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Review Article

Clinicopathological and prognostic importance of systemic immune inflammation index (SII) in breast cancer patients: a meta-analysis

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Abstract: Background: The relationship between systemic immune inflammation index (SII) and prognosis of malignancies is an original research topic that has intrigued great interests. However, the clinicopathological significance and prognostic value of it in breast cancer are still disputed. To solve this issue, a meta-analysis was performed on breast cancer patients. Methods: Suitable and relevant studies in PubMed, EMBASE, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), and SinoMed, were systematically retrieved. The endpoints set included disease-free survival (DFS), overall survival (OS), and clinicopathological features. Additionally, the hazard ratio (HR) and 95% confidence interval (CI) were incorporated into analyzing the correlation of pretreatment SII with OS and DFS in breast cancer patients, while the clinicopathological features were characterized by the odds ratio (OR). Results: 1,768 patients from eight studies were included. The results indicated that poor OS (pooled HR: 1.82, 95% CI: 1.28-2.59, P=0.0009) and DFS (pooled HR: 1.79, 95% CI: 1.26-2.54, P=0.001) had a considerable correlation with increased SII, and the role of SII in prognosis was further confirmed by subgroup analysis. Additionally, elevated pretreatment SII was also associated with T stage (T2-4), menstrual status (pre-menstrual), and ER status (ER+). Conclusions: A predictive biomarker for elevated pretreatment SII in worse survival of patients with breast cancer was suggested.

Keywords: Systemic immune inflammation index, breast cancer, prognosis, clinical pathology, meta-analysis

Introduction

As the world's highest incidence of feminine malignancies, breast cancer's fatality rate accounts for 15% of all malignant tumors [1]. The treatment of breast cancer depends on the stages of disease and characteristics of the tumor. Slow growth and favorable prognosis occur in some cases, while highly aggressive clinical outcomes present in others due to high heterogeneity in etiology and pathology. Accordingly, the prognosis of breast cancer receives more concerns from patients and doctors.

Previous studies have demonstrated that there is a certain relationship between inflammatory response and breast tumors [2, 3]. Inflammatory markers, such as platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and Glasgow score, have been demonstrated by researchers to be appreciably independent risk factors in malignant tumors [4-6]. However, systemic immune inflammation (SII) as a novel biomarker, which is based on neutrophils, platelets, and lymphocytes count, may be more comprehensive and objective than PLR or NLR in predicting the prognosis of diseases [7, 8].

Nonetheless, the discussion about the issue between pretreatment SII and prognosis of breast cancer is discrepant, and the value of SII as a prognostic marker remains elusive. The aim of the current study was devoted to further examine the effect of SII on the prognosis and clinicopathological characteristics of breast cancer patients through a meta-analysis of published suitable studies.

Methods

The meta-analysis was conducted in accordance with the statement of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

The strategy of search

A comprehensive literature search of related studies published before March 2020 was carried out by using PubMed, EMBASE, Web of Science, Cochrane Library, CNKI and SinoMed websites. The following individual keywords and their combinations were used for the search, including systemic immune inflammation index or SII and breast cancer or breast tumor or breast neoplasms or human mammary carcinomas or human mammary neoplasm or cancer of breast. Additionally, literatures in qualified publications were reviewed for possible studies. There were no restrictions on geographical areas. Moreover, the whole search work was independently completed by two reviewers (Yuan Wang and Zhujun Cong). The detailed retrieval strategies were illustrated in **Appendix 1**.

The criteria for study inclusion and exclusion

Eligible studies were reviewed based on the pre-specified inclusion and exclusion criteria. Moreover, the exhaustive decision on the inclusion and exclusion criteria was consented by all authors. If any disagreement between the two reviewers existed, a final decision was made by a senior reviewer (Guilin Huang).

The criteria for inclusion included: (1) Studies involving the investigation of the relationship between pretreatment SII and prognosis of breast cancer; (2) The diagnosis of breast cancer was confirmed by pathology; (3) According to the cut-off value of SII, patients were divided into high and low ratio groups; (4) Studies involving the assessment of the OS or DFS of breast cancer patients; (5) Studies directly provided HRs with corresponding 95% CIs or sufficient information for calculating them.

The criteria for exclusion contained: (1) Studies not involving the prognosis of breast cancer patients; (2) Studies provided inadequate SII data for further analysis; (3) Studies without data of interest (e.g. OS or DFS); (4) The types of literatures presented were abstract, comment, case report, review, editorial or duplicated studies; (5) Full or quality assessments of the literature were not available.

The extraction of data

The screening of literatures, the extraction of data, and the assessment of literature quality were performed by two independent researchers (Yuan Wang and Zhujun Cong).

The data extracted from the literature included: a) study characteristics such as name of the first author, country, sample size, and analysis method, year of publication; b) patients information containing age and menstrual status; c) clinical characteristics like therapies, the cut-off values of SII and follow-up time; d) pathological features consisting of histology grade, molecular subtype, AJCC stage, ER, PR and HER2 status, tumor progression; and associated 95% CIs for OS or DFS with HRs.

The assessment of quality

Two independent investigators (Zhujun Cong and Zhigang Li) respectively evaluated the quality of the included literatures using the Newcastle-Ottawa Quality Assessment Scale (NOS), which scored the studies separately according to the queue selection, comparability, and evaluation [9]. The scale of rate was set as 0-9 points and a score of 6 or higher was regarded as good. Accordingly, the higher the NOS score, the better the quality of the literatures was.

Statistical analysis

The relationship between pretreatment SII and prognosis in breast cancer patients was determined by HRs associated with 95% CIs. Pooled ORs in combination with 95% CIs were used to assess the association between SII and clinicopathological characteristics. If the survival analyses were reported in the literatures, we directly extracted HRs and 95% CIs from multivariate cox proportional hazard models; otherwise, Engauge Digitizer Software (version 4.1) was applied for the calculation in accordance with the method described by Tierney and Parmar [10, 11] based on the Kaplan-Meier diagram.

The Cochrane Collaboration's Review Manager (version 5.3) was utilized to pool the outcomes of primary studies. The heterogeneity was quantified by the chi-squared test and the I^2

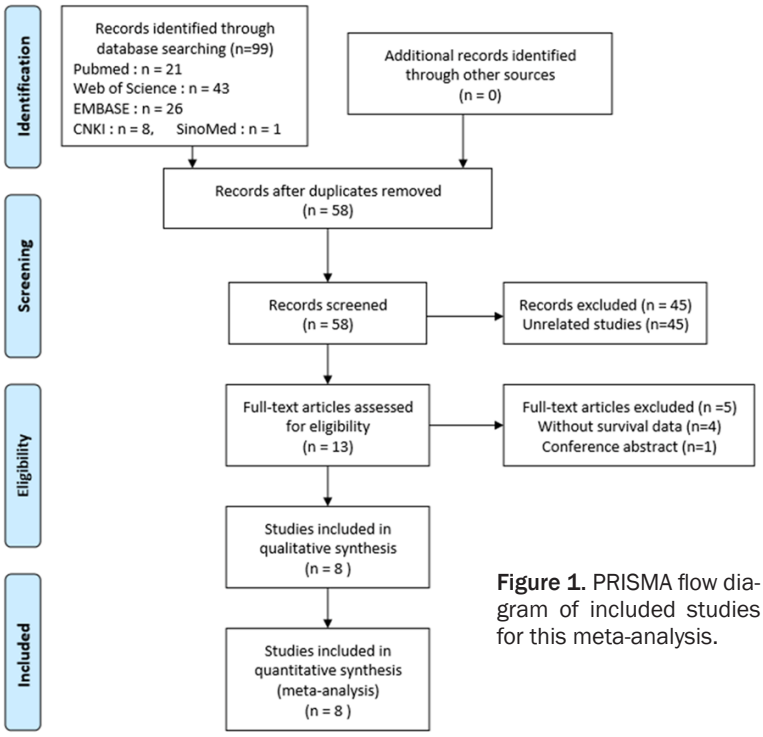


Figure 1. PRISMA flow diagram of included studies for this meta-analysis.

statistics. If $P<0.05$ and/or $I^2>40\%$, a random-effect model was adopted for the calculation of the pooled HRs; otherwise, a fixed-effect model was employed [12]. Potential causes of heterogeneity were further identified by subgroup and sensitivity analyses. The publications bias was evaluated by Begg and Egger tests.

Ethics

All procedures involving human participants in studies were complied with the ethical standards of institutions and/or national research councils and with the Declaration of Helsinki of 1964 and subsequent amendments or similar ethical standards.

Systemic reviews and meta-analyses do not require approval from a medical institution or ethics committee. The authors are responsible for all aspects of this work to make sure that issues associated with the completeness or accuracy are properly examined and resolved.

Results

Included literatures

Initially 99 records were identified from databases through examining titles and abstracts, among which 21, 43, 26, 8, 1 are from PubMed, Web of Science, Embase, CNKI and SinoMed, respectively. 45 unrelated studies and 41 duplications were then removed. Following the in-depth reading of the remaining 13 literatures, 4 of them without survival data and 1 conference abstract were further excluded. Finally, 8 eligible studies comprising 1768 patients were included [13-20], while the flow diagram of the literature search was presented in **Figure 1**.

Study characteristics

Among the 8 studies, 6 studies were evaluated for the prognostic value of SII on OS while 7 studies for DFS. Therefore, the HRs with an association of 95% CIs were directly extracted based on the multivariate cox proportional hazard models in these 7 studies [13-19], while 1 study [20] calculated them according to the Kaplan-Meier diagram using Engauge Digitizer. The cut-off values of SII had a range of 442 to 836, the NOS score of each study ranged from 7 to 8, indicating that the qualities of literatures were generally medium to high. The detailed quality assessment of each study was illustrated in **Appendix 2** and the primary characteristics of them were summarized in **Table 1**.

SII and OS in breast cancer

The relationship between SII and OS was reported in 6 studies comprising 1,455 patients with breast cancer. Due to the significant heterogeneity ($I^2=81\%$; $P=0.0001$), the random-effect model was therefore employed to estimate the pooled HR and corresponding 95% CI. Consequently, higher pretreatment SII was correlated with poorer OS (pooled HR: 1.82, 95% CI: 1.28-2.59, $P=0.0009$, **Figure 2**).

Subgroup analysis was performed to examine the sources of heterogeneity from the five aspects, including molecular subtype, cut-off value, tumor progression, sample size and follow-up time. The results demonstrated that the evaluated SII could predict worse OS in all the layered categories. First, molecular subtype

Table 1. Characteristics of the studies included in the meta-analysis

Author	Year	Country	Survival analysis endpoint	Sample size	Cut-off value	Follow-up (months)	Ages (Years)	Triple-negative tumors (%)	Tumor progression	Diagnosis	Therapies	NOS score
Sun	2019	China	OS/DFS/DMFS	155	578	124	≤35:31; >35:124	NA	non-metastatic	HR(-), HER2(+)	Sugury, Chemotherapy, Radiotherapy, Targeted therapy	8
Wang	2019	China	OS/DFS	215	624	89	≤50:155; >50:60	215 (100)	non-metastatic	TNBC	Sugury, Chemotherapy, Radiotherapy	7
Li	2020	China	DFS	161	518	63	Median:58	NA	non-metastatic	luminal breast cancer	Sugury, Chemotherapy Radiotherapy, Endocrine therapy	7
Chen	2019	China	OS/DFS	262	602	192	48 (27-73)	67 (25.5)	non-metastatic	advanced breast carcinoma	Sugury, Chemotherapy, Radiotherapy, Endocrine therapy, Targeted therapy	8
Jiang	2020	China	OS/DFS	147	442	54	≤35:7; >35:140	NA	non-metastatic	HER2(+)	Sugury, Chemotherapy, Radiotherapy, Endocrine therapy	8
DeGiorgi	2019	USA	OS	516	836	63	NA	124 (24)	metastatic	metastatic breast cancer	Chemotherapy, Endocrine therapy, Targeted therapy	7
Liu	2019	China	OS/DFS/DMFS	160	557	146	≤35:23; >35:137	160 (100)	non-metastatic	TNBC	Sugury, Chemotherapy, Radiotherapy	7
Xing	2018	China	DFS	152	632.32	63	≤35:7; >35:145	29 (19.08)	non-metastatic	Mix	Sugury, Chemotherapy, Radiotherapy, Endocrine therapy, Targeted therapy	7

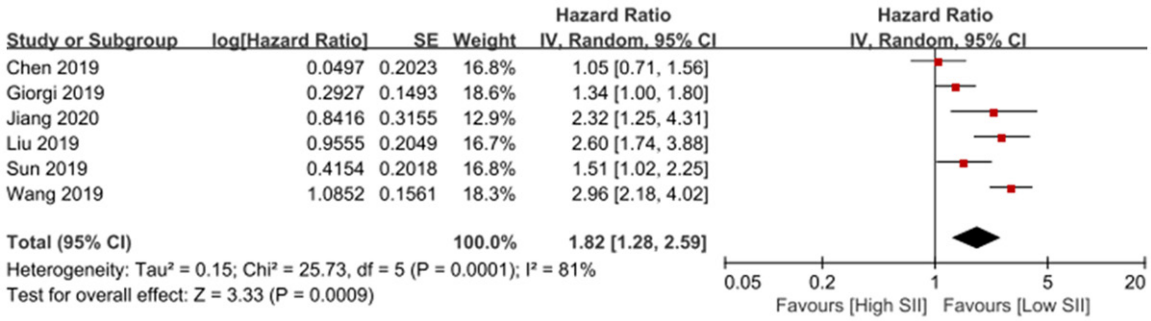


Figure 2. Forest plot of the correlation between SII and OS in breast cancer patients.

Table 2. Subgroup analyses of SII for OS

Subgroups	Independent Cohorts	Sample Size	HR (95% CI)	*P* value	Study heterogeneity			
					χ^2	df	I^2 (%)	P_h
Overall survival	6	1455	1.82 (1.28, 2.59)	0.0009	25.73	5	81	0.0001
Molecular subtype								
Triple-negative	2	375	2.83 (2.21, 3.61)	<0.00001	0.25	1	0	0.62
HER2 positive	2	302	1.71 (1.23, 2.39)	0.002	1.3	1	23	0.26
Other	2	778	1.40 (1.10, 1.78)	0.007	0.23	1	0	0.63
Cut-off value								
<600	3	462	2.03 (1.57, 2.63)	<0.00001	3.74	2	47	0.15
≥600	3	938	1.71 (1.41, 2.05)	<0.00001	20.81	2	90	<0.0001
Tumor progression								
Non-metastatic	5	939	2.02 (1.69, 2.41)	<0.00001	20.17	4	80	0.0005
Metastatic	1	516	1.34 (1.00, 1.80)	0.05	-	-	-	-
Sample Size								
<200	3	462	2.03 (1.57, 2.63)	<0.00001	3.74	2	47	0.15
≥200	3	993	1.71 (1.41, 2.05)	<0.00001	20.81	2	90	<0.0001
Follow-up (years)								
<10	3	878	1.99 (1.63, 2.43)	<0.00001	13.72	2	85	0.001
≥10	3	577	1.60 (1.27, 2.01)	<0.0001	10.00	2	80	0.007

based subgroup analysis predetermined that patients with triple-negative breast cancer (pooled HR: 2.83; 95% CI=2.21-3.61; P< 0.00001), HER2+ breast cancer (pooled HR: 1.71; 95% CI=1.23-2.39; P=0.002) and other molecular subtypes (pooled HR: 1.40; 95% CI=1.10-1.78; P=0.007) were all essentially associated with worse OS. Second, stratified analysis by the cut-off value of SII indicated that worse OS could also be found in SII <600 (pooled HR: 2.03; 95% CI=1.57-2.63; P<0.0001) and SII ≥600 (pooled HR: 1.71; 95% CI=1.41-2.05; P<0.0001). Then, higher pretreatment SII predicted worse OS in patients with breast cancer regardless of tumor progression, sample size and the time of follow-up. Furthermore, the forecasting ability of SII is stronger in triple-negative, non-metastatic breast cancer patients, together with the subgroups of cut-off value <600 and sample size <200 (**Table 2**).

SII and DFS in breast cancer

Among the 7 studies comprising 1,252 breast cancer patients investigating the predictive effect of SII for DFS, the pooled results similarly demonstrated that breast cancer patients with higher pretreatment SII were linked to worse DFS (HR: 1.79; 95% CI: 1.26-2.54; P=0.001) (**Figure 3**).

Subgroup analysis was conducted from the four aspects like molecular subtypes, cut-off value, sample size and the follow-up time. The

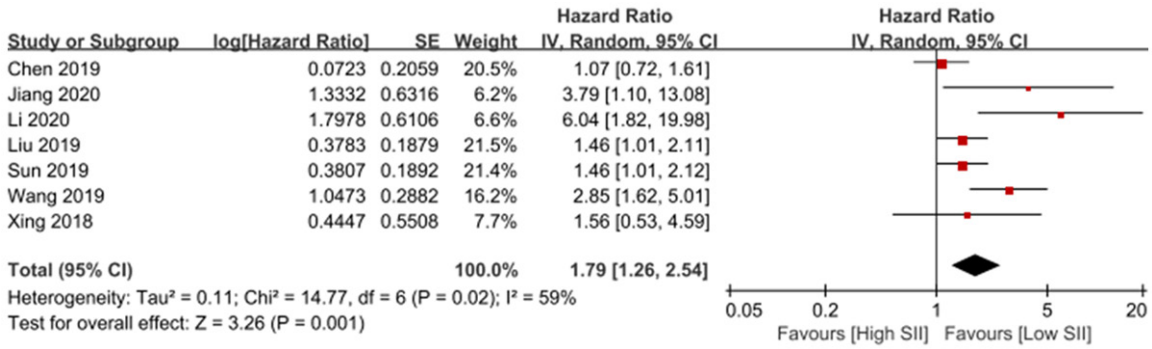


Figure 3. Forest plot of the correlation between SII and DFS in breast cancer patients.

Table 3. Subgroup analyses of SII for DFS

Subgroups	Independent Cohorts	Sample Size	HR (95% CI)	*P* value	Study heterogeneity			
					χ^2	df	I^2 (%)	P_h
Disease-free survival	7	1252	1.79 (1.26, 2.54)	0.001	14.77	6	59	0.02
Molecular subtype								
Triple-negative	2	375	1.78 (1.31, 2.43)	0.0002	3.78	1	74	0.05
HER2 positive	2	302	1.58 (1.11, 2.26)	0.01	2.09	1	52	0.15
Other	3	575	1.31 (0.91, 1.88)	0.14	7.28	2	73	0.03
Cut-off value								
<600	4	623	1.62 (1.26, 2.08)	0.0002	7.05	3	57	0.07
≥600	3	629	1.50 (1.10, 2.05)	0.01	7.58	2	74	0.02
Sample Size								
<200	5	775	1.61 (1.26, 2.06)	0.0001	7.06	4	43	0.13
≥200	2	477	1.49 (1.08, 2.08)	0.02	7.58	1	87	0.006
Follow-up (years)								
<10	4	675	2.96 (1.92, 4.55)	<0.00001	2.89	3	0	0.41
≥10	3	577	1.33 (1.07, 1.66)	0.010	1.57	2	0	0.46

results showed that higher SII was markedly associated with shorter DFS in triple-negative and HER2+ breast cancer, and also predicted worse DFS regardless of the SII cut-off value, sample size and follow-up time. Stronger predictive ability of SII was presented in the subgroup of follow-up time <10 years (**Table 3**).

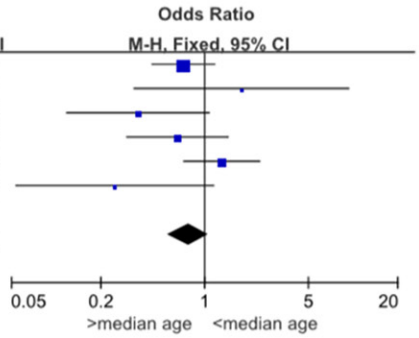
SII and clinicopathological characteristics

In this study, we investigated the association between higher pretreatment SII and clinicopathological characteristics. Total 10 variables of this meta-analysis were included, such as age, the stages of T, N and AJCC stage, histology grade, surgery, menstrual status, ER, PR, and HER2 status. The results indicated that higher pretreatment SII had a stronger correlation with T stage (T2-4 vs. T1; OR=1.91, 95% CI: 1.33-2.75, P=0.0005), menstrual status (pre-menstrual vs. post-menstrual; OR=1.90, 95% CI: 1.29-2.82, P=0.001), and ER status (ER+ vs. ER-; OR=0.58, 95% CI: 0.38-0.88, P=0.01). However, there was no obvious association between SII and age (>median vs. <median; OR=0.77, 95% CI: 0.57-1.05, P=0.10), N stage (N1-3 vs. N0; OR=1.38, 95% CI: 0.90-2.13, P=0.14), AJCC stage (II-III vs. 0-I; OR=0.44, 95% CI: 0.15-1.28, P=0.13), histology grade (III vs. I-II; OR=2.23, 95% CI: 0.82-6.06, P=0.12), surgery (breast-conserving vs. non-breast-conserving; OR=0.72, 95% CI: 0.46-1.14, P=0.16), PR status (PR+ vs. PR-; OR=1.04, 95% CI: 0.69-1.56, P=0.85) and HER2 status (HER2+ vs. HER2-; OR=1.45, 95% CI: 0.94-2.22, P=0.09). The details of the relationship between higher pretreatment SII and these clinicopathologic characteristics were shown in **Figure 4** and **Table 4**.

A

Study or Subgroup	>median age Events	Total	<median age Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen 2019	45	124	61	138	40.2%	0.72 [0.44, 1.18]
Jiang 2020	58	140	2	7	2.4%	1.77 [0.33, 9.43]
Li 2020	92	120	37	41	14.1%	0.36 [0.12, 1.08]
Sun 2019	59	124	18	31	16.5%	0.66 [0.30, 1.45]
Wang 2019	33	60	75	155	20.6%	1.30 [0.72, 2.37]
Xing 2018	36	145	4	7	6.3%	0.25 [0.05, 1.16]
Total (95% CI)		**713**		**379**	**100.0%**	**0.77 [0.57, 1.05]**
Total events	323		197			

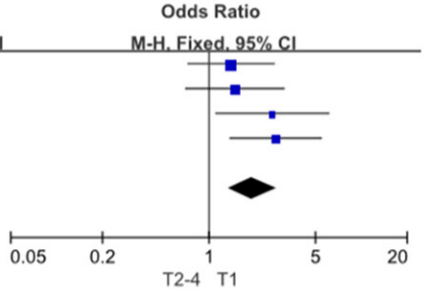
Heterogeneity: Chi² = 8.07, df = 5 (P = 0.15); I² = 38%
Test for overall effect: Z = 1.62 (P = 0.10)



B

Study or Subgroup	T2-4 Events	Total	T1 Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen 2019	90	215	16	47	35.2%	1.40 [0.72, 2.70]
Jiang 2020	46	106	14	41	26.4%	1.48 [0.70, 3.13]
Sun 2019	68	126	9	29	15.5%	2.61 [1.10, 6.16]
Wang 2019	94	170	14	45	22.8%	2.74 [1.36, 5.51]
Total (95% CI)		**617**		**162**	**100.0%**	**1.91 [1.33, 2.75]**
Total events	298		53			

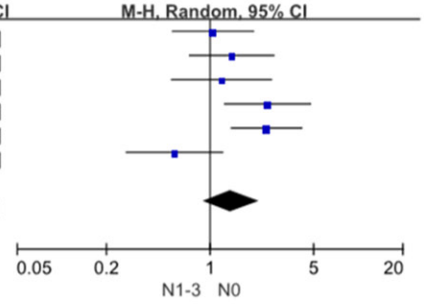
Heterogeneity: Chi² = 2.83, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 3.48 (P = 0.0005)



C

Study or Subgroup	N1-3 Events	Total	N0 Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen 2019	87	214	19	48	17.5%	1.05 [0.55, 1.98]
Jiang 2020	36	81	24	66	16.9%	1.40 [0.72, 2.73]
Li 2020	58	71	71	90	14.6%	1.19 [0.54, 2.62]
Sun 2019	57	99	20	56	16.7%	2.44 [1.24, 4.81]
Wang 2019	75	127	33	88	19.2%	2.40 [1.38, 4.20]
Xing 2018	13	64	27	88	15.1%	0.58 [0.27, 1.23]
Total (95% CI)		**656**		**436**	**100.0%**	**1.38 [0.90, 2.13]**
Total events	326		194			

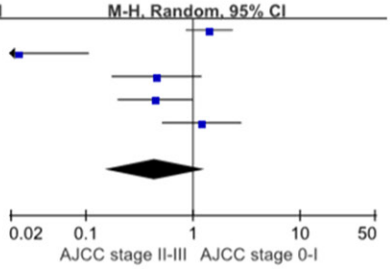
Heterogeneity: Tau² = 0.17; Chi² = 12.37, df = 5 (P = 0.03); I² = 60%
Test for overall effect: Z = 1.47 (P = 0.14)



D

Study or Subgroup	AJCC stage II-III Events	Total	AJCC stage 0-I Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen 2019	68	155	38	107	22.6%	1.42 [0.85, 2.36]
Li 2020	30	135	24	26	16.1%	0.02 [0.01, 0.11]
Sun 2019	7	21	70	134	19.8%	0.46 [0.17, 1.20]
Wang 2019	10	30	98	185	20.9%	0.44 [0.20, 1.00]
Xing 2018	31	114	9	38	20.6%	1.20 [0.51, 2.83]
Total (95% CI)		**455**		**490**	**100.0%**	**0.44 [0.15, 1.28]**
Total events	146		239			

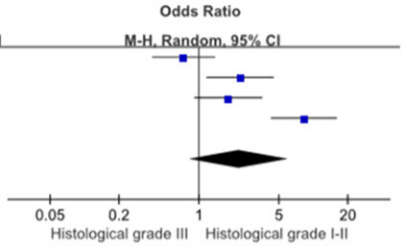
Heterogeneity: Tau² = 1.23; Chi² = 31.34, df = 4 (P < 0.00001); I² = 87%
Test for overall effect: Z = 1.50 (P = 0.13)



E

Study or Subgroup	Histological grade III Events	Total	Histological grade I-II Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen 2019	18	52	88	210	25.3%	0.73 [0.39, 1.38]
Jiang 2020	39	78	21	69	24.9%	2.29 [1.16, 4.50]
Sun 2019	30	52	40	93	24.8%	1.81 [0.91, 3.59]
Wang 2019	62	77	46	138	25.0%	8.27 [4.25, 16.09]
Total (95% CI)		**259**		**510**	**100.0%**	**2.23 [0.82, 6.06]**
Total events	149		195			

Heterogeneity: Tau² = 0.92; Chi² = 27.06, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.57 (P = 0.12)



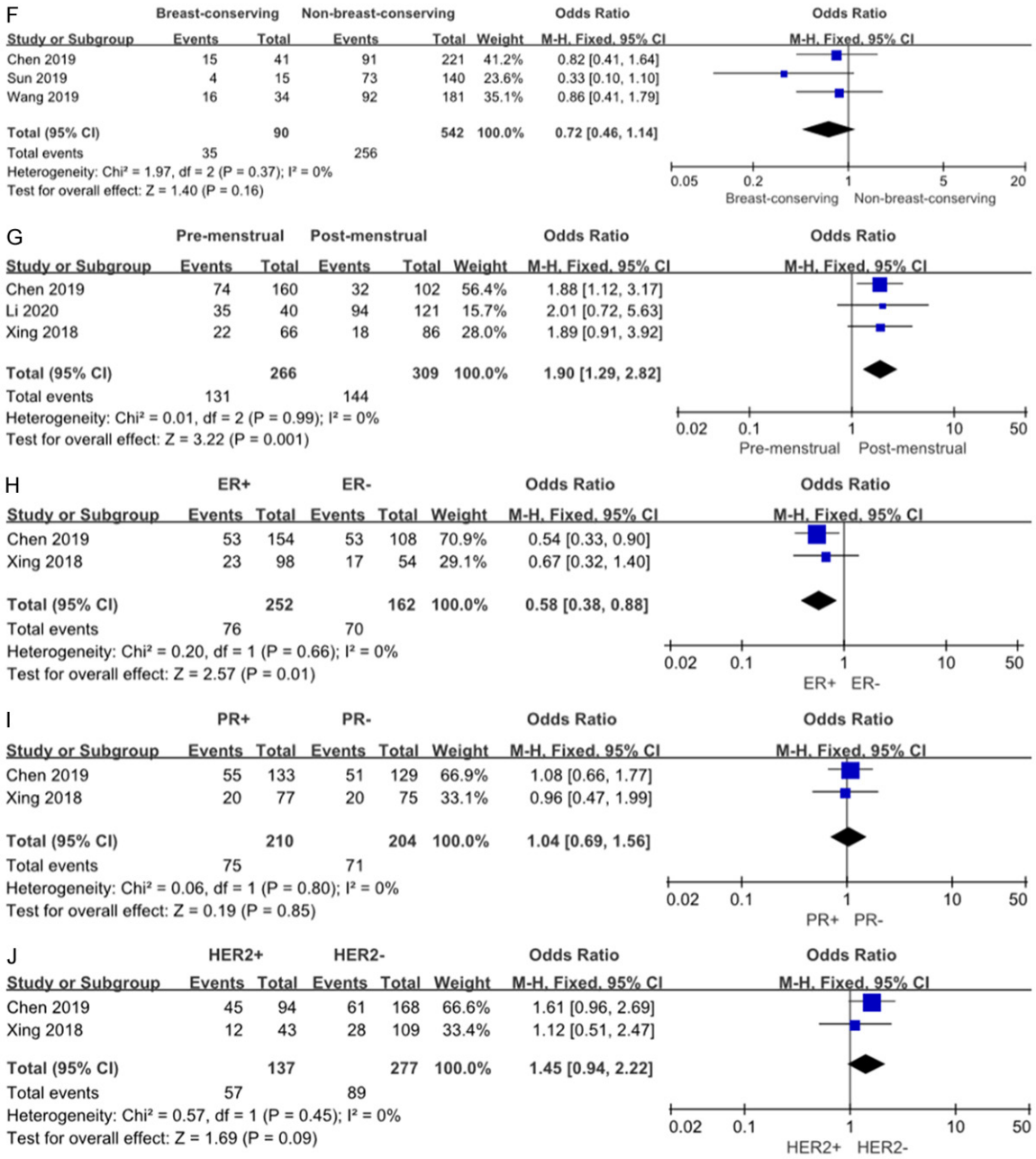


Figure 4. Forest plots of the association between SII and clinicopathological features of breast cancer. A. Age; B. T stage; C. N stage; D. AJCC stage; E. Histological grade; F. Surgery; G. Menstrual status; H. ER status; I. PR status; J. HER2 status.

Sensitivity analyses

Due to the considerable heterogeneity among the selected studies, sensitivity analyses were further performed to figure out the effect of individual studies on the overall conclusion. The stability of the pooled HRs of OS and DFS was tested by alternately removing enrolled studies. Interestingly, the results demonstrated that no obvious alterations appeared after getting rid of the selected studies in turn, thereby confirming the stability of our conclusion (**Figure 5**).

Publication bias

The funnel plots of studies included in this meta-analysis indicated no significant publica-

Table 4. Meta-analysis of the association between SII and clinicopathological features of breast cancer

Characteristics	Independent Cohorts	Sample Size	OR (95% CI)	*P* value	Heterogeneity	
					I^2 (%)	P_h
Age (>median vs. <median)	6	1092	0.77 (0.57, 1.05)	0.10	38	0.15
T stage (T2-4 vs. T1)	4	779	1.91 (1.33, 2.75)	0.0005	0	0.42
N stage (N1-3 vs. N0)	6	1092	1.38 (0.90, 2.13)	0.14	60	0.03
AJCC Stage (II-III vs. 0-I)	5	945	0.44 (0.15, 1.28)	0.13	87	<0.00001
Histology grade (III vs. I-II)	4	769	2.23 (0.82, 6.06)	0.12	89	<0.00001
Surgery (Breast-conserving vs. Non-breast-conserving)	3	632	0.72 (0.46, 1.14)	0.16	0	0.37
Menstrual status (Pre-menstrual vs. Post-menstrual)	3	575	1.90 (1.29, 2.82)	0.001	0	0.99
ER (ER+ vs. ER-)	2	414	0.58 (0.38, 0.88)	0.01	0	0.66
PR (PR+ vs. PR-)	2	414	1.04 (0.69, 1.56)	0.85	0	0.8
HER2 (HER2+ vs. HER2-)	2	414	1.45 (0.94, 2.22)	0.09	0	0.45

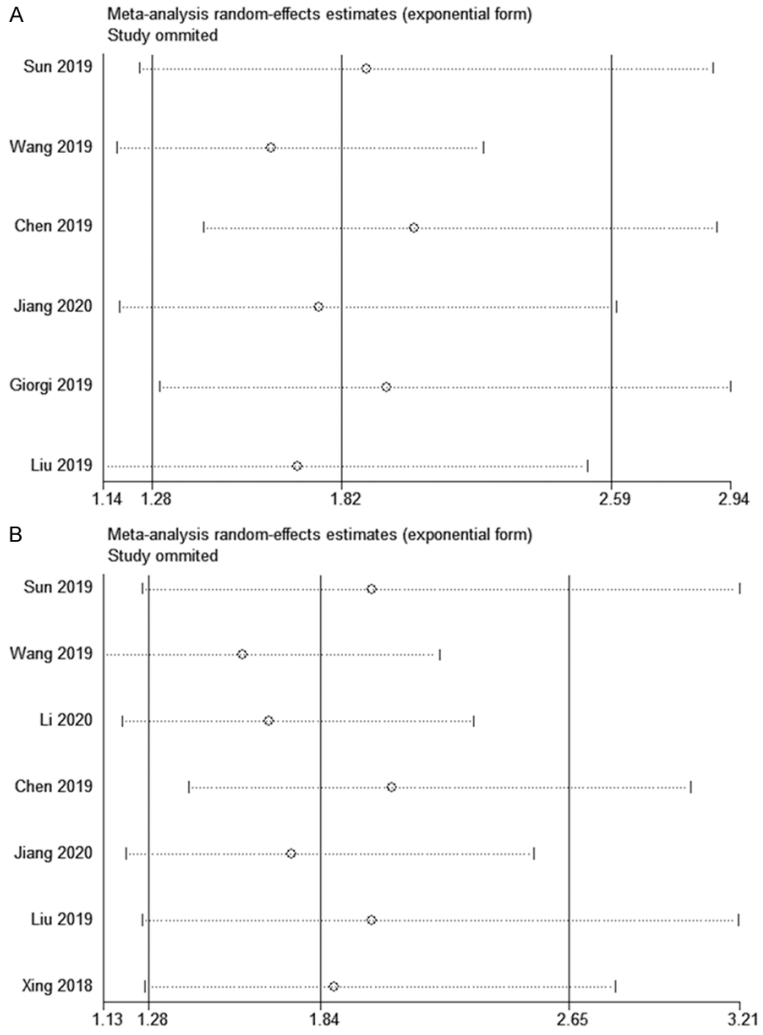


Figure 5. Sensitivity analyses. A. Sensitivity analysis of OS for SII; B. Sensitivity analysis of DFS for SII.

tion bias in the enrolled studies, as demonstrated by the distribution of studies around the centerline symmetrically in **Figure 6**. Additionally, Egger and Begg tests also confirmed no great publication bias in terms of OS and DFS (**Figures 6**, **7**, **Table 5**).

Discussion

Rudolf Virchow, a German medical scientist, initially proposed the relationship between the inflammatory response and the progression of cancers in 1960s. Systemic inflammation boosts the development of tumors at almost every step, such as initiation, progression, and metastasis [21-23]. Severe inflammatory response is one of the factors that lead to the worse prognosis of tumors [24]. Consequently, the immune-inflammatory response in tumor microenvironment plays a vital role in the proliferation and invasion of tumor cells and may be a significant cause of breast tumor metastasis [25-27].

To our knowledge, the current study should be the first meta-analysis to explore the clinicopathological and prognostic significance of SII in breast cancer patients. This present meta-analysis revealed a significant correlation between the higher pretreatment SII with the worse survival of breast cancer patients. Meanwhile, increased pre-

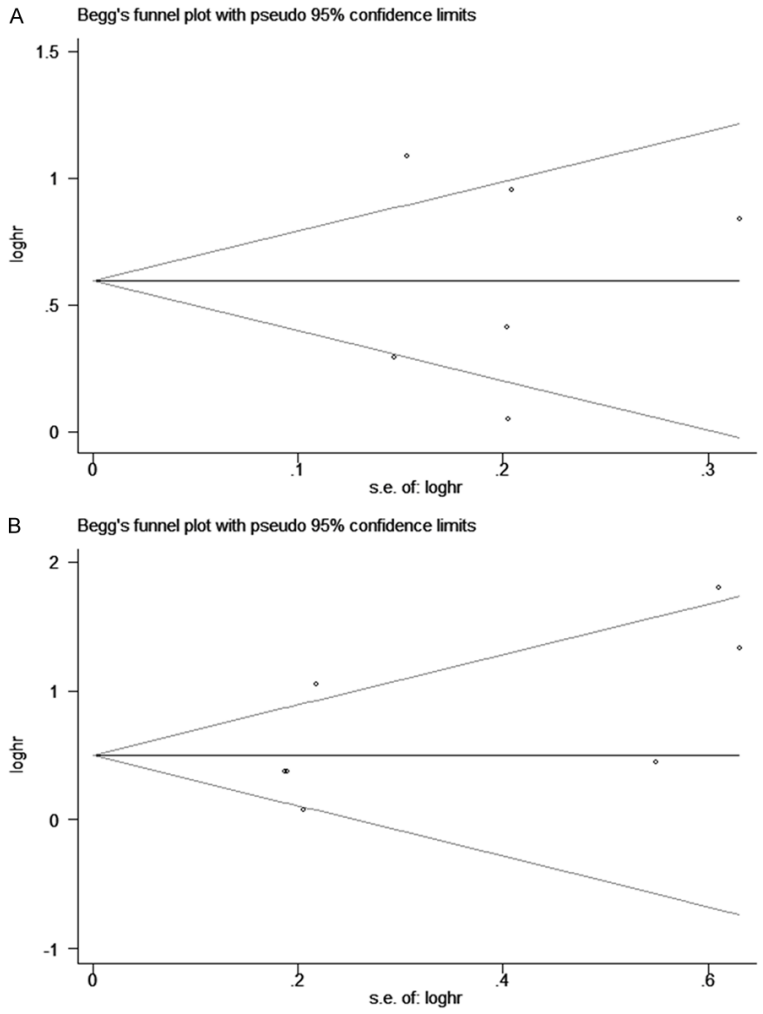


Figure 6. Begg's funnel plots. A. Begg's funnel plot of OS for SII; B. Begg's funnel plot of DFS for SII.

treatment SII also had a stronger correlation with clinicopathological characteristics, such as T stage (T2-4), menstrual (Pre-menstrual) and ER status (ER+). Since SII is calculated according to the formula: neutrophils count × platelets/lymphocytes count, a reasonable explanation for the underlying mechanism therefore tended to be that higher SII represents a higher count of neutrophils and platelets, as well as a lower count of lymphocytes.

Neutrophils play a crucial role in the host immune response, which suppress the immune system by inhibiting T-cell response, thereby leading to tumor progression and metastasis [28]. Likewise, neutrophils are the main sources of circulating chemokines (e.g. transforming growth factor-β, hepatocyte growth factor, and IL-8), which are engaged in various stages of tumor development [29, 30]. The occurrence and progress of malignancies are often accompanied by increased platelets, which in turn interact directly with circulating tumor cells, facilitate the exosmosis of the tumor cells to the metastasis site, and mediate the metastasis of the malignant tumors [31]. Moreover, the interplay of activated platelets with cancer cells in the tumor microenvironment via paracrine pathway often promotes the growth and survival of tumor cells [32]. Lymphocytes are responsible for immune surveillance, while tumor-infiltrating lymphocytes are primarily involved in the local immune response of tumors with the phenotypic characteristics of $CD8^+$ and $CD4^+$, therefore, lower count of tumor-infiltrating lymphocytes may reflect the weak immune response and lead to tumor progression [33]. Furthermore, circulating lymphocytes can also secrete cytokines, which in turn inhibit the proliferation and metastasis of tumor cells through their cytotoxic effects [34].

Though our efforts of a comprehensive analysis were made, there were still some limitations in terms of our findings. First, most of the included studies were conducted in China and USA; therefore, more prospective studies including other populations around the world are needed. Second, further studies are also required to incorporate more different types of molecular subtype of breast cancer. Similarly, the determination of uniform cut-off values of SII may significantly advance the final consensus. Finally, all included studies were retrospective, which are more susceptible to some degrees biases, thus, international multi-center studies with larger sample sizes are required to further verify our findings in the future.

In conclusion, increased SII before treatment may be an important biomarker for poor prog-

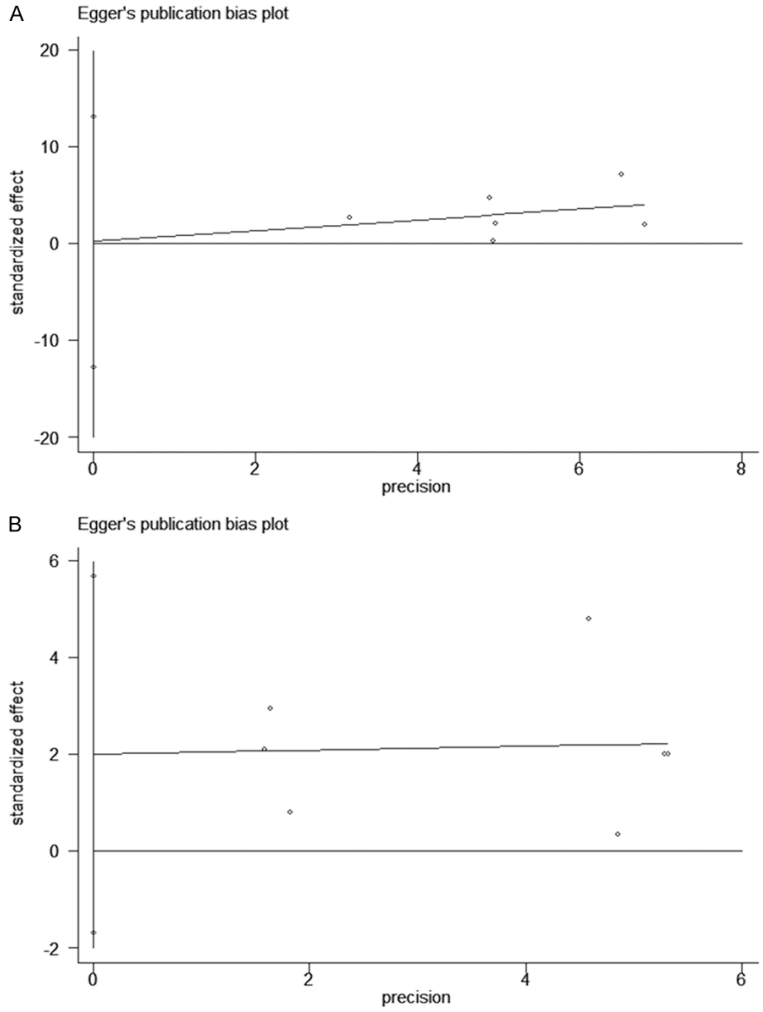


Figure 7. Egger's publication bias plots. A. Egger's publication bias plot of OS for SII; B. Egger's publication bias plot of DFS for SII.

Table 5. Assessment for publication bias

	Number of studies	Z value	P for Begg test	t	P for Egger test
SII for OS	6	0.0	1.00	0.04	0.968
SII for DFS	7	1.2	0.23	1.40	0.220

nosis in breast cancer patients. With the features of non-invasive and low-cost, SII can be considered a useful biomarker in the management of breast cancer. Considering the limitations of the conclusion in current study, more prospective and well-designed studies are required to determine the SII cut-off value, to investigate what effect of SII dynamic alterations has on breast cancer treatment, as well as whether the survival of patients can be extended by therapeutically altering the counts of neutrophils, platelets, and lymphocytes (required for SII calculation).

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Disclosure of conflict of interest

None.

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tion and promotes metastasis. Cancer Cell 2011; 20: 576-590.
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Appendix 1

Retrieval Strategies

Pubmed (21)

1. "Breast Neoplasms"[Mesh]
2. Breast Neoplasm[Title/Abstract]
3. Neoplasm, Breast[Title/Abstract]
4. Neoplasms, Breast[Title/Abstract]
5. Tumors, Breast [Title/Abstract]
6. Breast Tumors[Title/Abstract]
7. Breast Tumor[Title/Abstract]
8. Tumor, Breast[Title/Abstract]
9. Mammary Neoplasms, Human[Title/Abstract]
10. Human Mammary Neoplasm[Title/Abstract]
11. Human Mammary Neoplasms[Title/Abstract]
12. Neoplasm, Human Mammary[Title/Abstract]
13. Neoplasms, Human Mammary[Title/Abstract]
14. Mammary Neoplasm, Human[Title/Abstract]
15. Mammary Carcinoma, Human[Title/Abstract]
16. Carcinoma, Human Mammary[Title/Abstract]
17. Carcinomas, Human Mammary[Title/Abstract]
18. Human Mammary Carcinomas[Title/Abstract]
19. Mammary Carcinomas, Human[Title/Abstract]
20. Human Mammary Carcinoma[Title/Abstract]
21. Breast Cancer[Title/Abstract]
22. Cancer, Breast[Title/Abstract]
23. Cancer of Breast[Title/Abstract]
24. Mammary Cancer[Title/Abstract]
25. Malignant Neoplasm of Breast[Title/Abstract]
26. Malignant Tumor of Breast[Title/Abstract]
27. Breast Carcinoma[Title/Abstract]
28. Cancer of the Breast[Title/Abstract]
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. "systemic immune inflammation index"[Mesh]
31. systemic immune inflammation index[Title/Abstract]
32. SII[Title/Abstract]
33. 30 or 31 or 32
34. 29 and 45

(("Breast Neoplasms"[Mesh]) OR ((((((((((((((((((((((((((Breast Neoplasm[Title/Abstract]) OR Neoplasm, Breast[Title/Abstract]) OR Neoplasms, Breast[Title/Abstract]) OR Tumors, Breast[Title/Abstract]) OR Breast Tumors[Title/Abstract]) OR Breast Tumor[Title/Abstract]) OR Tumor, Breast[Title/Abstract]) OR Mammary Neoplasms, Human[Title/Abstract]) OR Human Mammary Neoplasm[Title/Abstract]) OR Human Mammary Neoplasms[Title/Abstract]) OR Neoplasm, Human Mammary[Title/Abstract]) OR Neoplasms, Human Mammary[Title/Abstract]) OR Mammary Neoplasm, Human[Title/Abstract]) OR Mammary Carcinoma, Human[Title/Abstract]) OR Carcinoma, Human Mammary[Title/Abstract]) OR Carcinomas, Human Mammary[Title/Abstract]) OR Human Mammary Carcinomas[Title/Abstract]) OR Mammary Carcinomas, Human[Title/Abstract]) OR Human Mammary Carcinoma[Title/Abstract]) OR Breast Cancer[Title/Abstract]) OR Cancer, Breast[Title/Abstract]) OR Cancer of Breast[Title/Abstract]) OR Mammary Cancer[Title/Abstract]) OR Malignant Neoplasm of Breast[Title/Abstract]) OR Malignant Tumor of Breast[Title/Abstract]) OR Breast Carcinoma[Title/Abstract]) OR Cancer of the Breast[Title/Abstract])))) AND (("systemic immune inflammation index"[Mesh]) OR ((systemic immune inflammation index[Title/Abstract]) OR SII[Title/Abstract]))

Web of Science [43]

TS=(Breast Neoplasm OR Neoplasm, Breast OR Breast Tumors OR Breast Tumor OR Tumor, Breast OR Tumors, Breast OR Neoplasms, Breast OR Breast Cancer OR Cancer, Breast OR Mammary Cancer OR Cancer, Mammary OR Cancers, Mammary OR Mammary Cancers OR Malignant Neoplasm of Breast OR Breast Malignant Neoplasm OR Breast Malignant Neoplasms OR Malignant Tumor of Breast OR Breast Malignant Tumor OR Breast Malignant Tumors OR Cancer of Breast OR Cancer of the Breast OR Mammary Carcinoma, Human OR Carcinoma, Human Mammary OR Carcinomas, Human Mammary OR Human Mammary Carcinomas OR Mammary Carcinomas, Human OR Human Mammary Carcinoma OR Mammary Neoplasms, Human OR Human Mammary Neoplasm OR Human Mammary Neoplasms OR Neoplasm, Human Mammary OR Neoplasms, Human Mammary OR Mammary Neoplasm, Human OR Breast Carcinoma OR Breast Carcinomas OR Carcinoma, Breast OR Carcinomas, Breast)AND TS=(systemic immune inflammation index OR SII)

Embase (26)

1. 'breast tumor'/exp
2. 'Breast Neoplasms':ab,ti
3. 'Breast Neoplasm':ab,ti
4. 'Neoplasm, Breast':ab,ti
5. ' Neoplasms, Breast':ab,ti
6. 'Tumors, Breast':ab,ti
7. 'Breast Tumors':ab,ti
8. 'Breast Tumor':ab,ti
9. 'Tumor, Breast':ab,ti
10. 'Mammary Neoplasms, Human':ab,ti
11. 'Human Mammary Neoplasm':ab,ti
12. 'Human Mammary Neoplasms':ab,ti
13. 'Neoplasm, Human Mammary':ab,ti
14. 'Neoplasms, Human Mammary':ab,ti
15. 'Mammary Neoplasm, Human':ab,ti
16. 'Mammary Carcinoma, Human':ab,ti
17. 'Carcinoma, Human Mammary':ab,ti
18. 'Carcinomas, Human Mammary':ab,ti
19. 'Human Mammary Carcinomas':ab,ti
20. 'Mammary Carcinomas, Human':ab,ti
21. 'Breast Cancer':ab,ti
22. 'Cancer, Breast':ab,ti
23. 'Cancer of Breast':ab,ti
24. 'Human Mammary Carcinoma':ab,ti
25. 'Mammary Cancer':ab,ti
26. 'Malignant Neoplasm of Breast':ab,ti
27. 'Cancer of the Breast':ab,ti
28. 'Breast Carcinoma':ab,ti
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 'systemic immune inflammation index'/exp
31. 'systemic immune inflammation index':ab,ti
32. 'SII':ab,ti
33. 30 or 31 or 32
34. 29 and 33

('breast neoplasm':ab,ti OR 'neoplasm, breast':ab,ti OR 'breast tumors':ab,ti OR 'breast tumor':ab,ti OR 'tumor, breast':ab,ti OR 'tumors, breast':ab,ti OR 'neoplasms, breast':ab,ti OR 'breast cancer':ab,ti OR 'cancer, breast':ab,ti OR 'mammary cancer':ab,ti OR 'cancer, mammary':ab,ti OR 'cancers, mammary':ab,ti OR 'mammary cancers':ab,ti OR 'malignant neoplasm of breast':ab,ti OR 'breast malignant neoplasm':ab,ti

OR 'breast malignant neoplasms':ab,ti OR 'malignant tumor of breast':ab,ti OR 'breast malignant tumor':ab,ti OR 'breast malignant tumors':ab,ti OR 'cancer of breast':ab,ti OR 'cancer of the breast':ab,ti OR 'mammary carcinoma, human':ab,ti OR 'carcinoma, human mammary':ab,ti OR 'carcinomas, human mammary':ab,ti OR 'human mammary carcinomas':ab,ti OR 'mammary carcinomas, human':ab,ti OR 'human mammary carcinoma':ab,ti OR 'mammary neoplasms, human':ab,ti OR 'human mammary neoplasm':ab,ti OR 'human mammary neoplasms':ab,ti OR 'neoplasm, human mammary':ab,ti OR 'neoplasms, human mammary':ab,ti OR 'mammary neoplasm, human':ab,ti OR 'breast carcinoma':ab,ti OR 'breast carcinomas':ab,ti OR 'carcinoma, breast':ab,ti OR 'carcinomas, breast':ab,ti) AND ('systemic immune inflammation index':ab,ti OR sii:ab,ti)

The Cochrane Library [0]

1. MeSH descriptor: [Breast Neoplasms]
2. Breast Neoplasm:ti,ab,kw
3. Neoplasm, Breast:ti,ab,kw
4. Neoplasms, Breast:ti,ab,kw
5. Tumors, Breast:ti,ab,kw
6. Breast Tumors:ti,ab,kw
7. Breast Tumor:ti,ab,kw
8. Tumor, Breast:ti,ab,kw
9. Mammary Neoplasms, Human:ti,ab,kw
10. Human Mammary Neoplasm:ti,ab,kw
11. Human Mammary Neoplasms:ti,ab,kw
12. Neoplasm, Human Mammary:ti,ab,kw
13. Neoplasms, Human Mammary:ti,ab,kw
14. Mammary Neoplasm, Human:ti,ab,kw
15. Mammary Carcinoma, Human:ti,ab,kw
16. Carcinoma, Human Mammary:ti,ab,kw
17. Carcinomas, Human Mammary:ti,ab,kw
18. Human Mammary Carcinomas:ti,ab,kw
19. Mammary Carcinomas, Human:ti,ab,kw
20. Human Mammary Carcinoma:ti,ab,kw
21. Breast Cancer:ti,ab,kw
22. Cancer, Breast:ti,ab,kw
23. Cancer of Breast:ti,ab,kw
24. Mammary Cancer:ti,ab,kw
25. Malignant Neoplasm of Breast:ti,ab,kw
26. Malignant Tumor of Breast:ti,ab,kw
27. Breast Carcinoma:ti,ab,kw
28. Cancer of the Breast:ti,ab,kw
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. MeSH descriptor: [systemic immune inflammation index]
31. systemic immune inflammation index:ti,ab,kw
32. SII:ti,ab,kw
33. 30 or 31 or 32
34. 29 and 33

Appendix 2

Newcastle-Ottawa quality assessment scale

1. Sun 2019 (8 socres)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * 1 score
b) yes, eg record linkage or based on self reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls * 1 score
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) * 1 score
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for tumor grade, ER status PR status and HER-2 status (Select the most important factor.) * 1 score
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.) 1 score

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) * 1 score
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description

2) Same method of ascertainment for cases and controls
a) yes * 1 score
b) no

3) Non-Response rate
a) same rate for both groups * 1 score
b) non respondents described
c) rate different and no designation

2. Wang 2019 (7 scores)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * 1 score
b) yes, eg record linkage or based on self reports

c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls * 1 score
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) * 1 score
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for tumor grade, ER status PR status and HER-2 status (Select the most important factor.) * 1 score
b) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) * 1 score
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description

2) Same method of ascertainment for cases and controls
a) yes * 1 score
b) no

3) Non-Response rate
a) same rate for both groups * 1 score
b) non respondents described
c) rate different and no designation

3. Li 2020 (7 scores)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * 1 score
b) yes, eg record linkage or based on self reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls * 1 score

b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) * 1 score
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for tumor grade, ER status PR status and HER-2 status (Select the most important factor.) * 1 score
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) * 1 score
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description

2) Same method of ascertainment for cases and controls
a) yes * 1 score
b) no

3) Non-Response rate
a) same rate for both groups * 1 score
b) non respondents described
c) rate different and no designation

4. Chen 2019 (8 scores)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * 1 score
b) yes, eg record linkage or based on self reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls * 1 score
b) hospital controls
c) no description

4) Definition of Controls

a) no history of disease (endpoint) * 1 score
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for tumor grade, ER status PR status and HER-2 status (Select the most important factor.) * 1 score
b) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.) 1 score

Exposure

Ascertainment of exposure

1) secure record (eg surgical records) * 1 score
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description

2) Same method of ascertainment for cases and controls
a) yes * 1 score
b) no

3) Non-Response rate
a) same rate for both groups * 1 score
b) non respondents described
c) rate different and no designation

5. Jiang 2020 (8 scores)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * 1 score
b) yes, eg record linkage or based on self reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls * 1 score
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) * 1 score
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for tumor grade, ER status PR status and HER-2 status (Select the most important factor.) * 1 score
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.) 1 score

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) * 1 score
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description

2) Same method of ascertainment for cases and controls
a) yes * 1 score
b) no

3) Non-Response rate
a) same rate for both groups * 1 score
b) non respondents described
c) rate different and no designation

6. Giorgi 2019 (7 scores)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * 1 score
b) yes, eg record linkage or based on self reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls * 1 score
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) * 1 score
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for tumor grade, ER status PR status and HER-2 status (Select the most important factor.) * 1 score
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) * 1 score
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description

2) Same method of ascertainment for cases and controls
a) yes * 1 score
b) no

3) Non-Response rate
a) same rate for both groups * 1 score
b) non respondents described
c) rate different and no designation

7. Liu 2019 (7 scores)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * 1 score
b) yes, eg record linkage or based on self reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls * 1 score
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) * 1 score
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for tumor grade, ER status PR status and HER-2 status (Select the most important factor.) * 1 score
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) * 1 score
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description

2) Same method of ascertainment for cases and controls
a) yes * 1 score
b) no

3) Non-Response rate
a) same rate for both groups * 1 score
b) non respondents described
c) rate different and no designation

8. Xing 2018 (7 scores)

Selection

1) Is the case definition adequate?
a) yes, with independent validation * 1 score
b) yes, eg record linkage or based on self reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls * 1 score
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) * 1 score
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for tumor grade, ER status PR status and HER-2 status (Select the most important factor.) * 1 score
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Exposure

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2) Same method of ascertainment for cases and controls
a) yes * 1 score
b) no

3) Non-Response rate
a) same rate for both groups * 1 score
b) non respondents described
c) rate different and no designation