Systemic Immune-Inflammation Index is a Promising Noninvasive Biomarker for Predicting the Survival of Urinary System Cancers: A Systematic Review and Meta-Analysis

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Abstract

**Purpose:** Systemic immune-inflammation index (SII) has been reported in numerous studies to effectively predict the pathological features and survival outcomes of urinary system cancers, but no agreement has been reached. The aim of this meta-analysis is to explore the prognostic significance of pretreatment SII in tumours of the urinary system.

**Methods:** Relevant published articles were selected from Web of Science, PubMed, Embase, and the Cochrane Library up to August 30, 2020. The pooled hazard ratios (HRs), odds ratios (ORs), and standard mean differences (SMDs) with 95% confidence intervals (CIs) were computed to estimate the associations of pretreatment SII with overall survival (OS), progression-free survival (PFS), cancer-specific survival (CSS), and clinicopathological parameters in urinary system cancers.

**Results:** Overall, a total of 13 papers published from 2016 to 2020 involving 15 datasets comprising 3974 patients were finally included in our meta-analysis. From the combined data, we found that high SII prior to treatment indicated markedly worse OS (HR = 1.98, 95% CI: 1.75–2.23, \( p < 0.001 \)), PFS (HR: 2.08, 95% CI: 1.32–3.26, \( p = 0.002 \)) with high heterogeneity (\( I^2 = 80.8%, p < 0.001 \)), and CSS (HR: 2.41, 95% CI: 1.73–3.35, \( p < 0.001 \)). In addition, patients who have an elevated SII value before receiving treatment might have undesirable pathological characteristics, including large tumour size, poor differentiation grade, and advanced tumour stage (all \( p < 0.001 \)).

**Conclusion:** Pretreatment SII could be used as a noninvasive and promising biomarker for indicating the prognosis of patients with urinary system cancers.

Background

Currently, the incidence and death rates of human urinary system cancers are increasing each year and have become a major health concern in both developed and developing countries.[1, 2] Based on the most recent Cancer Statistics in the United States, an estimated 59,120 new cancer cases and 33,820 cancer-related deaths due to urinary system cancers will occur in 2020 alone.[3] The statistics show that prostate cancer (PC) is already the leading cause of cancer among men in the United States and some other Western countries.[4] Meanwhile, the rest of the common malignancies of the urinary system, such as kidney, bladder, and upper urinary tract cancers, also pose a serious threat to human health.[5–7]

Although surgical techniques and medical therapies (chemotherapy, radiotherapy, immunotherapy and so on) have been rapidly developed in the last ten years, the five-year survival rate of patients with urinary system cancers is still not optimistic.[8, 9] Therefore, especially useful new biomarkers that could be helpful for the diagnosis, evaluation and even improvement of prognosis in urinary system cancers should be identified in clinical practice.

Recently, several parameters and molecules associated with the immune response extracted from blood samples have been proven to serve as new biomarkers for predicting the treatment effect or prognosis of patients with different kinds of cancer regardless of the therapeutic regimen.[10–13] Systemic immune-inflammation index (SII), a novel inflammatory marker, has been demonstrated to be associated with the clinicopathological features and prognosis of several cancers, such as colorectal cancer, breast cancer, hepatocellular carcinoma and PC.[14–17] Generally, SII can be calculated by the following formula: SII = platelet count × neutrophil count/lymphocyte count. Compared with other common inflammatory parameters, such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and C-reactive protein/albumin ratio, this parameter contains three types of peripheral blood inflammatory cells simultaneously, which can reflect the balance of inflammation and the immune response of the body better while still being easy to measure at a low cost.

In recent years, the relation of SII with urinary system malignancies has been explored and analysed in numerous studies.[18–20] However, due to the various experimental regions and subjects, the results of previous studies are not entirely consistent. To the best of our knowledge, there have not been any systematic reviews or meta-analyses researching SII in urinary system tumours until now. Hence, the purpose of this study was to comprehensively analyse the prognostic significance of SII in patients with common urinary system cancers through previous relevant studies.

Materials And Methods

**Information sources and search strategy**

A systematic literature search of relevant publications up to August 30, 2020, was carried out in Web of Science, PubMed, Embase, and the Cochrane Library by 2 authors independently with the following terms: (“systemic immune-inflammation index” OR “SII”) AND (“cancer” OR “tumor” OR “carcinoma” OR “neoplasm”). Moreover, additional studies were searched manually by scanning the reference lists of eligible original publications, review articles, and other relevant studies. There was no need for ethical approval and informed consent because all analyses in this study were based on previously published reports. In addition, we prospectively registered the review methodology of this meta-analysis in PROSPERO (registration number: CRD42020203389).
Inclusion And Exclusion Criteria

Articles would be included if they met the following criteria: (1) articles investigated the relationship of pretreatment SII with prognosis in any histologically confirmed urinary system cancer; (2) a specific cut-off value of SII divided the patients into high and low groups; and (3) articles had sufficient data for evaluating the hazard ratio (HR) and 95% confidence interval (CI) of survival.

Furthermore, publications were considered unqualified if they met the following criteria: (1) duplicate articles, reviews, conference summaries and letters; (2) basic medical experiments, non-human studies, case reports and editorials; and (3) studies with unavailable data.

Data Extraction

Two investigators of our research team independently evaluated the study characteristics and extracted the survival data from the retrieved publications. Any disagreements were resolved by discussion and negotiation between them or eventually reviewed by a third individual. The following data were extracted from each qualified article: name of the first author, year of publication, region, study period, type of cancer, sample size, treatment strategy, cut-off value, survival outcomes, and median follow-up time. Moreover, if only Kaplan-Meier curves were presented in a study, the survival data were collected from the graphical survival plots utilizing the software Engauge Digitizer 10.8 and the method of Tierney et al.[21] In addition, if both multivariate analysis and univariate analysis data were provided simultaneously, the HR and 95% CI data were extracted from the former analysis rather than from the latter.

Quality Assessment

The quality of each study was carefully assessed by the two authors with the use of the Newcastle-Ottawa Scale (NOS; Stang, 2010) on a score scale of 0 to 9 points. A high-quality study was identified as one with a score of 6 and over.

Statistical analysis

All statistical analyses of the data were performed utilizing Stata version 14.0 software (Stata Corporation, College Station, TX). Cochran’s Q-test and Higgin’s $I^2$ statistic were employed to measure the heterogeneity among the selected articles. The estimation of the HR and 95% CI would be pooled using the fixed-effects model if the heterogeneity was not statistically significant ($p \geq 0.05$ or $I^2 \leq 50\%$). Otherwise, the random-effects model would be used. Moreover, the presence of publication bias was evaluated visually by Begg’s funnel plot and Egger's test. In addition, we performed a sensitivity analysis to assess the reliability and stability of the results. Statistical significance was defined as $p < 0.05$.

Result

Search results and study characteristics

The selection procedure is presented in Fig. 1. Initially, a total of 412 published articles were identified through the electronic database search. After removing duplicate records and screening the titles and/or abstracts, nineteen studies were reviewed by full text. Subsequently, 6 studies were excluded for the following reasons: 3 studies did not provide sufficient data for calculating survival outcomes, 1 study did not divide patients into high and low groups, and 2 studies had NOS scores of less than 6. Finally, a total of 13 publications involving 3974 patients were enrolled in the current meta-analysis. Notably, among these 13 studies, two contained training and validation cohorts simultaneously, and thus, we eventually conducted a comprehensive analysis and statistical processing of 15 datasets.

The included studies were published from 2016 to 2020, with a sample size between 70 and 646 and a cut-off value of SII between 200 and 1375. Of them, six studies assessed the relationship between SII and prognosis in renal cell carcinoma (RCC) patients,[19, 22–26] two investigated upper tract urothelial carcinoma (UTUC),[20, 27] two focused on bladder cancer (BC),[28, 29] and three explored PC.[18, 30, 31] In terms of the research quality evaluation, the NOS score was 9 for three datasets, 8 for six datasets, 7 for one dataset, and 6 for five datasets, demonstrating that the included articles were overall of high quality. Other more detailed features of the enrolled studies are listed in Table 1.
Table 1
Basic characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Region</th>
<th>Study period</th>
<th>Cancer type</th>
<th>Sample size</th>
<th>Treatment strategy</th>
<th>Cut-off value</th>
<th>Cut-off selection</th>
<th>Data extraction</th>
<th>Survival analysis</th>
<th>Follow-up time</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teishima</td>
<td>2020</td>
<td>Japan</td>
<td>2008–2018</td>
<td>RCC</td>
<td>179</td>
<td>NS</td>
<td>730</td>
<td>Previous studies</td>
<td>MVA</td>
<td>OS</td>
<td>&lt; 5 years</td>
<td>8</td>
</tr>
<tr>
<td>Ozbek</td>
<td>2020</td>
<td>Turkey</td>
<td>N</td>
<td>RCC</td>
<td>176</td>
<td>WS</td>
<td>800</td>
<td>ROC analysis</td>
<td>SC</td>
<td>OS, CSS</td>
<td>≥ 5 years</td>
<td>9</td>
</tr>
<tr>
<td>Hu</td>
<td>2020</td>
<td>China</td>
<td>2010–2013</td>
<td>RCC</td>
<td>646</td>
<td>WS</td>
<td>529</td>
<td>ROC analysis</td>
<td>MVA</td>
<td>OS, CSS</td>
<td>≥ 5 years</td>
<td>8</td>
</tr>
<tr>
<td>De Giorgi</td>
<td>2019</td>
<td>Italy</td>
<td>2015–2016</td>
<td>RCC</td>
<td>313</td>
<td>NS</td>
<td>1375</td>
<td>X-tile software</td>
<td>MVA</td>
<td>OS</td>
<td>&lt; 5 years</td>
<td>6</td>
</tr>
<tr>
<td>Chrom</td>
<td>2019</td>
<td>Poland</td>
<td>2008–2016</td>
<td>RCC</td>
<td>502</td>
<td>NS</td>
<td>730</td>
<td>Previous studies</td>
<td>MVA</td>
<td>OS</td>
<td>≥ 5 years</td>
<td>7</td>
</tr>
<tr>
<td>Lolli</td>
<td>2016</td>
<td>Italy</td>
<td>N</td>
<td>RCC</td>
<td>335</td>
<td>NS</td>
<td>730</td>
<td>X-tile software</td>
<td>MVA</td>
<td>OS, PFS</td>
<td>&lt; 5 years</td>
<td>6</td>
</tr>
<tr>
<td>Zheng</td>
<td>2020</td>
<td>China</td>
<td>2006–2015</td>
<td>UTUC (TC)</td>
<td>253</td>
<td>WS</td>
<td>672.44</td>
<td>ROC analysis</td>
<td>MVA</td>
<td>OS, CSS, PFS</td>
<td>&lt; 5 years</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2004–2016</td>
<td>UTUC (VC)</td>
<td>272</td>
<td>WS</td>
<td>672.44</td>
<td>ROC analysis</td>
<td>MVA</td>
<td>OS, CSS, PFS</td>
<td>&lt; 5 years</td>
<td>8</td>
</tr>
<tr>
<td>Jan</td>
<td>2018</td>
<td>Taiwan</td>
<td>2007–2017</td>
<td>UTUC</td>
<td>424</td>
<td>WS</td>
<td>580</td>
<td>ROC analysis</td>
<td>MVA</td>
<td>OS, CSS, PFS</td>
<td>&lt; 5 years</td>
<td>8</td>
</tr>
<tr>
<td>Yilmaz</td>
<td>2020</td>
<td>Turkey</td>
<td>1999–2019</td>
<td>BC</td>
<td>152</td>
<td>WS</td>
<td>768</td>
<td>ROC analysis</td>
<td>MVA</td>
<td>OS, PFS</td>
<td>&lt; 5 years</td>
<td>6</td>
</tr>
<tr>
<td>Zhang</td>
<td>2019</td>
<td>China</td>
<td>2005–2019</td>
<td>BC</td>
<td>139 (PC)</td>
<td>WS</td>
<td>507</td>
<td>X-tile software</td>
<td>MVA</td>
<td>OS</td>
<td>≥ 5 years</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70 (VC)</td>
<td>WS</td>
<td>507</td>
<td>X-tile software</td>
<td>MVA</td>
<td>OS</td>
<td>≥ 5 years</td>
<td>9</td>
</tr>
<tr>
<td>Man</td>
<td>2019</td>
<td>China</td>
<td>2010–2018</td>
<td>PC</td>
<td>179</td>
<td>NS</td>
<td>535</td>
<td>Previous studies</td>
<td>MVA</td>
<td>OS</td>
<td>&lt; 5 years</td>
<td>8</td>
</tr>
<tr>
<td>Fan</td>
<td>2017</td>
<td>China</td>
<td>2013–2017</td>
<td>PC</td>
<td>104</td>
<td>NS</td>
<td>200</td>
<td>ROC analysis</td>
<td>MVA</td>
<td>OS, PFS</td>
<td>&lt; 5 years</td>
<td>6</td>
</tr>
<tr>
<td>Lolli</td>
<td>2016</td>
<td>Italy</td>
<td>2011–2015</td>
<td>PC</td>
<td>230</td>
<td>NS</td>
<td>535</td>
<td>X-tile software</td>
<td>MVA</td>
<td>OS</td>
<td>&lt; 5 years</td>
<td>6</td>
</tr>
</tbody>
</table>


Prognostic significance of SII for OS in urinary system cancers

All studies reported the association between pretreatment SII and overall survival (OS) in urinary system cancer patients. As shown in Fig. 2, the combined HR was 1.98 with the corresponding 95% CI (1.75–2.23), demonstrating that patients with high SII would have worse OS than those with low SII (p < 0.001). Since there was no remarkable heterogeneity, the fixed-effects model was used (I^2 = 17.0%, p = 0.263). In addition, subgroup analysis of OS based on the sample size, treatment strategy, cut-off value, and follow-up years further supported the above results and revealed that the sample size and treatment strategy might be potential causes of the slight heterogeneity (Table 2).
### Table 2
Subgroup analysis of the pooled HR and 95% CI between SII and OS in urinary system cancers.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Included datasets</th>
<th>Patients (n)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity test (I² (%))</th>
<th>P-value</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>15</td>
<td>3974</td>
<td>1.98 (1.75–2.23)</td>
<td>&lt; .001</td>
<td>17.0</td>
<td>0.263</td>
<td>Fixed-effects</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200</td>
<td>7</td>
<td>999</td>
<td>2.09 (1.60–2.75)</td>
<td>&lt; .001</td>
<td>35.0</td>
<td>0.161</td>
<td>Fixed-effects</td>
</tr>
<tr>
<td>≥ 200</td>
<td>8</td>
<td>2975</td>
<td>1.95 (1.70–2.23)</td>
<td>&lt; .001</td>
<td>5.8</td>
<td>0.386</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fixed-effects</td>
</tr>
<tr>
<td>NS</td>
<td>7</td>
<td>1842</td>
<td>1.95 (1.70–2.25)</td>
<td>&lt; .001</td>
<td>44.0</td>
<td>0.098</td>
<td></td>
</tr>
<tr>
<td>WS</td>
<td>8</td>
<td>2132</td>
<td>2.05 (1.62–2.59)</td>
<td>&lt; .001</td>
<td>0</td>
<td>0.534</td>
<td></td>
</tr>
<tr>
<td>Cut-off value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 600</td>
<td>7</td>
<td>1792</td>
<td>2.25 (1.80–2.81)</td>
<td>&lt; .001</td>
<td>0</td>
<td>0.447</td>
<td></td>
</tr>
<tr>
<td>≥ 600</td>
<td>8</td>
<td>2182</td>
<td>1.88 (1.63–2.17)</td>
<td>&lt; .001</td>
<td>24.9</td>
<td>0.230</td>
<td></td>
</tr>
<tr>
<td>Follow-up years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>10</td>
<td>2441</td>
<td>2.01 (1.73–2.34)</td>
<td>&lt; .001</td>
<td>21.0</td>
<td>0.250</td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td>5</td>
<td>1533</td>
<td>1.92 (1.57–2.34)</td>
<td>&lt; .001</td>
<td>25.0</td>
<td>0.255</td>
<td></td>
</tr>
</tbody>
</table>

SII: systemic immune-inflammation index, OS: overall survival, HR: hazard ratio, 95% CI: 95% confidence interval, NS: no surgery, WS: with surgery.

### Prognostic significance of SII for PFS in urinary system cancers

There were six datasets involving 1540 patients focusing on the correlation of pretreatment SII with progression-free survival (PFS). The combined result showed that high SII indicated poor PFS in patients (HR: 2.08, 95% CI: 1.32–3.26, \( p = 0.002 \)) (Fig. 3). A random-effects model was used due to the existence of obvious heterogeneity (\( I^2 = 80.8\%, \ p < 0.001 \)). Therefore, we carried out a subgroup analysis to evaluate whether the heterogeneity was related to the same variables as above. The results demonstrated that sample size less than 200, non-surgical treatment, cut-off value less than 600, and median follow-up not more than 5 years may be the major sources of heterogeneity, but these did not reverse the final conclusion (Table 3).
Table 3
Subgroup analysis of the pooled HR and 95% CI between SII and PFS in urinary system cancers.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Included datasets</th>
<th>Patients (n)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity test I² (%)</th>
<th>P-value</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6</td>
<td>1540</td>
<td>2.08 (1.32–3.26)</td>
<td>0.002</td>
<td>80.8</td>
<td>&lt; 0.001</td>
<td>Random-effects</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Random-effects</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>2</td>
<td>256</td>
<td>4.21 (0.58–30.80)</td>
<td>0.156</td>
<td>94.5</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>4</td>
<td>1284</td>
<td>1.64 (1.35–1.99)</td>
<td>&lt; 0.001</td>
<td>0</td>
<td>0.958</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Random-effects</td>
</tr>
<tr>
<td>NS</td>
<td>2</td>
<td>439</td>
<td>4.35 (0.66–28.82)</td>
<td>0.128</td>
<td>95.7</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>WS</td>
<td>4</td>
<td>1101</td>
<td>1.54 (1.18–2.01)</td>
<td>0.001</td>
<td>0</td>
<td>0.998</td>
<td></td>
</tr>
<tr>
<td>Cut-off value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Random-effects</td>
</tr>
<tr>
<td>&lt; 600</td>
<td>2</td>
<td>528</td>
<td>4.21 (0.58–30.56)</td>
<td>0.155</td>
<td>94.9</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>≥ 600</td>
<td>4</td>
<td>1012</td>
<td>1.64 (1.34–1.99)</td>
<td>0</td>
<td>0</td>
<td>0.958</td>
<td></td>
</tr>
<tr>
<td>Follow-up years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Random-effects</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>6</td>
<td>1540</td>
<td>2.08 (1.32–3.26)</td>
<td>0.002</td>
<td>80.8</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

SII: systemic immune-inflammation index, PFS: progression-free survival, HR: hazard ratio, 95% CI: 95% confidence interval, NS: no surgery, WS: with surgery.

Prognostic significance of SII for CSS in urinary system cancers

Only four studies involving five datasets investigated the relationship between pretreatment SII and cancer-specific survival (CSS). As shown in Fig. 4, the pooled data suggested that compared with low SII, high SII was definitely related to worse CSS (HR: 2.41, 95% CI: 1.73–3.35, \( p < 0.001 \)). Fortunately, no significant heterogeneity was observed among these studies and thus, a random-effects model was used to analyse the prognostic value of SII for CSS in urinary system cancer patients (\( I^2 = 0, p = 0.904 \)).

Correlations between SII and clinicopathological factors in urinary system cancers

Overall, 9 datasets comprising 2378 patients reported the associations of SII with clinicopathological characteristics, and the major features in our study included age (old versus young) in nine datasets, sex (male versus female) in eight datasets, tumour size (large versus small) in five datasets, differentiation grade (poor versus well) in five datasets, and tumour stage (III/IV versus I/II) in six datasets. The fixed-effects model or the random-effects model was used based on the presence or absence of heterogeneity. As shown in Table 4 and Fig. 5, there was no obvious correlation between pretreatment SII and the age of urinary system cancer patients regardless of whether the binary variables or continuous variables were used for calculation (OR = 1.12, 95% CI: 0.90–1.39, \( p = 0.315 \); SMD = -0.05, 95% CI: -0.43–0.34, \( p = 0.817 \), respectively). However, the pooled results revealed that high SII prior to treatment was significantly related to large tumour size (OR = 1.89, 95% CI: 1.49–2.40, \( p < 0.001 \)), poor differentiation grade (OR = 1.66, 95% CI: 1.31–2.12, \( p < 0.001 \)), and advanced tumour stage (OR = 2.36, 95% CI: 1.67–3.34, \( p < 0.001 \)). In addition, males may generally have a high pretreatment SII value compared to females (OR = 1.37, 95% CI: 1.13–1.67, \( p = 0.002 \)).
Table 4  
Correlation between SII and clinicopathological features in urinary system cancers

<table>
<thead>
<tr>
<th>Variables</th>
<th>Included studies</th>
<th>Patients (n)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity test</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (old vs. young)</td>
<td>Binary variables</td>
<td>6</td>
<td>1337</td>
<td>1.12 (0.90–1.39)</td>
<td>0.315</td>
<td>0</td>
</tr>
<tr>
<td>Continuous variables</td>
<td></td>
<td>3</td>
<td>1001</td>
<td>-0.05 (-0.43–0.34)*</td>
<td>0.817</td>
<td>84.3</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td></td>
<td>8</td>
<td>2159</td>
<td>1.37 (1.13–1.67)</td>
<td>0.002</td>
<td>0</td>
</tr>
<tr>
<td>Tumour size (large vs. small)</td>
<td></td>
<td>5</td>
<td>1158</td>
<td>1.89 (1.49–2.40)</td>
<td>&lt; 0.001</td>
<td>35.6</td>
</tr>
<tr>
<td>Differentiation grade (poor vs. well)</td>
<td></td>
<td>5</td>
<td>1774</td>
<td>1.66 (1.31–2.12)</td>
<td>&lt; 0.001</td>
<td>45.9</td>
</tr>
<tr>
<td>Tumour stage (III/IV vs. I/II)</td>
<td></td>
<td>6</td>
<td>1804</td>
<td>2.36 (1.67–3.34)</td>
<td>&lt; 0.001</td>
<td>55.7</td>
</tr>
</tbody>
</table>

OR: odds ratio, SMD: standard mean difference, 95% CI: 95% confidence interval, vs: versus, *SMD

Publication Bias

Both Egger's tests and Begg's funnel plot were carried out to evaluate the potential publication bias of the included studies. For the meta-analysis of the relationship of pretreatment SII with OS, no obvious publication bias was detected by Egger's test (p = 0.060), but Begg's funnel plot appeared to be asymmetric (p = 0.029) (Fig. 6A). Hence, we used the “trim and fill” method to explore the potential “missing” studies. Finally, 5 hypothetically missing studies were identified, and the recombined HR was 1.80 with the corresponding 95% CI (1.61–2.01), which did not obviously differ from the initial results (Fig. 6B). In addition, no remarkable bias was observed in the analysis of the associations of pretreatment SII with PFS (Egger's test: p = 0.396; Begg's test: p = 0.133) (Fig. 6C) and CSS (Egger's test: p = 0.729; Begg's test: p = 0.806) (Fig. 6D).

Sensitivity Analysis

As shown in Fig. 7, sensitivity analysis was conducted to evaluate the reliability of the combined HRs of OS, PFS and CSS by omitting each study from the analysis sequentially. No single study affected the final conclusions, which supported that the pooled results were relatively steady and reliable.

Discussion

Although several studies have previously reported the association of SII with urinary system cancers, we found that there were some slight inconsistencies in the various results. In this meta-analysis, we systematically evaluated the potential value of SII for predicting the clinicopathological features and prognosis of urinary system cancer patients who underwent non-surgical or surgical treatment. The statistical analysis results of our study showed that elevated levels of pretreatment SII are more likely to be associated with some poor survival outcomes, such as shorter OS, PFS, and CSS, and some undesirable pathological features, such as large tumour size, poor differentiation grade, and advanced tumour stage. To our knowledge, this meta-analysis is the first to investigate whether SII can be used as an independent prognostic marker for patients with urinary system cancer regardless of the treatment strategy.

As early as 1863, Virchow found abnormal leucocyte cells in cancerous tissues and built a hypothesis that there was a correlation between the inflammatory response and cancer progression. Later, an increasing number of studies began to explore the potential mechanisms by which inflammation affects tumours through animal models and clinical trials. SII, as a new inflammatory index that is simple, economic, and easily detected, has been proposed and has received more attention in recent years; it is calculated based on the counts of peripheral neutrophils, platelets, and lymphocytes. SII has been reported to be related to the occurrence, progression, and prognosis of several diseases, such as bleeding disorders, connective tissue diseases, and various malignant tumours in humans.

In 2014, through retrospective and prospective studies, Hu and his colleagues first demonstrated that SII was a great prognostic indicator of adverse outcomes for hepatocellular carcinoma (HCC) patients and could be used as a promising tool to aid in the decision making of therapeutic strategies for HCC. Although the precise mechanism by which SII affects cancer prognosis has not been fully clarified at present, it is related to the three inflammatory biomarkers involved in the SII calculation at least. First, neutrophils can secrete various inflammatory factors, such as vascular endothelial growth factor, interleukin (IL)-6, IL-10, and prostaglandin, to accelerate the construction of the tumour...
microenvironment, which plays a critical role in promoting tumour angiogenesis, enhancing tumour cell adhesion and facilitating distant metastasis.[11, 12] Second, platelets, as the shield of circulating tumour cells, may prevent them from endogenous and exogenous immune attacks, leading to the multiplication, invasion and metastasis of the tumour.[39] At the same time, platelets can also release several chemokines and cytokines and have a similar effect to neutrophils in vivo.[40] Thus, the enhanced neutrophil and platelet counts reflect the opening of immune pathways and activation of the immune state in the organism. In contrast, lymphocytes, especially tumour-infiltrating lymphocytes, may induce the apoptosis of tumour cells and eliminate them through specific cellular immunity and humoral immunity, which is essential for immune defence and immune surveillance in the host.[41, 42] Based on the above mechanisms, it easily understandable that high SII indirectly symbolizes the inadequate immunological function of cancer patients and the intensification of tumour invasiveness. Therefore, this kind of compound immunity index is more likely to predict the undesirable pathological features and worse survival of cancer patients.

Previously, several studies have explored the prognostic impact of SII in tumours of different organs and systems by systematic reviews and meta-analyses. In 2017, Zhong et al. first demonstrated that high SII predicted poor outcomes of patients with solid tumours and could be considered a new cost-effective prognostic indicator.[43] Zhang and his colleagues provided evidence in 2018 that SII, as an easily obtained and noninvasive biomarker, was observably associated with short OS (HR: 1.52, 95% CI: 1.29–1.74, p < 0.01), DFS (HR: 2.28, 95% CI: 1.46–3.10, p < 0.01) and recurrence-free survival (RFS) (HR: 1.60, 95% CI: 1.19–2.00, p < 0.01) in patients with gastrointestinal (GI) cancers and could become a powerful tool in predicting the survival of GI cancers in clinical practice.[44] Not long ago, the prognostic value of pretreatment SII in non-small cell lung cancer patients was also proven by Wang et al. They supported that this immune parameter was helpful for physicians to develop therapeutic strategies, and patients with high SII should be recommended for immunotherapy compared to those with low SII.[45] In recent years, a vast number of studies have successively explored the correlation between SII and urinary malignant tumours. An Italian scientific research team performed a retrospective study involving 335 patients with terminal RCC receiving sunitinib and suggested that SII and its changes during immunological therapy could effectively predict the prognosis of patients with metastatic RCC.[26] In patients with UTUC undergoing radical nephroureterectomy, the results of Zheng's study supported that patients with high SII before surgery might have a markedly shorter OS, PFS, and CSS than those with low SII (all p < 0.05).[20] The findings of Man et al. and Fan et al. directly proved that pretreatment SII could assist in predicting the survival of metastatic castration-resistant PC patients treated with chemotherapy in both the training and validation cohorts, which combined with other indices (prostate-specific antigen, albumin, and fibrinogen) might guide clinicians in the identification of high-risk populations and selection of the best treatment protocols.[30, 18] In 2020, Yilmaz et al. found that SII as well as other parameters, such as NLR, prognostic nutritional index, and red cell distribution, were all associated with poor survival outcomes in patients with muscle-invasive bladder cancer (MIBC) in univariate analysis. Unfortunately, SII was not found to be an independent prognostic indicator for either OS (HR: 1.551, 95% CI: 0.877–2.774, p = 0.131) or PFS (HR: 1.240, 95% CI: 0.670–2.294, p = 0.493) in multivariate analysis.[28] However, in a similar study of MIBC, Zhang et al. revealed that elevated preoperative SII could be considered an independent predictor for patients undergoing radical cystectomy in both univariate and multivariate Cox regression analyses, and SII was more predictive than NLR and PLR.[29] The existence of heterogeneity may be caused by the difference in study regions, the inconsistency of SII cut-off values, and the variety of tumour types. The results of our meta-analysis further confirmed the critical prognostic value of SII for urinary system cancers. Therefore, we recommend that SII should be brought into the prognostic risk assessment system for urinary system cancer patients.

Nevertheless, there were still several limitations in the present meta-analysis. First, most of the articles included in our meta-analysis were retrospective studies, which inevitably led to potential defects and deviations in the original data. Second, only 13 studies involving 15 datasets comprising 3974 patients were enrolled, which might cause bias due to the limited sample size. Third, because of the difference in cut-off selection, the critical values of SII have not yet been unified. Fourth, the treatment strategies are not exactly the same in various cancer types, and these inconsistencies might have an influence on the survival of patients and thus give rise to some heterogeneity. Finally, potential publication bias cannot be avoided entirely. Therefore, the prognostic role of pretreatment SII in urinary system cancers needs to be further explored by conducting more large-scale and high-quality prospective trials in the future.

**Conclusion**

In this relatively detailed comprehensive study, our findings provide evidence that elevated SII prior to treatment is remarkably correlated with unfavourable survival outcomes and adverse pathological characteristics in patients with urinary system cancers. Hence, SII can serve as an effective prognostic indicator to help clinicians assess prognosis and develop treatment strategies for these patients.

**Abbreviations**

SII: Systemic immune-inflammation index; HR: hazard ratio; OR: odds ratio; SMD: standard mean difference; CI: Confidence interval; OS: overall survival; PFS: progression-free survival; CSS: cancer-specific survival; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; NOS: Newcastle-Ottawa Scale; RCC: renal cell carcinoma; UTUC: upper tract urothelial carcinoma; BC: bladder cancer; PC: prostate cancer; HCC: hepatocellular carcinoma; IL: interleukin; GI: gastrointestinal; MIBC: muscle-invasive bladder cancer
Declarations

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Competing interests
The authors declare that they have no competing interests.

Ethics approval
Since all analyses were based on previously published studies, ethical approval and informed consent were not required.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The data that support the findings of this study are available on request from the corresponding author.

Code availability
Not applicable.

Author contributions
XL: project development, data collection, data analysis, manuscript writing/editing. LJG: data collection, data analysis, manuscript editing. YHC: data collection, data analysis, manuscript editing. YC: data collection, data analysis, manuscript editing. XYW: data analysis, manuscript editing. PG: project development, data analysis, manuscript writing/editing. DLH: project development, data analysis, manuscript writing/editing. All authors have read and approved the manuscript.

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References


Figure 1

Flow diagram of the study selection process
Figure 2

Forest plot reflecting the prognostic significance of SII for OS
Figure 3

Forest plot reflecting the prognostic significance of SII for PFS

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lolli (2016)</td>
<td>1.71 (1.33, 2.21)</td>
<td>20.15</td>
</tr>
<tr>
<td>Zheng (TC) (2020)</td>
<td>1.58 (1.02, 3.01)</td>
<td>16.45</td>
</tr>
<tr>
<td>Zheng (VC) (2020)</td>
<td>1.48 (1.02, 2.89)</td>
<td>16.75</td>
</tr>
<tr>
<td>Jan (2018)</td>
<td>1.56 (0.94, 2.58)</td>
<td>16.97</td>
</tr>
<tr>
<td>Yilmaz (2020)</td>
<td>1.55 (0.88, 2.74)</td>
<td>16.07</td>
</tr>
<tr>
<td>Fan (2017)</td>
<td>11.80 (5.60, 24.80)</td>
<td>13.60</td>
</tr>
<tr>
<td>Overall (I-squared = 80.8%, p = 0.000)</td>
<td>2.08 (1.32, 3.26)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
Figure 4

Forest plot reflecting the prognostic significance of SII for CSS
Figure 5

Forest plots showing the correlations between SII and clinicopathological factors (A, Age: binary variables; B, Age: continuous variables; C, Gender; D, tumour size; E, differentiation grade; F: tumour stage)
Figure 6

Detection of publication bias for meta-analysis of survival outcomes (A, OS: Begg’s funnel plot; B, OS: Filled funnel plot with “trim-and-fill” method; C, PFS; D, CSS)
Figure 7

Sensitivity analysis of the relationship between SII and survival outcomes (A, OS; B, PFS; C, CSS)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAChecklist.doc
- PRISMAFlowDiagram.doc