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Relationship between systemic immune-inflammation Index and contrast-induced acute kidney injury in cardiovascular patients: systematic review and meta-analysis

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ABSTRACT

Introduction: Contrast-induced acute kidney injury (CI-AKI) imposes high costs and various complications on individuals and society. Considering that inflammation is a significant risk factor for CI-AKI incidence, the present research aimed to investigate the relationship between the systematic immune-inflammation (SII) index and the CI-AKI risk in cardiovascular patients using the systematic review and meta-analysis method.

Materials and Methods: In the present study, ProQuest, PubMed, Embase, Web of Science, Cochrane, Scopus, and Google Scholar databases were used to search for articles published until October 16, 2024. Data analysis was conducted using the STATA 14 software, and tests with *P* values < 0.05 were considered statistically significant.

Results: There was no significant association between the SII index and risk of CI-AKI in patients who underwent carotid artery angiography (OR: 1; 95% CI: 1, 1.01) or coronary angiography (OR: 1.96; 95% CI: 0.94, 4.11). However, in patients undergoing percutaneous coronary intervention (PCI) (OR: 1.01; 95% CI: 1, 1.02), high SII index levels increased the risk of CI-AKI. High SII index levels (OR: 1.01; 95% CI: 1.01, 1.02), higher ages (OR: 1.04; 95% CI: 1.02, 1.06), high-sensitivity C-reactive protein (hs-CRP) (OR: 1.01; 95% CI: 1, 1.02), hypertension (OR: 1.63; 95% CI: 1.31, 2.03), diabetes mellitus (OR: 1.73; 95% CI: 1.12, 2.68), neutrophil to lymphocyte ratio (NLR) (OR: 1.09; 95% CI: 1.01, 1.17), and neutrophil count (OR: 1.12; 95% CI: 1.08, 1.16) increased the risk of CI-AKI in cardiovascular patients. On the other hand, estimated glomerular filtration rate (eGFR) (OR: 0.98; 95% CI: 0.98, 0.99), lymphocyte count (OR: 0.47; 95% CI: 0.31, 0.71), and hemoglobin (OR: 0.97; 95% CI: 0.96, 0.98), albumin (OR: 0.96; 95% CI: 0.93, 0.99) in individuals with CIN were lower than those in the no-CIN group.

Conclusion: High systemic immune-inflammation index levels, age, NLR, hs-CRP, hypertension, diabetes mellitus, and neutrophil count were among the risk factors of CI-AKI incidence in cardiovascular patients.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024604243) and Research Registry (UIN: reviewregistry1904) website.

Meta-analysis

Introduction

Interventional strategies, especially coronary angiography and percutaneous coronary intervention (PCI), improve clinical outcomes in patients with coronary artery diseases (1). It has been decades that iodinated radio-contrast agents cause acute kidney injury (AKI). This issue was previously called contrast-induced nephropathy (CIN); however, it is currently referred to as Contrast-Induced Acute Kidney Injury (CI-AKI) (2). This condition is critical among the coronary angiography and PCI complications

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Implication for health policy/practice/research/medical education:
In a review of 15 studies, several key risk factors were identified as significant contributors to the incidence of contrast-induced acute renal failure among cardiovascular patients, including high levels of the systemic immune-inflammation index, age, neutrophil to lymphocyte ratio (NLR), high-sensitivity C-reactive protein (hs-CRP), hypertension, diabetes mellitus, and neutrophil count. The systemic immune-inflammation index, which is calculated as the product of neutrophil count and platelet count divided by lymphocyte count, serves as a crucial marker of systemic inflammation and has been associated with adverse renal outcomes following contrast exposure. Older age was found to increase susceptibility to contrast-induced acute kidney injury (CI-AKI), while elevated neutrophil-to-lymphocyte ratio and C-reactive protein levels further indicated heightened inflammatory states that correlate with kidney injury risk. Additionally, the presence of comorbid conditions such as hypertension and diabetes mellitus significantly exacerbated the likelihood of developing CI-AKI. An increased neutrophil count also contributed to this risk profile, underscoring the importance of monitoring these inflammatory and clinical parameters in cardiovascular patients undergoing procedures involving contrast agents to effectively mitigate the risk of acute kidney injury.
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and is the third most common cause of kidney damage in hospitalized individuals (3,4). The frequency of CI-AKI in patients without risk factors is between 3% and 7%. However, in patients with chronic kidney disease, diabetes mellitus, intravascular volume deficit, proteinuria, anemia, and older patients, the frequency of CI-AKI reaches 50% (5).

Incidence of CIN is related to the prolonged hospitalization periods, increased costs, and higher mortality rates (6,7). CIN progression can increase cardiovascular diseases, renal failure, and mortality rate (8). Studies have reported that among CI-AKI-related factors, inflammation is a significant risk factor, and inflammation-based predictors can predict CI-AKI incidence (9,10). Some blood parameters, including neutrophil, lymphocyte, platelet, and other derived parameters, such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), can predict CIN (11-13). Recent articles have suggested the systematic immune-inflammation (SII) index as a new inflammatory parameter to evaluate inflammatory and immune conditions (14).

The SII index consists of three inflammatory parameters (i.e., neutrophils, lymphocytes, and platelets) (15). Different studies demonstrated that compared with NLR and PLR, the SII index has the upper hand in determining the inflammatory status in cardiovascular diseases (16,17). Early identification of at-risk individuals can promote patients' prognosis after PCI (16,18,19). Accordingly, the present systematic review and meta-analysis research examines the association between the SII index and CI-AKI risk in cardiovascular patients for the first time; hence, by combining the results of previous studies into a larger and more generalizable population, we can discuss the association between the SII index and CI-AKI risk in cardiovascular patients.

Materials and Methods

Study protocol

The present systematic review and meta-analysis used the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) protocol (20). The research protocol was registered at the websites The International Prospective Register of Systematic Reviews (PROSPERO) and Research Registry.

PICO elements

- **Population:** Studies on the association amongst the SII index and CI-AKI in cardiovascular patients.
- **Intervention/Exposure:** High SII index levels.
- **Comparison:** Healthy individuals.
- **Outcomes:** The risk of CI-AKI in cardiovascular patients.

Search strategy

Databases including ProQuest, PubMed, Embase, Web of Science, Cochrane, Scopus, and Google Scholar Search Engine were used for searches using the keywords and their Medical Subject Headings (MeSH) equivalents. There was no limitation for the time or location of the studies in the search for resources, and the search was updated to include articles published until October 16, 2024. The keywords used in the search operation included: Systemic immune-inflammation index, acute kidney injury, acute renal failure, contrast-induced acute kidney injury, cardiovascular, and percutaneous coronary intervention. The keywords were combined using 'AND' and 'OR' operators. The primary studies were screened, and those that were not duplicates were included in the review. The search strategy utilized in the Web of Science database was as follows: Systemic immune-inflammation index (All Fields) AND Contrast-induced acute kidney injury OR Contrast-induced nephropathy OR CI-AKI OR CIN OR acute kidney injury (All Fields)

Inclusion criteria

Studies that examined the relationship between the SII index and CI-AKI in cardiovascular patients met the inclusion criterion of the current research.

Exclusion criteria

Duplicate or low-quality studies, those that examined the effect of the SII index on outcomes other than CI-AKI in cardiovascular patients, articles without accessible full-texts, studies that lacked sufficient data for analysis, those that investigated the effect of the combination of two indices (i.e., SII and another index) on CI-AKI incidence in cardiovascular patients and did not report the effect of each index separately, were excluded from the present research.

Qualitative assessment

Two authors conducted this step independently. The Newcastle-Ottawa Scale (NOS) was conducted to evaluate the quality of the investigations. 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 (21).

Data extraction

Two authors carried out this task. First author, type of the study, patient's age, type of operation, publication year, country of origin, research duration, number of patients, the association between the SII index, high-sensitivity C-reactive protein (hs-CRP), estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), neutrophil count, lymphocyte count, high-density lipoprotein (HDL) cholesterol, NLR, albumin, body mass index (BMI), diabetes mellitus, and the risk of CI-AKI (in addition to their upper and lower limits) were among the extracted information from the reviewed researches.

Statistical analysis

Odds ratio (OR) logarithm was conducted to analyze the obtained data. Then, the 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 large heterogeneity. The subgroup analysis was used to investigate the relationship between the SII index and CI-AKI risk based on the variables study type, type of intervention, and country of origin. Further analysis was conducted using meta-regression. Data was analyzed using the STATA 14 software, and tests with P value < 0.05 were considered statistically significant.

Results

A total of 198 studies were found in the resource search stage. Among them, 96 were duplicates and were removed from the research, and 102 entered the next stage. Examination of abstracts showed that the presented data in the abstracts of 19 studies were insufficient, and as their full texts were not available, they were excluded. The full texts of 83 articles were reviewed, and 43 studies that did not report the necessary data for data analysis were removed. From the remaining 40 studies, 25 met other exclusion criteria and were excluded, and 15 studies remained (Figure 1).

The present meta-analysis reviewed fifteen

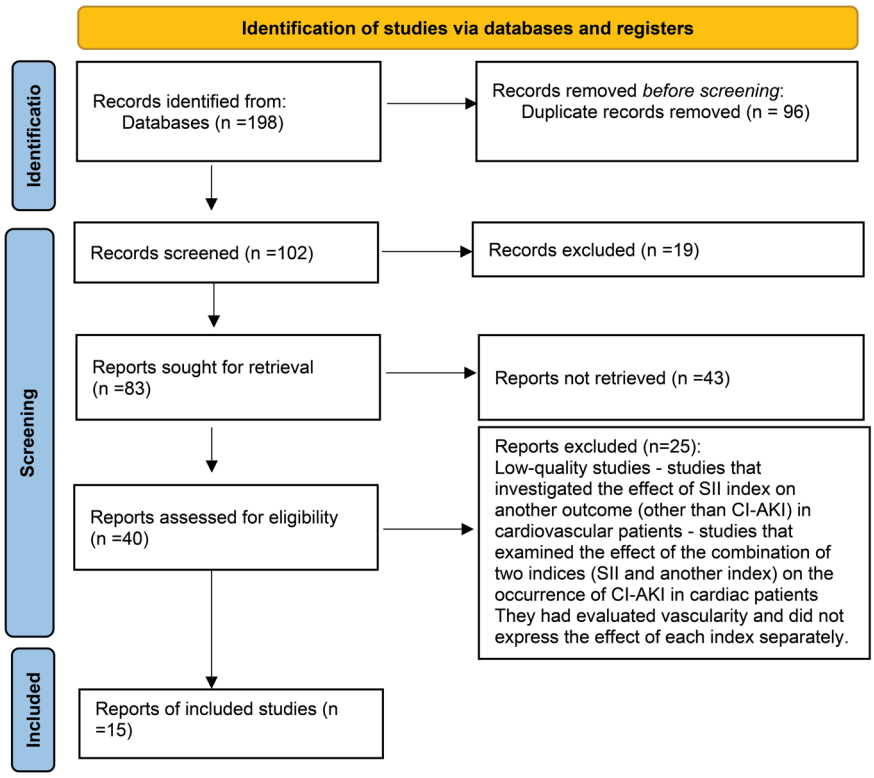

Figure 1. PRISMA flowchart of the study.

observational, nine case-control, three cohort, and three cross-sectional studies. Despite the fact that there was no limitation on the geographical location of the research, eight were conducted in China, and the remaining seven were in Turkey (Table 1).

High SII index levels slightly raised the risk of CI-AKI in cardiovascular patients (OR: 1.01; 95% CI: 1.01, 1.02) (Figure 2).

High SII index levels in cardiovascular patients in Turkey (OR: 1; 95% CI: 1, 1.01) did not affect the risk of CI-AKI incidence. In Chinese patients (OR: 1.76; 95% CI: 1.46, 2.11), on the other hand, it significantly increased CI-AKI risk. Accordingly, the patient's ethnicity may affect the relationship between the SII index and CI-AKI incidence (Figure 3).

There was no correlation between the SII index and CI-AKI risk in case-control studies (OR: 1; 95% CI: 1, 1.01). In cohort (OR: 1.39; 95% CI: 1.29, 1.49) and cross-sectional (OR: 2.71; 95% CI: 2.20, 3.32) studies, on the other hand, high SII index levels significantly increased the risk of CI-AKI (Figure 4).

In patients who underwent carotid artery angiography (OR: 1; 95% CI: 1, 1.01) or coronary angiography (OR: 1.96; 95% CI: 0.94, 4.11), there was no association between the SII index and the risk of CI-AKI. On the contrary, in patients who received PCI (OR: 1.01; 95% CI: 1, 1.02), high SII index levels slightly increased the risk of CI-AKI (Figure 5).

High SII index levels in female (OR: 1.60; 95% CI: 0.89, 2.88) and male (OR: 1.86; 95% CI: 0.58, 5.93) patients did not increase CI-AKI risk. Nevertheless, it must be noted that only a limited number of reviewed studies reported the association between the SII index and CI-AKI risk separately for each gender (Figures 6 and 7).

Table 1. A summary of the information of the reviewed articles

Author, year	Country	Type of study	Duration of study	Sample size in object group	Mean age in object group	Sample size in comparison group	Mean age in comparison group	Type of surgery	Relationship between SII index and CI-AKI		
									OR	Low	Up
Shen G, 2024 (22)	China	Case-control	from Feb. 2019 to Dec. 2022	95	69.22	990	62.54	PCI	1.07	1.046	1.096
Wang L, 2024 (23)	China	Cross-sectional	between Jan. 2020 and May 2023	89	69.36	888	62.23	PCI	2.358	1.677	3.361
Zhu Y, 2023 (24)	China	Cohort	from Jan. 2019 to Dec. 2021	259	67.18	1272	63.11	PCI	1.596	1.01	1.905
Qiu H, 2023 (25)	China	Cohort	from Jan. 2019 to Jun. 2022	53	73.75	327	73.68	PCI	1.774	1.131	2.781
Ma X, 2023 (26)	China	Case-control	from Mar. 2018 to Jul. 2020	40	62	201	67.5	PCI	2.686	1.457	4.953
Jiang H, 2022 (27)	China	Cross-sectional	From Dec. 2006 to Dec. 2019	786	69.34	3595	66.62	Coronary angiography	2.914	2.121	4.003
Lai W, 2022 (28)	China	Cohort	From Jan. 2007 to Dec. 2020	NR	NR	NR	NR	Coronary angiography	1.37	1.32	1.42
Shen G, 2022 (29)	China	Case-control	from Nov. 2019 to Oct. 2021	103	65.87	347	62.73	PCI	2.471	1.661	3.676
Ozturk R, 2022 (30)	Turkey	Cross-sectional		343	60.5	1278	57.6	PCI	2.906	1.903	4.437
Yilmaz Y, 2022 (31)	Turkey	Case-control	between Jan. 2018 and Dec. 2020	40	58.5	222	53	Carotid artery angiography	1.003	1.001	1.005
Ertem AG, 2022 (32)	Turkey	Case-control	between Feb. 2019 and Mar. 2021	20	79	110	76	PCI	1.002	1.001	1.003
Ketenciler S, 2022 (33)	Turkey	Case-control	between Aug. 2018-Dec. 2021	41	62.84	259	56.81	NR	1.002	1.001	1.002
Karauzum I, 2022 (34)	Turkey	Case-control	between Mar. 2015 and May 2021	67	67.1	565	58.3	PCI	1.007	1.004	1.011
Kelesoglu S, 2021 (15)	Turkey	Case-control	From Jan. 2018 to Jun. 2020	49	59.2	380	54.1	PCI	1.009	1.006	1.012
Gucun M, 2021 (35)	Turkey	Case-control	between Jun. 2019 and Apr. 2020	33	70	157	63	PCI	1.002	1.001	1.004

NR: Not reported; PCI: Percutaneous coronary intervention; OR: Odds ratio; SII: systemic immune-inflammation; CI-AKI: Contrast-induced acute kidney injury.

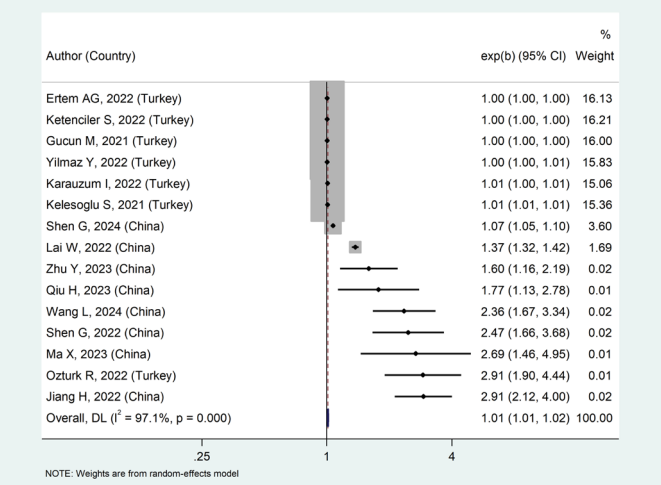

Figure 2. Forest plot showing the relationship between SII index and CI-AKI in cardiovascular patients.

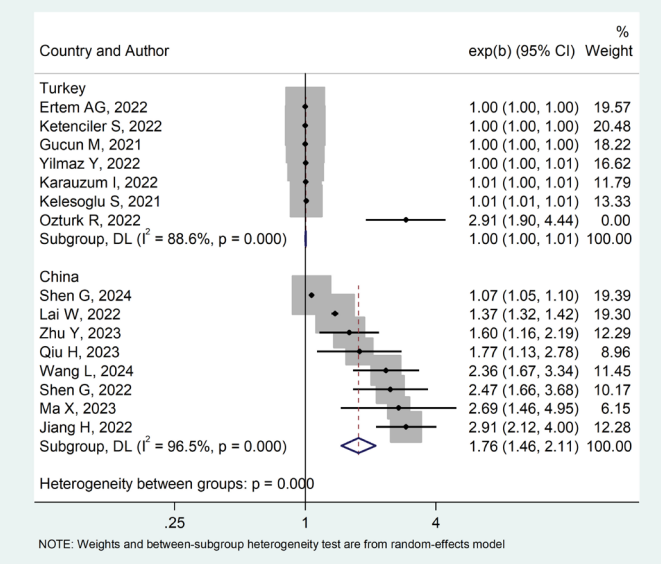

Figure 3. Forest plot showing the association between SII index and CI-AKI in cardiovascular patients by country.

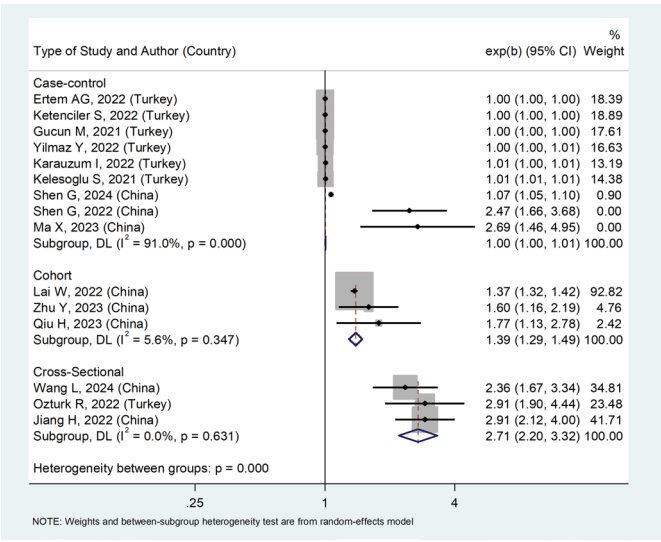

Figure 4. Forest plot showing the association between SII index and CI-AKI in cardiovascular patients by type of study.

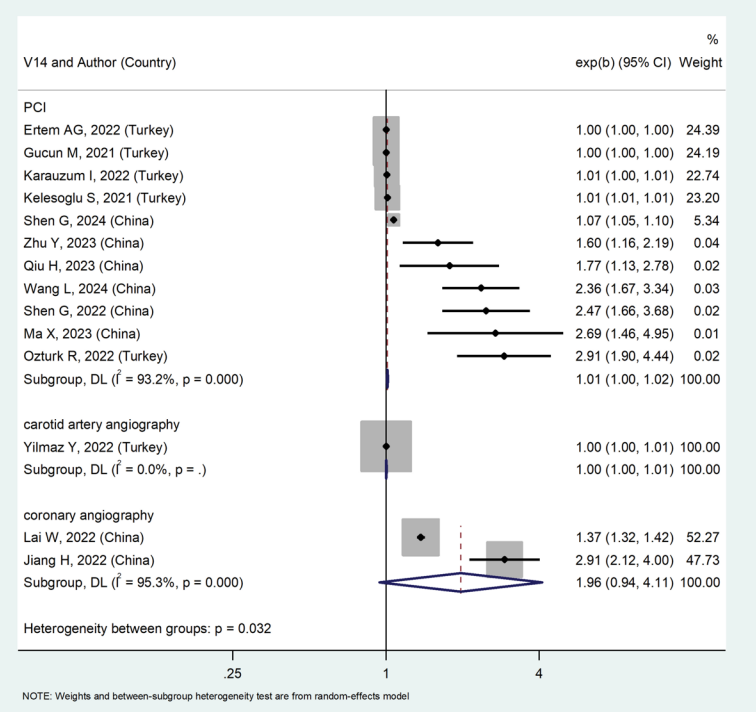

Figure 5. Forest plot showing the association between SII index and CI-AKI in cardiovascular patients by type of surgery.

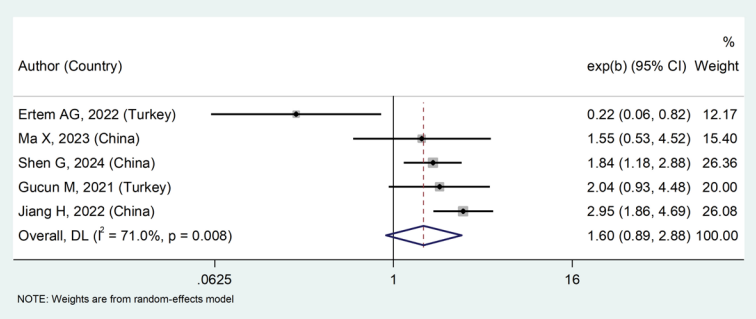

Figure 6. Forest plot showing the association between SII index and CI-AKI in females.

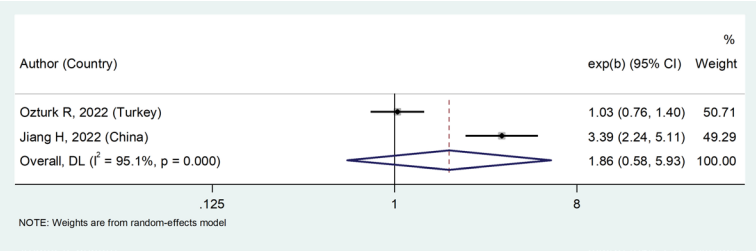

Figure 7. Forest plot showing the association between SII index and CI-AKI in males.

Examinations of the secondary outcomes demonstrated that high ages (OR: 1.04; 95% CI: 1.02, 1.06) and hs-CRP (OR: 1.01; 95% CI: 1, 1.02) increased CI-AKI risk in cardiovascular patients (Figures 8 and 9). Nevertheless, eGFR (OR: 0.98; 95% CI: 0.98, 0.99) in individuals with CIN were lower than those in the no-CIN group (Figure 10).

Table 2 demonstrated no significant association between HDL-C (high-density lipoprotein cholesterol) or BMI and CI-AKI risk in cardiovascular patients. Nonetheless, lymphocyte count, hemoglobin, and albumin in patients with CIN were lower than those in the no-CIN group.

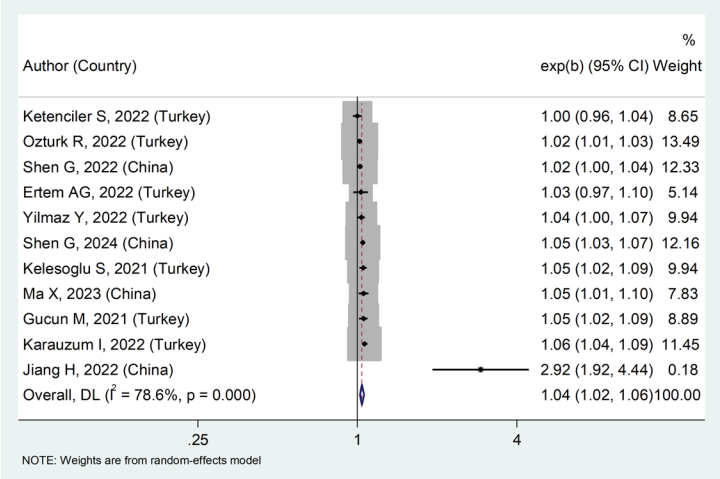

Figure 8. Forest plot showing the association between age and CI-AKI in cardiovascular patients.

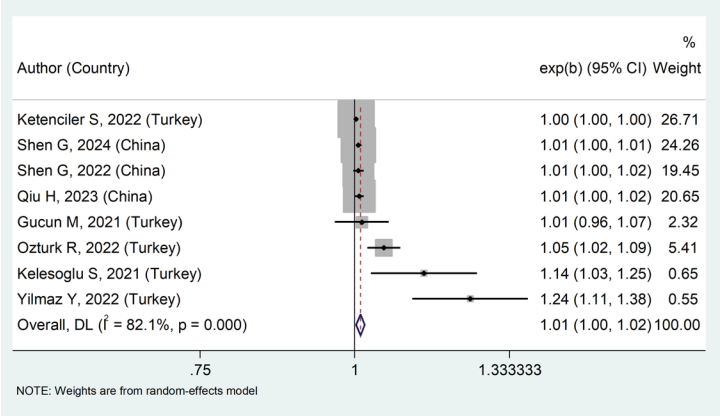

Figure 9. Forest plot showing the association between hs-CRP and CI-AKI in cardiovascular patients.

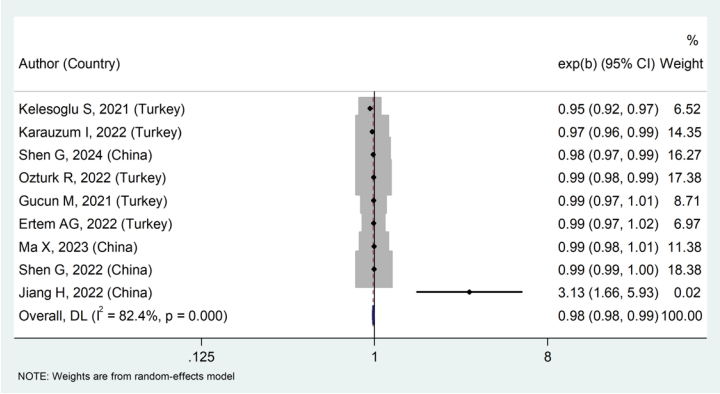

Figure 10. Forest plot showing the association between eGFR and CI-AKI in cardiovascular patients.

While hypertension, diabetes mellitus, NLR, and neutrophil count increased the risk of CI-AKI incidence. In Figure 11 meta-regression revealed no significant association between the 'association between the SII index and CI-AKI risk' and the publication year of the articles (*P* value = 0.261).

Discussion

In our study, high SII index levels (1%), high ages (4%), hs-CRP (1%), hypertension (63%), diabetes mellitus (73%), NLR (9%), and neutrophil count (12%) increased CI-AKI risk in cardiovascular patients. However, eGFR, lymphocyte count, hemoglobin, and albumin in patients

Table 2. Other secondary outcomes examined in the context of the relationship between the SII index and the risk of CI-AKIA in cardiovascular patients

Variables	OR	Low	Up	*P* value	I^2 (%)
BMI	1.11	0.06	1.16	0.577	0
HDL-C	0.96	0.88	1.05	0.008	79.5
Neutrophil count	1.12	1.08	1.16	0.415	0
Lymphocyte count	0.47	0.31	0.71	0.737	0
NLR	1.09	1.01	1.17	0.000	85.3
Albumin	0.96	0.93	0.99	0.492	0
Hemoglobin	0.97	0.96	0.98	0.244	26.3
Hypertension	1.63	1.31	2.03	0.351	4.4
Diabetes mellitus	1.73	1.12	2.68	0.000	81

OR: Odds ratio; HDL-C: high-density lipoprotein cholesterol; NLR: Neutrophil/Lymphocyte; BMI: body mass index.

with CIN were lower than those in the no-CIN group.

Findings of a cohort study by Qiu et al demonstrated that SII and hs-CRP increased the risk of CI-AKI (25). This study was consistent with the present research concerning the SII index, and hs-CRP results. Yet, their results regarding diabetes mellitus were inconsistent with the findings of the current research. However, the study type, kind of cardiovascular disease, and investigated intervention by Qiu et al and the current research were different.

Results of a meta-analysis by Wu et al examining the inflammatory indices and blood parameters in CIN patients who received coronary interventions showed that patients with higher CRP (OR: 1.06; 95% CI: 1.01, 1.12), hs-CRP (OR: 1.03; 95% CI: 1.01, 1.06), and NLR (OR: 1.11; 95% CI: 1.01, 1.20) levels faced higher risks of CIN incidence (36). According to the findings of a meta-analysis by Lun et al investigating the correlation between hypertension and CI-AKI, hypertension was a risk factor for CI-AKI incidence (OR: 1.37; 95% CI: 1.21, 1.56) (37). In another research by Butt et al on acute coronary syndrome patients who received PCI, higher NLR levels were directly associated with increased CIN risks (OR: 2.03; 95% CI: 1.40, 3.17) (38). In the study by Tanık et al, NLR was an independent predictor for CI-AKI in patients with STEMI (OR: 1.78; 95% CI: 1.21, 2.61) (39). Findings of a cohort study by Zhu et al determining the value of predicting the SII index in addition to CHA2DS2-VASC score for CI-AKI in patients with acute coronary syndrome who received PCI revealed that albumin (OR: 0.96; 95% CI: 0.93, 1) and SII index (OR: 1.59; 95% CI: 1.01, 1.90) levels were correlated with CI-AKI incidence (24). Shen et al conducted a case-control research to examine the effect of the SII index level of CI-AKI risk in patients with STEMI after primary PCI. They reported that increased SII index levels before the surgery were a risk factor for CI-AKI after PCI (HR: 1.07; 95% CI: 1.04, 1.09) (22). In another case-control study, Kelesoglu et al demonstrated that increased SII index level was an independent predictor of CIN incidence in patients with non-ST-elevation myocardial infarction. Besides, higher ages (OR: 1.07; 95% CI: 1.01, 1.12), GFR (OR: 0.87; 95% CI: 0.82, 0.93), lymphocyte count (OR: 0.42; 95% CI: 0.20, 0.87), and high NLR (OR: 2.74; 95% CI: 1.93, 3.09) were associated with CIN incidence (15). The mentioned studies indicated that higher ages, high SII index levels, hs-CRP, hypertension, and NLR increased CI-AKI risk. On the contrary, GFR, albumin, and lymphocyte count in individuals with CIN were lower than those in the no-CIN group. Accordingly, the findings of these studies were consistent with the results of the current meta-analysis.

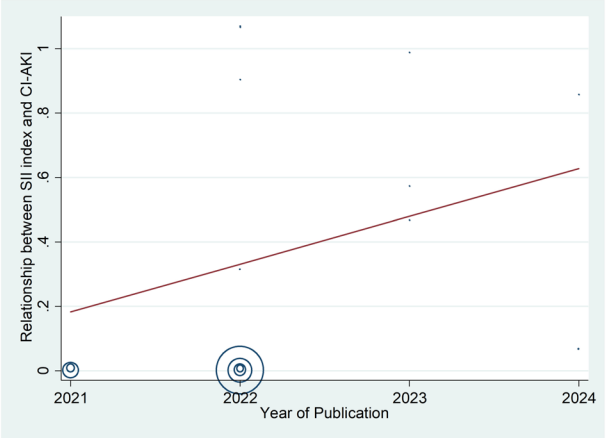

Figure 11. Meta-regression of the association between SII index and CI-AKI with year of publication.

Cross-sectional research by Jiang et al on the association between the SII index and CI-AKI risk reported that high SII index levels were correlated with increased CI-AKI risk (OR: 2.91; 95% CI: 2.12, 4.00) (27). The findings of their study were consistent with the current research, as in the present meta-analysis, high SII index levels in cross-sectional studies increased CI-AKI risk.

Results of a meta-analysis by Wang et al indicated that higher SII index levels were associated with increased risk of adverse short-term (HR: 1.61; 95% CI: 1.28, 2.03) and long term (HR: 2.43; 95% CI: 1.74, 3.40) cardiovascular outcomes (40). According to the study by Shi et al, high SII index levels were correlated with major adverse cardiovascular events in acute coronary syndrome patients

with chronic kidney disease (HR: 1.86; 95% CI: 1.19, 2.90) (41). Based on the study by Adali et al, high SII index levels were associated with poor coronary collateral circulation (42). In the meta-analysis by Chen et al, high SII index levels increased the risk of postoperative atrial fibrillation (OR: 3.24; 95% CI, 1.6, 6.55) (43). The mentioned studies confirmed the results of the present research, indicating that in addition to CI-AKI, high SII index levels are a risk factor for adverse cardiovascular outcomes, atrial fibrillation, and coronary collateral circulation.

Conclusion

Diabetes and hypertension were the most significant risk factors for CI-AKI, and neutrophil count, NLR, high age, SII index, and hs-CRP were among the causes that increased CI-AKI risk in cardiovascular patients, respectively.

Furthermore, high SII index levels in cardiovascular patients in Turkey did not affect the CI-AKI incidence risk. In Chinese patients, on the other hand, high SII index levels significantly increased the risk of CI-AKI. There was no association between the SII index and CI-AKI risk in patients who underwent carotid artery or coronary angiography. However, high SII index levels increased CI-AKI risk in PCI patients. Accordingly, the ethnicity and type of surgery may be among the factors affecting the relationship between the SII index and CI-AKI risk, and we recommend addressing this issue in future studies.

Limitations of the study

The study limitations regarding the association between the SII Index and the risk of CI-AKI are noteworthy. Firstly, only a limited number of studies have specifically reported this association while considering the gender of patients, which restricts the understanding of potential gender differences in SII's predictive value for CI-AKI. Additionally, the full text of some relevant studies was not publicly accessible, which may hinder a comprehensive analysis of the existing literature. Furthermore, most of the reviewed research was conducted exclusively in China and Turkey, raising concerns about the generalizability of the findings to other populations and healthcare settings. These limitations highlight the need for further studies that include diverse populations and explicitly examine gender-specific effects to better elucidate the role of SII in predicting CI-AKI risk.

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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 with (ID: CRD42024604243) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1904). Besides, the authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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