Systemic Immune-Inflammation Index Has Prognostic Significance In Pancreatic Carcinoma Patients: A Meta-Analysis

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Research

Keywords: systemic immune-inflammation index, pancreatic carcinoma, prognosis, meta-analysis

Posted Date: December 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-117731/v1>

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Abstract

Background: Systemic immune-inflammation index (SII) is reportedly a prognostic indicator for several malignancies, including pancreatic carcinoma, although there exists no consensus regarding its significance. In the current study, we used a systematically meta-analysis to evaluate the association between SII and prognosis in pancreatic carcinoma patients.

Methods: We screened PubMed, Embase and Cochrane Library databases, through May 2020, and retrieved studies describing the prognostic role of SII in pancreatic carcinoma. We calculated pooled hazard ratio (HR) and 95% confidence interval (CI) using a random or fixed effects models to reveal the correlation between SII and prognosis.

Results: A total of 4 studies, comprising 1,749 patients, met our inclusion criteria and were therefore eligible for inclusion. Our meta-analysis showed that elevated SII indicated significantly worse overall survival in patients with pancreatic carcinoma (HR: 1.43, 95% CI: 1.24-1.65, $P < 0.001$), with subgroup analyses, stratified by the TNM stage and treatment, further validating these results. In addition, patients with high SII had poorer cancer-specific survival (HR: 2.32, 95% CI: 1.55-3.48, $P < 0.001$). However, we found no significant associations between SII with disease-free and relapse-free survival.

Conclusions: These findings indicate that SII is a potential non-invasive and promising tool for predicting clinical outcomes of pancreatic carcinoma patients. However, further studies using adequate designs and larger sample sizes are required to validate our findings.

Introduction

Pancreatic carcinoma is the seventh highest cause of cancer-related mortalities in the world, and one of the most devastating gastrointestinal tumors with a 5-year survival rate of only 9% [1, 2]. Despite advancements in approaches for early diagnosis and therapy, there has been no significant improvement in survival benefits of pancreatic carcinoma patients, owing to distal metastases or local recurrence [3]. Therefore, it is critical to develop novel and specific prognostic biomarkers for risk stratification in pancreatic carcinoma patients.

Recent studies have demonstrated that inflammatory response is closely associated with tumorigenesis, development and metastasis of various tumors [4–7]. For example, hematological biomarkers, such as the level of lymphocytes, neutrophils, platelets, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and C-reactive protein, are now commonly measured and applied in the assessment of systemic inflammatory response [8, 9]. In fact, previous studies have confirmed that parameters are potential prognostic markers in patients with solid tumors [10–13]. Conversely, other research works have reported contradictory results on the prognostic values [14–17]. Numerous studies have also implicated systemic immune-inflammation index (SII), combining platelet, lymphocyte, and neutrophil counts, as a promising inflammation-based biomarker and a prognostic indicator for clinical outcomes in several malignancies, including pancreatic carcinoma [16, 18–20]. Therefore, we sought to comprehensively assess the clinical prognostic effect of SII in pancreatic carcinoma patients using a meta-analysis.

Methods

Search strategy and study selection

Two investigators (XC Li and HP Lin) independently performed a systematic online literature search and data extraction. Specifically, electronic scientific databases, including PubMed, Embase and Cochrane Library, were searched and relevant studies identified up to May 2020. The search terms used included “systemic immune-inflammation index”, “SII”, “pancreatic neoplasms”, “pancreatic”, and “pancreas”, with all searches conducted using a combination of MeSH terms and free-text words. Furthermore, references of both relevant systematic reviews and included studies were manually reviewed and additional studies identified.

Inclusion and exclusion criteria

Inclusion criteria include studies that: (1) described the relationship between SII and prognosis of patients with pancreatic tumors; (2) reported no laboratory or clinical evidence of infection, autoimmune or blood disease; (3) included an optimal cutoff value of SII; (4) reported outcomes of interest, including cancer-specific survival (CSS), overall survival (OS), disease-free survival (DFS) or relapse-free survival (RFS); (5) in which the hazard ratios (HRs) with 95% confidence intervals (CIs) of prognostic factors could be extracted or calculated; (6) were written in the English language. On the other hand, exclusion criteria were as follows: (1) studies on cell lines, tissues, or animals; (2) necessary data were not available; (3) continuous variables for SII; (4) the publication type was case series, review articles, letter, editorial, or commentary.

Data extraction and quality assessment

All data required for meta-analysis were independently extracted by the aforementioned authors using a prespecified table, and any disagreements resolved through a group discussion to reach a consensus. The collected information included, name of the first author, country of origin, publication year, study period, sample size, study design, baseline characteristics of patients, follow-up time, tumor-node-metastasis (TNM) stage, treatment methods, SII cut-off value, outcome, HRs and the corresponding 95% CIs.

We obtained HRs and 95% CIs for univariate and multivariate analyses in two ways. Firstly, HRs and their corresponding 95% CIs were directly obtained from the reported literature. Secondly, in cases where the article only provided the Kaplan–Meier curves, HRs and 95% CIs were calculated from the survival curves using Engauge Digitizer version 4.1 [21]. Methodological quality for each eligible article was independent assessed by the two reviewers using the Newcastle–Ottawa Scale (NOS). NOS scores of the ranging from 1 to 9 points were considered low to high quality [22], with a score ≥ 6 denoted high quality.

Statistical analysis

Meta-analysis was conducted using the RevMan software, version 5.3 (The Nordic Cochrane Center, Cochrane Collaboration, and Copenhagen, Denmark). Summary statistics were assessed using standard meta-analysis methods, with HRs used as an effect measure to assess the association between SII with prognosis in pancreatic carcinoma patients. Between-study statistical heterogeneity was evaluated using the Higgins I2 statistic and Cochran’s Q test, with data followed by P < 0.10 and/or I2 > 50% considered to have significant heterogeneity. In cases where studies showed a significant homogeneity, a fixed-effect model was adopted, otherwise a random-effect model was applied. Presence of publication bias was determined using the funnel plot, whereas stability and reliability of the results were assessed using sensitivity analysis through the leave-one-out strategy. Data followed by P < 0.05 were considered statistically significant.

Results

Search results and study characteristics

Our search yielded 43 articles, comprising 23, 13, 3 and 4 studies from EMBASE, PubMed, Cochrane Library, and other sources, respectively. A total of 19 articles remained, following exclusion of duplicates, whereas reviewing abstracts and full text resulted in exclusion of 14 more articles owing to the fact that they were systematic reviews, case reports, comments, and irrelevant studies. We also excluded Zhou et al [11], a recent study considered SII a continuous variable. A summary of the search procedures is illustrated in Fig. 1. Finally, a total of four studies [16, 18–20], involving 1749 patients were included in our analysis. Three of the studies reported OS, whereas the remaining one reported CSS and RFS. One of the studies involved two independent patient cohorts, comprising 197 and 222 patients in the training and validation cohorts, respectively [19]. For this meta-analysis, we treated these two patient cohorts as two studies for further evaluation. The included articles were all retrospective cohort studies and were published between 2018–2020, with a sample size ranging between 321 and 590, and SII cut-off values ranging from 440 to 900. All included studies had NOS scores ≥ 6. A detailed description of all included studies is outlined in Table 1.

Table 1 Characteristics of included trials in the review												
Author	Study design	Study period	Country/region	No. of Sample	Age (years)	Treatment	Tumor type	TNM stage	Median follow-up (months)	Outcome	Cut-off value	NOS score
Murthy et al, 2020 ^[18]	Retrospective study	2007–2017	USA	419	65.17 ± 9.7	Mixed	PDAC	I–II	39.1(32.6–48.1)	OS	900	8
Jomrich et al, 2019 ^[16]	Retrospective study	1995–2014	Austria	321	68.5(35.9–92.3)	Surgery	PDAC	I–II	60	OS, DFS	873	8
Zhang et al, 2019 ^[19]	Retrospective study	2011–2015	China	419	61(25–84)	Mixed	PA	I–II	48	OS	440	8
Aziz al, 2018 ^[20]	Retrospective study	2004–2015	Netherlands	590	65.5(35.5–82.4)/ 65.6(36.6–84.7)	Surgery	PDAC	I–II	43.3/44.8	CSS, RFS	900	8
Abbreviations: TNM, tumor-node-metastasis; NOS, Newcastle-Ottawa Scale; PDAC, pancreatic ductal adenocarcinoma; PA, pancreatic adenocarcinoma; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; RFS, relapse-free survival												

The relationship between SII and OS in pancreatic carcinoma patients

A total of three cohort studies, comprising 1,159 patients, were combined to evaluate the relationship between SII and OS in pancreatic carcinoma patients. We found no significant heterogeneity among the studies (I2 = 0), hence we applied a fixed-effect model. Univariate analysis revealed a pooled HR of 1.44 with the corresponding 95%CI (1.25–1.65) (P < 0.001), whereas multivariate analysis resulted in a HR of 1.43 with the corresponding 95%CI (1.24–1.65) (P < 0.001). Based on these results, it was evident that higher SII indicated poor OS in pancreatic carcinoma (Fig. 2).

The relationship between SII and CSS/DFS/ RFS in pancreatic carcinoma patients

Only one study reported the prognostic impact of SII on CSS/DFS/ RFS in pancreatic carcinoma patients. Results indicated that a high SII acts as an independent prognostic marker for CSS (HR: 2.32, 95% CI: 1.55–3.48, P < 0.001), although no significant differences were recorded between SII and DFS (HR: 1.27, 95% CI: 0.95–1.70, P = 0.103) or RFS (HR: 1.49, 95% CI: 1.00-2.20, P = 0.048) in pancreatic carcinoma (Table 2).

Table 2
Meta and subgroup analyses for SII in pancreatic carcinoma

Analysis	No. of studies	No. of cases	HR (95% CI)	P-value	Heterogeneity	
					I ² (%)	P-value
OS	3	1159	1.43(1.24–1.65)	< 0.001	0	0.97
TNM stage						
I-II	2	740	1.39(1.13–1.69)	0.001	0	0.91
III-IV	1	419	1.48(1.21–1.80)	< 0.001	-	-
Treatment						
Mixed	2	838	1.44(1.22–1.70)	< 0.001	0	0.90
Surgery	1	321	1.40(1.07–1.84)	0.016	-	-
CSS	1	590	2.32(1.55–3.48)	< 0.001	-	-
DFS	1	321	1.27(0.95–1.70)	0.103	-	-
RFS	1	590	1.49(1.00-2.20)	0.048	-	-
Abbreviations: SII, systemic immune-inflammation index; TNM, tumor-node-metastasis; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval						

Subgroup and sensitivity analyses

A summary of results from subgroup analyses stratified by the TNM stage and treatment is outlined in Table 2. Summarily, higher SII was a poor prognostic indicator for OS in patients with stage I-II (HR: 1.39, 95% CI: 1.13–1.69, $P = 0.001$) and III-IV (HR: 1.48, 95% CI: 1.21–1.80, $P < 0.001$). When the treatment method was considered, HRs for the impact of SII on OS were 1.44 (95% CI: 1.22–1.70, $P < 0.001$) and 1.40 (95% CI: 1.07–1.84, $P = 0.016$) for the mixed and surgery groups, respectively. Moreover, all subgroups revealed significant association between SII levels and OS of pancreatic carcinoma (Table 2). Subsequent exclusion of a single trial did not alter pooled HRs for the aforementioned associations. Particularly, a comparison among the random and fixed effects models resulted in identical pooled risk estimate of OS. Overall, subgroup and sensitivity analyses indicated that the current pooled evidence from meta-analysis were robust and credible.

Publication bias

Funnel plots in our meta-analysis revealed no evidence of publication bias among the included studies (Fig. 3).

Discussion

Numerous studies have suggested that inflammatory response plays a pivotal role in development and progression of tumors [6, 23, 24]. This interaction is reportedly mediated by a series of inflammatory cells, which form major cellular components of the tumor microenvironment [25], and either directly or indirectly affect tumor cell proliferation, migration and angiogenesis by releasing various inflammatory mediators [26, 27]. Other studies have implicated peripheral blood inflammatory cell count, including neutrophils, and lymphocytes in prognosis of many tumors [28–31]. SII, a combined marker based on platelet, lymphocyte, and neutrophil counts, was first identified as an independent factor for predicting clinical outcomes of hepatocellular carcinoma patients [32]. Thereafter, its prognostic value was revealed in various tumors, including colorectal, renal cell, esophageal squamous cell, lung, prostate, and gastrointestinal cancers [33–38].

SII is a novel and convenient marker, that is easily accessible and inexpensive, and has recently been shown to be a prognostic marker for pancreatic carcinoma. In the present study, literature review-based analysis of the relationship between SII and prognosis of pancreatic carcinoma patients indicated that patients with higher SII levels have worse prognostic tendency, possibly due to several reasons. Firstly, neutrophils have been proven to promote release of a variety of inflammatory factors, such as vascular epithelial growth factor, neutrophil elastase, interleukin-8, and matrix metalloproteinase-9, which play an important role in promoting the invasion, proliferation, progression, and metastasis of cancer cells, as well as helping these cells to escape immune surveillance [39, 40]. In addition, platelets not only promote adhesion of tumor cells to microvascular endothelium, but also form a defense barrier around circulating tumor cells, helping tumor cells escape the host's immune surveillance [41]. Consequently, they directly promote tumor growth and metastasis by secreting pro-angiogenic factors and platelet-derived growth factors [42]. Conversely, lymphocytes play an important role, defending the body against cancer cells by inducing cell death, inhibiting cell proliferation and migration [5]. Therefore, a reduction in the number of lymphocytes may weaken the antitumor immune response and immune surveillance function, thereby providing a good microenvironment for tumor growth [43, 44]. Based on these mechanisms, presence of high levels of SII, platelets and neutrophils and low levels of lymphocytes, enhances tumor invasion, adhesion, progression, metastasis and weakens antitumor immune response. Thus, an elevated SII is associated with adverse clinical outcomes in tumor patients.

In the present study, we determined SII's prognostic value in pancreatic carcinoma patients, using a total of 4 published studies comprising 1,749 patients. Pooled results indicated that pancreatic cancer patients with high levels of SII had worse OS rates than those with low SII levels. Furthermore, results from subgroup analyses, applied to explore the prognostic significance of SII in patients with different stages and treatment options, suggested that high SII levels were a potential independent poor prognostic marker for OS in patients with resectable or advanced pancreatic tumors. This trend remained, even when

treatment was considered as a stratification factor, regardless of whether the patient has received surgery or mixed treatment. In addition, we also found that a high SII value was associated with CSS in patients with pancreatic tumors, although these results need further validation.

This study had several limitations. Firstly, the four included articles were retrospective cohort studies, and could have inherent defects. Secondly, the total number of included studies and the sample size was relatively small, especially for some subgroup analyses. Therefore, more large-sample studies are needed to further confirm our findings. Thirdly, we did not make stratified comparisons based on other factors, such as age, gender, and pathological type of tumor owing to the paucity of original data from individual studies. Fourthly, the optimal cut-off value of the SII was inconsistent across different studies. Finally, although the funnel plots suggested no evidence of publication bias, this may be inevitable because funnel plots lacked adequate statistical power owing to the small number of studies included. Given these several limitations, our study findings should be treated with caution.

In summary, high SII levels are associated with poor prognosis of OS and CSS in pancreatic carcinoma patients. However, SII is no significantly associated with DFS and RFS. The exact biological mechanisms underlying the observed associations are still poorly understood, although previous studies have implicated the inflammatory response pathway in their regulation. Our findings indicate that SII might be a non-invasive and valuable prognostic marker for pancreatic carcinoma for clinical practice. However, well designed, large-scale, and prospective studies are needed to validate the association between SII levels and the prognostic outcomes of pancreatic carcinoma patients.

Abbreviations

- SII
- systemic immune-inflammation index
- NLR
- neutrophil to lymphocyte ratio
- PLR
- platelet to lymphocyte ratio
- CSS
- cancer-specific survival
- OS
- overall survival
- DFS
- disease-free survival
- RFS
- relapse-free survival
- HRs
- hazard ratios
- CIs
- confidence intervals
- TNM
- tumor-node-metastasis
- NOS
- Newcastle-Ottawa Scale

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

This work was funded by Clinical Medical Technology Demonstration Base for Minimally Invasive Treatment of Hepatobiliary and Pancreatic Diseases in Huaihua.

Acknowledgments

The authors are grateful to Ms. Shanqiongyao Wang for her consistent support and help during this study. This work was funded by Clinical Medical Technology Demonstration Base for Minimally Invasive Treatment of Hepatobiliary and Pancreatic Diseases in Huaihua.

Author Contributions

Conception and design: XCL, HPL, JP. Data collection and drafting: XCL, HPL. Statistical analysis: XCL, YWY, RBOY. Manuscript writing: XCL, HPL. Final approval of manuscript: All authors.

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Figures

Figure 1
Flow chart of study selection

Figure 1

Flow chart of study selection

Figure 2

Forest plots describing the association between SII and overall survival. (A) Univariate analysis and (B) multivariate analysis; SII, systemic immune-inflammation index

Figure 2

Forest plots describing the association between SII and overall survival. (A) Univariate analysis and (B) multivariate analysis; SII, systemic immune-inflammation index

Figure 3

Funnel plots describing the association between SII and overall survival; SII, systemic immune-inflammation index