Association of Clinical Parameters and Prognosis with the Pretreatment Systemic Immune-inflammation Index (SII) in Patients with Gastric Cancer

Xihuang Cao[1], Jiaming Xue[2], Huiliang Yang[2], Xiao Han[2] and Guo Zu[2]

[1]*Department of Emergency Surgery, The Dalian Municipal Central Hospital, China*
[2]*Department of General Surgery, The Dalian Municipal Central Hospital, China*

ABSTRACT

This study explored the relationship between the pretreatment systemic immune-inflammation index (SII) and overall survival (OS) in gastric cancer (GC) patients. A systemic literature search was performed to find out the articles that estimated the relationship of SII with specific clinical parameters and OS in GC patients. Nine articles (including 10 studies) were included. A total of 3,850 cases were eventually included. In GC patients, there was no association between pretreatment SII and gender (OR=0.991, p=0.944) or differentiation (OR=1.093, p=0.687). However, pretreatment SII was related to depth of tumor invasion (OR=0.340, p <0.001), lymph node metastasis (OR=0.447, p <0.001) and TNM stage (OR=0.361, p <0.001) in GC patients. The ORs of 1-year, 3-year and 5-year OS were 0.467 (I^2=0.0%; p=0.682), 0.355 (I^2=85.6%; p <0.001) and 0.507 (I^2=56.4%; p=0.057). The pretreatment SII could be used as an indicator of the depth of tumor invasion, lymph node metastasis, TNM stage and overall of gastric cancer patients. However, more multi-centres researches are needed to confirm these findings.

Key Words: *Systemic immune-inflammation index (SII), Prognosis, Gastric cancer.*

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INTRODUCTION

As one of the most common digestive tract cancers, gastric cancer (GC) is still one of the leading causes of cancer-associated mortality worldwide.[1] Although prognosis of GC patients has improved during the past decades, radical gastrectomy is still the most important treatment for GC, and the survival rate is still much less than 30%.[2] Recurrence and metastasis occur in 35-70% of GC patients within 5 years and are the most important poor prognostic factors, even after radical resection.[3] Therefore, there is a strong need to find out new markers and to predict the overall survival (OS) of GC patients.

Several studies have shown that inflammatory factors and cells are involved in the tumor microenvironment.[4,5] In recent years, clinical studies have confirmed that the immune and inflammatory cells play important roles in the progression, invasion and metastasis of several tumors.[6-8] Some inflammatory biomarkers, such as the lymphocyte-to-monocyte ratio (LMR), are used to predict the OS, tumor recurrence and metastasis of cancers, including GC.[9,10]

Correspondence to: Dr. Guo Zu, Department of General Surgery, The Dalian Municipal Central Hospital, China
E-mail: zushanghai@163.com

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Recently, a novel index named SII (SII = neutrophil × platelet / lymphocyte), which is based on systemic immune-inflammation index, has become a better marker to reflect the inflammation and immune status of host; it has been used as a prognostic index in bladder cancer, colorectal cancer and lung cancer.[11-13] However, it has not reached a consensus between the pretreatment SII and OS of several tumor patients, including GC patients. Chen *et al*. reported that a low pretreatment SII was significantly related to gender, lymph node stage, and tumor size.[14] Wang *et al*. reported that pretreatment SII was related to age, Borrmann type, lymph node and distant metastasis, high CEA levels, TNM stage, tumor size, and tumor invasion.[15] Therefore, the present meta-analysis was performed to check the relationship of clinical parameters and prognostic values of GC patients to the pretreatment SII.

METHODOLOGY

The studies about pretreatment SII and GC were searched in the databases of Cochrane Library, PubMed, Springer, EMBASE, Elesevier, Web of Science, and Chinese databases (including CNKI, Wanfang and VIP). The time of literature retrieval was until Dec 15, 2019. The key words were used as stomach, gastric, tumor, cancer, carcinoma, neoplasm and systemic immune-inflammation index or SII.

The inclusion criteria of the relevant studies were: articles including data on the pretreatment SII, clinical parameters and OS of GC patients; the data of neutrophil, platelet and lympho-

cyte must be included and measured before treatment, such as chemoradiotherapy, surgery or targeted therapy; and the articles were estimated by Newcastle-Ottawa Quality Assessment Scale (NOS) score >6. The exclusion criteria for the article were: lack of data on clinical parameters or OS and articles; duplicated data; patients with infection, hematological or autoimmune diseases; and those patients who took medicine that could influence the neutrophil, platelet and lymphocyte counts.

The included articles in this study were independently completed by two authors (Xihuang Cao and Jiaming Xue). Two authors (Xihuang Cao and Jiaming Xue) extracted the needed data independently. Any disagreement was resolved by another author (Huiliang Yang). The following information extracted from the articles included: name of authors, journal, published year, country of the patients, gender, number of cases, depth of tumor invasion, TNM stage, lymph node metastasis, methods of treatment, period of follow-up, cut-off value of pretreatment SII, and OS of GC patents.

The quality evaluation of the eligible articles was independently done by two researchers (Xihuang Cao and Jiaming Xue) according to the NOS. Study with a score ≥6 was included in this study.

STATA 10.0 (Stata Corporation) software was used in this analysis. The relationship between pretreatment SII and OS of GC patients were evaluated by odds ratios (ORs) and 95% confidence intervals (CIs) with the fixed effects model. The heterogeneity analysis was checked by Higgins I^2 and Cochran's Q test. I^2>50% and/or p <0.10 were defined as significant heterogeneity. If I^2 >50% and/or p <0.10, the random effects model was used.

We used the Begg's test and Egger's test to estimate the publication bias, and p <0.05 was considered to significant statistical differences.

RESULTS

The literature review and flow diagram of this analysis are shown in Figure 1. Twenty-nine articles were retrieved from the database. After eliminating two duplicate studies and other 18 articles, including lack of clinical data and review, nine studies were included by reading the full-texts. One article included two validation cohorts; so finally, nine articles (including 10 studies) including 3,850 patients were included.[14-22]

The eligible 10 studies were published from 2015 to 2019. The included number of patients varied between 60 and 1,032. The studies were conducted in Korea (one study) and China (nine studies).[14-22] The cut-off values of pretreatment SII were checked from 320 to 888. The characteristics and results of the eligible studies were listed in Table I.

To analyse the relationship between pretreatment SII and clinical parameters and OS of GC patients, the correlation of pretreatment SII and parameters were assessed in more than three studies. As shown in Table II and Figure 2, there was no association between pretreatment SII and gender (OR=0.991, p=0.944) or differentiation (OR=1.093, p=0.687) in GC patients. However, pretreatment SII was related to depth of tumor invasion (OR=0.340, p <0.001), lymph node metastasis (OR=0.447, p <0.001) and TNM stage (OR=0.361, p <0.001).

As shown in Figure 3, the Begg's funnel plot was symmetric, and the Egger's test of gender, differentiation, T, N and TNM also showed p values of 0.599, 0.116, 0.112, 0.796 and 0.293, respectively. The publication bias was not significant.

Seven studies have estimated the relationship between pretreatment SII and the 1-year, 3-year and 5-year OS of GC patients. The results of eligible studies are shown in Table II and III. Patients with high pretreatment SII have higher relative risks of poor OS than patients with low pretreatment SII. The 1-year, 3-year and 5-year patients OS had OR of 0.467 (I^2= 0.0%; p =0.682), 0.355 (I^2=85.6%; p <0.001) and 0.507 (I^2=56.4%; p=0.057, Figure 4).

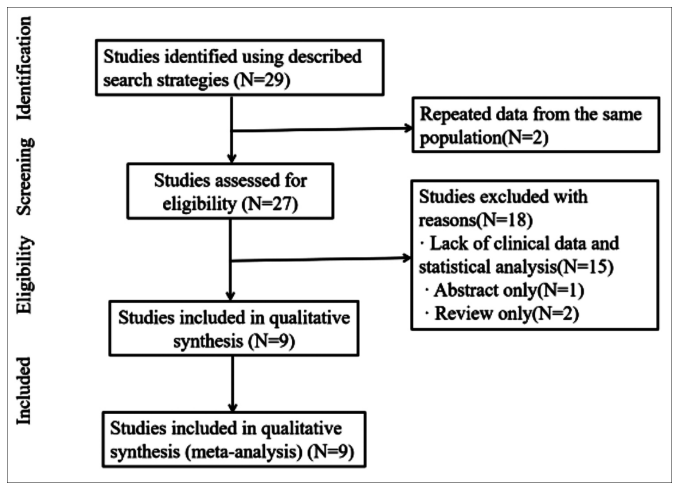

Figure 1: Flow diagram of the literature review.

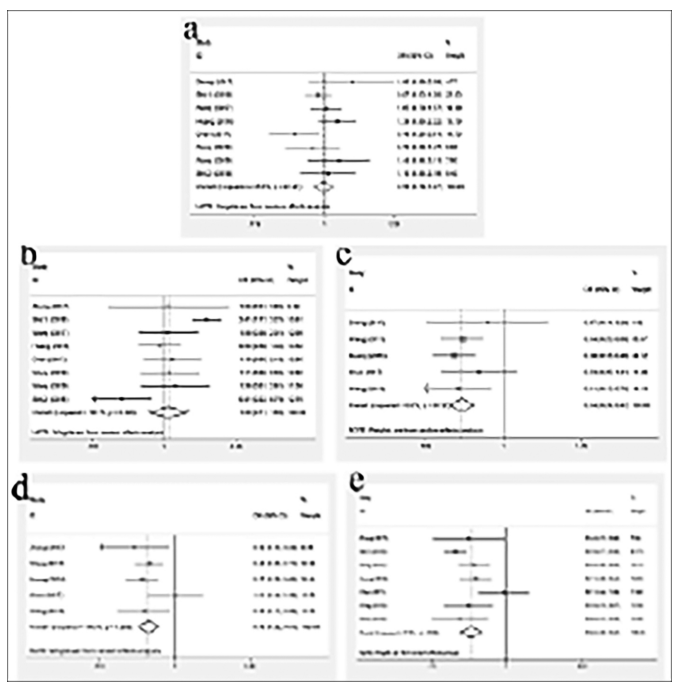

Figure 2: Forest plots showing the correlation between pretreatment SII and gender (a), differentiation (b), depth of invasion (c), lymph node metastasis (d), and TNM stage (e).

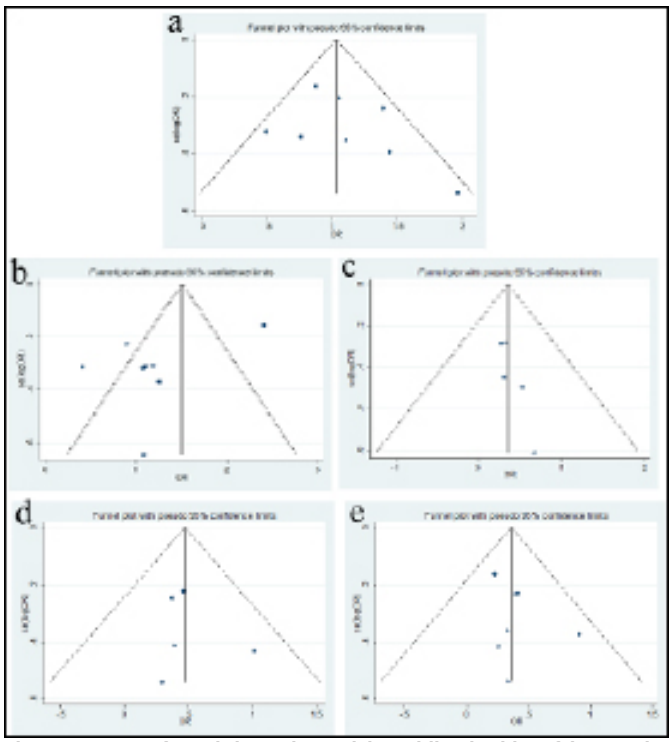

Figure 3: Egger's funnel plot estimated the publication bias of the correlation between pretreatment SII and gender (a), differentiation (b), depth of tumor invasion (c), lymph node metastasis (d), and TNM stage (e).

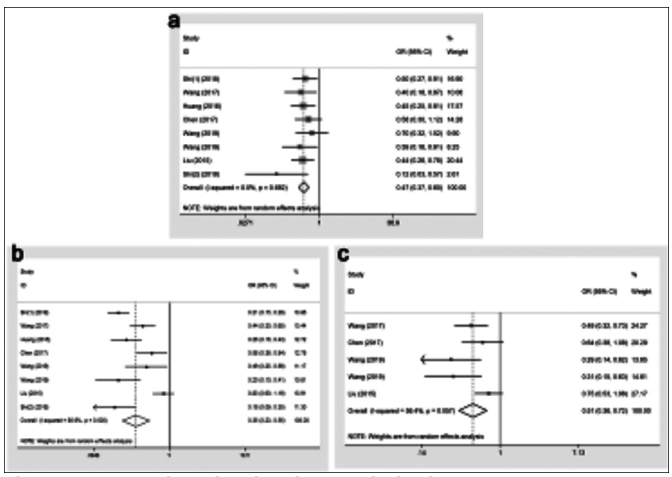

Figure 4: Forest plots showing the correlation between pretreatment SII and 1-year OS (a), 3-year OS (b), and 5-year OS (c).

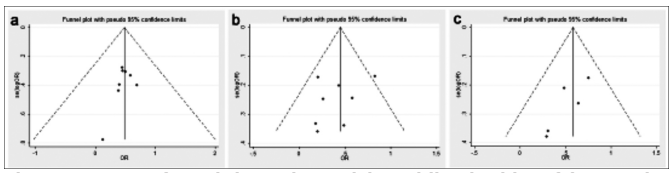

Figure 5: Egger's funnel plot estimated the publication bias of the correlation between pretreatment SII and 1-year OS (a), 3-year OS (b), and 5-year OS (c).

As shown in Figure 5, Begg's funnel plots of OS (1-year, 3-year and 5-year) were symmetric, and the Egger's test for the 1-year, 3-year and 5-year OS indicated no significant publication bias (p=0.102, 0.459 and 0.063, respectively).

DISCUSSION

It has been reported that cancer-related immunity and inflammation are essential components of the tumor microenvironment which is related to tumor development. Immunity and inflammation is associated with tumor progression.[23,24] As an immune and inflammation-related biomarker, pretreatment high SII is a poor prognostic factor of several tumors, including GC. In this study, the association between preoperative SII and clinical parameters, and OS of GC patients were confirmed. In GC patients, it was found that high pretreatment SII was related to depth of invasion, lymph node metastasis and TNM stage; and a high pretreatment SII was associated with poorer OS of GC patients.

In GC, many immune and inflammatory cells compose the tumor stroma and microenvironment.[25,26] They can also secrete cytokines and inflammatory factors, which may contribute to the recurrence and metastasis of tumor.[27] For example, CXCR1/CXCR2 and interleukin-6 are involved in the processes of tumor cell proliferation, invasion and metastasis.[28,29] As an inflammation-related biomarker, pretreatment SII has been shown as an important indicator in several cancers.[11-13] It has been reported that SII is associated with clinical parameters in GC, but there is still controversy. In this meta-analysis, high pretreatment SII was correlated with depth of invasion, lymph node metastasis, and TNM stage. However, there was no association between pretreatment SII and gender (p=0.944) or differentiation (p=0.687) in GC patients.

Several studies have investigated the association between the pretreatment SII and the OS of malignant tumors patients, and the high pretreatment SII predicted prognostic value in many types of tumors. High pretreatment SII is related to poor OS in several kinds of malignant cancer patients.[30-32] The pretreatment SII is an immune and inflammation-related index and has been used to reflect inflammation and immune status. The tumor-associated neutrophils are involved in progression of tumor.[33] The platelet count and mean platelet volume is related to the regional details of the microenvironment of pancreatic neuroendocrine tumor.[34] Moreover, lymphocytes are involved in infiltrating the tumor environment.[35] In this study, a meta-analysis was conducted to detect the association of pretreatment SII and OS in GC patients. The results showed that high pretreatment SII had poorer OS than those with low pretreatment SII in GC patients.

This meta-analysis also has several limitations. First, only 10 studies were from China or Korea, which involved 3,850 patients, all from East Asia, and the results from other countries or regions remain unclear. So the bias cannot be ignored.

Second, the data was just from the published paper, and lacked the original data for some parameters. The subgroup analysis could not be performed, which may also cause bias.

Table I: Main characteristics and results of the eligible studies.

No.	First author	Year	Case No.	M/F	During	Country	Cutoff value	Treatment	NOS
1	Zheng[16]	2017	60	36/24	2015.4-2016.3	China	888	Surgery	9
2	Shi(1)[17]	2018	688	471/217	2012-2014	China	320	Surgery	7
3	Shi(2)[17]	2018	174	131/43	2012-2014	China	320	Surgery	8
4	Guner[18]	2018	1032	667/365	2009.3-2015.12	Korea	-	Surgery	9
5	Wang[19]	2017	444	281/163	1994.1-2005.12	China	660	Surgery	6
6	Huang[20]	2016	455	305/150	2013.1-2014.12	China	572	Surgery	6
7	Chen[14]	2017	185	125/60	2007.7-2015.9	China	600	Surgery	7
8	Wang[15]	2019	182	133/49	2009.1-2012.12	China	600	Surgery	7
9	Wang[21]	2019	175	127/48	2008.1-2015.8	China	782	Surgery	6
10	Liu[22]	2015	455	314/141	2005.1-2010.12	China	660	Surgery	6

Table II: Results of clinical parameters and prognostic value of SII in patients with GC.

Clinical parameters	No. of studies	Overall OR (95%CI)	Heterogeneity test (Q, I^2, P)
Gender	1, 2, 3, 5, 6, 7, 8, 9	0.991 (0.776-1.266)	10.82, 35.3%, 0.944 (random)
Differentiation	1, 2, 3, 5, 6, 7, 8, 9	1.093 (0.708-1.688)	32.03, 78.1%, 0.687 (random)
T	1, 5, 6, 7, 9	0.340 (0.244-0.474)	2.05, 0.0%, <0.001 (random)
N	1, 5, 6, 7, 9	0.447 (0.325-0.614)	4.95, 19.2%, <0.001 (random)
TNM	1, 2, 3, 5, 6, 7, 9	0.361 (0.259-0.504)	14.02, 57.2%, <0.001 (random)
1-year OS	2, 3, 5, 6, 7, 8, 9,10	0.467 (0.365-0.597)	4.82, 0.0%, <0.001 (random)
3-year OS	2, 3, 5, 6, 7, 8, 9,10	0.355 (0.230-0.548)	48.51, 85.6%, <0.001 (random)
5-year OS	5, 7, 8, 9,10	0.507 (0.359-0.716)	9.18, 56.4%, <0.001 (random)

Table III: Prognostic values of the SII in GC patients.

Author (year)	1-Year		3-Year		5-Year	
	OR (95%CI)	Weight	OR (95%CI)	Weight	OR (95%CI)	Weight
Shi (1) (2018)	0.499 (0.275-0.908)	16.90%	0.207 (0.148-0.289)	13.86%	-	-
Wang (2017)	0.401 (0.185-0.871)	10.06%	0.439 (0.295-0.651)	13.44%	0.485 (0.321-0.733)	24.27%
Huang (2016)	0.452 (0.251-0.812)	17.57%	0.263 (0.162-0.428)	12.72%	-	-
Chen (2017)	0.584 (0.300-1.119)	14.28%	0.584 (0.362-0.942)	12.78%	0.645 (0.385-1.081)	20.29%
Wang (2019)	0.696 (0.319-1.519)	9.90%	0.494 (0.254-0.960)	11.17%	0.295 (0.140-0.620)	13.65%
Wang (2019)	0.385 (0.164-0.907)	8.25%	0.204 (0.101-0.414)	10.81%	0.310 (0.153-0.626)	14.61%
Liu (2015)	0.443 (0.257-0.763)	20.44%	0.832 (0.598-1.157)	13.91%	0.752 (0.534-1.060)	27.17%
Shi (2) (2018)	0.124 (0.027-0.568)	2.61%	0.182 (0.095-0.348)	11.30%	-	-
Overall	0.467 (0.365-0.597)	100%	0.355 (0.230-0.548)	100%	0.507 (0.359-0.716)	100%

CONCLUSION

A high pretreatment SII was related to the depth of invasion, lymph node metastasis and TNM stage of GC patients. High pretreatment SII in GC patients indicated poor OS. The pretreatment SII could be used as a valuable index to predict the prognosis of GC patients. However, more research is still needed to further verify the findings of this meta-analysis.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

ETHICAL APPROVAL:

This article does not contain any studies with human participants or animals performed by any of the authors.

PATIENTS' CONSENT:

Informed consents were obtained from all individual participants included in the study.

AUTHORS' CONTRIBUTION:

GZ: Design the study; assisted in interpreting the results; assessed the data quality.

XC, JX: Did the literature search, screening and data extraction; drafted the manuscript.

XC, HY, XH: Performed critical appraisal of all included studies.

XC: Analysed data and assisted in the writing of paper.

All authors read and approved the final manuscript.

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