Prognostic value of the systemic immune-inflammation index in patients with biliary tract cancer: a systematic review and meta-analysis

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Research

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Abstract

Background: The systemic immune-inflammation index (SII) has been found to predict outcomes in many tumors. The purpose of this study was to determine the prognostic value of SII in biliary tract cancer.

Methods: We searched PubMed, EMBASE, Web of Science, Cochrane Library, CNKI, CBM, Wanfang and VIP databases from its inception until May 18, 2020. Pooled hazard ratio and 95% confidence interval were calculated to assess the prognostic role of SII in patients with BTC. The main outcomes included the overall survival, cancer-specific survival, disease-free survival and recurrence-free survival. Stata 12.0 was used for statistical analysis.

Results: A total of 8 studies involving 2249 patients were eventually included. The results showed that elevated SII was significantly associated with poorer OS (HR=1.56, 95% *CI*: 1.23–1.99, *P*<0.001, I^2 = 68.1%), poorer DFS/RFS (HR=1.42, 95%*CI*:1.09–1.84, *P*=0.009) and poorer CSS (HR =1.55, 95% *CI*: 1.09–2.21, *P*<0.014). Subgroup analysis further verified the above results.

Conclusions: Higher SII is a predictor of poor prognosis in BTC patients. SII can serve as a useful prognostic indicator and help to evaluate the prognosis and formulate treatment strategies.

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Introduction

Biliary tract cancer (BTC) is the second most common tumor in hepatobiliary tumors, it includes intrahepatic cholangiocarcinoma (ICCA), extrahepatic cholangiocarcinoma (ECCA), gallbladder cancer (GBC) and Ampulla of Vater Cancer (AoV Ca) [1–3]. Insidious early symptoms and rapid progression are the characteristics of biliary tract cancer. The prognosis of BTC is dismal, because most patients are in advanced stages at the time of first diagnosis. Not only were less than 20% of patients considered resectable at presentation, but also the postoperative recurrence rate is very high[4, 5]. When considering all patients, the five-year survival is around 5–15%. Part of the reason for this poor prognosis may be the lack of efficient prognostic markers[6, 7]. Therefore, finding new biomarkers predicting prognosis may be crucial for better therapeutic strategies.

It is widely accepted that inflammation plays a crucial role in tumor development and progression, and is one of the hallmarks of cancer[8–10]. Some risk factors have been identified mainly associated with chronic gallbladder or biliary tract inflammation. For example, adult flukes can stay in the biliary tract for several years, stimulating the host immune response, leading to chronic biliary tract inflammation. These results lead to a 15-fold increased risk of intrahepatic/extrahepatic cholangiocarcinoma[6]. The systemic immune-inflammation index (SII) is a recently proposed inflammatory biomarker and is defined as the platelet count × neutrophil count/lymphocyte count[11]. It has been proved to be an independent prognostic factor in a number of malignancies, such as hepatocellular carcinoma and lung cancer[11, 12]. However, regarding BTC the conclusion has been controversial, and there is a lack of evidence to systematically prove the prognostic value of SII in patient with BTC. Hence, this study was conducted to systematically review the prognostic value of SII in biliary tract cancer, which could be favourable for improved prognosis and the individualized therapy.

Methods

1. Search strategy

We searched PubMed, EMBASE, Web of Science, Cochrane Library, CNKI, CBM, Wanfang and VIP databases from its inception until may 18, 2020. No language restrictions were applied. The following terms were used in the searches: “cholangiocarcinoma”, “biliary tract cancer”, “bile duct cancer”, “gallbladder cancer”, “gallbladder carcinoma”, “intrahepatic cholangiocarcinoma”, “extrahepatic cholangiocarcinoma”, “ampulla of Vater cancer”, “systemic immune-inflammation index” and “SII”. Both MeSH terms and free-test words were used to increase the sensitivity. Furthermore, we cross-checked reference of articles and then included potential additional studies.

2. Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) types of studies: published studies exploring the relationship between SII and BTC prognosis; (2) subjects: pathologically diagnosed BTC patients;(3) outcome indicator: overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS) or Recurrence-free survival (RFS).

Exclusion criteria were as follows: (1) the types of articles were abstract, comment, case report, review, systematic review; (2) information provided was insufficient; (3) duplicate papers and the analysis with overlapping data.

3. Study selection

Two reviewers independently screened the titles and abstracts of papers during the search. Then, we assessed the full texts of the selected studies to identify related studies. Disagreements were resolved through consensus or by a third reviewer serving as final arbitrator. The reasons for exclusion were recorded at the full-text screening stage.

4. Data extraction and quality assessment

Two reviewers extracted study data following a pre-established data collection form independently, and any disagreement was resolved by discussion. The following information was collected: the name of the first author, year of publication, study period, country, sample size, gender of subjects, treatment, follow-up period, SII cut-off, outcome, source of hazard ratio (HR).

Quality assessment of the included studies was performed according to the NOS by two independent researchers to evaluate the process in terms of queue selection, comparability of queues, and evaluation of results. Studies with a score of 6 or higher were defined as high-quality studies[13].

5. Statistical analysis

Stata 12.0 was used to analyze the data. Hazard ratio (HR) and 95% confidence intervals (CIs) were combined to evaluate the association of the SII with prognosis in patients with PC. Among studies, heterogeneity was assessed using the I^2 statistic and Q test for each pooled estimate. Significant heterogeneity was defined as $P < 0.1$ and/or $I^2 > 50\%$, and the random-effects model was used in the appearance of significant heterogeneity; otherwise, the fixed-effects model was used[14]. To further explore the prognostic value of SII, subgroup analysis was conducted from the following aspects: cut-off value, sample, country, treatment method, tumor type and analysis method. Sensitivity analysis were assessed by excluding single study to evaluate the stability of pooled HRs for OS. Begg's test and Egger's test were performed to evaluate potential publication bias, and significant publication bias was defined as $P < 0.05$[15].

Results

1. Search results

The initial literature search revealed 310 records, and 293 papers were further screened after deleting duplicate papers. After reviewing the titles and abstracts, 264 reports were excluded. Subsequently, we evaluated the full text of the remaining 29 studies, 21 of which were excluded for the following reasons: 15 studies did not provide available data, 3 studies were reviews, 1 study was meeting abstract, 1 study was comment and 1 study was duplicate publication. Finally, a total of 8[16–23] studies were included for the meta-analysis (Fig. 1).

2. Characteristics of included studies

The 8[16–23] included studies were all retrospective and published during 2016–2020. 3 studies were conducted in china, 3 studies were conducted in Korea, 1 study were conducted in America and 1 study was an international multi-institutional analysis. 8 studies focused on OS as primary endpoints. One study reported the relationship between SII and CSS/RFS. Also, another paper studied the correlation between SII and DFS in BTC. The cutoff values of the SII ranged from 456 to 1150 in the included studies. The quality assessment of the included studies showed that all studies were considered to be of high-quality with a score of 6 or higher based on NOS. More detailed information is shown in Table 1.

Table 1
Characteristics of included studies.

Study	Year	Study design	Country	Study period	Sample	Sex (F/M)	endpoint	Cut-off value	Treatment methods	Tumor site	Stage	Analysis	NOS
Ha1	2016	Re	Korea	1997—2012	227	125/102	OS/DFS	780	Surg	AOV Ca	1A-3	MV	7
Ha2	2016	Re	Korea	2004—2009	158	103/55	OS	572.38	No surg	Mixed	Advanced	MV	7
Hu	2018	Re	China	2012—2017	113	75/38	OS	456	No surg	ECCA	Advanced	MV	8
Ha	2019	Re	Korea	2001—2016	90	61/29	OS	686	No surg	Mixed	NA	UV	6
Sellers	2019	Re	Germany	2005—2016	131	68/63	OS	867	Mixed	ICCA	1–4	UV	7
Kong	2019	Re	China	2005—2019	312	120/192	OS	510.42	Surg	GBCA	1–4	MV	7
Li	2020	Re	China	2009—2017	530	256/274	OS/RFS	459	Surg	ICCA	1A-3B	MV	8
Tsilimigras	2020	Re	Multi	2000—2017	688	416/272	OS/CSS	1150	Surg	ICCA	1A-4	MV	9

Re, Retrospective; F, female; M, male; OS, overall survival; CSS, cancer-specific survival, DFS, disease-free survival; RFS, recurrence-free survival; Surg, surgery; No surg, no surgery; NA, not available; HR, hazard ratio; NOS, Newcastle-Ottawa Scale.

3. Meta-analysis results

3.1 Impact of SII on OS of BTC

There were 8 studies, involving 2249 persons with BTC, which reported the relationship between SII and OS. Results showed significant heterogeneity (I^2 = 68.1%, P = 0.003), and thus a random-effects model was adopted. A pooled HR showed that patients with elevated SII were significantly associated with poorer OS (HR:1.56, 95%*CI*:1.23–1.99, P <0.001) (Fig. 2).

3.2 Impact of SII on DFS/RFS and CSS of BTC

There were 2 studies, involving 757 persons with BTC, reporting the relationship between SII and DFS/RFS. There was no significant heterogeneity (I^2 = 0.0%, P = 0.807), and thus a fixed-effects model was used. A pooled HR showed that patients with higher SII values were significantly associated with poorer DFS/RFS (HR:1.42, 95%*CI*:1.09–1.84, P =0.009). One study reported that higher SII values were associated with pooerer CSS (HR:1.55, 95%*CI*:1.09–2.21, P <0.014). Because of the lack of relevant studies, we did not conduct a combined analysis of CSS in our study (Table 2).

Table 2
Meta and subgroup analyses

Analysis	No. of studies	HR (95%*CI*)	*P*	Heterogeneity	
				I^2(%)	P_h
OS					
Total	8	1.56 (1.23—1.99)	< 0.001	68.1	0.003
Cut-off value					
< 600	4	1.72 (1.10—2.68)	0.017	79.9	0.002
≥ 600	4	1.44 (1.22—1.70)	< 0.001	0.0	0.467
Sample					
< 200	4	1.34 (1.13—1.60)	0.001	26.1	0.255
≥ 200	4	1.81 (1.30—2.53)	< 0.001	67.2	0.027
Country					
China	3	2.20 (1.79—2.71)	< 0.000	39.0	0.194
Korea	3	1.10 (0.82—1.48)	0.533	0.0	0.379
America	1	1.37 (1.02—1.84)	0.037	NA	NA
multi	1	1.70 (1.23—2.34)	0.001	NA	NA
Treatment					
Surg	4	1.81 (1.30—2.53)	< 0.001	67.2	0.027
No-surg	3	1.29 (0.97—1.71)	0.080	49	0.141
Mixed	1	1.38 (1.11—1.73)	0.004	NA	NA
Tumor type					
AOV Ca	1	0.92 (0.44—1.93)	0.833	NA	NA
Mixed	2	1.14 (0.82—1.60)	0.438	40.6	0.195
ECC	1	1.88 (1.06—3.32)	0.031	NA	NA
GBC	1	2,65 (1,98—3,54)	< 0.05	NA	NA
ICC	3	1.54 (1.31—1.81)	< 0.001	0.0	0.388
Analysis method					
UV	2	1.39 (1.13—1.70)	0.001	0.0	0.891
MV	6	1.61 (1.16—2.23)	0.004	72	0.003
DFS/RFS	2	1.42 (1.09—1.84)	0.009	0.0	0.807
CSS	1	1.55 (1.09—2.21)	< 0.014	NA	NA

OS, overall survival; CSS, cancer-specific survival, DFS, disease-free survival; RFS, recurrence-free survival; Surg, surgery; No surg, no surgery; NA, not available; HR, hazard ratio; MV, multivariate analysis; UV, univariate analysis NOS, Newcastle-Ottawa Scale.

4. Subgroup analysis

Subgroup analyses showed that high SII remained an important factor for poorer OS in patients with ECCA (HR:1.88, 95%*CI*:1.06–3.32, *P* = 0.031), ICCA (HR:1.54, 95%*CI*:1.31–1.81, *P* < 0.001) and GBC (HR:2.65, 95%*CI*:1.98–3.54, P < 0.05), but not in patients with AOV Ca (HR:0.92, 95%*CI*:0.44–1.93, *P* = 0.833) and the mixed type (HR:1.14, 95%*CI*:0.82–1.60, *P* = 0.438). On stratification by treatment method, the results showed that higher SII were a significant factor of poorer OS for patients with surg (HR:1.81, 95%*CI*:1.30–2.53, *P* < 0.001) and mixed treatment (HR:1.38, 95%*CI*:1.11–1.73, *P* < 0.004), but not for patients with no-surg (HR:1.29, 95%*CI*:0.97–1.71, *P* = 0.080). Furthermore, higher SII predicted poorer OS in BTC patients regardless of cut-off values, sample size and analysis methods (Table 2).

5. Sensitivity analysis

By sequentially removing individual eligible studies, we observed that no individual study altered the primary results, with HR range from 1.44 (95%*CI*:1.21–1.72) to 1.68 (95%*CI*:1.34–2.12) (Fig. 3).

6. Publication bias

Begg's (*P* = 0.711) and Egger's test (*P* = 0.527) results indicated that no significant asymmetry was found in the pooled analysis which showed impact of SII on OS of BTC (Fig. 4).

Discussion

By including 8 studies which involved 2249 participants, our results showed a significant association between higher SII and poorer OS, DFS/RFS and CSS in patients with BTC. In addition, subgroup analyses showed that a higher SII was a significant factor of poorer OS for patients with ECCA, GBC and ICCA, but not in patients with AOV Ca and mixed type ones. On stratification by treatment method, the results showed that higher SII was a significant factor of poorer OS for patients with surg and patients with mixed treatment, but not in patients with no-surg. Furthermore, higher SII predicted poorer OS in patient with BTC, regardless of cut-off values < 600 or ≥ 600, sample size < 200 or ≥ 200, analysis methods univariate or multivariate.

The prognostic effect of SII has also been studied in other cancers in meta-analysis. A recent meta-analysis—from 9 studies involving 2441 patients—showed that higher SII could predict worse survival outcomes in patients with non-small cell lung cancer[11]. Another study also showed that higher SII was associated with poorer OS in patients with hepatocellular carcinoma[12]. A comprehensive meta-analysis of 8 studies involving 2642 patients showed that in breast cancer patients, higher SII was associated with poorer OS and some clinicopathological factors [24]. In our meta-analysis, the pooled results showed that higher SII was predictive of poorer OS, which is consistent with previous studies on other cancers. However, due to the lack of data, we did not analyze the correlation between SII and clinical factors in BTC patients.

Relevant studies have shown that the inflammatory cell is one of the main characteristics of tumor and plays a crucial role in tumor growth, progression, and metastasis. Moreover, deletion or inhibition of inflammatory cytokines inhibits development of experimental cancer[25, 26]. SII, as a combination of NLR and PLR, can fully reflect the balance between immunity and inflammation. High SII is caused by thrombocytopenia, neutropenia and lymphocytopenia, suggesting an increase in inflammatory state and a decrease in immune system response. Some evidence suggested that neutrophilia and thrombocythemia were associated with pro-cancer effects[27–30]. In addition to the above reasons, BTC patients with higher SII may have a poorer survival due to the micro-metastasis. Such as patients with pancreatic cancer, platelets conduce to the adhesion of tumor cells to escape host immune surveillance[31–33]. On the contrary, lymphocytes play a vital role in tumor defense. Lymphocytopenia indicates that the immune surveillance system is ineffective and has been reported to be associated with poor survival in some malignant tumors[34–36]. SII can be detected by routine blood test, and the cost is low, so it can help clinicians to predict the prognosis of patients better and easier for reasonable systematic treatment strategies.

There are also some limitations in this study. First of all, there was some heterogeneity in these included articles, and we used subgroup analysis and so on, but still failed to explore all the heterogeneity; Secondly, fewer studies were included, and fewer studies were included in subgroup analysis, which affected the accuracy of the results. Third, there was still no unified standard for the optimal demarcation value of SII, and it was easily affected by patients' own conditions, such as infection, chemotherapy and so on.

In summary, the prognostic value of SII on BTC was analyzed by meta for the first time, and current evidence suggested that SII could serve as a useful prognostic indicator in BTC. However, limited by the quantity and quality of included studies, the above conclusions need to be further verified by more high-quality studies.

Abbreviations

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index; OS: Overall survival; DFS: Disease-free survival; RFS: Recurrence-free survival; CSS: Cancer-specific survival; HR: Hazard ratio; CI: Confidence interval; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; NOS: Newcastle-Ottawa Scale; BTC: Biliary tract cancer;

Declarations

Acknowledgements

Not applicable.

Authors' Contributions

Shi Chen and Fa-quan Zhou contributed equally to this study. (I) Conception and design: FQ Zhou, S Chen, LJ Tang, HY Sun; (II) Administrative support: LJ Tang, HY Sun;(III) Provision of study materials or patients: FQ Zhou, S Chen; (IV) Collection and assembly of data: FQ Zhou, S Chen; (V) Data analysis and interpretation: FQ Zhou, S Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Availability of data and materials

All data generated or analyzed during this study are included in this

published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

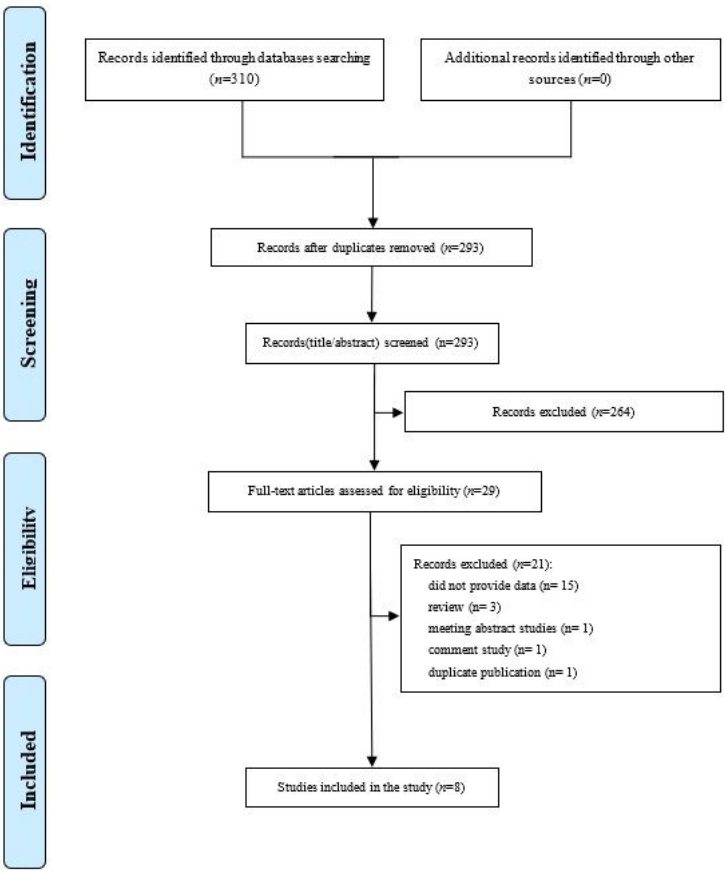

Figure 1

Flowchart of the selection process in this study.

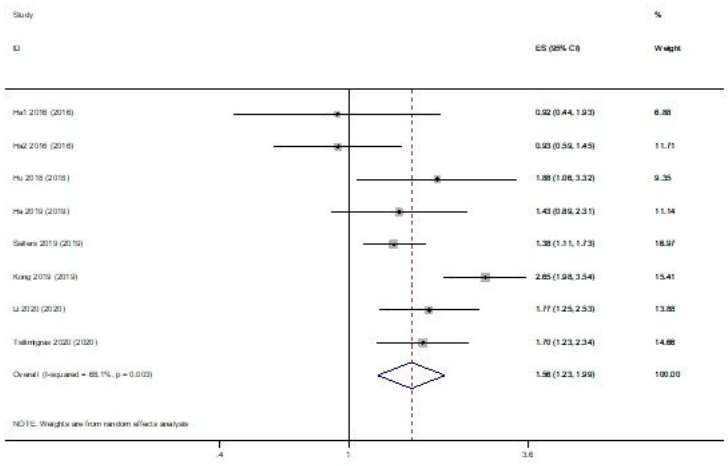

Figure 2

Forest plot of the association between SII and overall survival.

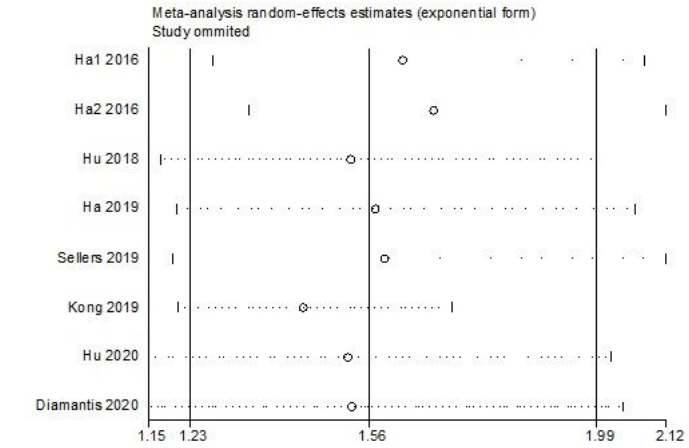

Figure 3

Sensitivity analysis of the association between SII and OS

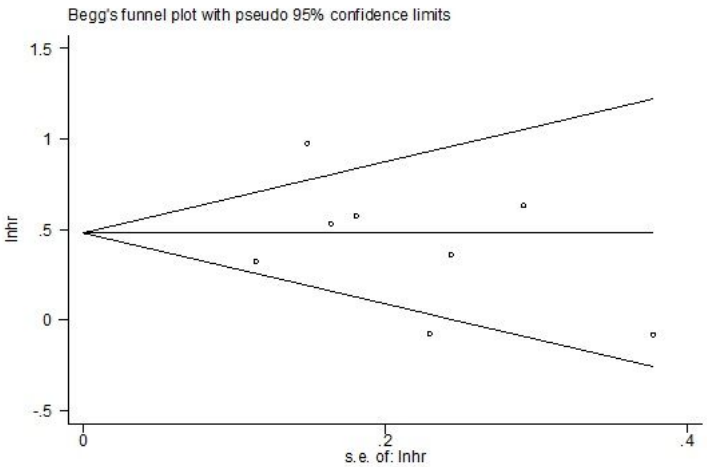

Figure 4

Begg's funnel plot of the association between SII and overall survival.