mixed	OS, DFS	557	ROC analysis	61.7	6
Sun et al[25] 2019	China	HER2	155	NR	I-III	Mixed	OS, DFS	578	Median value	57.6	6
Wang et al[26] 2019	China	TNBC	215	NR	I-III	Mixed	OS, DFS	624	Median value	49.2	7
Chen et al[22] 2020	China	Mixed	262	48	II-III	Non-Surgical	OS, DFS	602	ROC analysis	NR	8
Hua et al[23] 2020	China	Mixed	1,026	47	I-III	Mixed	OS, DFS	601.7	ROC analysis	68.5	7
Jiang et al[21] 2020	China	HER2	147	NR	I-III	Mixed	OS, DFS	442	ROC analysis	42	7
Jiang et al[17] 2020	China	Mixed	249	NR	I-III	Mixed	OS	547	ROC analysis	28-34	8
Pang et al[28] 2021	China	TNBC	231	NR	I-III	Mixed	DFS	474	Median value	NR	7
Li et al[18] 2021	China	Mixed	784	49	I-III	Surgery	OS, DFS	514	ROC analysis	65.5	8
Zhu et al[19] 2022	China	Mixed	785	47	I-III	Mixed	OS, DFS	560	ROC analysis	NR	7
Xu et al[20] 2022	China	Mixed	508	49	I-III	Surgery	OS, DFS	429.4	NR	NR	7

TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor-2; OS, overall survival; DFS, disease-free survival; ROC, receiver operating characteristics; NR not reported, NOS Newcastle-Ottawa Scale.

Table II. Details of included studies on PIV.

Study	Location	Molecular type	Sample size	Median Age	Stage	Treatment	Outcomes	Cut-off	Cut-off determination	Median follow-up (months)	NOS score
Provenzano et al[29] 2023	Italy	Mixed	78	NR	IV	Chemotherapy	OS, DFS	NR	Median value	47.4	8
Lin et al[32] 2022	China	Mixed	1,312	48	I-III	Surgery	OS	310.2	MSR	NR	7
Sahin et al[31] 2021	Turkey	Mixed	743	48	I-III	Mixed	OS, DFS	306.4	ROC analysis	67.5	8
Ligorio et al[30] 2021	Italy	HER2	57	53	NR	Chemotherapy	OS, DFS	205	Median value	36.6	8

OS, overall survival; DFS, disease-free survival; ROC, receiver operating characteristics; NR not reported; HER2, human epidermal growth factor receptor-2; NOS Newcastle-Ottawa Scale; MSR, maximally selected rank statistics.

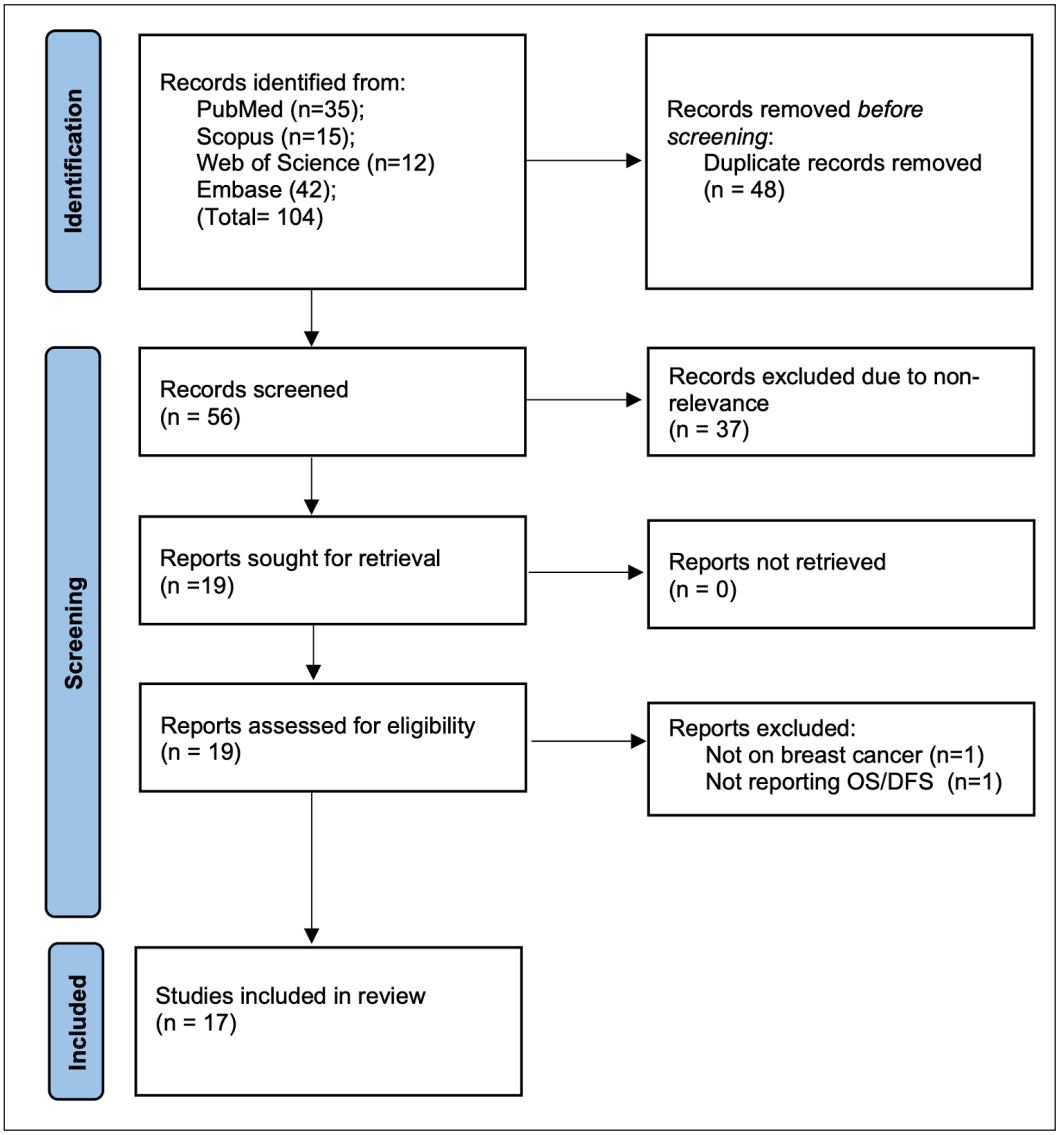

Figure 1. Study flowchart.

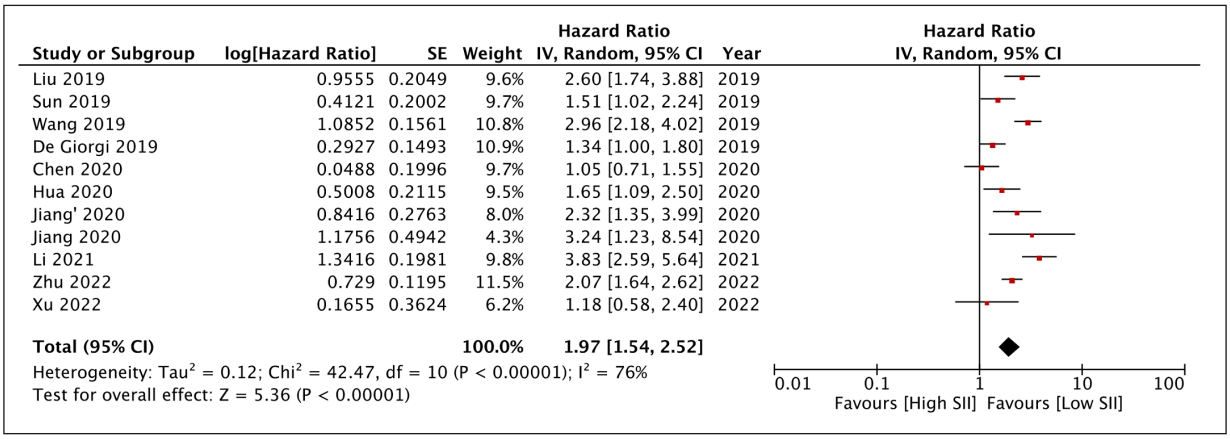

Figure 2. Meta-analysis of the association between SII and OS.

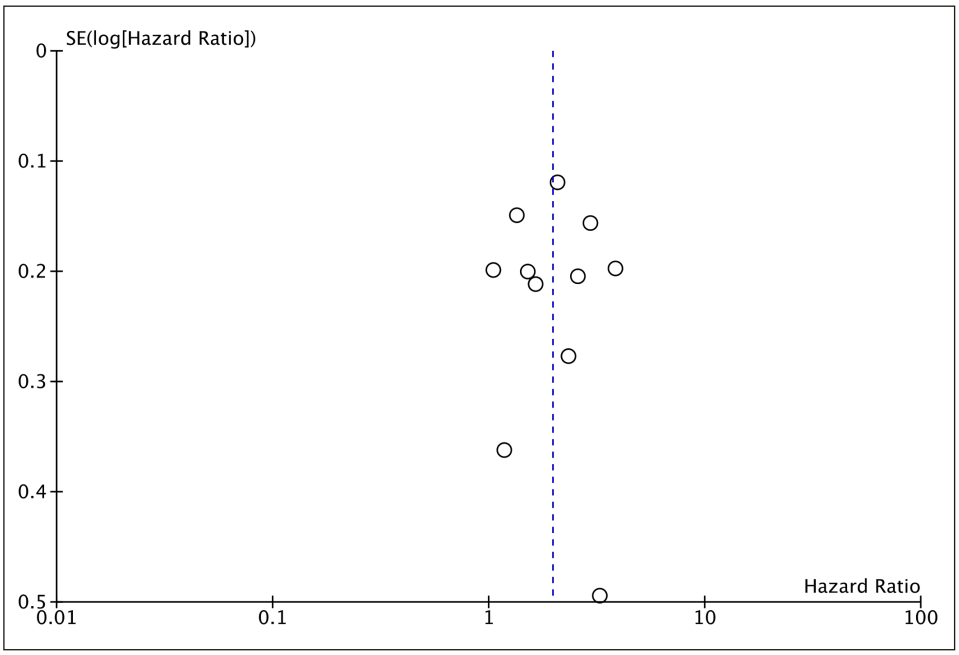

Figure 3. Funnel plot for the meta-analysis of the association between SII and OS.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Li 2019	1.7984	0.612	4.7%	6.04 [1.82, 20.04]	2019
Liu 2019	0.3853	0.1915	11.3%	1.47 [1.01, 2.14]	2019
Sun 2019	0.3784	0.188	11.3%	1.46 [1.01, 2.11]	2019
Wang 2019	1.0473	0.2882	9.4%	2.85 [1.62, 5.01]	2019
Chen 2020	0.077	0.2069	11.0%	1.08 [0.72, 1.62]	2020
Hua 2020	0.4886	0.1824	11.4%	1.63 [1.14, 2.33]	2020
Jiang' 2020	1.3297	0.6298	4.5%	3.78 [1.10, 12.99]	2020
Jian 2021	0.7971	0.3847	7.7%	2.22 [1.04, 4.72]	2021
Li 2021	1.5107	0.1649	11.8%	4.53 [3.28, 6.26]	2021
Zhu 2022	0.7352	0.1622	11.8%	2.09 [1.52, 2.87]	2022
Xu 2022	0.207	0.5731	5.1%	1.23 [0.40, 3.78]	2022
Total (95% CI)			**100.0%**	**2.07 [1.50, 2.86]**	

Heterogeneity: Tau² = 0.20; Chi² = 46.73, df = 10 (P < 0.00001); I² = 79%
Test for overall effect: Z = 4.45 (P < 0.00001)

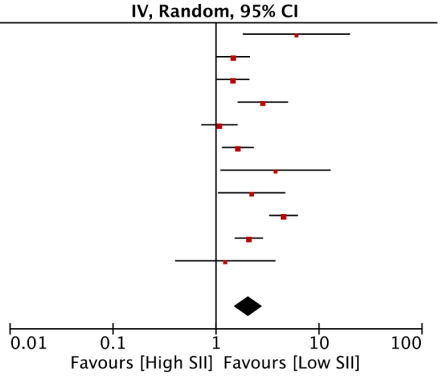

Figure 4. Meta-analysis of the association between SII and DFS.

IL-10, IL-22, and vascular endothelial growth factor, have shown[35] tumor-nurturing behavior. Neutrophils can be reprogrammed by the tumor microenvironment and may facilitate the transport of cancer cells into various tissues, leading to cancer progression and metastasis[36]. Likewise, platelets may support cancer growth by inhibiting the lysis of malignant cells by natural killer cells[37]. Recent research[38] has shown that platelet-derived extracellular vesicles can aid in distant metastasis of cancer by upregulating integrin β3. Contrastingly, lymphocytes are cancer-protective cells on account of their immune-surveillance property. These cells are also known[39] to modulate response to breast cancer therapy, with every 10% increase in tumor-infiltrating lymphocytes increasing OS.

The PIV is an upgrade to SII by the inclusion of monocyte counts. It is calculated by "neutrophil count × monocyte count x platelet count/lymphocyte count". The addition of monocytes adds value to the overall equation as these cells are known to have multiple functions aiding tumor growth and progression. Similar to neutrophils, these are reprogrammed by the malignancy to aid in tumorigenesis by increasing immunosuppression, angiogenesis, and tumor cell intravasation[40]. Therefore, by using multiple immune-inflammatory markers in the form of neutrophils, monocytes, platelets,

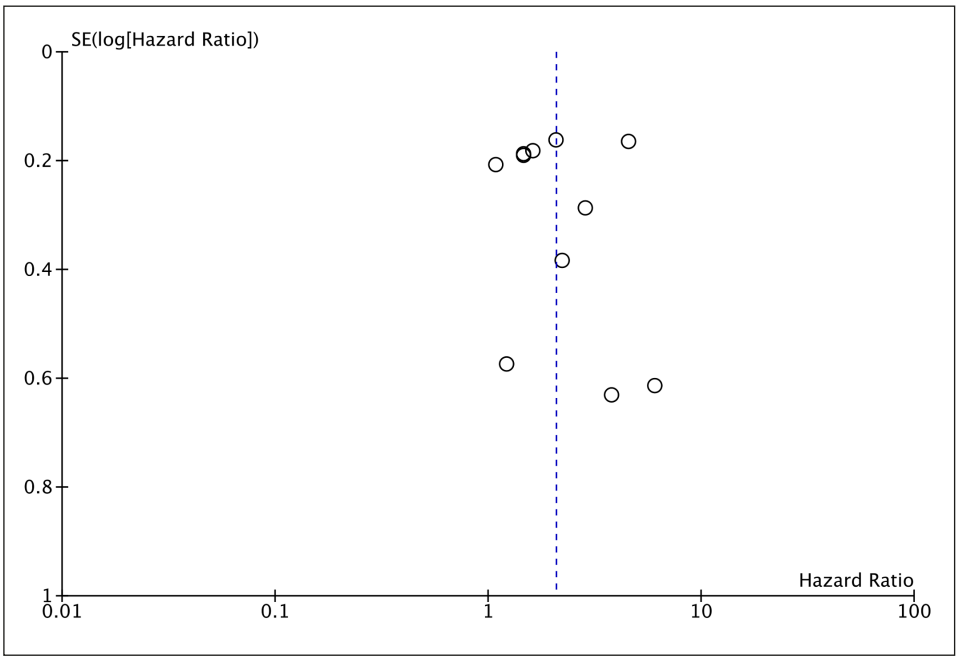

Figure 5. Funnel plot for the meta-analysis of the association between SII and DFS.

Table V. Subgroup analysis of SII.

Variable	Groups	Number of studies	HR (95% CI)	I^2 (%)
Overall Survival				
Breast cancer type	Mixed	7	1.79 (1.27, 2.52)	80
	TNBC	2	2.82 (2.21, 3.60)	0
	HER2	2	1.79 (1.19, 2.71)	37
Treatment	Mixed	7	2.18 (1.79, 2.66)	43
	Surgery	2	2.21 (0.70, 6.98)	88
	Non-surgery	2	1.23 (0.97, 1.55)	0
Cut-off determination	ROC	8	2.00 (1.49, 2.70)	78
	Median	2	2.14 (1.11, 4.14)	86
Cut-off	>550	7	1.79 (1.37, 2.34)	78
	<550	4	2.47 (1.47, 4.16)	66
Disease free survival				
Breast cancer type	Mixed	5	1.92 (1.12, 3.29)	89
	TNBC	3	1.99 (1.28, 3.10)	49
	HER2	2	1.94 (0.83, 4.57)	52
Treatment	Mixed	7	1.82 (1.50, 2.21)	22
	Surgery	2	2.65 (0.75, 9.32)	79
	Non-surgery	2	2.32 (0.43, 12.40)	86
Cut-off determination	ROC	7	2.21 (1.41, 3.44)	85
	Median	3	1.99 (1.77, 3.11)	51
Cut-off	>550	6	1.64 (1.30, 2.07)	53
	<550	5	3.26 (1.97, 5.40)	47

TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor-2; ROC, receiver operating characteristics; HR, hazard ratio; CI, confidence intervals; I^2, heterogeneity.

and lymphocytes, the SII and PIV aim to be better prognostic indices for breast cancer as compared to binary values like neutrophil:lymphocyte ratio, platelet:lymphocyte ratio, and monocyte:lymphocyte ratio. Indeed, a meta-analysis has shown[13] that the SII can predict OS and DFS in urinary cancer patients. Similarly, individual studies have validated the prognostic value of SII for endometrial cancer[12], pancreatic cancer[41], and lung cancer[42]. Likewise, PIV has been found to independently predict outcomes in melanomas[11] and colorectal cancer[10].

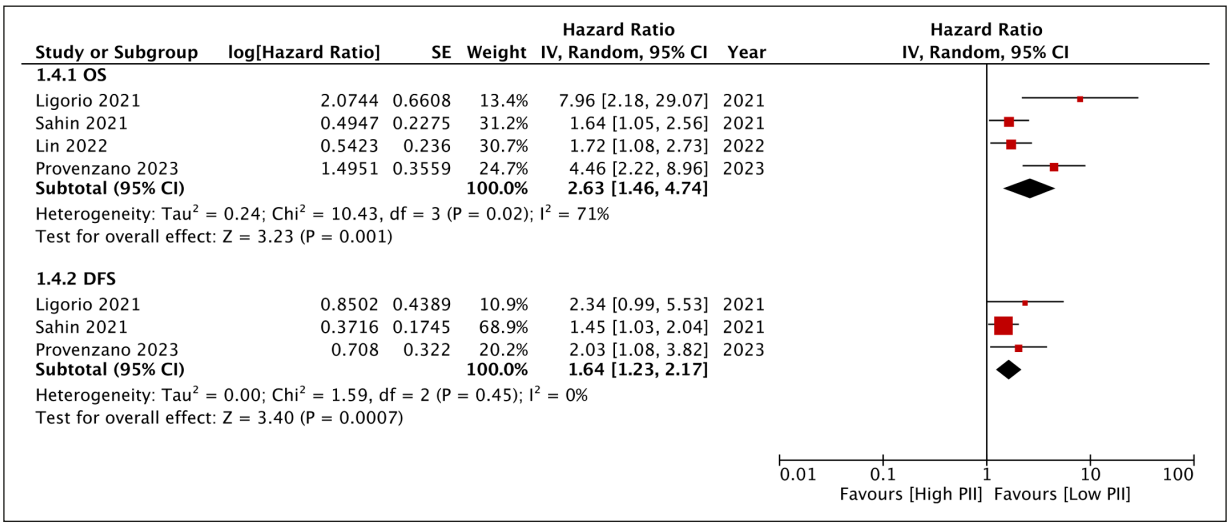

Figure 6. Meta-analysis of the association between PIV and OS and DFS.

The results of this review concur with the outcomes of these previous literature[43]. It was seen in our review that patients with high SII and PIV had poor OS and DFS as compared to those with lower values. Previously, Zhang et al[43], in a meta-analysis of eight studies, have also noted poor OS and DFS with high SII in breast cancer patients. By including 13 studies, our review is a significant update on this prior meta-analysis. Furthermore, for the first time, studies on PIV for breast cancer have been pooled in a meta-analysis in this review. On examining the forest plot, it was noted that the direction of the results was consistent across all included studies, with a few exceptions of non-significant outcomes. The lack of change in effect size on sensitivity analysis and publication bias increases the credibility of the results.

Owing to high heterogeneity in the meta-analysis of SII, multiple subgroup analyses were conducted. However, there was no change in the results of the subgroup analysis based on the cut-off and cut-off determination method. Nevertheless, some subgroups of both OS and DFS turned non-significant, which could be attributed to the low number of studies in these subgroups. The overall effect size was still above 1 with a high ranging upper 95% CI, indicating that the results could not achieve statistical significance owing to the small number of studies.

Our results have important clinical significance as both SII and PIV are easy to calculate and readily available worldwide without any additional laboratory costs. Blood counts are a routine requirement in the pre-treatment work-up of all breast cancer patients, and these can be rapidly converted to SII or PIV to predict the prognosis of the patient. Individuals with high SII or PIV should receive personalized treatment protocols and close follow-up owing to the high tendency of poor OS and DFS.

The retrospective and observational nature of included studies is an important limitation to consider while interpreting the results. Such studies are prone to selection bias, which can skew the results. Also, despite focusing on breast cancer only, there was significant heterogeneity among studies concerning the type of breast cancer, the therapy, and follow-up duration. Also, all studies used different cut-offs based on their study population, which was mostly Chinese. This not only limits the wide interpretation of the results but also suggests that clinicians should derive specific cut-offs in their patient populations to achieve the desired results. Lastly, most studies in the review were on SII, and only four studies on PIV could be included. Additional analyses could not be conducted for PIV due to limited data. Thus, at this point, the value of PIV may not be conclusively proven, and further studies may help in strengthening the results.

Conclusions

High SII and PIV can predict poor OS and DFS in breast cancer patients. High heterogeneity and the observational nature of data are important limitations of the review. Further studies are needed specifically on PIV to increase the strength of the evidence. Also, future studies

on SII and PIV should be conducted on different ethnic populations, focusing on specific breast cancer types to supplement our results.

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Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions
HC conceived and designed the study. TW, GY, LX and BS collected the data and performed the literature search. HC was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethics Approval and Informed Consent
Not applicable.

Conflict of Interest
The authors declare that they have no competing interests.

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