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The association between systemic immune-inflammation index and risk of prostate carcinoma; a systematic review and meta-analysis

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Abstract

Introduction: Prostate carcinoma is the second most common cancer in the world, and the association between the systemic immune inflammation (SII) index and prostate cancer is not clear.
Objectives: The present study aimed to investigate the relationship between the SII index and prostate carcinoma using systematic review and meta-analysis methods.
Materials and Methods: Databases ProQuest, Embase, PubMed, Web of Science, Cochrane, and Google Scholar Search Engine were used to find articles published by November 10, 2024. There was no limitation for the time or location of the studies in the search for resources. Data was analyzed using STATA software version 14, and tests with *P* values<0.05 were considered statistically significant.
Results: In general, high SII index levels increased the risk of prostate carcinoma (Odds ratio [OR]: 1.44; 95% CI: 1.22, 1.70). High SII index levels in the United States and cross-sectional studies increased the risk of prostate cancer by 44 percent; however, there was no significant relationship between the SII index and prostatic neoplasms in China or case-control (OR: 1.27; 95% CI: 0.47, 3.43) studies. Furthermore, the increase of the SII index in the middle one-third (OR: 1.35; 95% CI: 1.11, 1.64), upper one-third (OR: 1.57; 95% CI: 1.16, 2.10), and the fourth quartile (OR: 2.17; 95% CI: 1.44, 3.27) increased in the risk of prostate carcinoma. However, in the second quartile (OR: 0.91; 95% CI: 0.53, 1.55) and third quartile (OR: 1.26; 95% CI: 0.59, 2.70), there was no significant association between the SII index and the risk of prostatic neoplasms. High neutrophil-to-lymphocyte ratio (NLR) levels increased the risk of prostate carcinoma (OR: 1.50; 95% CI: 1.24, 1.82), but there was no statistically significant relationship between total prostate specific antigen and prostate cancer (OR: 1; 95% CI: 0.72, 1.39).
Conclusion: High SII index levels and high NLR levels increased the risk of prostate carcinoma by 44% and 50%, respectively, and those with elevated SII and NLR were at higher risk.
Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024616273) and Research Registry (UIN: reviewregistry1921) websites.

Introduction

Prostate carcinoma is the second most common cancer and the fifth primary cause of death and mortality due to cancer in men (1,2). In 2023, a total of 288 300 patients were diagnosed with prostatic neoplasms, and the mortality rate of prostatic cancer was estimated as 34 700 for the year (2), which will increase with the global trend of population aging (3). The interaction between systemic inflammation and local immune response is primarily considered the seventh sign of cancer (4). From the perspective of various methodologies, including genetic, epidemiologic, and molecular methods, inflammation is the primary cause of prostatic carcinogenesis and the progression of prostate carcinoma (5). Recent studies suggested inflammatory factors, including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), as prostate carcinoma predictors (6). Convenient preparation, quick access, and low costs are among the prominent advantages of blood-based indicators (7), such as various immune cells interacting with cancer cells

Key point

In a review of five articles, findings consistently indicated that elevated levels of the systemic immune-inflammation index (SII) and the neutrophil-to-lymphocyte ratio (NLR) significantly increased the risk of developing prostatic carcinoma. The examination of various SII index levels demonstrated a clear correlation, where higher SII values were associated with an increased likelihood of prostate cancer incidence. Consequently, both elevated SII and NLR are identified as independent risk factors for the development of prostatic neoplasms, underscoring the importance of these biomarkers in assessing prostate cancer risk and potentially guiding clinical decision-making in patient management.

and the inflammation-related environment (8,9). The systemic immune-inflammation index (SII), which is a combination of NLR and platelet-to-lymphocyte ratio (PLR) components, is a more potent method to predict the incidence and progression of several types of cancers (10-12).

On the other hand, the association between the SII index and prostatic neoplasms is unclear, as in 2022, researchers conducted a case-control study in China and reported no significant relationship between the SII index and the risk of prostate cancer (13). However, a cross-sectional study in the USA showed that high SII index levels in the upper third increased the risk of prostatic carcinoma (14). Hence, the present study used the systematic review and meta-analysis methods to present a general estimate of a larger population at the global level.

Materials and Methods

Study protocol

The protocol of the current systematic review and meta-analysis was registered at the PROSPERO (The International Prospective Register of Systematic Reviews) and Research Registry websites, and the study was designed based on the Preferred reporting items for systematic review and meta-analysis (PIRSMA) (15).

PICO elements

Our target population included studies examining the association between the SII index and prostate cancer; a high SII index level was our intended exposure. Healthy individuals were the comparison group. Investigating the risk of prostate carcinoma was our primary outcome, and examining the relationship between high NLR or total serum prostate-specific antigen (sPSA) and the risk of prostate cancer was the secondary outcome.

Search strategy

ProQuest, Embase, PubMed, Web of Science, Cochrane, and Google Scholar Search databases were searched using the Medical Subject Headings (MeSH) keywords and their equivalents to find articles published by November 10, 2024. There was no limitation for the time or location of the studies in the search for resources. Nonetheless, the articles were published from 2022 to 2024, and out of the five studies examined, four were conducted in the US and one in China. Advanced search was conducted by combining keywords using the operators (AND, OR). A manual search was conducted by examining the references of the primary articles. The search strategy used in the PubMed database was as follows: (Prostatic Neoplasms OR Prostate Neoplasm OR Cancer of Prostate) AND (Systemic immune-inflammation OR SII index)

Inclusion criteria

Studies that examined the association between the SII index and risk of prostatic carcinoma.

Exclusion criteria

Literature reviews, letters to the editor, low-quality studies, and articles published in congress or conferences, duplicate studies, those without accessible full text, studies that investigated the combined effect of the SII index and another indicator, and studies that lacked the data required for analysis were excluded.

Qualitative assessment

Two authors assessed the studies using the Newcastle-Ottawa Scale (NOS). In this checklist, a maximum of one star was assigned to each question, and only the question related to the comparison could receive two stars. Accordingly, the lowest score, zero, indicated the lowest quality, and the highest score, ten, denoted the highest quality. The cut-off score of the questionnaire was six (16).

Data extraction

Two authors extracted the following information: author's name, study duration, publication year, study type and location, age and number of samples, and the odds ratio of association between the SII index and risk of prostate cancer (in addition to its upper and lower limits).

Statistical analysis

Odds ratio (OR) logarithm was utilized to analyze the data, and studies were combined. The heterogeneity of the studies was examined using the I^2 index. The random-effects model was used in the present research due to the high heterogeneity. A subgroup analysis was used to examine the correlation between the SII index and the risk of prostatic neoplasms based on the variables study type, location, and research stages. Further analysis was conducted using meta-regression and publication bias. Data was analyzed using the STATA 14 software, and tests with p-values < 0.05 were considered statistically significant.

Results

Searches in databases and the Google Scholar Search Engine resulted in 193 studies, among which 111 were duplicates. After reviewing the abstracts of the remaining

82 studies, 13 were removed as their abstracts did not present complete information, and their full texts were not available. The complete text of 69 studies was reviewed, and 26 articles that lacked the necessary data for analysis were removed. A total of 38 studies were excluded due to other exclusion criteria, and five studies remained (Figure 1).

Table 1 examines the five studies, among which four were cross-sectional and one was case-control.

As Figure 2 demonstrates, high SII index levels increased the risk of prostatic carcinoma (OR: 1.44; 95% CI: 1.22, 1.70).

High SII index levels increased the risk of prostate cancer in the United States (OR: 1.44; 95% CI: 1.21, 1.71); however, there was no significant association between the SII index level and prostatic neoplasms in China (OR: 1.27; 95% CI: 0.47, 3.43) (Figure 3).

High SII index levels increased the risk of prostatic neoplasms in cross-sectional (OR: 1.44; 95% CI: 1.21, 1.71) studies, though there was no significant association between the SII index and prostate cancer in case-control (OR: 1.27; 95% CI: 0.47, 3.43) studies (Figure 4). In different stages of the research we concluded that increased SII index levels elevated the risk of prostate cancer in the middle third (OR: 1.35; 95% CI: 1.11, 1.64), upper third (OR: 1.57; 95% CI: 1.16, 2.10), and fourth quartile (OR: 2.17; 95% CI: 1.44, 3.27); however, in second quartile (OR: 0.91; 95% CI: 0.53, 1.55) and third quartile (OR: 1.26; 95% CI: 0.59, 2.70) there was no statistically significant relationship between the SII index and prostatic carcinoma (Figure 5).

Elevated NLR increased the risk of prostate cancer (OR: 1.50; 95% CI: 1.24, 1.82), but there was no statistically significant association between tPSA and prostatic neoplasms (OR: 1; 95% CI: 0.72, 1.39) (Figures 6 and 7).

Meta-regression in Figure 8 demonstrated that there was no statistically significant relationship between the research objective and publication year of the articles ($P=0.351$).

Figure 9 showed that there was no publication bias ($P=0.612$). Therefore, in the resource search section,

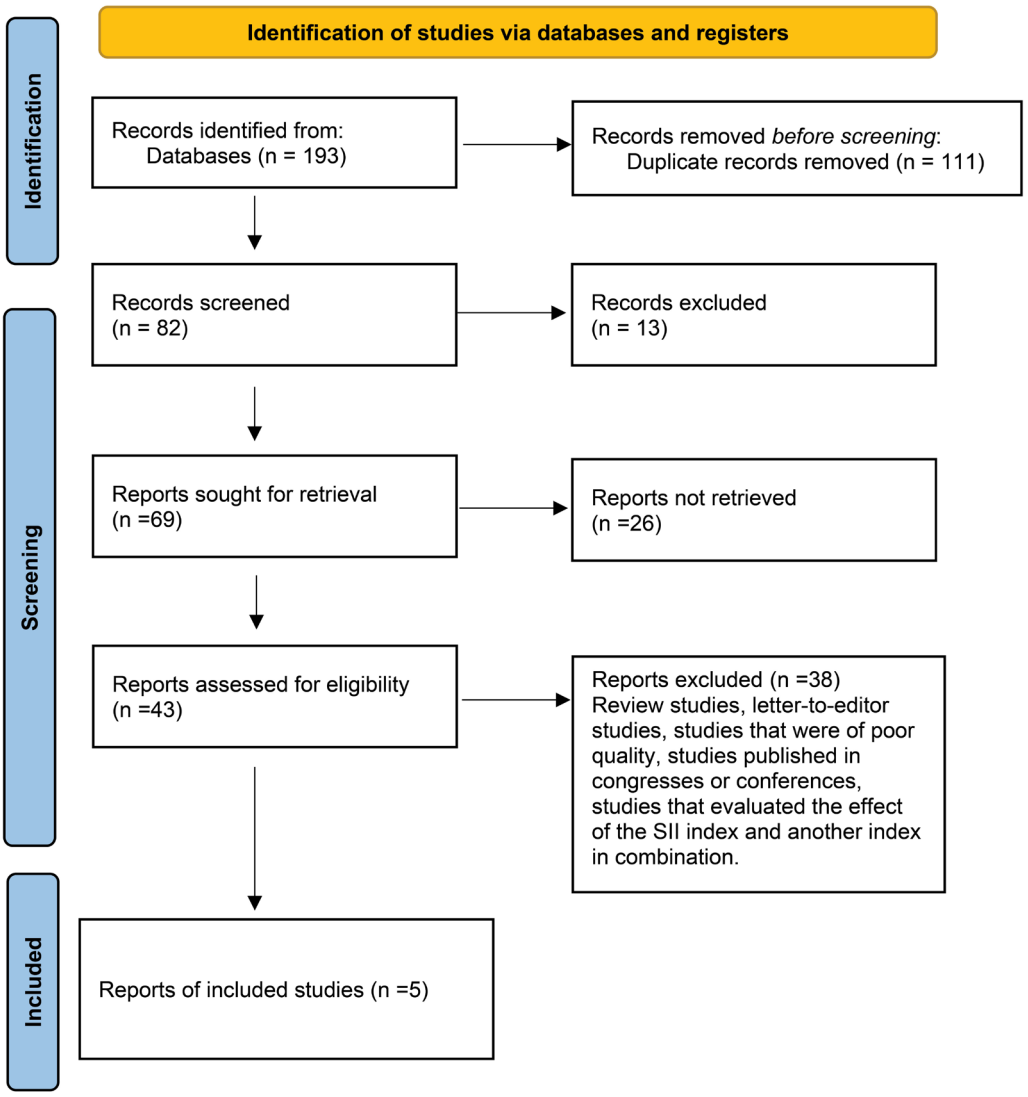

Figure 1. PRISMA flowchart of the study.

Table 1. Information of articles reviewed in this systematic review and meta-analysis

Author, year	Country	Type of study	Duration of study	Sample size	Levels of SII (Mean)	Stage of study	Association between SII index and risk of prostate carcinoma		
							OR	Low	Up
Wang L, 2024 (17)	USA	Cross-sectional	1999–2020	NR	NR	Tertile 2	1.42	1.11	1.83
				NR	NR	Tertile 3	1.8	1.41	2.28
He R, 2024 (18)	USA	Cross-sectional	between 2001 and 2010	2664	8.519-9.0255	Quartile 2	0.8	0.39	1.65
				NR	9.0255-9.5332	Quartile 3	0.88	0.49	1.57
				NR	9.5332-13.514	Quartile 4	1.96	1.19	3.24
Yao W, 2024 (19)	USA	Cross-sectional	from 2007 to 2010	NR	NR	Quartile 2	1.06	0.48	2.34
				NR	NR	Quartile 3	1.92	0.93	3.97
				NR	NR	Quartile 4	2.68	1.32	5.46
Luo Z, 2023 (14)	USA	Cross-sectional	1999–2010	2673	NR	Tertile 2	1.24	0.91	1.7
				2674	NR	Tertile 3	1.33	1.01	1.81
Wang S, 2022 (13)	China	Case-Control	Between Jan 2014 and Dec 2019	NR	≥471.86	Total	1.27	0.47	3.43

NR: Not reported; OR: Odds ratio.

published studies in this field were reviewed, regardless of whether they were in line with our research hypothesis or not.

Discussion

Elevated SII index levels and high NLR increased the risk of prostate cancer by 44% and 50%, respectively. Americans with high SII index levels are exposed to higher risks of prostatic neoplasms. Furthermore, higher SII index levels increased the risk of prostate cancer in the middle third, upper third, and fourth quartile. However, there was no significant association between the SII index and prostatic carcinoma in the second and third quartiles.

A cross-sectional study by He et al on older adults reported that demonstrated inflammation through the SII index was associated with higher risks of prostate cancer (OR: 1.96, 95% CI: 1.19, 3.24) (18). In another cross-sectional study by Yao et al on male middle-aged and older adults in the United States, results showed that elevated SII index levels increased the risk of prostatic carcinoma by 52% (OR: 1.52, 95% CI: 1.13, 2.04) (19). The results of the mentioned studies were consistent with the present research, indicating that high SII index levels in men can play a prognostic role in prostate cancer incidence. Accordingly, we can identify male patients at risk of prostatic neoplasms by examining the SII index and taking necessary measures to prevent prostate cancer.

According to a cross-sectional study by Luo et al, there was no significant association between the SII index and prostate cancer (OR: 1.07, 95% CI: 0.99, 1.15) (14). Based on the retrospective research by Wang et al investigating the values of SII index and NLR, the relationship between

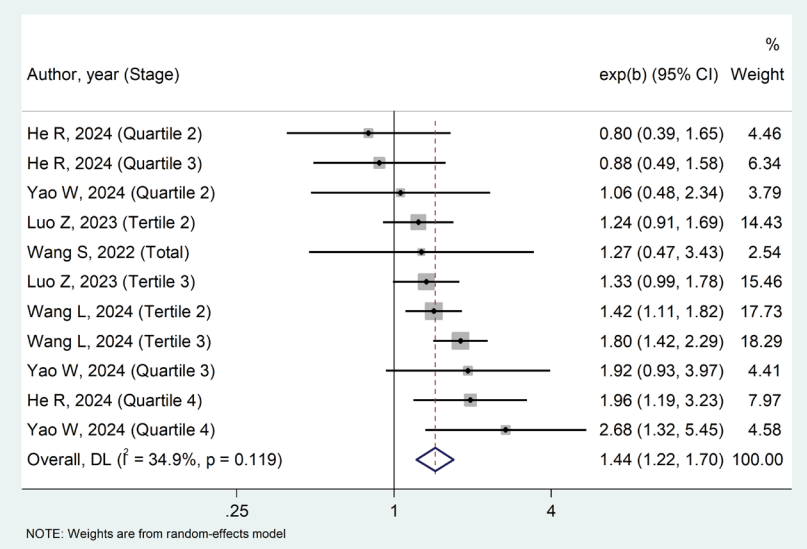

Figure 2. Forest plot showing the association between SII index and risk of prostate carcinoma.

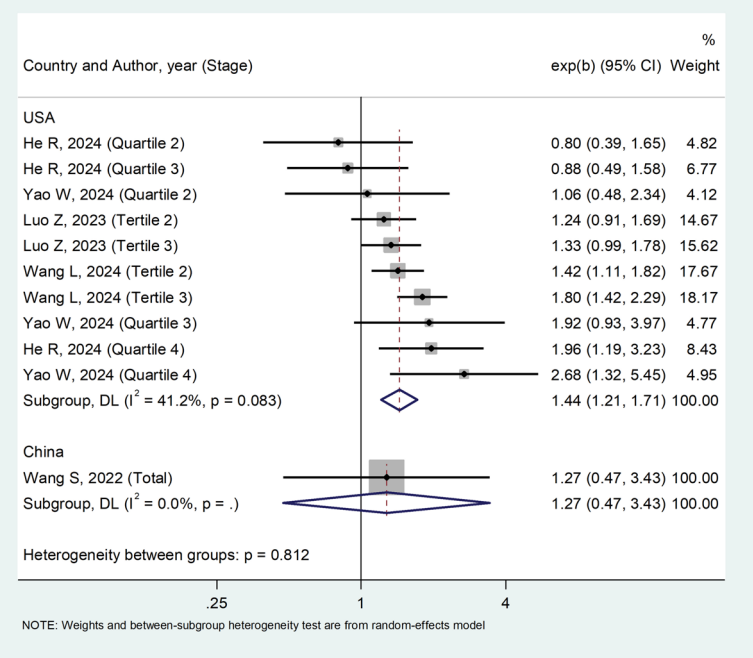

Figure 3. Forest plot showing the association between SII index and risk of prostate carcinoma by country.

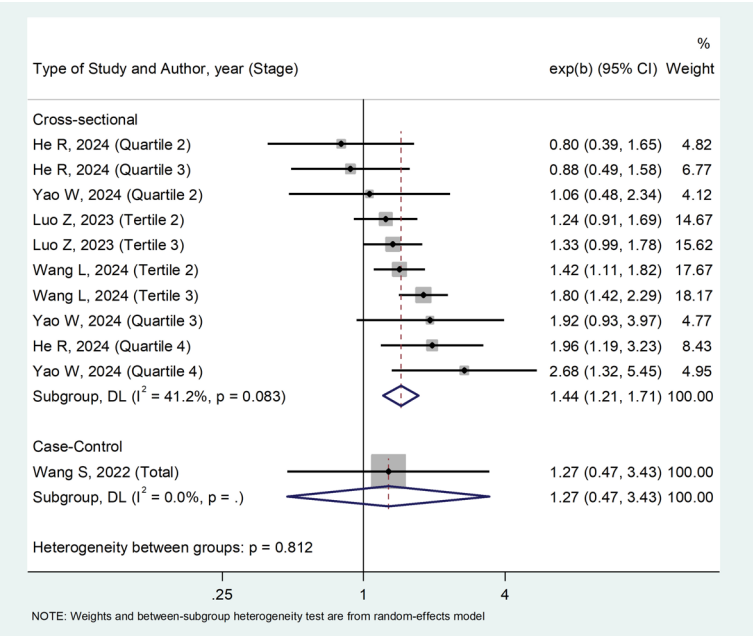

Figure 4. Forest plot showing the association between SII index and risk of prostate carcinoma by design.

prostate cancer and NLR ≥1.6 (OR: 2.73; 95% CI: 0.93, 7.96), SII ≥471.86 (OR: 1.27; 95% CI: 0.47, 3.43), and PSA ≥12.89 ng/mL (OR: 1.44; 95% CI: 0.62, 3.94) was not significant (13). The results of the mentioned studies were inconsistent with our findings. However, influential variables, including the patient's age, type of study, and the level of SII and NRL in the mentioned studies, were different from the present meta-analysis and could have caused differences in the results. However, in our study, there was no significant association between PSA and risk of prostatic carcinoma, which was consistent with the study by Wang et al.

In a meta-analysis by Qi et al, the combined results revealed that elevated SII index was associated with the aggravation of overall survival and biochemical recurrence-free survival of patients with prostate cancer. However, there was no significant relationship between the SII index and progression-free survival (20). Based

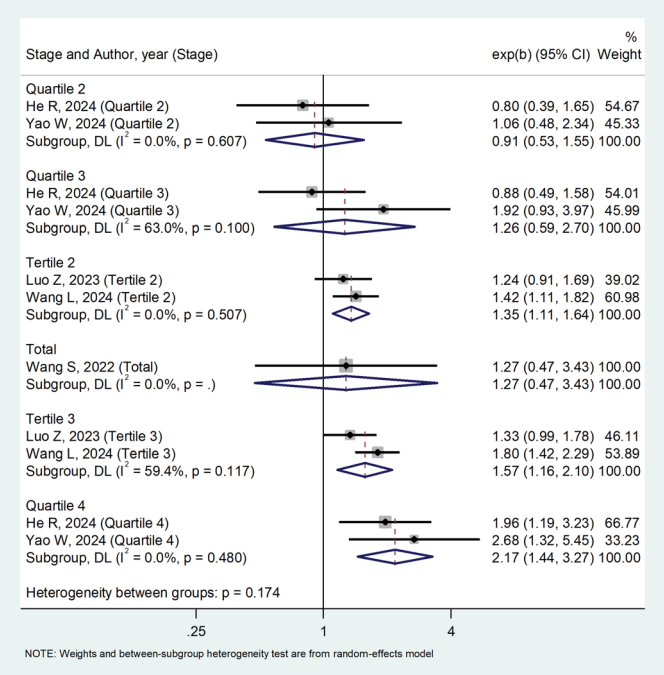

Figure 5. Forest plot showing the association between SII index and risk of prostate carcinoma by stage of study.

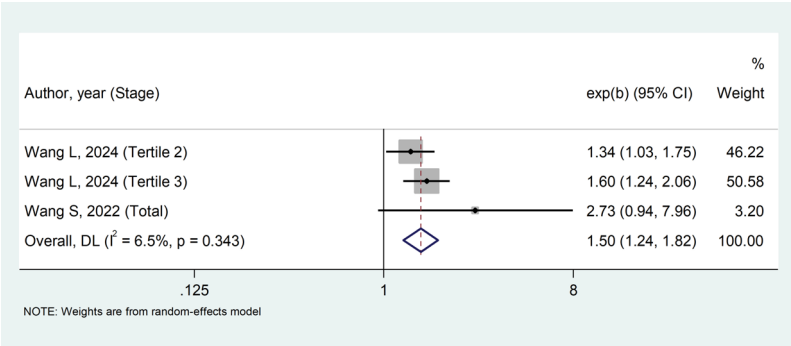

Figure 6. Forest plot showing the association between NLR and risk of prostate carcinoma.

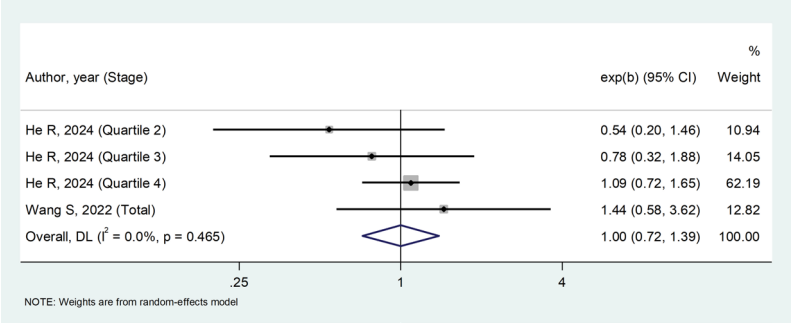

Figure 7. Forest plot showing the association between total prostate specific antigen (tPSA) and risk of prostate carcinoma.

on the results of a meta-analysis by Zhang et al on a population of patients with prostate cancer, elevated SII index levels were associated with poor overall survival and worse progression-free survival/ biochemical recurrence-free survival (21). The findings of a meta-analysis by Meng et al showed that high SII index levels were correlated with poor overall survival (22). A meta-analysis by Wang et al investigating the importance of the SII index in urothelial carcinoma indicated that elevated SII index levels before surgery was associated with poor survival outcomes in patients with urothelial carcinoma, including overall survival, cancer-specific survival, recurrence-free survival, and progression-free survival (23). Results of another meta-analysis by Yu et al evaluating the importance of the

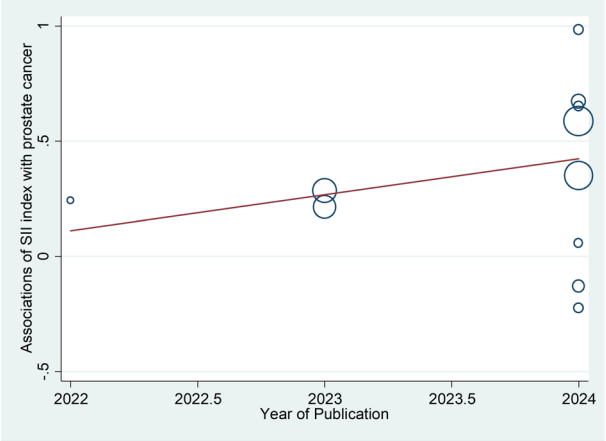

Figure 8. Meta-regression plot of the association between SII index and risk of prostate carcinoma with year of publication.

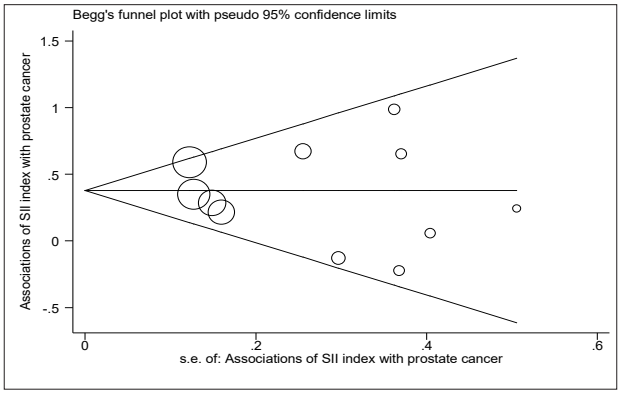

Figure 9. Publication bias.

SII index in upper tract urothelial carcinoma demonstrated that high SII index levels before treatment predict poor overall survival, cancer-specific survival, and recurrence-free survival (24). The findings of the mentioned studies showed that elevated SII index level was a risk factor for the survival of patients with prostate cancer and could reduce patient survival and increase mortality due to prostatic carcinoma. Accordingly, high SII index levels in male patients before prostate cancer incidence increase the risk of prostatic carcinoma and reduce patient's survival after prostate cancer incidence.

Study limitations

The reviewed studies were merely conducted in two countries (i.e., the United States and China). The number of examined articles was extremely low. Subgroup analysis based on the patient's age and level of SII index was not possible.

Conclusion

High SII index and NLR increased the risk of prostatic carcinoma. Examination of different SII index levels revealed that higher SII index levels increased the risk of prostate cancer; therefore, elevated SII index and NLR are independent risk factors for the incidence of prostatic neoplasms. And those with both a high SII and NLR are at greater risk. Therefore, by identifying people at risk, they can be prevented from developing prostate cancer.

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Authors' contribution

Conceptualization: Atefeh Nourmohammadi and Sajad Ataei Azimi.
Data curation: Armin Attar and Seyed Sohrab Vahdati.
Formal analysis: Seyed Sohrab Vahdati and Roozbeh Roohinezhad.
Investigation: Roozbeh Roohinezhad and Atefeh Nourmohammadi.
Methodology: Radhwan Abdul Kareem and Seyed Sohrab Vahdati.
Project management: Seyed Sohrab Vahdati.
Supervision: Atefeh Nourmohammadi.
Validation: Sarah Qutaiba Badraldeen and Rasoul Jafari Arismani.
Visualization: Sarah Qutaiba Badraldeen and Hossein Pourmasomi.
Writing–original draft: All authors.
Writing–reviewing and editing: All authors.

Conflicts of interest

There are no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42024616273) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1921). Besides, the authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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