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Review Article

Predictive Value of Hyperuricemia in Cardiac Patients with Post-Contrast Acute Kidney Injury (PC-AKI) and Different Basic Renal Functions: A Meta-Analysis

Angshu Cai [1], ****Tian Zhou*** [2]

1. *Queen Mary School, Nanchang University, Nanchang 330031, China*
2. *School of Basic Medical Sciences, Nanchang University, Nanchang, 330031, China*

***Corresponding Author:** Email: zhoutian@ncu.edu.cn

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Abstract

Background: Uric acid level has shown a certain relationship with the incidence of post-contrast acute kidney injury (PC-AKI), whereas it remains controversial whether hyperuricemia can function as a predictor of PC-AKI in patients with different basic creatinine serum level. The present meta-analysis aimed to investigate whether hyperuricemia is an independent risk factor for PC-AKI and to explore the relationship between hyperuricemia and basic renal function.

Methods: Relevant studies were retrieved via searching in PubMed, Embase, Cochrane Library, and WAN FANG electronic databases from inception to Jan 2022. Only studies published in English and Chinese languages were selected.

Results: Overall, 11892 patients from 15 studies were included. The results of the pooled analysis revealed that the incidence of PC-AKI was significantly higher in the hyperuricemia group than that in the normouricemic group (20.62% vs. 13.05%). Hyperuricemia was associated with an increased risk of the incidence of PC-AKI (odds ratio (OR): 2.48 [95% confidence interval (CI): 1.77-3.46%]). The pooled ORs for mortality and incidence of undergoing renal replacement therapy were 2.33 (95% CI:1.81-3.00) and 8.69 (95% CI:3.22-23.44%), respectively. Comparatively, the pre-existing renal dysfunction subgroup had a lower relative risk in the hyperuricemia population.

Conclusion: Hyperuricemia was found to be significantly associated with the incidence of PC-AKI. The effect of serum uric acid level on the incidence of PC-AKI was higher in patients with normal renal function, which could lay a foundation for the establishment of individualized schemes to prevent PC-AKI by urate-lowering therapy.

Keywords: Hyperuricemia; Post-contrast acute kidney injury; Creatinine serum

Introduction

Post-contrast acute kidney injury (PC-AKI) is an important adverse effect appearing after various radiographic procedures (1, 2). The latest recommended definition of PC-AKI by the Contrast Media Safety Committee of the European Society of Urogenital Radiology is an increase in serum

creatinine ≥ 0.3 mg/dl (26.5μmol/ l), or ≥ 1.5 times the basic serum creatinine value within 48–72h of exposure to a contrast medium (CM) (3). PC-AKI was used to be defined as contrast-induced nephropathy (CIN) or contrast-induced nephropathy and described as an elevation in the creatinine serum level of more than 0.5 mg/dL or 25% increase over the baseline within a few days after the procedure in some clinical studies (4-6). PC-AKI is the third leading cause of hospital-acquired acute renal injury, accounting for 12% of cases(7). An episode of PC-AKI typically indicates increased short- and long-term morbidity and mortality and prolonged hospitalization (8, 9). The incidence of PC-AKI is remarkably associated with some known risk factors, such as administration of contrast agents (e.g., intravenous or intra-arterial), basic renal function (basic creatinine serum level or glomerular filtration rate (GFR)), old age. Prevention is essential and valuable to reduce the incidence or adverse results of PC-AKI. Identification of patients who are at high risk is the critical first step.

In recent years, the relationship between hyperuricemia and PC-AKI has noticeably attracted scholars' attention. Hyperuricemia was associated with PC-AKI and suggested that serum uric acid level could be a novel independent predictor of PC-AKI (10, 11). However, similar studies were conducted, while controversial results were reported (12, 13), and the causal role in AKI remains elusive. Notably, the relevant studies were mainly conducted based on a direct comparison of the uric acid level between the PC-AKI group and the non- PC-AKI group (12). The high incidence of PC-AKI may wrongly be attributed to hyperuricemia by this kind of grouping. The association between PC-AKI and hyperuricemia was strongly confounded by baseline clinical features that were predisposed to both kidney injury and mortality. To date, few meta-analyses have specifically evaluated the association between hyperuricemia and basic creatinine serum level based on the risk of PC-AKI development.

We aimed to perform a meta-analysis to indicate whether serum uric acid level is associated with PC-AKI, and to further compare the influence of uric acid in patients with different basic creatinine serum level.

Methods

Literature Search

In the present meta-analysis, PubMed, Cochrane Library, Embase, and WAN FANG (Chinese) databases were searched, and this meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). All the relevant observational studies that investigated the association between serum uric acid level and PC-AKI from inception to Jan 2022 were included. Only studies published in English and Chinese languages were selected. The following search terms were used: "contrast-induced nephropathy, radiographic contrast nephropathy, renal diseases, contrast associated nephropathy, contrast-induced renal dysfunction, contrast-induced renal failure, acute renal injury, acute kidney injury, uric acid, urate, hyperuricemia, risk factors, and renal status." Furthermore, the reference lists of all the included articles were checked to identify further potentially relevant studies. Overlapping data were identified as well.

Selection Criteria

Retrieved studies were first screened independently by two unblinded researchers, and disagreements between researchers were resolved by consensus. Only original articles published in peer-reviewed scientific journals were included. The inclusion criteria were as follows: 1) studies related to iodine contrast agent; 2) studies that compared the incidence of PC-AKI between hyperuricemia group and normouricemia group; 3) clear diagnosis of PC-AKI and defining hyperuricemia for human participants; 4. studies that enrolled patients who underwent coronary angiography (CAG) and/or Percutaneous coronary intervention (PCI). The exclusion criteria were as follows: 1) laboratory studies, review articles, case reports, letters, animal studies, and other irrelevant clinical trials 2) Lack of the description of

incidence rate of PC-AKI in hyperuricemia group and low uric acid group respectively.

Data extraction and quality assessment

Data from each study were abstracted by two independent reviewers using a standardized spreadsheet. Disagreements between reviewers were resolved by consensus. Dichotomous variables were extracted in absolute numbers and were recalculated when percentages were reported. Continuous variables were extracted and weighted mean differences for the total study population were calculated.

The following data were extracted from each study: study design, the first author's name, country, publication year, study subjects' details (population, age, sex distribution, basic renal function), sample size, administration of contrast agents (e.g. volume, category), definitions of hyperuricemia and PC-AKI, and the incidence, mortality and incidence of undergoing renal replacement therapy of PC-AKI. The primary endpoint was the development of PC-AKI in the hyperuricemia group and normouricemia group. Due to the close relationship between basal renal function and incidence rate of PC-AKI, the included studies were divided into three subgroups: normal renal function subgroup, pre-existing renal dysfunction subgroup, and mix group which regardless of renal function status.

In order to assess the quality of the included studies, the standard Newcastle-Ottawa Scale (NOS) was used (15).

Statistical analysis

All the statistical analyses were performed using Review Manager 5.4 software. The main evaluation indexes were dichotomous variables, and the pooled estimate of the odds ratio (OR) and the corresponding 95% confidence interval (CI) was carried out (16). The OR was calculated to quantitatively evaluate the association between serum uric acid level and the incidence rate of PC-AKI. The overall pooled effect was assessed using the Z statistic. A P-value<0.05 was considered statistically significant. Heterogeneity was considered significant with P<0.10 or I^2>50 (17). When the heterogeneity was significant, the random-effects model was used; otherwise, the fixed-effects model was utilized. The sensitivity analysis and subgroup analysis were conducted to further explain the heterogeneity in the results. The values of OR and 95% CI of the PC-AKI incidence, mortality rate, and incidence of undergoing renal replacement therapy (RRT) were compared between the hyperuricemia group and normouricemia group. Sensitivity analysis refers to a method to determine the robustness of an assessment by examining the extent to which results are affected by changes in methods, models, values of unmeasured variables, or assumptions.

Results

Search Results

Overall, 2023 duplicate studies were removed from the 4188 initial search results. After the review of the title, abstract, and full-text, ineligible studies were excluded. Overall, 11892 patients from 15 studies were included. (10, 11, 13, 18-29). Fig. 1 illustrates the flowchart of study selection. The subjects of those studies were users of arterial iodinated contrast agents who received CAG and/or PCI, the basic characteristics of the included studies was shown in Table 1.

The 15 selected studies that assessed the incidence of PC-AKI in hyperuricemia group and normouricemia group were divided into three subgroups according to the renal status (normal renal function (3 studies), pre-existing renal dysfunction (7 studies), and mix group (5 studies)) (Table 2). Besides, 6 articles provided the proof for the sample size of >1000 patients (10, 19-22, 25). The majority of the included studies were conducted in China (33%), five studies were published in the past five years (Fig. 2). In addition, two studies were published in Chinese (28, 29), and other studies were published in English. Moreover, seven studies assessed the mortality (3 in normal renal function subgroup and 4 in pre-existing renal dysfunction subgroup), and 5 studies compared the data of RRT.

Table 1: Characteristics of the included studies

Firs author, Year	*Country*	*Cohort Design*	*Patient Status*	*Patients(n)*	*HUA diagnostic Basis*	*PC-AKI diagnostic basis*				*NOS Score*
					male> 7 mg /dL;female>6 mg / dL	>0.3 mg/dL	≥0.5mg /dL	>25 %	Time of hour	
Liu,2013	China	PC	PCI	788	YES	No	YES	No	48-72h	9
Mir-bolouk,2021	Iran	CC	CAG	211	Yes	No	YES	YES	48h	8
Guo,2015	China	CC	PCI	1772	Yes	No	YES	YES	48h	9
L.Barbier,2014	Italy	CC	CAG +PCI+CKD	1296	Yes	No	YES	No	7day	9
Park,2010	Korea	RC	PCI	290	Yes	YES	No	No	48h	9
Mandurino-Mirizzi,2021	Italy	PC	PCI +CKD	1247	No	No	YES	YES	48h	8
R. Sadineni,2021	India	CC	PCI+ CAG	2433	Yes	YES	No	YES	24 or 48h	8
Yacov,2016	Israel	RC	PCI	1372	No	YES	No	No	48h	9
To-prak,2006	Turkey	PC	PCI	266	Yes	No	YES	YES	48h	9
Mendi,2017	Turkey	PC	PCI	450	No	No	YES	YES	72h	9
Kow-alczyk,2010	Poland	PC	PCI +CKD	1372	Yes	No	YES	YES	48h	9
Okino,2010	Japan	RC	PCI+CKD	139	Yes	No	YES	YES	48h	8
Chen,2011	China	PC	PCI+ACS	266	Yes	No	YES	YES	72h	9
Liu YH,2013	China	PC	PCI+CKD	450	Yes	No	YES	YES	72h	8
Zheng,2019	China	CC	PCI+ACS	146	Yes	No	YES	YES	48h	9

HUA: hyperuricemic; PC: prospective cohort study; CC:Case–control study; RC: retrospective cohort study; PCI: percutaneous coronary intervention; CAG coronary angiography; CKD: Chronic kidney disease; ACS: angiotensin-converting enzyme. NOS:the standard Newcastle-Ottawa Scale

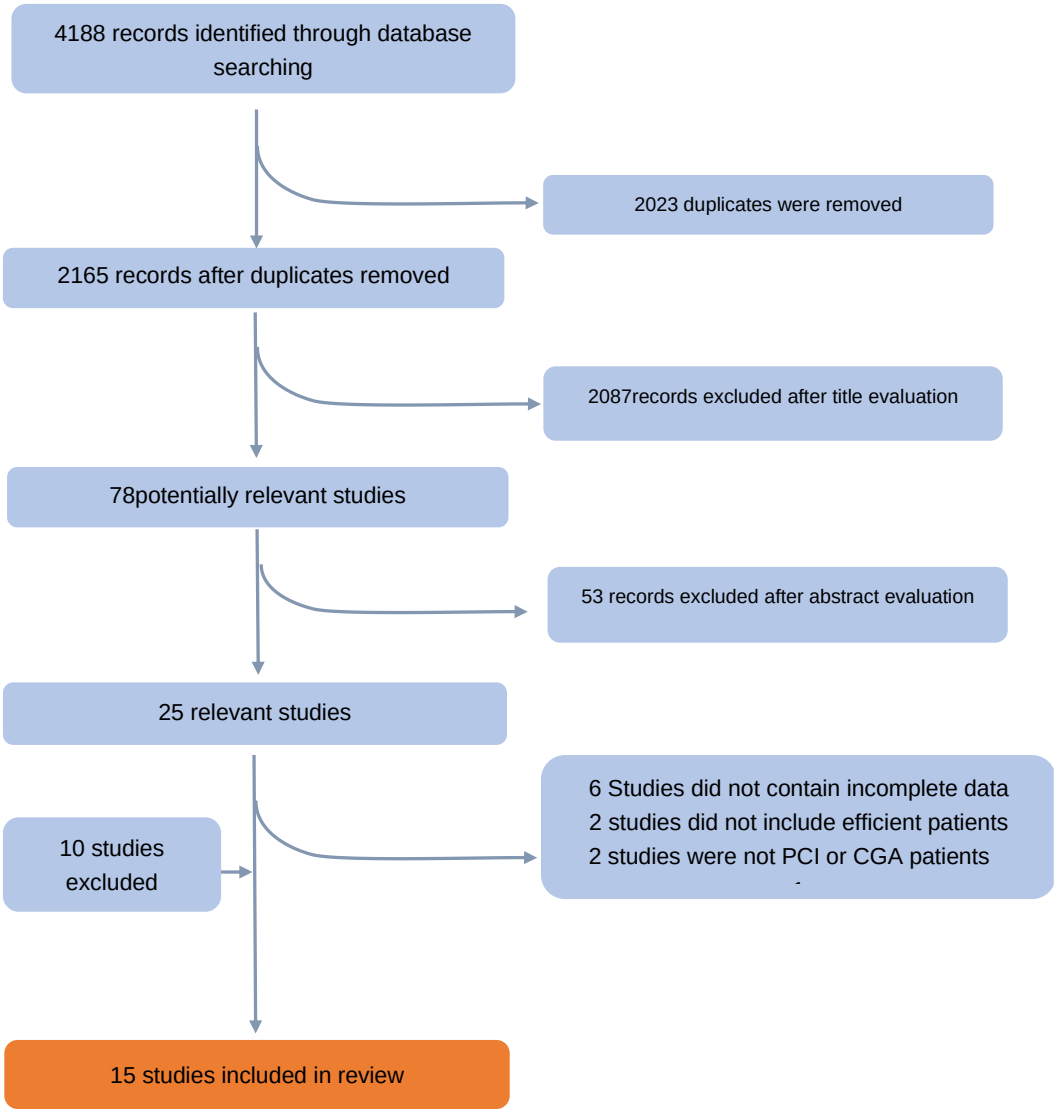

Fig. 1: Flow diagram of the literature search and study selection process

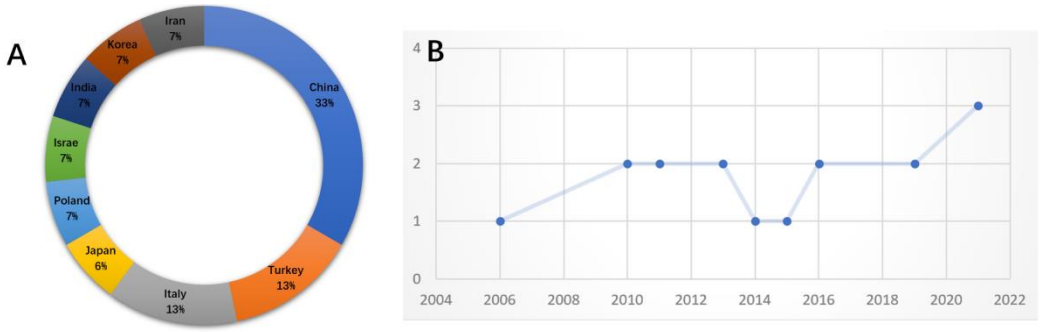

Fig. 2: Distribution of studies according to the country (A) and publication year (B)

Table 2: Subgroup meta-analysis of hyperuricemic and PC-AKI

Author	*Baseline Scr(μmol/l)*		*Incidence of PC-AKI n(%)*		*Mortality n(%)*		*Renal replacement therapy n(%)*		*Adjusted OR*
	HUA	NUA	HUA	NUA	HUA	NUA	HUA	NUA	
				Normal renal function subgroup					
MENDI,2017	72.5±13	71.6±10	48(20%)*	25(12%)*	10(4%)	4(1%)	2(1%)	1(1%)	2.1
MIRBOLOUK 2021	97.25±4.33*	86.63±3.26*	7(8.04%)	9(7.2%)	—	—	—	—	1.12
CHEN 2011	106.1 ±29.4	87.6 ±27.4	22(37%)*	31(20%)*	1(1.7%)	0(0%)	4(6.8%)	0(0%)	2.42
				Pre-existing renal dysfunction subgroup					
KOWALCZYK,2010	125.48±59.8*	98.78±73.9*	24(69%)	450 (67.9%)	51(14.5%)*	47(7.1%)*	—	—	1.06
OKINO 2010	145.86±54*	114.92±46.85*	5(8.5%)	4(5%)	—	—	—	—	1.76
TOPRAK2006	128.2±17.68	125.53±14.14	19(15.1%)*	4(2.9%)*	2(1.6%)	1(0.7)	5(4%)*	0(0%)*	6.04
LIU YH2013	141.19±12*	124.14±±18*	49(23.9%)*	25(10.4%)*	10(4.9%)	6(2.5%)	12(5.9%)*	2(0.8%)*	2.71
L.BARBIER 2014	—	—	102(16%)	80(12.3%)	—	—	—	—	1.35
R. SADINENI2021	—	—	10(35.7%)*	13(19.4%)*	—	—	—	—	2.31
MANDURINO-MIRIZZI 2021	97.25±5.76*	80.45±3.62*	120(20.8%)*	300(16.2%)*	34(5.8%)*	37(2%)*	—	—	1.35
				Mix group					
LIU 2013	94±19*	85±18*	17(8.1%)*	8(1.4%)*	5(2.4%)*	2(0.3%)*	3(1.4%)*	0(0)*	6.23
PARK 2011	—	—	24(13.04%)*	25(2.35%)*	—	—	—	—	6.23
GUO 2015	105.87±46.51*	85.14±27.13*	33(5.78%)*	21(1.76%)*	—	—	—	—	3.42
YACOV 2016	114.04±31*	99.65±3.48*	83(24%)*	70(6.78%)*	—	—	—	—	4.46
ZHENG2019	—	—	12(38.7%)*	19(16.81%) *	—	—	—	—	2.83

Values are mean±standard deviation or n(%);HUA: hyperuricemic; NUA:normouricemic; OR:odd ratio *P<0.05

Association of hyperuricemia with the incidence of PC-AKI

The incidence of PC-AKI was assessed in all the included studies. The results of pooled analysis revealed that hyperuricemia was significantly associated with the incidence of PC-AKI(ORs=2.48; 95% CI:[1.77, 3.46], *P*<0.00001). As there was a significant heterogeneity between studies (I^2=84%, *P*<0.00001), the sensitivity and subgroup analyses were conducted. Sensitivity analysis refers to the assessment of the combined results of the remaining studies by removing one study in turn. The combined results of the I^2 and ORs (I^2:84~86%; ORs:2.37~2.68) did not change significantly in the sensitivity analysis when a single study was excluded, which indicated that the conclusion was robust. A higher incidence of PC-AKI was found in the hyperuricemia group among all the three subgroups. The heterogeneity was satisfied in the normal renal function subgroup (I^2=0%, *P*=0.45) and mixed subgroup (I^2=0%, *P*=0.43) after subgroup analysis, and the detailed results are shown in Fig. 3. However, the normal renal function subjects with hyperuricemia were found to be at a higher risk of PC-AKI.

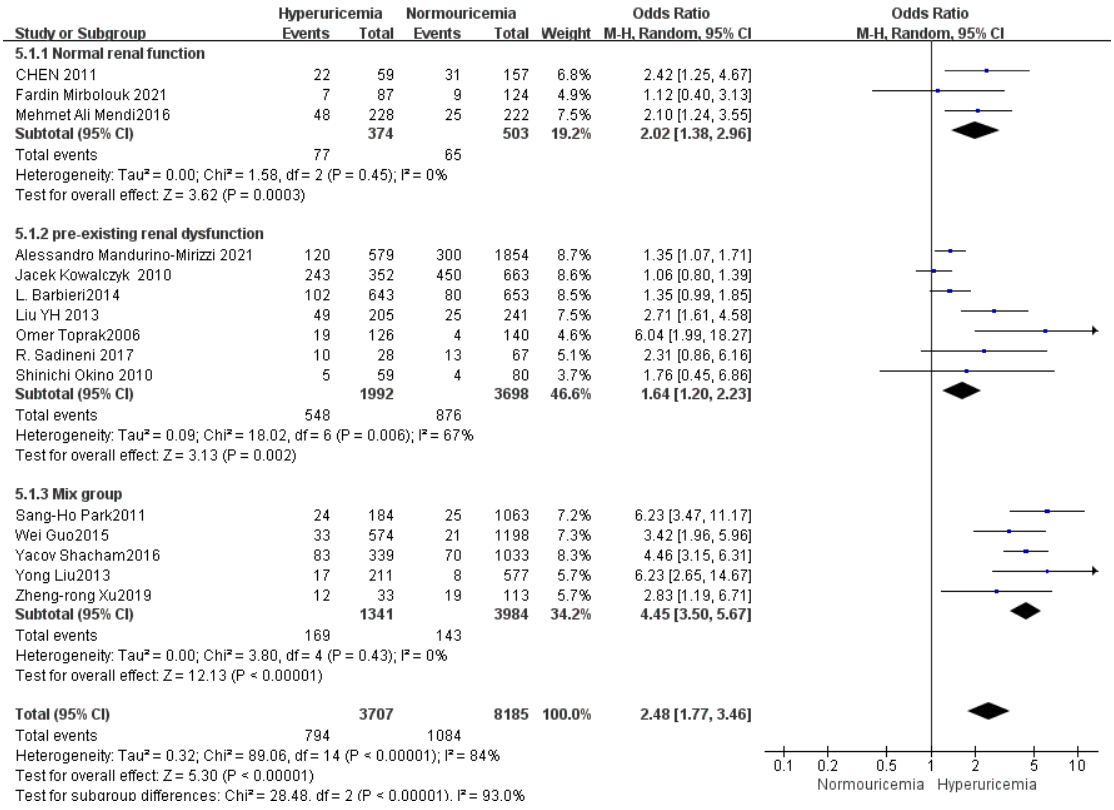

Fig. 3: Forest plot showed the total and subgroups results of association between hyperuricemia and the incidence of PC-AKI

Association of hyperuricemia with mortality and incidence of undergoing RRT

Seven studies assessed the association between hyperuricemia and mortality rate. The fixed-effects model was chosen, and the pooled OR for mortality was 2.33 (95% CI:1.81-3.00). The heterogeneity analysis reached statistical outcomes (I^2=0%, *P*=0.87). Similar results with the incidence of PC-AKI were found in subgroup analysis that normal renal function subjects with hyperuricemia were shown a higher risk of mortality (Fig. 4A).

Besides, five studies reported the incidence rates of RRT, which were significantly different be-

tween the hyperuricemia group and normoglycemia group. The pooled OR for the risk of RRT was 8.69 (95% CI: 3.22–23.44). There was no heterogeneity between studies (I^2 = 0.0%, *P*=0.67) (Fig.4B).

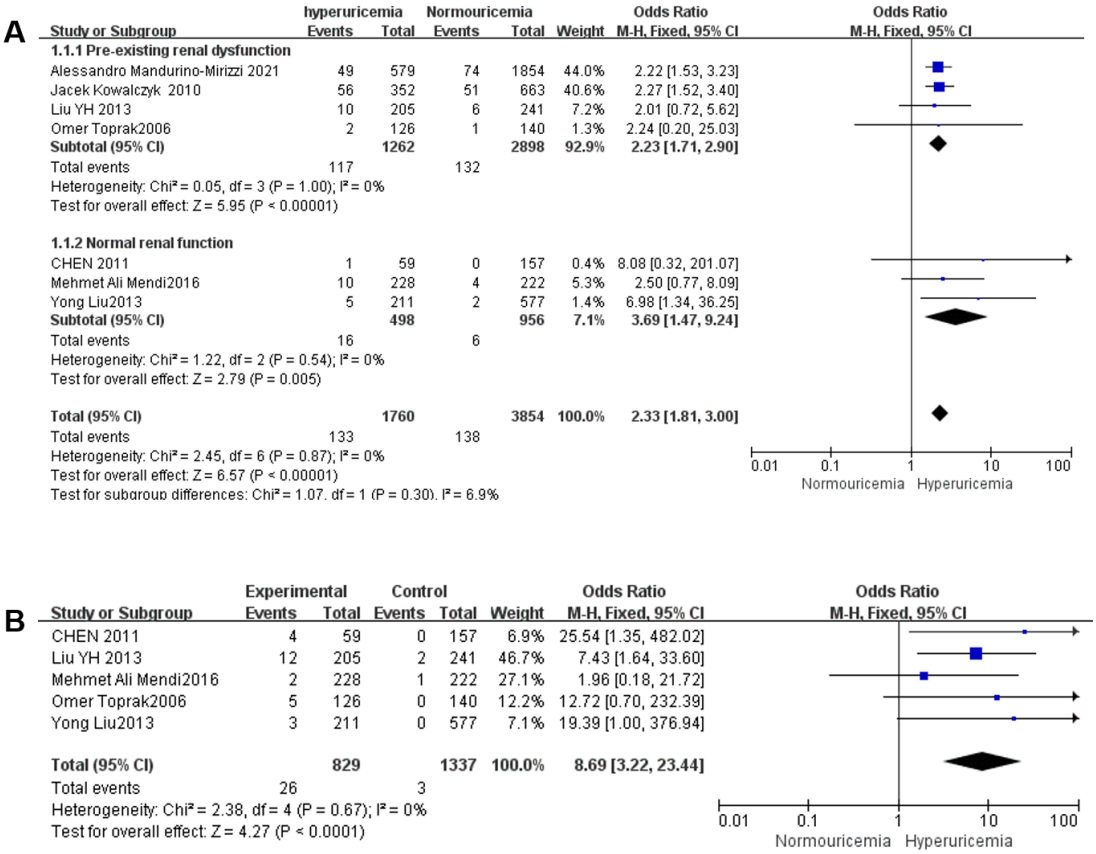

Fig. 4: Forest plot showed the total and subgroups results of association between hyperuricemia with mortality (A) and RRT(B)

Discussion

The present meta-analysis of 15 relevant studies that involved a total of 11892 participants demonstrated that hyperuricemia was an independent risk factor for PC-AKI development. The pooled OR of hyperuricemia for PC-AKI incidence was 2.48 (95% CI: [1.77, 3.46]). Additionally, the present meta-analysis also suggested that mortality rate and incidence of undergoing RRT were higher in patients with hyperuricemia. Compared with traditional grouping methods depending on the occurrence of PC-AKI events (PC-AKI group and Non-PC-AKI group), the studies included in the present meta-analysis were grouped by serum uric acid level (Normouricemic group and Hyperuricemic group). This method of grouping can better reflect the independent association between serum uric acid level and incidence of PC-AKI. To date, few studies have concentrated on the relationship between serum uric acid level and incidence of PC-AKI based on this grouping method (30). This is the first meta-analysis that has fully considered the influence of basic renal function when exploring the relationship between hyperuricemia and incidence of PC-AKI.

Association of hyperuricemia with the incidence of PC-AKI

The analysis of 10 of 15 included studies showed that the incidence rate of PC-AKI in the hyperuricemia group was significantly higher than that in the normal uric acid group (10, 18, 19, 21-24, 27-29). On the contrary, other 5 studies indicated that hyperuricemia was not directly related to the incidence of contrast-induced nephropathy (11, 13, 20, 25, 26). The results of the subgroup analysis showed that the overall effect of hyperuricemia was statistically significant, which proved that hyperuricemia was an independent risk factor of PC-AKI, and this is consistent with most of the previously reported results (22-24, 27-29). However, the cut-off point values of uric acid in different studies are inconsistent. Some study suggested a possible detrimental threshold effect of SUA >5.4mg/dl, while some advised >6.7mg/dl (22, 24). More researches in the future are needed to focus on this aspect. The results of the present meta-analysis revealed that the relationship between hyperuricemia and incidence of PC-AKI was not affected by study design and sample size, while it was significantly affected by basic renal function. In the current meta-analysis, the association of PC-AKI incidence with hyperuricemia was fluctuated from 5.78% to 69%, which could be related to the difference in basic renal function of the included subjects. Renal dysfunction is the most important risk factor for PC-AKI (3, 30). The incidence of PC-AKI increases from 8% to 92% along with the elevation of Scr level from 1.5 to 6.8 mg/dL (31). However, few studies have compared the influences of hyperuricemia on different renal function statuses (32). In order to more accurately evaluate the independent effects of hyperuricemia on the incidence of PC-AKI, the included studies were divided into three subgroups according to the basic renal function. The subgroup results showed that the incidence rate of AKI between the hyperuricemia group and the normal uric acid group was significantly different, and the heterogeneity was also significant (I^2=84%, P<0.00001). However, the results of the sensitivity analysis indicated that the study was relatively stable. The results of the heterogeneity analysis changed significantly, and I^2 was 0% in both the normal renal function and mixed subgroups. The basic renal function status could be the main cause of the overall heterogeneity. Unexpectedly, the results of the subgroup analysis revealed that compared with the normal renal function subgroup, a lower incidence of PC-AKI was found in the pre-existing renal dysfunction subgroup. This might be related to more adequate pretreatments (i.e., hydration had always been carried out in the renal dysfunction group before injection of contrast media) (33-35) . In addition, the small sample size could also lead to the biased results. In the present meta-analysis, the normal renal function subgroup only included 3 studies, of which one study included patients with emergency PCI, which was considered to have a higher risk of PC-AKI than primary PCI and elective PCI (36). Additional studies are therefore required to explore the relationship between renal function and serum uric acid level.

Apart from basic renal function, diabetes, hypertension, dehydration were also the well-known risk factor of PC-AKI. Due to the limited original data, this study did not further explore the comprehensive impact of these factors and uric acid on PC-AKI. However, a large meta-regression study revealed an independent and significant association between uric acid and PC-AKI, not mediated by other risk factors (i.e. diabetes, hypertension, ejection fraction, hemoglobin) (12).

Association of hyperuricemia with mortality and RRT

PC-AKI was reported as the most important risk factor for persistent renal dysfunction, chronic kidney disease, end-stage renal disease, or death (37). Further attention has been recently paid to the risk factors for major adverse kidney events (38, 39), while the concentration was shifted from short-term to long-term, as well as involvement of more patient-centered endpoints (40, 41). Besides, 7 of 15 studies assessed the relationship between hyperuricemia with mortality rate. The pooled OR for mortality was 2.33 (95% CI:[1.81,3.00]), which is similar to another finding (32). However, the subsequent subgroup analysis

unexpectedly showed that the pre-existing renal dysfunction subgroup had a lower OR (renal dysfunction (2.23) vs. normal renal function (3.69)). As no subgroup analysis has yet been conducted according to the renal function status to explore the influence of hyperuricemia on mortality, the results of the present meta-analysis could not be further compared with those reported previously. In the current meta-analysis, 5 of the 15 studies assessed RRT with different serum uric acid levels. The total pooled OR for the risk of RRT was 8.69 (95% CI:[3.22,23.44]), which was higher than Zuo et al.'s result (32). Due to the small sample size, we could not perform the subgroup analysis based on renal function status. In short, hyperuricemia increases the incidence of renal adverse outcomes. The specific damage mechanism may be due to hyperuricemia, the accumulation of urate crystals, macrophage infiltration, endothelial cell apoptosis, and increased expressions of inflammatory mediators (42, 43).

Similar results were found in the subgroup analysis of incidence rate of PC-AKI and mortality, in which the pre-existing renal dysfunction subgroup had a relatively low risk. The specific mechanism has still remained elusive, while some studies hypothesized that the renal dysfunction might offset the influence of hyperuricemia on PC-AKI to some extent (32). In addition, we speculated that in patients with existing renal function injury, the indicators of renal function status, such as SCr or glomerular filtration rate, have the greatest influence on PC-AKI incidence or short- and long-term renal adverse events. The influence of blood uric acid level on PC-AKI was weakened in this case. A larger sample size is urgently required to prove these hypotheses, especially for the study of normal renal function.

Quality assessment and publication bias

The quality of the included studies was assessed using the Newcastle-Ottawa (NOS) which consisted three parts: selection of the study groups (0–4 points), Study group comparison (0–2 points), and Exposure method assessment (0–4 points). All studies included in our study were of high quality with 8–9 stars (Table 1). For any meta-analysis, publication bias cannot be completely eliminated as non-English studies with negative results are less likely to be published or appear in international databases, thus, some articles could be missed. The asymmetric funnel plot in the meta-analysis suggested the existence of publication bias.

Several intrinsic limitations of the present meta-analysis should be acknowledged. First, the majority of the including studies were case-control or observational studies, thus, the differences in methodology, subjects, and the definitions of hyperuricemia and PC-AKI could influence the final results. Different multivariable factors were found in the included studies, which could result in confounding effects. Second, the high heterogeneity among the included studies due to the difference in the sample size, definition, or frequency of PC-AKI could lead to a reduction in the credibility of the results. However, the 'leave-one-out' sensitivity analysis demonstrated that the omission of each study did not change the overall results. Third, this meta-analysis mainly concentrated on the intracoronary administration of the iodine contrast agent, therefore, the risk models reviewed might not be applied to other procedures, such as contrast-enhanced computed tomography (CT), CT angiography, and non-coronary angiography. Last but not least, the sample size was insufficient, especially for performing subgroup analysis. The small sample size hindered us from reliably explaining the effects of basic renal function on the relationship between hyperuricemia and the incidence of PC-AKI.

Conclusion

Hyperuricemia was independently associated with the incidence of PC-AKI, and it significantly increased the mortality rate and the risk of RRT among patients who received CAG and/or PCI. In addition, the effect of serum uric acid level on the incidence and mortality of PC-AKI was higher in patients with normal renal function. In the next study, the effects of serum uric acid level on

the incidence of PC-AKI in patients with different renal functions will be particularly studied, so as to establish a more accurate individualized prevention scheme for PC-AKI.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that there is no conflict of interests.

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