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Prognostic value of systemic immune-inflammation index in patients with urinary system cancers: a meta-analysis

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Abstract. – OBJECTIVE: The systemic immune-inflammation index (SII), an inexpensive and widely available hematologic marker of inflammation, has been linked to tumor progression, metastatic spread, and poor patient prognosis. The objective of this study is to explore the prognostic value of SII in patients with urinary system cancers (USCs).

MATERIALS AND METHODS: A comprehensive literature search was conducted by searching the PubMed, EMBASE, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases from inception to May 10, 2020, to identify potential studies that assessed the prognostic role of the SII in USCs. The hazard ratio (HR) with a 95% confidence interval (CI) were used to evaluate the correlation between SII and overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS) in USCs patients.

RESULTS: A total of 12 studies, including 2,693 USCs patients, were eventually included in the meta-analysis. Elevated SII index was significantly associated with poor OS (HR=1.28, 95% CI: 1.17-1.39, $p<0.001$), PFS (HR=1.51, 95% CI: 1.25-1.82, $p<0.001$) and CSS (HR=3.42, 95% CI: 1.49-7.91, $p<0.001$). Furthermore, subgroup analysis indicated that higher SII than a cut-off value could predict poor OS in renal cell carcinoma (HR=1.23, $p<0.001$), prostate carcinoma (HR=1.95, $p<0.001$), bladder carcinoma (HR=5.40, $p<0.001$), testicular cancer (HR=6.09, $p<0.001$) and upper tract urothelial carcinoma (HR=2.19, $p<0.001$). Besides, these associations did not vary significantly by tumor subtypes and stages of USCs, sample sizes, study types, cut-off value defining elevated NLR, treatment methods, and NOS scores.

CONCLUSIONS: SII may serve as a useful prognostic indicator in USCs and contribute to prognosis evaluation and treatment strategy formulation. However, more well-designed studies are warranted to verify our findings.

Key Words:
Urinary system cancer, Systemic immune-inflammation index, Meta-analysis, Prognosis.

Introduction

Urinary system cancers (USCs), mainly including prostate cancer (PCa), bladder cancer (BCa), and renal cell carcinoma (RCC), are responsible for approximately 734,000 cancer-related deaths per year[1]. Prostate cancer (PCa) is a heterogeneous disease and ranked as the second leading cause of cancer-related deaths in males worldwide. In 2018 alone, there were 1.3 million new PCa cases and 359,000 PCa deaths worldwide[2]. Meanwhile, BCa and RCC are in fourth and seventh place in men, respectively[3]. According to GLOBOCAN data in 2018, the number of BCa patients was approximately 550,000, accounting for 3% of global cancer diagnoses[4]. Additionally, RCC is an insidious neoplasm, accounting for about 2% of global cancer diagnoses and deaths, and projected to increase in burden worldwide[5]. Despite significant progress of treatment, the prognosis and clinical outcome of urological cancers remain unsatisfactory because of local recurrence or

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distal metastasis[6,7]. Therefore, it is pivotal for us to identify better predictors for prognosis in patients with USCs.

Recently, emerging evidence has indicated the crucial role of the inflammatory response in tumor progression, invasion, and metastasis[8]. Inflammation increases cancer risk and affects cancer stages, triggering the initial genetic mutation or epigenetic mechanism, promoting cancer initiation, progression, and metastatic diffusion[9]. Therefore, some inflammation parameters may be potential candidates to predict cancer outcomes. In recent years, inflammatory markers, such as C-reaction protein (CRP), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) have been reported to be associated with poor prognosis of cancers[10-13]. The systemic immune-inflammation index (SII), defined as neutrophil×platelet/lymphocyte, is a new and promising inflammatory biomarker linked to poor outcomes in USCs patients[14-17]. SII reflects systemic inflammation in a more balanced way and has a higher predictive value than PLR and NLR in USCs patients[18,19]. Whereas, due to the difference in the study design, demographic characters, or limited sample size, there are still some contrary views[15,16,18]. Therefore, we carried out a meta-analysis to evaluate the prognostic role of SII in patients with USCs.

Materials and Methods

Search Strategy

We searched the PubMed, EMBASE, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases up to May 10, 2020, to identify potential studies that assessed the prognostic role of the SII in USCs. Both the Medical Subject Heading (MeSH) and free text words were used to increase the sensitivity of the searching. Qin Wang and Sirui Zhu independently performed the literature search. Search terms used were: (systemic immune-inflammation index OR SII) AND (bladder carcinomas OR bladder cancer OR prostate carcinoma OR prostate cancer OR renal cell cancer OR renal cell carcinoma OR testicular cancer OR testicular carcinoma OR upper-tract urothelial cancer OR upper-tract urothelial carcinoma OR urinary system carcinoma OR urinary system cancer OR urogenital tumors OR urogenital cancer OR urogenital neoplasm) AND (prognosis OR outcome OR mortality OR survival OR recurrence OR metastasis OR progression). The language was limited to English. Furthermore, we also manually screened the reference lists of the retrieved articles to identify other relevant publications.

Inclusion and Exclusion Criteria

Articles that met the following inclusion criteria were selected: (1) exploring the relationship between SII and prognosis in USCs patients; (2) providing a definite cutoff value of SII; (3) the hazard ratio (HR) with 95% confidence interval (CI); (4) overall survival (OS), progression-free survival (PFS) or cancer-specific survival (CSS) of USCs patients. The exclusion criteria were as follows: (1) duplicate publications; (2) review articles, conference abstracts, letters, meta-analysis, editorials, and expert opinions; (3) studies with insufficient data; (4) animal studies.

Data Extraction and Quality Assessment

Two independent reviewers evaluated all identified publications, and a third reviewer resolved any disagreement between reviewers. The information included the first author's surname, year of publication, country of the population, sample size, tumor stage, treatment methods, SII cutoff value, outcome index, and corresponding HR value with 95% CI. In this meta-analysis, HR and the related 95% CI for prognosis was acquired directly from the papers that reported the HRs with 95% CI in univariate and/or multivariate analysis. The quality of studies was evaluated by the Newcastle-Ottawa scale (NOS)[20]. The NOS scores ranged from 0 to 9 points, and studies with NOS scores ≥ of 6 points was assigned to be of high quality.

Statistical Analysis

All data analysis was performed using the Stata 12.0 software (Stata Corp, College Station, TX). An observed HR >1.0 indicated a worse prognosis for the USC patients with a higher SII level, and 95% CI not including the value of 1.0 was regarded as statistically significant. Cochran's Q test and Higgins-I-squared statistics were applied to measure the heterogeneity of the combined studies. When $p \geq 0.05$ or $I^2 < 50\%$, it showed no heterogeneity, and therefore we used the fixed-effect model for a merger. On the

contrary, we used the random-effect model for a combination because of significant heterogeneity. Additionally, Egger's test and Begg's tests were conducted to evaluate publication bias. We also performed a sensitivity analysis to assess the stability of the results. A *p*-value of less than 0.05 was considered statistically significant.

Results

Process of Study Selection and Description of Qualified Studies

A total of 163 records were identified from the initial database search and additional records from other sources. After excluding duplication and reading the texts for further examination, 12 studies were included for analysis, including 2693 cases[14-19,21-26] (Figure 1). All the included studies reported the OS, whereas only seven reported PFS and one covered CSS. We finally chose five different types of urinary system tumors in this meta-analysis, including BCa (n=209), PCa (n=699), RCC (n=1333), testicular cancer (TC, n=28), and upper tract urothelial carcinoma (UTUC, n=424). The mean NOS score for these studies was 7.11 (range 6-8), indicating the quality of all included studies was good. There were 11 retrospective studies and one prospective study. These studies were published between 2016 and 2019 with a sample size between 28 and 502, and a medium age of 68.7 (range 62-74). Seven out of 12 studies were conducted in Asian countries (China, Japan, and India), and five studies in three European countries, including Italy, Poland, and Austria. The SII cutoff values ranged from 200 to 1375. The general characteristics of 12 included studies are summarized in Table I.

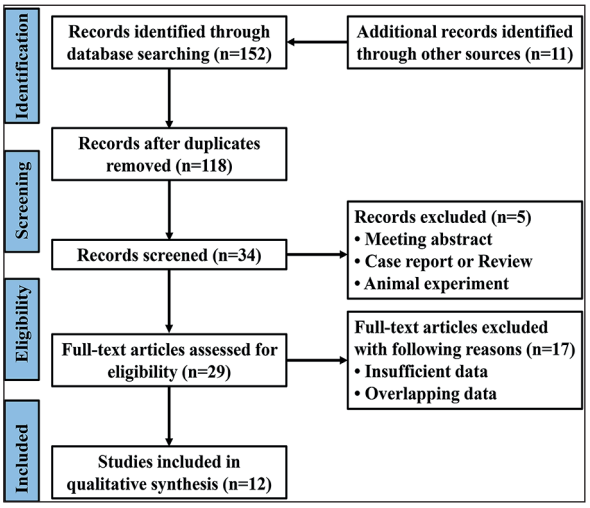

Figure 1. Flow diagram of the literature search and study selection.

Meta and Subgroup Analysis

A total of 12 studies involving 2,693 patients reported the association between the SII and OS in USCs patients. The results showed that elevated SII was significantly associated with poor OS (HR =1.28, 95% CI: 1.17-1.39, $p<0.001$; $I^2=92.0\%$, $p<0.001$) (Figure 2), poor PFS (HR=1.51, 95% CI: 1.25-1.82; $I^2=94.2\%$, $p<0.001$) in 7 studies including 1451 USCs patients (Figure 3), and poor CSS (HR =3.43, 95% CI: 1.49-7.91; $p<0.001$) in one study including 424 USCs patients. The subgroup analysis indicated that elevated SII was significantly associated with poor OS in RCC (HR=1.23, 95% CI: 1.12-1.38, $p<0.001$), PCa (HR=1.95, 95% CI: 1.05-3.61, $p<0.001$), BCa (HR=5.40, 95% CI: 1.26-23.11, $p<0.001$), TC (HR=6.09, 95% CI: 1.72–21.53, $p<0.001$) and UTUC patients (HR=2.19, 95% CI: 1.14-4.22, $p<0.001$). Besides, elevated SII was significantly associated with poor OS in Europe populations (HR=1.93, 95% CI: 1.04-3.58, $p<0.001$). Meanwhile, significantly elevated SII also indicated poor prognostic values in Male-specific USCs (HR=2.09, 95% CI: 1.14-3.83, $p=0.017$), early tumor stage (I–II) (HR=2.73, 95% CI: 2.30-3.74, $p<0.001$), and chemoradiotherapy (HR=2.15, 95% CI: 1.40-3.29, $p<0.001$). Additionally, pooled HR results were also >1.0 in the subgroups of study type, NOS scores, and cutoff value ($p<0.001$). The summary of the subgroup analysis between SII and OS was shown in Table II.

Publication Bias

Begg's funnel plot and Egger's test were used to assess potential publication bias in this meta-analysis. The *p*-value for OS was 0.161 in Begg's test and <0.001 in Egger's test, indicating potential publication bias. Therefore, the Duval and Tweedie nonparametric trim and fill procedure was undertaken to assess the effect of the possible missing studies on the results[27]. We filled likely missing studies, and the corresponding results were not changed, suggesting that the results about OS were stable and acceptable (Figure 4). There was no publication bias for PFS (*p*-value for Begg's and Eggers' tests was 0.072 and 0.05, respectively).

Table I. Basic characteristics of included studies.

Study No.	First author and year	Cancer	Country	Study period	No.	Outcome	Follow-up (months)	Cutoff	Treatment	Stage	NOS score
1	Lolli et al[14] 2016	PCa	Italy	2011-2015	230	OS	1–48	535	CRT	–	6
2	Barua et al[15] 2019	RCC	India	2012-2017	31	OS/PFS	M (16.5)	883	Surgery	I-IV	7
3	Stangl-kremser et al[16] 2020	PCa	Austria	2005-2016	156	OS/PFS	M (7.8)	200	CRT	I-III	7
4	Lolli et al[17] 2016	RCC	Italy	2006-2014	335	OS/PFS	1-96	730	CRT	–	6
5	Zhang et al[18] 2019	BCa	China	2005-2019	209	OS	1-168	507	Surgery	I-IV	7
6	Jan et al[19] 2019	UTUC	China	2007-2017	424	OS/CSS/PFS	M (35)	580	Surgery	T1–T4	8
7	Fan et al[21] 2018	PCa	China	2013-2017	104	OS/PFS	M (20.2)	200	CRT	–	7
8	Chrom et al22 2019	RCC	Poland	2008-2016	502	OS	M (52)	730	CRT	–	7
9	Man et al[23] 2019	PCa	China	2010-2018	179	OS	M (24)	535	CRT	I-II	7
10	De Giorgi et al[24] 2019	RCC	Italy	2015-2016	313	OS/PFS	1-12	1375	CRT	I-II	7
11	Yang et al[25] 2019	TC	China	2008-2016	28	OS/PFS	M (39.2)	428.4	CRT	I-IV	7
12	Fukuda et al[26] 2018	RCC	Japan	1986-2015	152	OS	M (14)	819	Surgery	I-III	8

BCa, bladder carcinoma; CRT, chemoradiotherapy; M, median; NOS, Newcastle–Ottawa quality assessment scale; PCa, prostate carcinoma; RCC, renal cell carcinoma; TC, testicular cancer; USCs, Urinary system cancers; UTUC, upper-tract urothelial carcinoma.

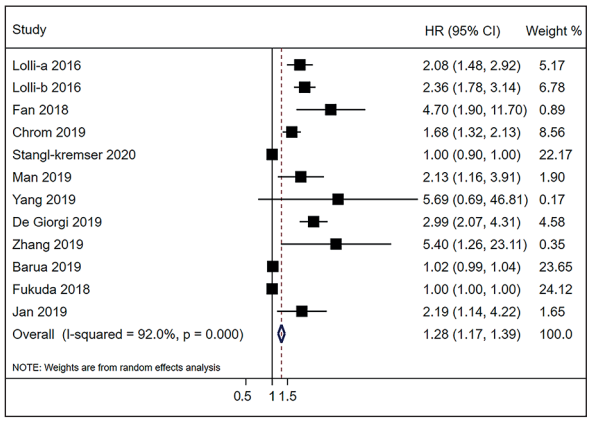

Figure 2. Forest plot of the association between SII and OS.

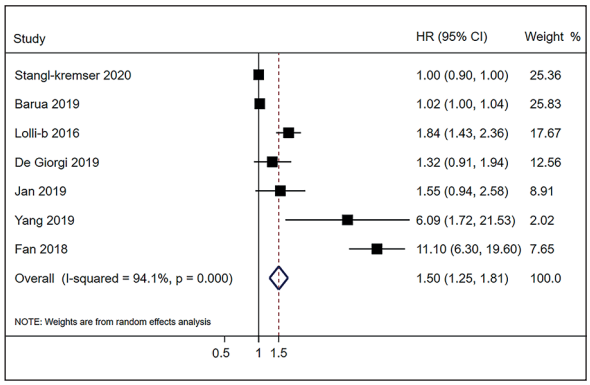

Figure 3. Forest plot of the association between SII and PFS.

Sensitivity Analysis

Due to considerable heterogeneity, a further sensitivity analysis was performed. Sensitivity analyses of OS were conducted after excluding two studies[15,25] with a small sample size in the exposure group (less than 31 patients), which indicated that these results were robust (**Supplementary Figure 1**). Sensitivity analyses of PFS conducted by excluding one study at a time

Table II. Summary of the subgroup analysis between SII and OS.

Analysis	Studies (n)	Cases (n)	HR (95% CI)	p_{HR}	I^2 (%)	p_I
Cancer type						
RCC	5	1333	1.23 (1.12-1.38)	< 0.001	95.5	< 0.001
PCa	4	699	1.95 (1.05-3.61)	< 0.001	91.1	< 0.001
BCa	1	209	5.40 (1.26-23.11)	–	–	–
TC	1	28	6.09 (1.72-21.53)	–	–	–
UTUC	1	424	2.19 (1.14-4.22)	–	–	–
Gender-specific USCs						
Male	5	727	2.09 (1.14-3.83)	0.017	89.0	< 0.001
Both	7	1966	1.27 (1.15-1.41)	< 0.001	94.0	< 0.001
Stage						
NA	4	1171	2.31 (1.64-2.77)	< 0.001	55.7	0.079
Mixed	6	1030	1.01 (0.98-1.04)	0.576	66.5	0.011
Early stage (I-II)	2	492	2.73 (2.30-3.74)	< 0.001	0	0.35
Study type						
Retrospective	11	2380	1.19 (1.10-1.29)	< 0.001	90.3	< 0.001
Prospective	1	313	2.99 (2.07-4.31)	–	–	–
Treatments						
Surgery	4	816	1.01 (0.97-1.05)	0.553	75.6	0.006
Chemoradiotherapy	8	1877	2.15 (1.40-3.29)	< 0.001	86.2	< 0.001
Countries						
Asian	7	1127	1.04 (0.97-1.10)	0.266	81.3	< 0.001
Europe	5	1566	1.87 (1.16-3.01)	< 0.001	95.8	< 0.001
NOS score						
6	2	565	2.24 (1.80-2.79)	< 0.001	0	0.576
7	8	1552	1.46 (1.22-1.73)	< 0.001	90.6	< 0.001
8	2	576	1.39 (0.63-3.03)	0.413	81.9	0.019
Cut-off value						
200-729	7	1360	2.28 (1.34-3.89)	0.002	87.1	< 0.001
730-1375	5	1333	1.23 (1.12-1.36)	< 0.001	95.5	< 0.001

BCa, bladder carcinoma; CI, confidence interval; HR, hazard ratio; I, inconsistency; NOS, Newcastle-Ottawa quality assessment scale; PCa, prostate carcinoma; RCC, renal cell carcinoma; TC, testicular cancer; USCs, Urinary system cancers; UTUC, upper-tract urothelial carcinoma.

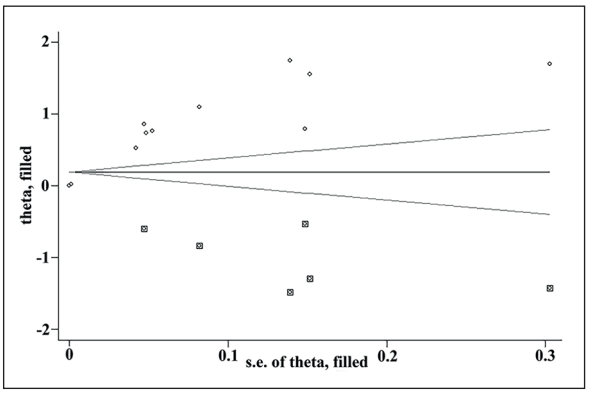

Figure 4. Funnel plot of Duval's trim and fill correction of OS. Included studies are illustrated as diamonds, and potential missing studies are presented as boxes outside the circle.

indicated that each dataset had no significant influence on the overall results (**Supplementary Figure 2**).

Discussion

The relationship between SII and the prognosis in USCs patients is still contentious. Therefore, we performed the meta-analysis, including 12 articles and 2693 patients, to investigate the predictive value of SII in USCs patients. Overall, SII over the cutoff was associated with worse OS, PFS, and CSS with the HR of 1.28, 1.51, and 3.43, respectively. Subgroup analysis also indicated that significantly elevated SII indicated poor OS in RCC (HR=1.23), PCa (HR=1.95), BCa (HR=5.40), TC (HR=6.09), and UTUC (HR=2.19) with all *p*-values were less than 0.001. Besides, there was more inferior OS in males specific USCs (PCa and TCa) than both the males and females (2.09 *vs.* 1.27), in the early tumor stage of the USC than the mixed (2.73 *vs.* 1.01). Additionally, the meta-analysis indicated that SII was a crucial prognostic indicator, especially in USCs patients treated by chemoradiotherapy (HR=2.15). Besides, we found that European populations were remarkably sensitive to SII than that in the Asian community (1.87 *vs.* 1.04). Finally, we found that different cutoff values of SII in these articles did not influence the pooled results. Taking these results together, the SII may serve as a useful prognostic index for OS and PFS in patients with USCs.

The mechanisms underlying the prognostic significance of SII for the OS and PFS in USCs remain unclear. The physiopathologic role of neutrophils, platelets, and lymphocytes might explain this to some extent. Many similar studies[28-31] indicate that neutrophils participate in the process of enhancing tumor cell proliferation, migration and invasion, and tumor immunosuppression in the stages of carcinogenesis. The increased neutrophils will promote the release of inflammatory factors of vascular epithelial growth factor (VEGF), interleukin-8 (IL-8), IL-16, and a series of proteases angiogenesis[32,33]. Furthermore, these inflammatory cytokines produced in the tumor microenvironment facilitate tumor development and progression[34].

Platelets play a crucial role in cancer progression and the prothrombotic state of cancer patients[35]. One of the most common manifestations of cancer is hypercoagulation[36]. On the one hand, tumor cells can directly activate blood clotting by activating some platelet activation markers. On the other hand, platelet-derived tumor growth factor-β (PDGF-β) can down-regulate the cytokine natural killer group 2 member D (NKG2D) to protect tumor cells from the immune system surveillance. Besides, increased platelet activation markers (e.g., P-selectin and β-thromboglobulin) and thrombopoietin also contributed to increased platelet in peripheral blood. The accumulation of platelets in peripheral blood, in turn, leads to stimulate angiogenesis of tumors and protects tumor cells from damage[37,38]. Additionally, platelets mediate tumor cell survival and growth at distant sites by governing the formation of metastatic niches[39,40]. Meanwhile, platelets can also recruit and activate granulocytic cells in the tumor tissues, and therefore, platelets may be essential for generating tumor-associated neutrophils[41].

Dunn et al[42] indicated that lymphocytes are responsible for the adaptive immune response and participate in cancer immunosurveillance and immunoediting. Lymphocytes play a crucial role in tumor defense by promoting cytotoxic cell death and inhibiting tumor cell proliferation and migration, thereby dictating the host's immune response to malignancy[43]. Lymphopenia usually indicates disease severity and helps cancer cells escape from the immune of tumor-infiltrating lymphocytes (TILs). As the formation of TILs is related to the process of lymphocytes migrating into the tumor microenvironment, decreased levels of TILs predict worse survival in cancer patients[44].

Our meta-analysis has some limitations. There was substantial heterogeneity between the in-

cluded studies, even though we tried our best to assess the source of heterogeneity based on subgroup analysis. Besides, most of the studies included in the meta-analysis were retrospective, which may cause selection bias. Finally, we only included English and Chinese publications with full text in this meta-analysis, which may leave out some eligible studies that were either unpublished or reported in other languages.

Conclusions

Our meta-analysis suggests that elevated SII indicated poor prognosis in patients with USCs. SII may serve as a useful prognostic indicator in USCs and contribute to prognosis evaluation and treatment strategy formulation. Nevertheless, given the limited number of studies included in the meta-analysis, future large-scale and multi-center studies are needed to verify our findings.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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Availability of Data and Materials

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

Authors' Contribution

SZ and QW conceived and designed the study. SZ, XH, and XL collected the data and performed the literature search. SZ and QW wrote the manuscript, and GT edited the manuscript. Additionally, professor JL provided suggestions for further modification.

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