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ORIGINAL ARTICLE

Systemic immune-inflammation index is a promising non-invasive biomarker for predicting the survival of urinary system cancers: a systematic review and meta-analysis

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ABSTRACT

Objective: Systemic immune-inflammation index (SII) has been reported in numerous studies to effectively predict the survival outcomes of urinary system cancers; however no agreement has been reached. This meta-analysis aimed to explore the prognostic significance of pre-treatment 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 30 August 2020. The hazard ratios (HRs) with 95% confidence intervals (CIs) were computed to estimate the associations of pre-treatment SII with overall survival (OS), progression-free survival (PFS), cancer-specific survival (CSS) in urinary system cancers.

Results: 13 papers were included in our meta-analysis. From the combined data, we found that a high pre-treatment SII indicated a markedly worse OS (HR = 1.98; 95% CI: 1.75–2.23; $p < .001$), PFS (HR: 2.08; 95% CI: 1.32–3.26; $p = .002$), and CSS (HR: 2.41, 95% CI: 1.73–3.35, $p < .001$). Additionally, patients with an elevated SII value might have undesirable pathological characteristics, including a large tumour size, a poor differentiation grade, and an advanced tumour stage (all $p < .001$).

Conclusions: Pre-treatment SII could be used as a non-invasive and promising biomarker to indicate the prognosis of urinary system cancer patients.

KEY MESSAGES:

- This meta-analysis evaluates the predictive value of systemic immune-inflammation index (SII) for patients with urinary system cancer.
- A high pre-treatment SII indicates a poor prognosis.
- SII can serve as a promising non-invasive biomarker to help clinicians assess the prognosis and develop treatment strategies for urinary system cancer 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.

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Introduction

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]. Prostate cancer (PC) is already the leading cause of cancer among men in the United States and some other Western countries [4]. Additionally, the remaining common malignancies of the urinary system, such as kidney, bladder, and upper urinary tract cancers, also pose a serious threat

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to human health [5–7]. Although surgical techniques and medical therapies (e.g. chemotherapy, radiotherapy, and immunotherapy) have been rapidly developed in the last 10 years, the 5-year survival rate of patients with urinary system cancers remains dismal [8,9]. Therefore, useful new biomarkers to diagnose, evaluatee and even the prognosis of 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 cancers regardless of the therapeutic regimen [10–13]. The systemic immune-inflammation index (SII), a novel inflammatory marker, is associated with the clinicopathological features and prognosis of several cancers, such as colorectal cancer, breast cancer, hepatocellular carcinoma and PC [14–17]. The SII is calculated using the following formula: SII = platelet count × neutrophil count/lymphocyte count. Compared with other common inflammatory parameters, such as the 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, reflecting 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 relationship of SII with urinary system malignancies has been explored and analysed in numerous studies [18–20]. However, because of the various experimental regions and subjects, the results of previous studies have been inconsistent. To our best knowledge, no systematic review or meta-analysis has been reported concerning the SII in urinary system tumours until now. Thus, this study aimed to comprehensively analyse the prognostic significance of the SII in patients with common urinary system cancers using previous relevant studies.

Materials and methods

Information sources and search strategy

A systematic literature search of relevant publications up to August 30, 2020, was performed by 2 authors independently using Web of Science, PubMed, Embase, and the Cochrane Library and the following terms: ("systemic immune-inflammation index" OR "SII") AND ("cancer" OR "tumour" OR "carcinoma" OR "neoplasm"). Additional studies were searched manually by scanning the reference lists of eligible original publications, review articles, and other relevant studies. The requirement for ethical approval and informed consent was waived because all the analyses in this study were based on previously published reports. Additionally, we prospectively registered the review methodology of this meta-analysis in PROSPERO (registration number: CRD42020203389).

Inclusion and exclusion criteria

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

Furthermore, publications were disqualified if they met the following criteria [1]: they were duplicate articles, reviews, conference summaries and letters [2]; they were basic medical experiments, non-human studies, case reports and editorials [3]; the studies had unavailable data.

Data extraction

Two of our research investigators 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. Additionally, if only Kaplan-Meier curves were presented in a study, the survival data were collected from the graphical survival plots utilising the software Engauge Digitiser 10.8 and the method of Tierney et al. [21] Additionally, if both multivariate and univariate analyses 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 using the Newcastle-Ottawa Scale (NOS; Stang, 2010) on a score scale of 0–9 points. A high-quality study was identified as one with a score of 6 and greater.

Statistical analysis

All statistical analyses of the data were performed utilising 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 was pooled using the fixed-effects model if the heterogeneity was not statistically significant ($p \geq .05$ or $I^2 \leq 50\%$). Otherwise, the random-effects model was used. Additionally, the presence of publication bias was evaluated visually by Begg's funnel plot and Egger's test. Furthermore, we performed sensitivity analysis to assess the reliability and stability of the results. Statistical significance was defined as $p < .05$.

Results

Search results and study characteristics

The selection procedure is presented in Figure 1. Initially, a total of 412 published articles were identified using 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 provide insufficient 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, 13 publications involving 3974 patients were enrolled in the current meta-analysis. Notably, among these 13 studies, two

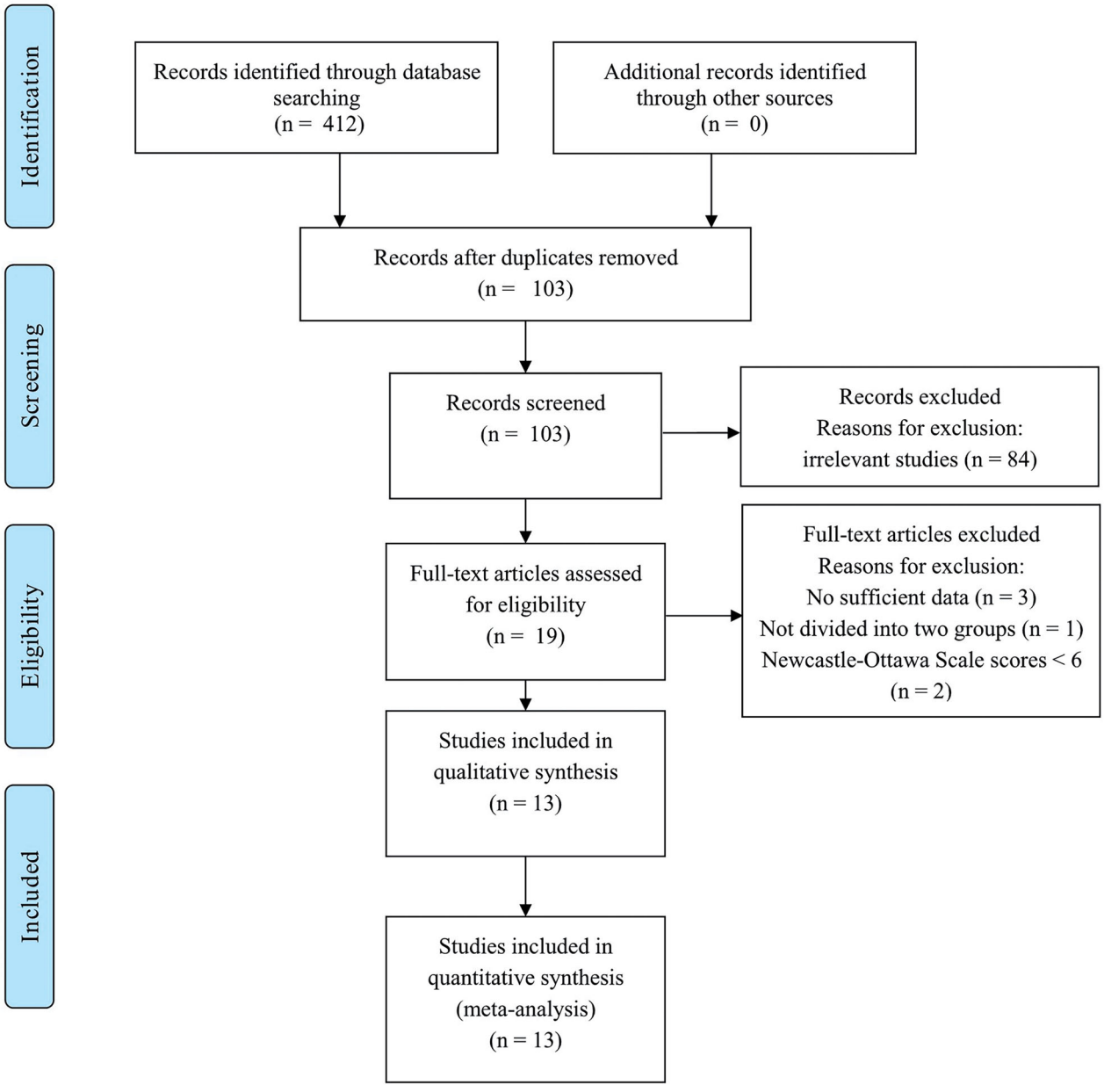

Figure 1. Flow diagram of the study selection process.

Table 1. Basic characteristics of the included studies.

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

RCC: renal cell carcinoma; UTUC: upper tract urothelial carcinoma; BC: bladder cancer; PC: prostate cancer; TC: training cohort; VC: validation cohort; MC: multi-centre; SC: single centre; DC: double centre; CC: case control; CS: cohort study; NS: no surgery; WS: with surgery; ROC: receiver operating characteristic; OS: overall survival; PFS: cancer-specific survival; CSS: progression-free survival; NOS: Newcastle-Ottawa quality assessment scale.

contained training and validation cohorts simultaneously; 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 the 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 focussed 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.

Prognostic significance of the SII for OS in urinary system cancers

All the studies reported the association between the pre-treatment SII and overall survival (OS) in urinary system cancer patients. As shown in Figure 2(A), the combined HR was 1.98 with the corresponding 95% CI (1.75–2.23), demonstrating that patients with a high SII would have a worse OS than those with a low SII ($p < .001$). Because there was no remarkable heterogeneity, the fixed-effects model was used ($I^2 = 17.0\%$; $p = .263$). Additionally, subgroup analysis of OS based on the sample size, tumour location, urothelial carcinoma (yes or no), treatment strategy, cut-off value, and follow-up years further supported the above results and revealed that the sample size, tumour location, urothelial carcinoma (yes or no) and treatment strategy might be potential causes of the slight heterogeneity (Table 2).

Prognostic significance of the SII for PFS in urinary system cancers

Six datasets involving 1540 patients focussing on the correlation of the pre-treatment SII with progression-free survival (PFS). The combined result showed that a high SII indicated a poor PFS in patients (HR: 2.08; 95% CI: 1.32–3.26; $p = .002$) (Figure 2(B)). A random-effects model was used because of heterogeneity ($I^2 = 80.8\%$; $p < .001$). Therefore, we performed subgroup analysis to evaluate whether the heterogeneity was related to the same variables as above. The results demonstrated that a sample size less than 200, lower urinary tract tumour, non-urothelial carcinoma, non-surgical treatment, a cut-off value less than 600, and a median follow-up not longer than 5 years might be the major sources of heterogeneity; however, these results did not reverse the conclusion (Table 3).

Prognostic significance of the SII for CSS in urinary system cancers

Only four studies involving five datasets investigated the relationship between the pre-treatment SII and cancer-specific survival (CSS). The pooled data suggested that, compared with a low SII, a high SII was related to a worse CSS (HR: 2.41; 95% CI: 1.73–3.35; $p < .001$; Figure 2(C)). Fortunately, no significant heterogeneity was observed among these studies. Thus, a random-effects model was used to analyse the prognostic value of the SII for CSS in urinary system cancer patients ($I^2 = 0$; $p = .904$).

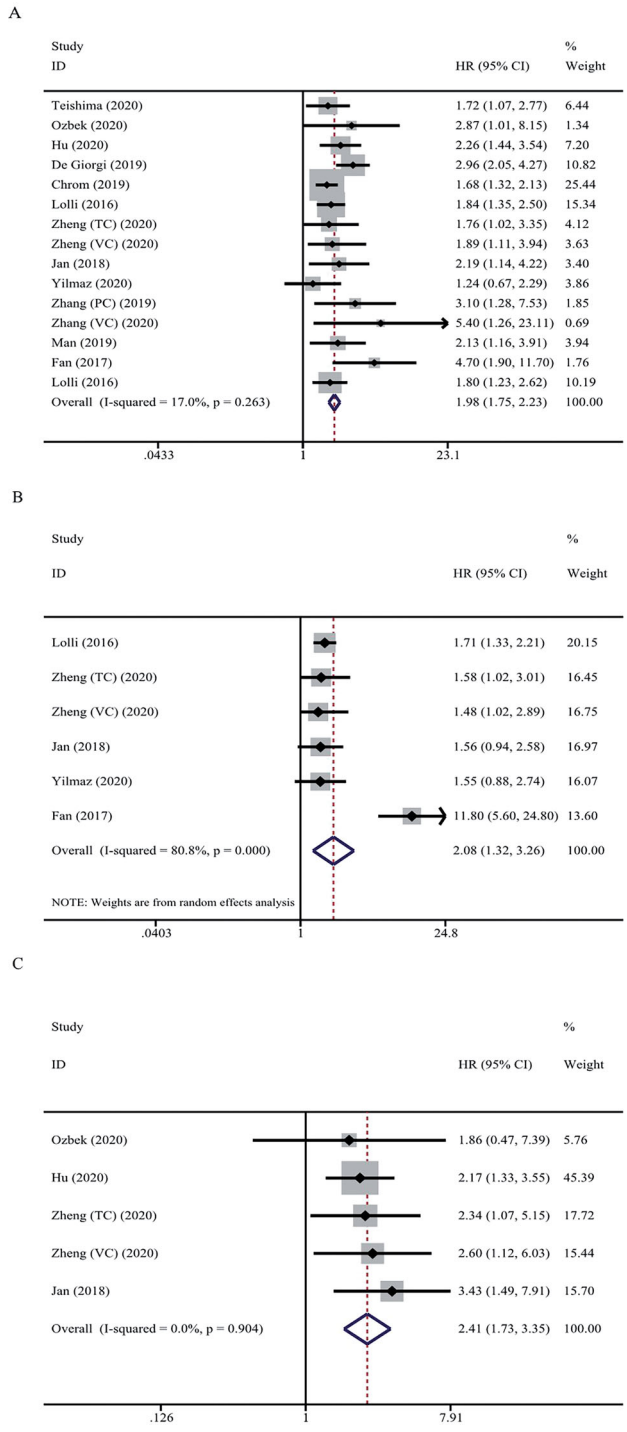

Figure 2. Forest plot reflecting the prognostic significance of SII for survival in patients (A, OS; B, PFS; C, CSS).

Correlations between the SII and clinicopathological factors in urinary system cancers

Overall, 9 datasets comprising 2338 patients reported the associations of the 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 random-effects model was used based on the presence or absence of heterogeneity. No obvious correlation was observed between the pre-treatment SII and 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, $p = .315$; SMD = −0.05, 95% CI: −0.43–0.34, $p = .817$; Table 4 and Figure 3). However, the pooled results revealed that a pre-treatment high SII was significantly related to a large tumour size (OR = 1.89; 95% CI: 1.49–2.40; $p < .001$), a poor differentiation grade (OR = 1.66; 95% CI: 1.31–2.12; $p < .001$), and an advanced tumour stage (OR = 2.36; 95% CI: 1.67–3.34; $p < .001$). Additionally, male patients generally had a high pre-treatment SII value compared with female patients (OR = 1.37; 95% CI: 1.13–1.67; $p = .002$).

Publication bias

Both Egger's tests and Begg's funnel plot were performed to evaluate the potential publication bias of the included studies. Regarding the meta-analysis of the relationship of the pre-treatment SII with OS, no obvious publication bias was detected by Egger's test ($p = .060$); however, Begg's funnel plot appeared to be asymmetric ($p = .029$) (Figure 4(A)). Thus, 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 differ from the initial results (Figure 4(B)). Additionally, no remarkable bias was observed in the analysis of the associations of pre-treatment SII with PFS (Egger's test: $p = .396$; Begg's test: $p = .133$) (Figure 4(C)) and CSS (Egger's test: $p = .729$; Begg's test: $p = .806$) (Figure 4(D)).

Sensitivity analysis

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 (Figure 5). No single study affected the conclusions, supporting that the pooled results were relatively steady and reliable.

Table 2. Subgroup analysis of the pooled HR and 95% CI between SII and OS in urinary system cancers.

					Heterogeneity test		
Variables	Included datasets	Patients (*n*)	HR (95% CI)	*p*-Value	I^2 (%)	*p*-Value	Model
Total	15	3974	1.98 (1.75–2.23)	<.001	17.0	.263	Fixed-effects
Sample size							Fixed-effects
<200	7	999	2.09 (1.60–2.75)	<.001	35.0	.161	
≥ 200	8	2975	1.95 (1.70–2.23)	<.001	5.8	.386	
Tumour location							Fixed-effects
Upper tract	9	3100	1.96 (1.71–2.24)	<.001	0.5	.429	
Lower tract	6	874	2.03 (1.57–2.26)	<.001	43.0	.118	
Urothelial carcinoma							Fixed-effects
N	9	2664	1.99 (1.74–2.27)	<.001	30.8	.172	
Y	6	1310	1.91 (1.44–2.55)	<.001	4.7	.386	
Treatment							Fixed-effects
NS	7	1842	1.95 (1.70–2.25)	<.001	44.0	.098	
WS	8	2132	2.05 (1.62–2.59)	<.001	0	.534	
Cut-off value							Fixed-effects
<600	7	1792	2.25 (1.80–2.81)	<.001	0	.447	
≥ 600	8	2182	1.88 (1.63–2.17)	<.001	24.9	.230	
Follow-up years							Fixed-effects
<5	10	2441	2.01 (1.73–2.34)	<.001	21.0	.250	
≥ 5	5	1533	1.92 (1.57–2.34)	<.001	25.0	.255	

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

Table 3. Subgroup analysis of the pooled HR and 95% CI between SII and PFS in urinary system cancers.

					Heterogeneity test		
Variables	Included datasets	Patient (n)s	HR (95% CI)	*p*-Value	I2 (%)	*p*-Value	Model
Total	6	1540	2.08 (1.32–3.26)	.002	80.8	<.001	Random-effects
Sample size							Random-effects
<200	2	256	4.21 (0.58–30.80)	.156	94.5	<.001	
≥200	4	1284	1.64 (1.35–1.99)	<.001	0	.958	
Tumour location							Random-effects
Upper tract	4	1284	1.64 (1.35–1.99)	<.001	0	.958	
Lower tract	2	256	4.21 (0.58–30.80)	.156	94.5	<.001	
Urothelial carcinoma							Random-effects
N	2	439	4.35 (0.66–28.82)	.128	95.7	<.001	
Y	4	1101	1.54 (1.18–2.01)	.001	0	.998	
Treatment							Random-effects
NS	2	439	4.35 (0.66–28.82)	.128	95.7	<.001	
WS	4	1101	1.54 (1.18–2.01)	.001	0	.998	
Cut-off value							Random-effects
<600	2	528	4.21 (0.58–30.56)	.155	94.9	<.001	
≥ 600	4	1012	1.64 (1.34–1.99)	0	0	.958	
Follow-up years							Random-effects
<5	6	1540	2.08 (1.32–3.26)	.002	80.8	<.001	
≥5	0	0	–	–	–	–	

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

Table 4. Correlation between SII and clinicopathological features in urinary system cancers.

					Heterogeneity test		
Variables	Included studies	Patients (*n*)	OR (95% CI) SMD (95% CI)*	*p*-Value	I^2 (%)	*p*-Value	Model
Age (old vs. young)							
Binary variables	6	1337	1.12 (0.90-1.39)	.315	0	.554	Fixed-effects
Continuous variables	3	1001	−0.05 (−0.43–0.34)*	.817	84.3	.002	Random-effects
Gender (male vs. female)	8	2159	1.37 (1.13–1.67)	.002	0	.430	Fixed-effects
Tumour size (large vs. small)	5	1158	1.89 (1.49–2.40)	<.001	35.6	.184	Fixed-effects
Differentiation grade (poor vs. well)	*5*	1774	1.66 (1.31–2.12)	<.001	45.9	.116	Fixed-effects
Tumour stage (III/IV vs. I/II)	6	1804	2.36 (1.67–3.34)	<.001	55.7	.046	Random-effects

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

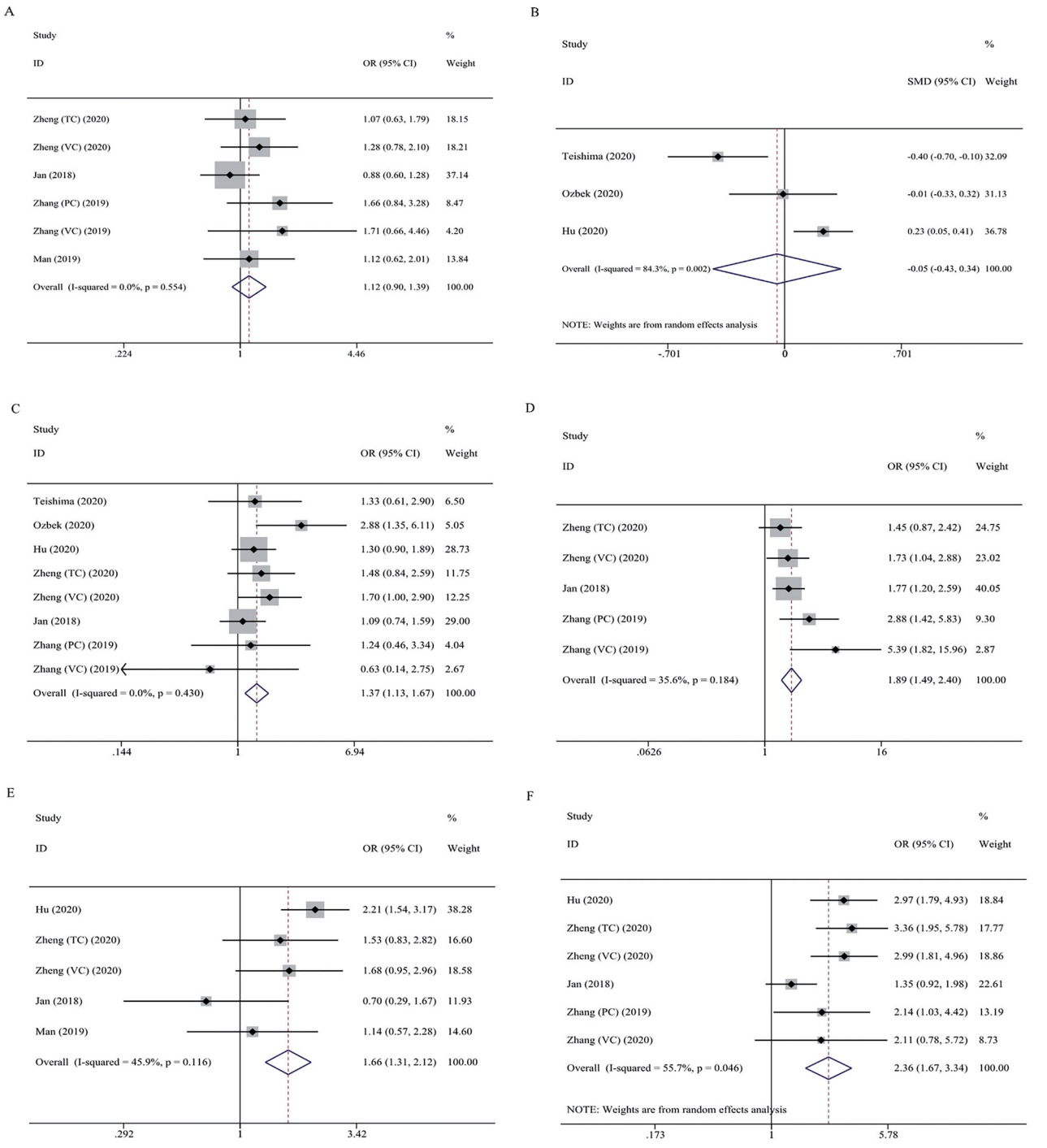

Figure 3. Forest plots showing the correlations between SII and clinicopathological factors (A, Age: binary variables; B, Age: continuous variables; C, Gender; D, tumour size; E, differentiation grade; F: tumour stage).

Discussion

Although several studies have previously reported the association of SII with urinary system cancers, we found some inconsistencies among the various results. In the present meta-analysis, we systematically evaluated the potential value of SII for predicting the clinicopathological features and prognosis of urinary system cancer patients who had undergone non-surgical or surgical treatment. Our statistical analyses showed that elevated levels of the pre-treatment SII are more likely to be associated with poor survival outcomes, such as shorter OS, PFS, and CSS, and undesirable pathological features, such as a large tumour size, a poor differentiation grade, and an advanced tumour stage. To our best knowledge, this meta-analysis is the first to investigate whether SII can

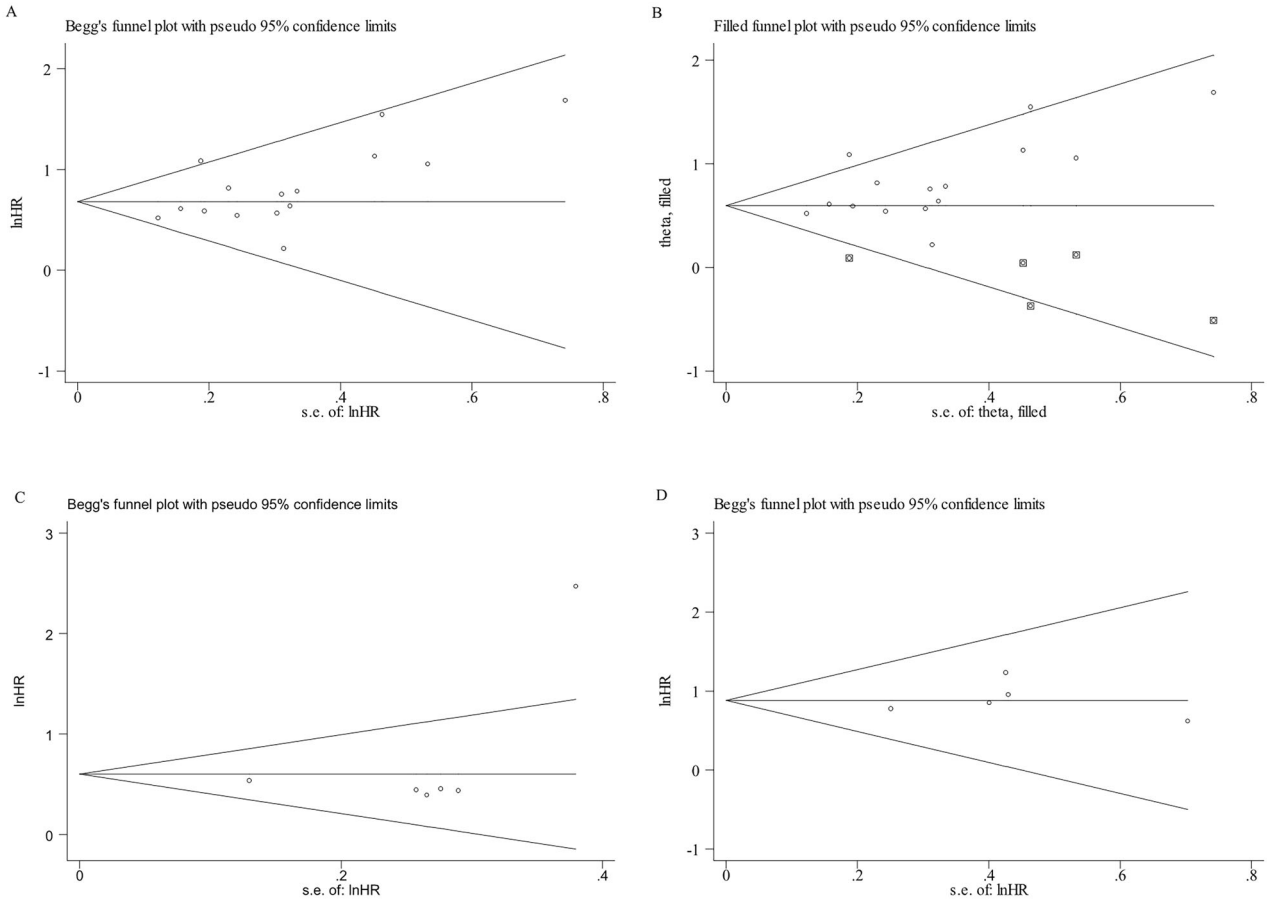

Figure 4. Detection of publication bias for meta-analysis of survival outcomes (A, OS: Begg's funnel plot; B, OS: Filled funnel plot with "trim-and-fill" method; C, PFS; D, CSS).

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 formulated a hypothesis that a correlation existed between the inflammatory response and cancer progression [32]. Later, an increasing number of studies began to explore the potential mechanisms by which inflammation affects tumours using animal models and clinical trials [33,34]. The 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. The SII is related to the occurrence, progression, and prognosis of several diseases, such as bleeding disorders, connective tissue diseases, and various malignant tumours in humans [35–37].

In 2014, using retrospective and prospective studies, Hu and his colleagues first demonstrated that the SII was a strong prognostic indicator of adverse outcomes for hepatocellular carcinoma (HCC) patients and could be a promising tool to aid in the decision making of therapeutic strategies for HCC [38]. Although the precise mechanism by which the SII affects cancer prognosis has not been fully clarified presently, it is at least related to the three inflammatory biomarkers involved in the SII calculation. 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 exert effects similar to those of neutrophils *in vivo* [40]. Thus, the enhanced neutrophil and platelet counts reflect the opening of the immune pathways and activation of the immune state in the organism. By contrast, lymphocytes, particularly tumour-infiltrating

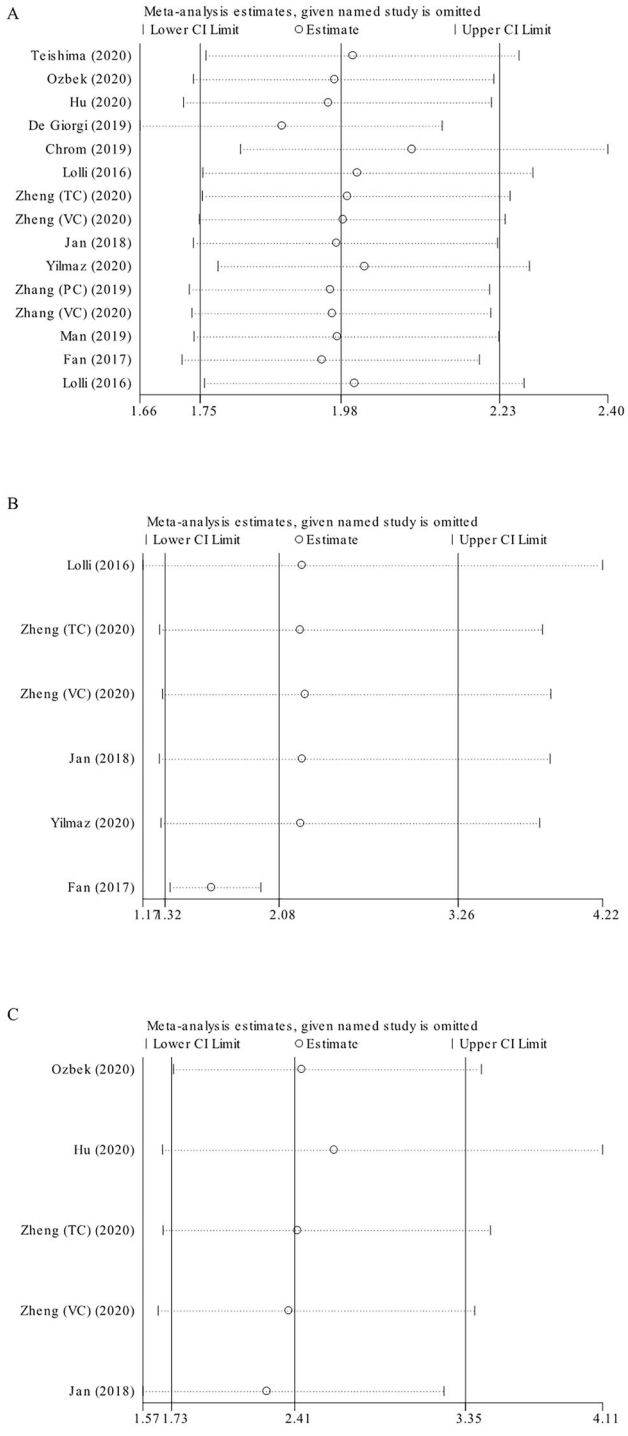

Figure 5. Sensitivity analysis of the relationship between SII and survival outcomes (A, OS; B, PFS; C, CSS).

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 is easily understandable that a high SII indirectly symbolises the inadequate immunological function of cancer patients and intensification of tumour invasiveness. Therefore, this 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 the SII in tumours of different organs and systems using systematic reviews and meta-analyses. In 2017, Zhong et al. first demonstrated that a high SII predicted the 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 the SII, as an easily obtained and non-invasive biomarker, was associated with a short OS (HR: 1.52; 95% CI: 1.29-1.74; $p < .01$), DFS (HR: 2.28; 95% CI: 1.46–3.10; $p < .01$) and recurrence-free survival (RFS) (HR: 1.60; 95% CI: 1.19–2.00; $p < .01$) in patients with gastrointestinal (GI) cancers and could become a powerful tool in predicting the survival of GI cancers in clinical practice [44]. Recently, the prognostic value of the pre-treatment 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 a high SII should be recommended for immunotherapy compared with those with a low SII [45]. In recent years, many studies have successively explored the correlation between the 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 Zheng's study of patients with UTUC undergoing radical nephroureterectomy, the patients with a high SII before surgery had a markedly shorter OS, PFS, and CSS than those with a low SII (all $p < .05$) [20]. The findings of Man et al. and Fan et al. directly proved that the pre-treatment SII could assist in predicting the survival of metastatic castration-resistant PC patients treated with chemotherapy in both the training and validation cohorts. Thus, the pre-treatment SII, 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 [18,30]. In 2020, Yılmaz et al. found that the SII and other parameters, such as the NLR, prognostic nutritional index, and red cell distribution, were associated with poor survival outcomes in patients with muscle-invasive bladder cancer (MIBC) in univariate analysis. Unfortunately, the SII was not found to be an independent prognostic indicator for either OS (HR: 1.551; 95% CI: 0.877–2.774; $p = .131$) or

PFS (HR: 1.240; 95% CI: 0.670–2.294; $p = .493$) in multivariate analysis [28]. However, in a similar study of MIBC, Zhang et al. revealed that an elevated preoperative SII could be considered an independent predictor for patients undergoing radical cystectomy in both univariate and multivariate Cox regression analyses, and the SII was more predictive than the NLR and PLR [29]. The heterogeneity may be caused by the differences in the study regions, inconsistency of the SII cut-off values, and various tumour types. The results of our meta-analysis further confirmed the critical prognostic value of the SII for urinary system cancers. Therefore, we recommend that SII should be applied to the prognostic risk assessment system for urinary system cancer patients.

However, the present meta-analysis has several limitations. 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, likely causing bias due to the limited sample size. Third, because of the differences in cut-off selection, the critical values of the SII have not yet been unified. Fourth, the treatment strategies are not exactly the same in various cancer types; these inconsistencies may influence the survival of patients, producing heterogeneity. Finally, potential publication bias cannot be avoided entirely. Therefore, the prognostic role of the pre-treatment 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 an elevated pre-treatment SII is markedly correlated with unfavourable survival outcomes and adverse pathological characteristics in patients with urinary system cancers. Hence, the SII can serve as an effective prognostic indicator to help clinicians assess the prognosis and develop treatment strategies for these patients.

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Ethical approval

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

Author contributions

Conceptualisation: XL, DLH; Data curation: XL, LJG, YHC, YC; Formal analysis: XL, LJG; Investigation: XL, LJG, YHC, YC, XYW, PG, DLH; Methodology: XL, LJG, YHC, YC, XYW, PG, DLH; Resources: DLH; Software: XL, LJG, YHC, YC; Supervision: DLH, PG; Writing – original draft: XL, LJG, YHC, YC, XYW, PG, DLH; Writing – review & editing: XL, LJG, YHC, YC, XYW, PG, DLH. All the authors have read and approved the manuscript.

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Data availability statement

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

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