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The association between hyperuricemia and the risk of acute kidney injury; a systematic review and meta-analysis

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ABSTRACT

Introduction: Acute kidney injury (AKI) is a prevalent clinical syndrome in hospitalized patients associated with uric acid levels in patients. This study aims to evaluate the relationship between hyperuricemia and the risk of AKI using a systematic review and meta-analysis approach.

Materials and Methods: This systematic review and meta-analysis was performed based on PRISMA guidelines. A query on international databases, including Cochrane, Web of Science, PubMed, Scopus, and the Google Scholar search engine, was conducted using relevant keywords. The literature search stage was updated until January 2023. Data were analyzed in STATA 14 software. A significance level of $P < 0.05$ was considered for all tests.

Results: A total of 22 articles published from 2006 to 2023 with a sample size of 82469 patients were reviewed. The estimated odds ratio (OR) was 1.96 (95% CI: 1.63, 2.35, $P = 0.000$, $I^2 = 89.6\%$) between hyperuricemia and the risk of AKI and 1.64 (OR: 1.64; 95% CI: 1.23, 2.20, $P = 0.012$, $I^2 = 63.2\%$) between hyperuricemia and AKI mortality and these relationships were statistically significant. In addition, the OR of hyperuricemia and AKI was 1.96 (95% CI: 0.97, 3.98, $P = 0.000$, $I^2 = 97.9\%$) in males and 2.34 (OR: 2.34; 95% CI: 1.14, 4.78, $P = 0.000$, $I^2 = 97.9\%$) in females. The OR of hyperuricemia and AKI was 1.07 (95% CI: 1.03, 1.10) in 30-39 years, 2.37 (95% CI: 1.04, 5.42) in 40-49 years, 4.71 (95% CI: 1.29, 17.20) in 50-59 years, 2.07 (95% CI: 1.58, 2.71) in 60-69 years, and 1.42 (95% CI: 1.04, 1.93) in 70-79 years age groups.

Conclusion: Hyperuricemia significantly increases the risk of AKI and mortality. Therefore, by reducing the serum level of uric acid, the risks caused by it can be avoided.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023393648).

Implication for health policy/practice/research/medical education:
Our meta-analysis showed that hyperuricemia raises the risk of AKI by nearly two times. Thus, elevated uric acid levels cause an increase in the incidence of AKI and mortality.

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Introduction

Acute kidney injury (AKI) is a prevalent clinical syndrome in hospitalized patients, independently associated with short-term and long-term mortality (1). The mortality risk of AKI patients is four times higher than that of non-AKI patients (2). AKI encompasses the whole spectrum of

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kidney injuries ranging from primary renal dysfunction to acute kidney failure (3). AKI is diagnosed by a rapid increase in serum levels of creatinine, decreased urinary output, or a combination of both and is characterized by a rapid decline of kidney function (4).

Chronic conditions, such as hypertension, diabetes, chronic renal disease, obesity, gout, and certain medications, particularly diuretics, can raise the uric acid level in the body (5). Uric acid is linked to AKI via crystalline-dependent pathways and crystalline-independent mechanisms, including decreased renal blood flow and glomerular filtration rate (GFR) (6). Serum uric acid (SUA) measurement has been proposed as a novel marker for early diagnosis of AKI (7). A SUA concentration of ≥6 mg/dL in women, ≥7 mg/dL in men, and ≥ 5.5 mg/dL in adolescents (below 18 years) is defined as hyperuricemia (8).

Clinical and empirical evidence collected over the past several decades has supported the relationship between SUA levels and hypertension, metabolic conditions, chronic renal disease, AKI, cardiovascular events (9), inflammation, and renal tubular obstruction (10). However, given the inconsistent findings of previous studies investigating the relationship between hyperuricemia and AKI, in the current study, we pooled previous studies using a systematic review and meta-analysis approach to evaluate the association between hyperuricemia and AKI and provide an overall assessment.

Materials and Methods

Study design

This research was a systematic review and meta-analysis evaluating the association between hyperuricemia and AKI. This study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist. The protocol was registered on the International Prospective Register for Systematic Reviews (PROSPERO) website, available at https://www.crd.york.ac.uk/prospero/#recordDetails with protocol number CRD42023393648.

Search strategy

A query on international databases, including Cochrane, Web of Science, Scopus, PubMed, and the Google Scholar search engine, was performed using standard keywords and Medical Subject Headings (MeSH) without time restriction. The searched keywords were "Hyperuricemia," "Uric Acid," "Urate," "Trioxopurine," "Acute Kidney Injury," "Acute Kidney Failure," "Acute Renal Injury," and "Acute Renal Insufficiencies."

For an advanced search, a combination of keywords using the Boolean operators (OR, AND) was used in the databases mentioned above. Finally, a manual search of the reference list provided at the end of each identified article was also conducted. See search strategy in PubMed as follows: (Hyperuricemia[Title/Abstract] OR Uric Acid[Title/Abstract] OR Urate[Title/Abstract] OR Trioxopurine[Title/Abstract]) AND (Acute Kidney Injury[Title/Abstract] OR Acute Kidney Failure[Title/Abstract] OR Acute Renal Injury[Title/Abstract] OR Acute Renal Insufficiencies[Title/Abstract]).

PICO (Patients, Intervention, Comparison, Outcome)

Patients: patients with heart disease, renal disease, and hospitalized patients with hyperuricemia. Intervention: none. Comparison: patients with a normal uric acid level. Outcomes: the chief outcome was the incidence risk of AKI, and the secondary outcome was the mortality rate.

Inclusion criteria

The current study included all cohort studies investigating the relationship between hyperuricemia and AKI.

Exclusion criteria

The following studies were excluded; studies lacking adequate data for analysis; poor-quality studies; case report studies; qualitative studies; studies reporting the mean and standard deviation measurements; studies that assessed the relationship between hyperuricemia and incidence of another disease; and studies with no full text available.

Qualitative assessment

After the identification of the initial studies, two researchers performed a qualitative assessment of the articles independently using the Newcastle Ottawa Scale checklist (11). This checklist uses a star system for quantitative evaluation of the study quality. According to this checklist, the scores assigned to each article range from zero (the lowest quality) to ten (the highest quality) stars. The cut-off point was set at six. The two researchers resolved any discrepancy by reaching a consensus on a single option.

Data extraction

Two researchers extracted data from the studies separately to minimize the risk of biased reporting and data collection errors. They entered data in a checklist containing the first author's name, study type, publication year, country, age, sample size, the number of men and women, study duration, eGFR, odds ratio between hyperuricemia and AKI incidence, and its upper and lower limits.

Statistical analysis

The odds ratio (OR) index was utilized to evaluate the association between hyperuricemia and AKI incidence. The logarithmic OR was applied in all studies to combine their results. The I^2 index was employed to examine the heterogeneity among studies. Given the high heterogeneity of this study (I^2 = 89.6%), the random effects model was chosen. Data analysis was performed in STATA 14 software. A significance level of $P < 0.05$ was considered for all tests.

Results

Selection of studies

Overall, 625 articles were retrieved from the initial search of the mentioned databases. After checking the titles, 215 duplicates were discarded. The abstracts of the remaining 410 studies were screened, and another 105 were excluded. Of the remaining 305 articles, ten were eliminated due to the unavailability of their full text. Additionally, 273 of 295 remaining articles met other exclusion criteria and were removed. Eventually, 22 articles with high quality were eligible to enter the meta-analysis process (Figure 1).

The information of the articles included in the systematic review and meta-analysis stage is shown in Table 1.

Twenty-two articles published from 2006 to 2023 with a sample size of 82 469 patients were reviewed. The estimated OR between hyperuricemia and AKI risk was 1.96 (95% CI: 1.63, 2.35, $P=0.000$, $I^2 = 89.6\%$), and this association was statistically significant (Figure 2).

The OR between hyperuricemia and mortality due to AKI was 1.64 (95% CI: 1.23, 2.20, $P=0.012$, $I^2 = 63.2\%$), indicating that hyperuricemia increases the mortality rate of AKI as well (Figure 3).

Subgroup analysis

The OR between hyperuricemia and the AKI risk was 1.96 (95% CI: 0.97, 3.98, $P=0.000$, $I^2 = 97.9\%$) in men compared to 2.34 (95% CI: 1.14, 4.78, $P=0.000$, $I^2 = 97.9\%$) in women. The association between hyperuricemia and the risk of AKI was statistically non-significant in men but significant in women (Figures 4 and 5).

In an analysis by age group, we divided patients into five categories. The OR between hyperuricemia and the AKI risk was 1.07 (95% CI: 1.03, 1.10) in 30-39 years, 2.37 (95% CI: 1.04, 5.42) in 40-49 years, 4.71 (95% CI: 1.29, 17.20) in 50-59 years, 2.07 (95% CI: 1.58, 2.71) in 60-69 years, and 1.42 (95% CI: 1.04, 1.93) in 70-79 years age groups. Although the OR between hyperuricemia and the risk of AKI was significant in all age groups, it did not show any statistically significant relationship with patients' age. Thus, this data was insufficient to conclude that the incidence risk of AKI increases with age in hyperuricemic patients (Figure 6).

In Figure 7, the publication bias diagram showed that the studies that reported a direct and significant relationship between hyperuricemia and the incidence of AKI had more chances to be published than the studies that reported the inverse relationship between hyperuricemia and the incidence of AKI, and the publication bias graph was significant ($P=0.003$).

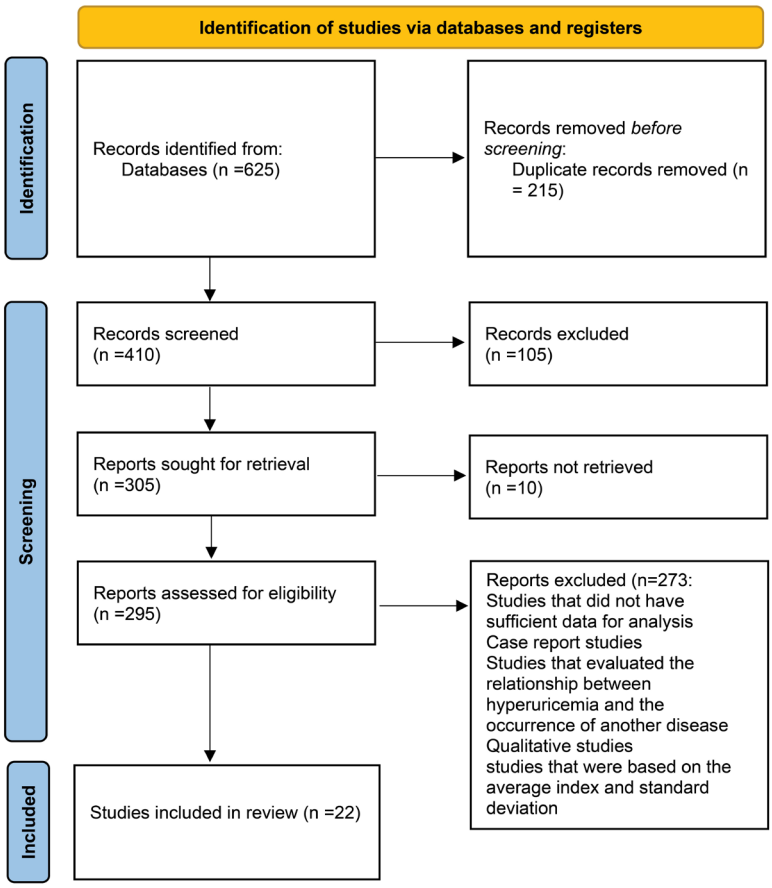

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Summary of the information available in the reviewed articles

Author	Country	Study period	Definition of hyperuricemia or grouping according to SUA	Sample size	Number of female	Number of male	Mean age (year)	eGFR mL/ min/1.73 m^2
Srivastava et al (12)	USA	Between October 2008 and December 2016	11.1 (IQR, 8.6–14.2) mg/dL	204	94	114	61.8	91.1
Puti et al (13)	Indonesia	From October 2019 to December 2019	>7.0 mg/dL in male and >5.7 mg/dL in female	158	34	124	>18	
He et al (14)	China	Between January 2014 and January 2019	≤2.2 mmol/L or >2.2 mmol/L	1887	395	1492	63.9	71.5
Kang et al (15)	Korea	From January 2013 to December 2013	male, UA > 6.7 mg/dL; female, UA > 5.4 mg/dL	4472	2155	2317	59	84.8
Mandurino-Mirizzi et al (16)	Italy	Between January 2006 and September 2017	SUA ≥ 6.8 mg/dL and SUA<6.8 mg/dL	2433	543	1900	63	
Kaufeld et al (17)	Germany	NR	≥373 µmol/L	247	82	165	67.82	
Shirakabe et al (18)	Japan	Between January 2000 and July 2017	UA N 7.0 mg/dL	1326	NR	NR	63-81	
Lapsia et al (19)	USA	Between 2004 and 2008	SUA ≥7 mg/dL	190	NR	NR	63.9	52.2
Liang et al (20)	China	Between January 2009 and November 2014	≥375.5 µmol/L	59	39	20	37.3	98.99
Guo et al (21)	China	Between January 2010 and October 2013	SUA ≥7 mg/dL	1772	336	1436	62.8	71.08
Park et al (22)	Korea	From August 2006 to December 2009	≥7 mg/dL for males and of ≥6.5 mg/dL for females	1247	470	777	61.01	45.32
Liu et al (23)	China	Between February 2010 and January 2011	>7 mg/dL for males and of >6 mg/dL for females	788	NR	NR	62.8	
Kim et al (24)	Korea	From January 2007 to December 2008	SUA ≥7.3 mg/dL in men or ≥5.3 mg/dL in women	247	129	118	46.1	
Lee et al (25)	Korea	Between January 1, 2006, and October 31, 2011	NR	2185	552	1633	63.6	
Ejaz et al (26)	USA	NR	SUA >5.77 mg/dL	100	40	60	61.4	
Otomo et al (27)	Japan	Between October 19, 1981 and April 30, 2011	SUA >7	59219	30549	28670	58.6	
Joung et al (28)	Korea	Between January 2011 and May 2012	≥6.5 mg/dL	1019	385	634	63	
Cheungpasitporn et al (29)	USA	From January 2011 through December 2013	SUA >9.4 mg/dL	1435	570	865	62	73.1
Xu et al (30)	China	Between January 2005 and May 2011	(436.6 ± 119.1) µmol/L vs. (398.0 ± 107.2) µmol/L	936	NR	NR	65.2	
Lazzeri et al (31)	Italy	From 1 April 2006 to 31 December 2013,	>7.4 mg/dL	329	152	177	77.2	
Barbieri et al (32)	Italy	From January 2007 to September 2011	≥7.0 mg/dL	1950	NR	NR	72.1	
Toprak et al (33)	Turkey	Between May 2004 and June 2005	≥7 mg/dL for males and of ≥6.5 mg/dL for females	266	96	170	58.33	55.2

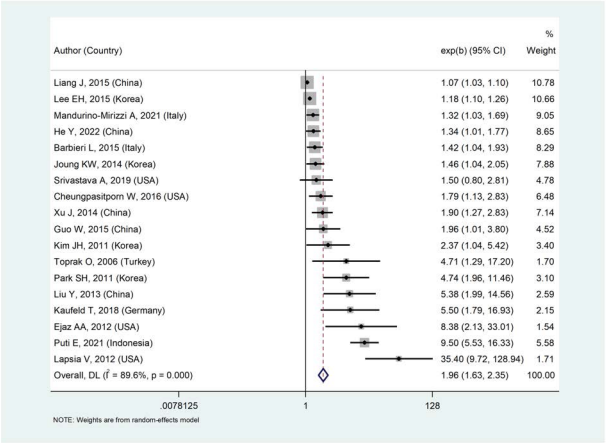

Figure 2. Relationship between hyperuricemia and risk of acute kidney injury.

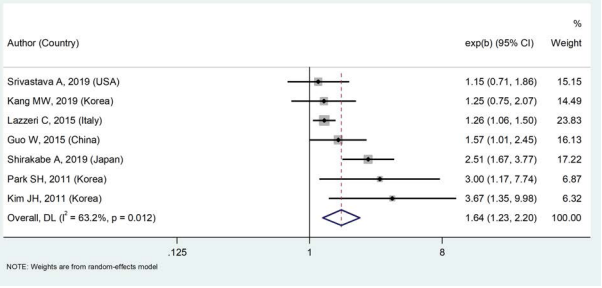

Figure 3. Relationship between hyperuricemia and mortality of acute kidney injury.

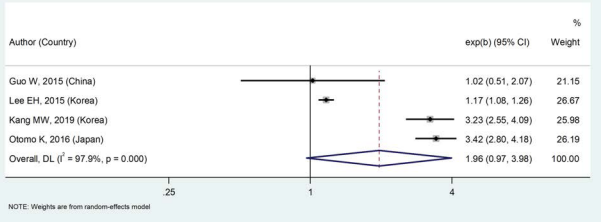

Figure 4. Relationship between hyperuricemia and risk of acute kidney injury in men.

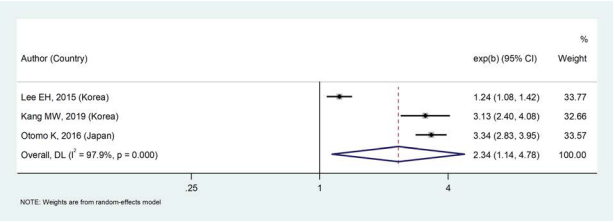

Figure 5. Relationship between hyperuricemia and risk of acute kidney injury in women.

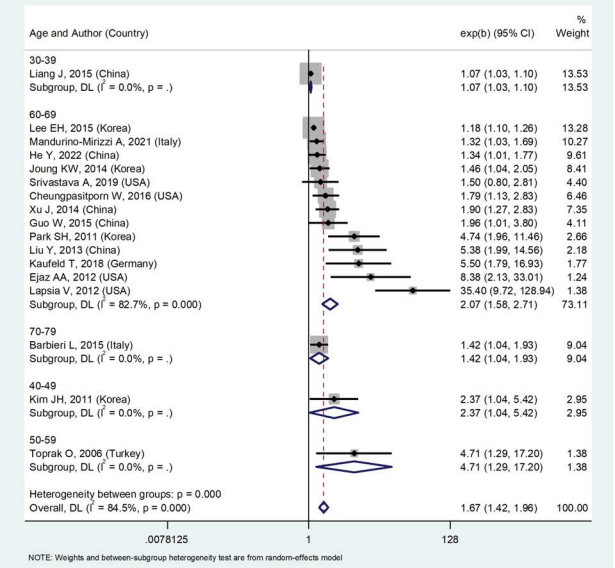

Figure 6. Relationship between hyperuricemia and risk of acute kidney injury by age group.

Discussion

The present meta-analysis has identified hyperuricemia as a risk factor for the incidence of AKI and its associated mortality. This result is supported by many previously published studies on this subject.

Xu et al conducted a meta-analysis in 2017 to evaluate the relationship between SUA level and AKI incidence. Their results demonstrated that hyperuricemia considerably increased the risk of AKI development compared to the control group (OR: 2.24, 95% CI 1.76-2.86, $P<0.01$) (34). A 2016 meta-analysis by Zuo et al, including 13084 patients, aimed to determine whether or not hyperuricemia was an independent risk factor for contrast-induced acute kidney injury (CI-AKI). Based on their results, hyperuricemia was associated with an increased risk of CI-AKI development (unadjusted OR: 2.08, 95% CI: 1.63–2.64; adjusted OR: 1.68, 95% CI: 1.38–2.04). Hyperuricemia and normouricemic patients showed a significant difference regarding in-hospital mortality and renal replacement treatment cases after coronary angiography and or percutaneous coronary intervention (35). In a systematic review, Hahn et al stated that uric acid might enhance the risk of AKI occurrence through systemic effects of hyperuricemia and its local crystalline and non-crystalline effects on the renal tubules. In conclusion, accumulating evidence suggests that hyperuricemia may play a significant role in the incidence of AKI (36).

Recently, Cai et al conducted a meta-analysis on 11 892 patients from 15 studies to establish whether hyperuricemia was an independent risk factor for post-contrast acute kidney injury (PC-AKI) and explore the relationship between hyperuricemia and basal renal function. The pooled analysis indicated that PC-AKI occurrence was significantly higher in the hyperuricemic group than in the normouricemic group (20.62% versus 13.05%). Hyperuricemia was accompanied by an increase

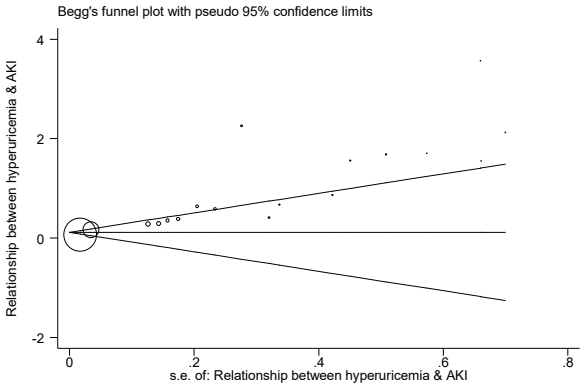

Figure 7. Publication bias.

in the incidence risk of PC-AKI (OR: 2.48; 95% CI: 1.77-3.46%) (37). In a meta-analysis in 2017, Kanbay et al assessed the pathogenic role of uric acid in CI-AKI and found that higher levels of SUA, as described by the authors, were associated with a 2-fold increase in the risk of AKI occurrence (pooled OR: 2.03; 95% CI: 1.48-2.78) (38). The results of the above studies corroborate those of the current study. As these findings suggested, a high uric acid level is alarming for AKI and its associated mortality. Uric acid level control, to some extent, can help prevent AKI incidence and mortality. This measure has a substantial effect in reducing hospital stays, hospital costs, and hyperuricemic complications.

Conclusion

Hyperuricemia raises the risk of AKI by nearly two times and its associated mortality by 1.5 times. Thus, elevated uric acid levels cause an increase in the incidence of AKI and mortality. Moreover, given the statistically significant association between the female gender and AKI occurrence, the female gender could serve as a risk factor for this condition. However, age did not enhance the increasing effect of hyperuricemia on the risk of AKI, and AKI occurred with a fluctuating trend in the 30-80 age groups. Though, the age group of 50 to 59 years are considered a high-risk group.

Limitations of meta-analysis

Analysis by study type was not possible, given the cohort nature of all studies. In addition, the full texts of some studies were unavailable.

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Authors' contribution

Conceptualization: MR and MF.
Methodology: HR, SM, and FF.
Validation: MR and MKH.
Formal analysis: FGh and PK.
Research: MKh, BR and FF.
Resources: MR, FGh and HR.
Data curation: SM and MKh.
Writing–original draft preparation: MR, FF, MKh, BR and MF.
Writing–reviewing and editing: HR, SM, PK and FGh.
Visualization: HR and SM.
Supervision: MR.
Project Management: FF.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author. This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD42023393648.)

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