

Uric acid and contrast-induced nephropathy: an updated review and meta-regression analysis

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Abstract

Introduction: Previous studies have suggested a relationship between serum uric acid and contrast-induced nephropathy (CIN).

Aim: We performed an updated review and a meta-regression analysis to assess whether serum uric acid is associated with CIN or there exists any relationship between serum uric acid and other risk factors for CIN.

Material and methods: We searched PubMed, Embase and Cochrane databases and reviewed cited references up to July 31, 2018 to identify relevant studies.

Results: A total of 6,705 patients from 10 clinical studies were included. CIN occurred in 774 of the 6,705 (12%) patients. Baseline uric acid levels were significantly higher in those who developed CIN (6.51 vs. 5.67 mg/dl; 95% CI: 0.55–1.22, $p = 0.00001$). Comparison of clinical features showed that patients with CIN were significantly older (69 vs. 63 years; $p < 0.00001$) and more often had diabetes (42% vs. 32%; $p = 0.002$) and hypertension (67% vs. 59%; $p = 0.03$). Also, patients who developed CIN had lower hemoglobin (12.5 vs. 13.6 mg/dl; $p < 0.00001$) and higher levels of baseline creatinine (1.27 vs. 1.01 mg/dl; $p < 0.00001$), but had similar levels of glycemia, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride. Also, they showed a lower ejection fraction (45% vs. 50%; $p < 0.00001$). Meta-regression analysis revealed that uric acid related only to age ($r = 0.13$, $p = 0.03$).

Conclusions: Our investigation indicates that uric acid is significantly associated with CIN. Uric acid correlated significantly with age only, and not with other major predictors of CIN. Further studies are therefore needed to verify the potential of uric acid to improve CIN risk stratification.

Key words: angiography, contrast-induced nephropathy, percutaneous coronary intervention, uric acid.

Summary

Uric acid relates to the occurrence of contrast-induced nephropathy (CIN), but it remains unclear whether it is merely related to traditional risk factors for CIN or plays an independent predictive role. We performed a meta-analysis and a meta-regression analysis of 10 clinical studies. Baseline uric acid levels were significantly higher in those who developed CIN. Statistical analysis revealed that uric acid correlated significantly with age only, but not with other major predictors of CIN, such as diabetes, hypertension, hemoglobin, creatinine, glycemia, cholesterol, and triglycerides. Uric acid seems to have the potential to improve CIN risk stratification.

Introduction

Contrast-induced nephropathy (CIN) is one of the most common complications of procedures that require the use of contrast media [1, 2]. Contrast-induced ne-

phropathy occurs in up to 25% of patients undergoing diagnostic and/or therapeutic coronary angiography, depending on the presence of known risk factors, such as chronic kidney disease, diabetes mellitus, high dose of

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contrast medium, congestive heart failure, and anemia [3, 4]. In recent years, several investigations and some systematic reviews and meta-analyses have shown that hyperuricemia relates to a greater frequency of CIN [5–7]. However, no previous investigation has assessed whether serum uric acid plays an independent role in CIN stratification or is merely related to presenting features and procedural characteristics of patients undergoing elective coronary angiography.

Aim

The aim of the current study was to perform an updated review and a meta-regression analysis in order to assess whether serum uric acid is associated with CIN or there exists any relationship between serum uric acid and other risk factors for CIN.

Material and methods

Study design

This meta-analysis was conducted following current guidelines, including the Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE), and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement [8–10]. All activities were carried out independently by two reviewers (FP and VP). Divergences were solved after consensus.

Data sources

We searched PubMed, Embase, and Cochrane databases as well as the National Institutes of Health Clinical Trials Registry (www.clinicaltrials.gov) up to July 31, 2018 to identify relevant studies. In addition, we searched the presentations at major cardiovascular scientific sessions including meetings of the American College of Cardiology, American Heart Association and European Society of Cardiology. Additional studies were searched in Google Scholar and Scopus. Editorials and reviews from major medical journals published within the last 5 years were also considered for further information on studies of interest. No language restriction was enforced in order to minimize the risk of publication bias. The following combinations of medical subject heading terms and text words were used: “contrast induced acute kidney injury”, “contrast induced acute renal failure”, “contrast nephropathy”, “contrast induced nephropathy”, “contrast induced nephrotoxicity”, “contrast associated nephropathy”, “contrast associated nephrotoxicity”, and “radiocontrast induced nephropathy”.

Study selection

Retrieved citations were first screened independently by two unblinded investigators (FP and GP) at the title

and/or abstract level, with divergences resolved after consensus. Studies were screened in order to identify potentially suitable articles that should be assessed for eligibility as full texts. Notably, a detailed review of study authors, dates, and locations was used to exclude redundancy. Studies with overlapping data were identified, and in cases of apparent serial reporting of a particular patient cohort, only the publication with the largest number of patients was included in the meta-analysis. Only studies published in original articles in peer-reviewed scientific journals were taken into consideration. Studies were then selected according to the following explicit inclusion criteria (all had to be met for inclusion): (i) case series of patients undergoing coronary angiography and/or PCI; (ii) comparison of clinical, laboratory and procedural features between patients with or without post-procedural evidence of CIN; (iii) baseline assessment of uric acid levels.

Data extraction and quality

Analysis was performed at the study level, as databases of the individual patients were not obtained. Data from each study were obtained by two independent reviewers (FP and GP) and entered into a structured spreadsheet. Disagreements were resolved by consensus. Dichotomous variables were extracted in absolute numbers and were recalculated when percentages were reported. Continuous variables were extracted and weighted means for the total study population were calculated. The primary endpoint was baseline uric acid levels in patients with or without CIN. Other endpoints were the differences in clinical, laboratory and procedural features between patients with and without CIN, with special emphasis on renal function. Study validity was tested according to recommendations distinguishing several sources of bias. In order to assess the quality of reporting of the studies, the standard Strengthening the Reporting of Observational Studies in Epidemiology checklist (STROBE) was used [11]. This checklist includes items assessing the study methodology, study type, study population, sample size, sample collection methods, statistical tests, and presentations.

Data analysis and synthesis

All analyses were performed using the Review Manager 5.2.10 software and Comprehensive Meta-analysis Version 3.1. Since heterogeneity of results was expected, the inverse variance method for random effects was used to estimate pooled risk ratios or relative risk for dichotomous variables or mean difference for continuous variables and 95% confidence intervals (CI) [12]. We tested the heterogeneity of the included studies with Q statistics and the extent of inconsistency between results with I^2 statistics. Significant heterogeneity was considered present in the case of $I^2 > 50\%$ and/or $p < 0.10$ [13].

However, we did not exclude outliers based on heterogeneity since heterogeneity is expected in meta-analyses of observational studies [14]. Accordingly, we performed a leave-one-out sensitivity analysis for each parameter in order to evaluate the robustness of the results and the impact of each single study on the summary estimate of effect. Briefly, we recalculated pooled estimates multiple times, using a random-effects model, each time with the removal of a single study from the original group. We also performed a sensitivity analysis stratified by sample size to exclude the possibility of overestimating the role of uric acid due to the inclusion of small studies (defined as those with a sample size < 500 patients). Presence of publication bias was estimated by the Rucker test (with arcsine transformation), which is best suited for binary outcomes and funnel plot analysis [15, 16]. Meta-regression analysis was conducted to assess whether there was a direct relationship between levels of uric acid and other variables associated with CIN [17]. Specifically, we performed a weighted random-effects meta-regression regressing uric acid and CIN against the difference of

each variable. Results are reported as beta coefficients and two-sided *p*-values. Statistical significance was set at *p* < 0.05 (two-tailed).

Results

Search results

From 2,046 initial citations that were retrieved from multiple databases, a total of 78 articles were analyzed as full reports according to predefined selection criteria. After excluding 68 studies because serum uric acid levels in patients with or without CIN were not reported, 10 investigations were finally deemed as eligible for inclusion in our systematic review (Figure 1) [18–27]. A total of 6,705 patients were included in the 10 studies. Selected studies were published between 2010 and 2015, and included series of patients from North America, Europe, and Asia (Table I). All included patients underwent either coronary angiography or percutaneous coronary intervention (PCI). Quality assessment by STROBE checklist revealed moderate to high quality in all studies (Table II).

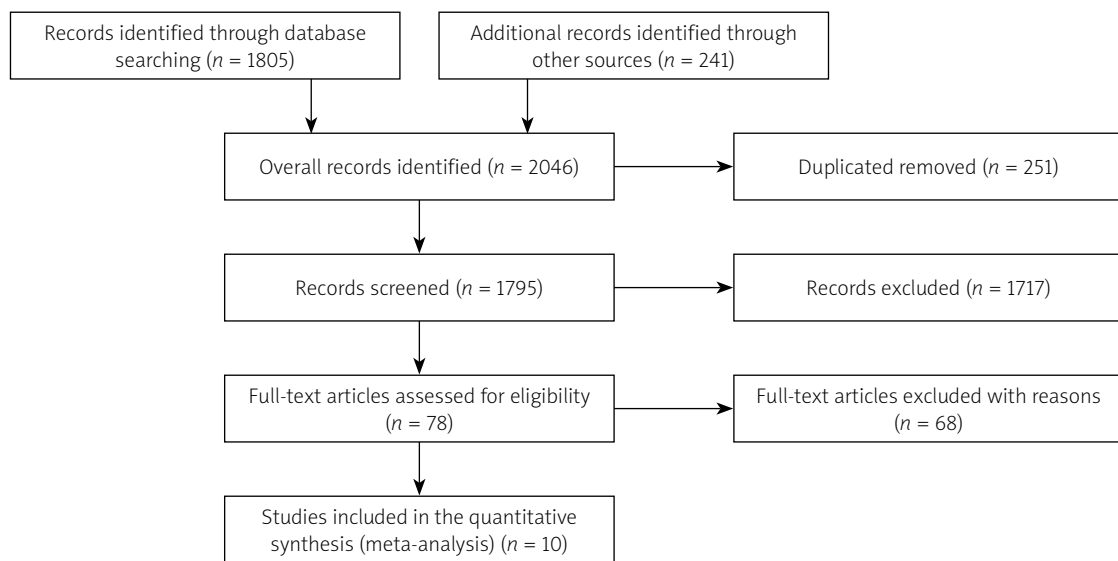


Figure 1. PRISMA diagram of study selection. The flow diagram demonstrates the study selection process in the systematic review and meta-analysis

Table I. List of included studies

Author	Country	Overall (n)	No CIN (n)	CIN (n)	Coro	PCI	Definition of CIN
Parkfetrat	Iran	290	245	45	Yes	Yes	SCr > 50% or > 0.5 mg/dl
Okino	China	139	130	9	Yes	Yes	SCr > 25% or > 0.5 mg/dl
Ma	China	69	43	26	Yes	Yes	SCr > 25% or > 0.5 mg/dl
Park	Korea	1247	1,196	51	Yes	Yes	SCr > 50% or > 0.5 mg/dl
Kurtul	Turkey	436	373	63	Yes	Yes	SCr > 25% or > 0.5 mg/dl
Elbasan	Turkey	835	755	80	Yes	Yes	SCr > 25%
Saritemur	Turkey	744	651	93	Yes	Yes	SCr > 25% or > 0.5 mg/dl
Ji	China	805	497	68	Yes	Yes	SCr > 25% or > 0.5 mg/dl
Barbieri	Italy	1950	1,699	251	Yes	Yes	SCr > 25% or > 0.5 mg/dl
Karabulut	Poland	430	342	88	Yes	Yes	SCr > 25% or > 0.5 mg/dl

Table II. STROBE Statement – checklist of items that should be included in reports of observational studies

Variable	Item No.	Recommendation	Score											
			Pakfetrat [18]	Okino [19]	Ma [20]	Park [21]	Kurtul [22]	Elbasan [23]	Saritemur [24]	Ji [25]	Barbieri [26]	Karabulut [27]		
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	1	1	1	1	1	1	1	1	1	1	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1	1	1	1	1	1	1	1	1	1	1	1
Introduction														
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1	1	1	1	1	1	1	1	1	1	1	1
Objectives	3	State specific objectives, including any pre-specified hypotheses	1	1	1	1	1	1	1	1	1	1	1	1
Methods														
Study design	4	Present key elements of study design early in the paper	1	1	0	1	0	1	1	0	1	1	1	1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	1	1	1	1	1	1	1	1	1	1	1	1
Participants	6	(a) <i>Cohort study</i> – Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) <i>Case-control study</i> – Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (c) <i>Cross-sectional study</i> – Give the eligibility criteria, and the sources and methods of selection of participants (d) <i>Cohort study</i> – For matched studies, give matching criteria and number of exposed and unexposed (e) <i>Case-control study</i> – For matched studies, give matching criteria and the number of controls per case	1	1	1	1	1	1	1	1	1	1	1	1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	1	1	0	1	1	1	1	1	1	1	0	0
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	1	1	1	1	1	1	1	1	1	1	1	1

Table II. Cont.

Variable	Item No.	Recommendation	Score										
			Pakfetrat [18]	Okino [19]	Ma [20]	Park [21]	Kurtul [22]	Elbasan [23]	Saritemur [24]	Ji [25]	Barbieri [26]	Karabulut [27]	
Bias	9	Describe any efforts to address potential sources of bias	1	1	0	1	0	1	0	1	0	0	0
Study size	10	Explain how the study size was arrived at	0	0	0	0	0	0	0	0	0	0	0
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	1	1	0	1	1	1	1	1	1	1	1
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	1	1	1	1	1	1	1	1	1	1	1
		(b) Describe any methods used to examine subgroups and interactions	1	1	1	1	1	1	1	1	1	1	1
		(c) Explain how missing data were addressed	1	1	1	1	1	1	1	1	1	1	1
		(d) Cohort study – If applicable, explain how loss to follow-up was addressed	0	0	0	0	1	0	1	0	0	0	0
		Case-control study – If applicable, explain how matching of cases and controls was addressed	0	0	0	0	1	0	1	0	0	0	0
Results	13*	Cross-sectional study – If applicable, describe analytical methods taking account of sampling strategy	1	1	1	1	1	1	1	1	1	1	1
		(e) Describe any sensitivity analyses	1	1	1	1	1	1	1	1	0	0	1
Participants	13*	(a) Report numbers of individuals at each stage of study, eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	1	1	1	1	1	1	1	1	1	1	1
		(b) Give reasons for non-participation at each stage	1	1	0	0	0	0	0	0	0	0	0
		(c) Consider use of a flow diagram	1	0	1	1	1	0	1	0	0	0	1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	1	1	0	1	1	1	1	1	1	1	0
		(b) Indicate number of participants with missing data for each variable of interest	1	1	1	1	1	1	1	1	1	1	1
		(c) Cohort study – Summarise follow-up time (eg, average and total amount)	–	–	–	–	–	0	–	–	–	–	–

Table II. Cont.

Variable	Item No.	Recommendation	Score												
			Pakfetrat [18]	Okino [19]	Ma [20]	Park [21]	Kurtul [22]	Elbasan [23]	Saritemur [24]	Ji [25]	Barbieri [26]	Karabulut [27]			
Outcome data	15*	<i>Cohort study</i> – Report numbers of outcome events or summary measures over time <i>Case-control study</i> – Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> – Report numbers of outcome events or summary measures	–	–	–	–	–	–	1	–	–	–	–	–	–
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	1	1	0	1	0	1	0	1	0	0	0	1	0
Other analyses	17	Report other analyses done, eg analyses of subgroups and interactions, and sensitivity analyses	1	1	1	1	1	1	1	1	1	1	1	1	1
Discussion															
Key results	18	Summarise key results with reference to study objectives	1	1	1	1	1	1	1	1	1	1	1	1	1
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	1	1	0	0	0	0	1	1	0	0	0	0	0
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	1	1	1	1	1	1	1	1	1	1	1	1	1
Generalisability	21	Discuss the generalisability (external validity) of the study results	1	1	1	1	1	1	1	1	1	1	1	1	1
Other information															
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	0	0	0	0	0	0	1	1	0	0	1	0	0
Total scores			28	26	19	25	24	28	23	25	19	24	25	19	24

Definition of CIN

CIN was defined variously in the studies. Most studies described CIN as an increase in serum creatinine levels of more than 25% or 0.5 mg/dl above the baseline 48–72 h following intravascular contrast medium administration [19, 20, 22, 24–27]. CIN was defined according to the RIFLE criteria by Pakfetrat *et al.* [18] as an increase in serum creatinine of ≥ 0.5 mg/dl or $\geq 50\%$ over baseline within 7 days by Park *et al.* [21], and as an increase $\geq 25\%$ in creatinine by Elbasan *et al.* [23].

Primary end-point

CIN occurred in 774 of the 6,705 (11.5%) patients. Frequency of CIN ranged between 4.1% and 37.7%. Baseline uric acid levels were significantly higher in those who developed CIN 6.51 (95% CI: 6.23–6.78) vs. 5.67 (95% CI: 5.25–6.09) mg/dl; mean difference: 0.88, 95% CI 0.55–1.22, $p < 0.00001$; $I^2 = 83\%$, $p < 0.00001$ (Table III; Figure 2).

Factors associated with CIN

Comparison of clinical features at referral showed that patients who experienced CIN were significantly older (69 (95% CI: 64–72) vs. 63 (95% CI: 59–67) years; mean difference: 5.25, 95% CI: 3.19–7.32, $p < 0.00001$; $I^2 = 81\%$, $p < 0.00001$), more often had diabetes (42% vs. 32%; risk ratio: 0.70, 95% CI: 0.56–0.88, $p = 0.002$; $I^2 = 81\%$, $p < 0.00001$) and hypertension (67% vs. 59%; risk ratio: 0.84, 95% CI: 0.72–0.98, $p = 0.03$; $I^2 = 81\%$, $p < 0.00001$), with no difference in prevalence of smoking and hyperlipidemia (Table III; Figure 3). With respect to laboratory findings at baseline, patients who developed CIN had lower hemoglobin (12.5 (95% CI: 12.1–12.9) vs. 13.6 (95% CI: 13.2–13.9) mg/dl; mean difference: 1.02, 95% CI: 0.61–1.42, $p < 0.00001$; $I^2 = 71\%$, $p = 0.0002$) and higher levels of baseline creatinine (1.27 (95% CI: 1.07–1.43) vs. 1.01 (95% CI: 0.86–1.16) mg/dl; mean difference: 0.22, 95% CI: 0.11–0.32, $p < 0.0001$; $I^2 = 94\%$, $p = 0.00001$), but had similar levels of glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride (Table IV; Figure 3). Also, they showed a lower ejection fraction (45% (95% CI: 42–47) vs. 50% (95% CI: 46–53); mean difference: 4.89, 95% CI: 2.77–7.01, $p < 0.00001$; $I^2 = 71\%$, $p = 0.002$) (Table V; Figure 4).

Meta-regression analysis

Meta-regression (Table VI) revealed that uric acid, apart from a relationship with age ($r = -0.75$, $p = 0.02$), was not associated with major risk factors for CIN, i.e. diabetes, hypertension, ejection fraction, hemoglobin and baseline creatinine (Figures 5 and 6).

Sensitivity analysis and publication bias

The leave-one-out analysis showed that the pooled results were not influenced by any single trial. In addition,

Table III. Baseline presenting features of overall population

Author	Uric acid [mg/dl]		Age [years]		Men		Diabetes		Smoking		Hypertension		Hyperlipidemia	
	No CIN \bar{x} (SD)	CIN \bar{x} (SD)	No CIN \bar{x} (SD)	CIN \bar{x} (SD)	No CIN n (%)	CIN n (%)	No CIN n (%)	CIN n (%)	No CIN n (%)	CIN n (%)	No CIN n (%)	CIN n (%)	No CIN n (%)	CIN n (%)
Pakfetrat	6.20 (1.60)	6.10 (2.00)	58 (12)	58 (11)	159 (88)	21 (12)	NA	NA	NA	NA	NA	NA	NA	NA
Okino	6.60 (1.60)	7.30 (2.70)	69 (8)	71 (11)	111 (93)	8 (89)	65 (50)	5 (56)	NA	NA	100 (77)	6 (67)	NA	NA
Ma	4.81 (1.15)	6.75 (1.99)	67 (9)	72 (8)	NA	NA	8 (19)	7 (27)	NA	NA	23 (54)	21 (81)	NA	NA
Park	5.12 (1.54)	6.51 (2.23)	64 (12)	69 (10)	NA	NA	378 (32)	34 (67)	NA	NA	NA	NA	NA	NA
Kurtul	5.49 (1.53)	6.53 (1.76)	61 (12)	72 (13)	241 (65)	39 (62)	119 (32)	23 (37)	176 (47)	10 (16)	161 (43)	35 (56)	110 (30)	11 (18)
Elbasan	5.10 (0.90)	6.20 (0.9)	58 (12)	65 (13)	564 (75)	51 (64)	221 (29)	37 (46)	298 (39)	31 (39)	290 (38)	30 (38)	195 (26)	22 (28)
Saritemur	4.89 (1.32)	6.09 (2.01)	55 (12)	64 (11)	475 (73)	55 (59)	135 (21)	39 (42)	361 (56)	51 (55)	265 (41)	57 (61)	242 (37)	37 (40)
Ji	6.02 (1.75)	6.78 (1.96)	66 (11)	73 (10)	232 (47)	38 (56)	132 (27)	26 (38)	NA	NA	262 (53)	52 (77)	NA	NA
Barbieri	6.35 (1.79)	6.60 (1.81)	72 (NA)	75 (NA)	1134 (67)	189 (75)	632 (37)	90 (36)	263 (15)	26 (10)	1287 (76)	189 (75)	928 (55)	135 (54)
Karabulut	6.08 (2.10)	6.83 (1.9)	64 (13)	66 (10)	208 (61)	62 (71)	129 (38)	42 (48)	248 (73)	64 (73)	248 (74)	65 (76)	171 (50)	40 (47)
Overall	5.67 95% CI: 5.25–6.09	6.51 95% CI: 6.23–6.78	63 95% CI: 59–67	69 95% CI: 64–72	3124/4510 (69%)	463/686 (67%)	1819/5686 (32%)	303/729 (42%)	1346/3638 (37%)	182/564 (32%)	2636/4490 (59%)	455/678 (67%)	1646/3638 (45%)	245/564 (43%)
P-value	< 0.00001		< 0.00001		0.970	0.002	0.105	0.03	0.864					

CIN – contrast-induced nephropathy, LV – left ventricular.

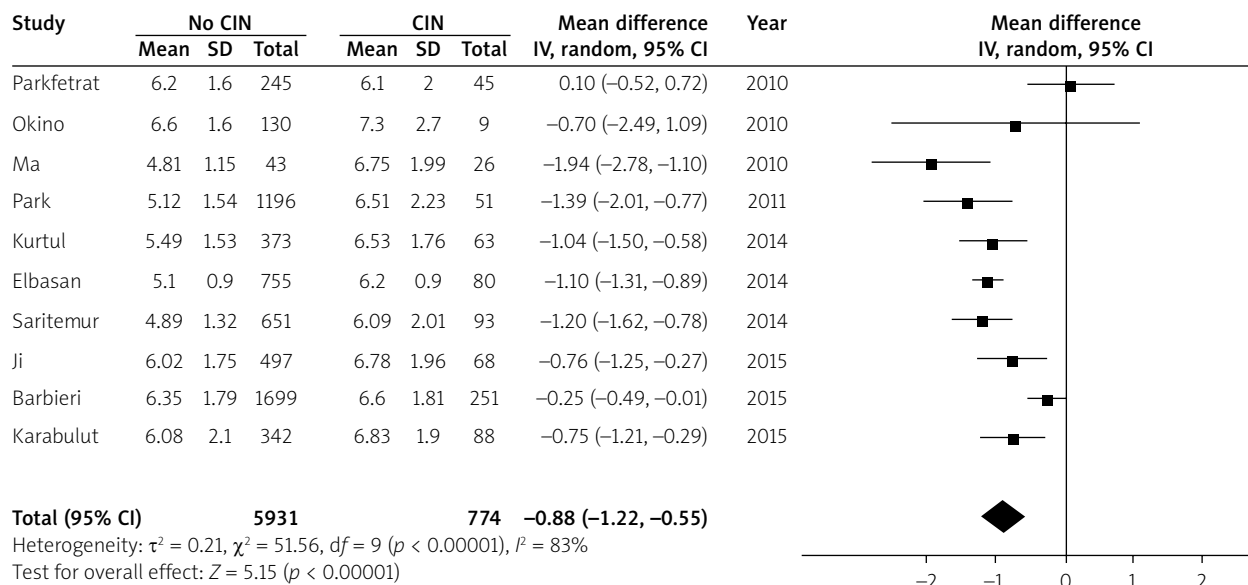


Figure 2. Forest plot of risk ratios for contrast-induced nephropathy according to uric acid. Markers represent point estimates of risk ratios, marker size represents study weight. Horizontal bars indicate 95% confidence intervals

tion, excluding studies with large (> 500 patients) or small (< 500 patients) sample sizes did not change results of the meta-analyses. Rucker’s test did not suggest publication bias ($p = 0.77$ for CIN). Funnel plot analysis showed no asymmetry suggesting a significant risk of publication bias, and that the end-points did not depend on the size of the studies (Figure 7).

Discussion

Serum uric acid is an underestimated and under-reported parameter in studies dealing with cardiac angiography and interventional procedures. Our study is the first meta-regression on this topic, showing that uric acid does not correlate with major predictors of CIN, with the exception of age, thus indicating that it might constitute a novel independent predictor to be included in CIN risk stratification.

Serum uric acid is the final product of purine metabolism, and uric acid levels depend on many factors, including diet, drug therapy, presence of kidney disease, increased purine turnover, etc. Hyperuricemia is associated with urate deposition, leading to gout arthritis and kidney stones [28]. Uric acid may also have a role in acute renal failure. Indeed, several studies have suggested a significant association between hyperuricemia and the development and progression of kidney disease and renal function impairment [29–31]. Uric acid can also impair endothelial function, as it inactivates nitric oxide, i.e. endothelium-derived relaxing factor, and inhibits release of nitric oxide from endothelial cells [32]. The relationship between hyperuricemia and renal failure may be helpful

for understanding the association between uric acid and CIN. However, to date, limited information is available on the effects of contrast media on uric acid metabolism. Two pioneer investigations in the 1970s showed that contrast agents have a uricosuric effect with enhanced renal tubular secretion of uric acid and a possible nephrotoxic effect [33, 34]. In addition, uric acid is associated with other factors that play a role in the pathogenesis of CIN, such as enhanced synthesis of reactive oxygen species, activation of the renin–angiotensin–aldosterone system, an increase in endothelin-1, and inhibition of the nitric oxide system [35].

Various patient- and procedure-related risk factors may contribute to CIN. Pre-existing renal insufficiency and diabetes mellitus are the two main patient-related risk factors. In a retrospective review of 938 patients with stable renal insufficiency, the overall incidence of CIN was 6.1%, while the incidence was 4.4%, 10.5% and 10.0% in patients whose eGFR was 45–60, 30–45 and ≤ 30 ml/min, respectively [36]. In the present study, baseline factors significantly associated with CIN included age, creatinine, lower hemoglobin, lower ejection fraction, diabetes and hypertension. It may be hypothesized that uric acid might be a marker for the presence of one or more of these well-known risk factors. However, our meta-regression analysis showed only a moderate significant association between uric acid and age, as expected, while other risk factors, including baseline creatinine, diabetes and hypertension, did not show any relationship with uric acid. These results suggest an independent association between uric acid and CIN, not mediated by other risk factors. It is worth noting the lack of associa-

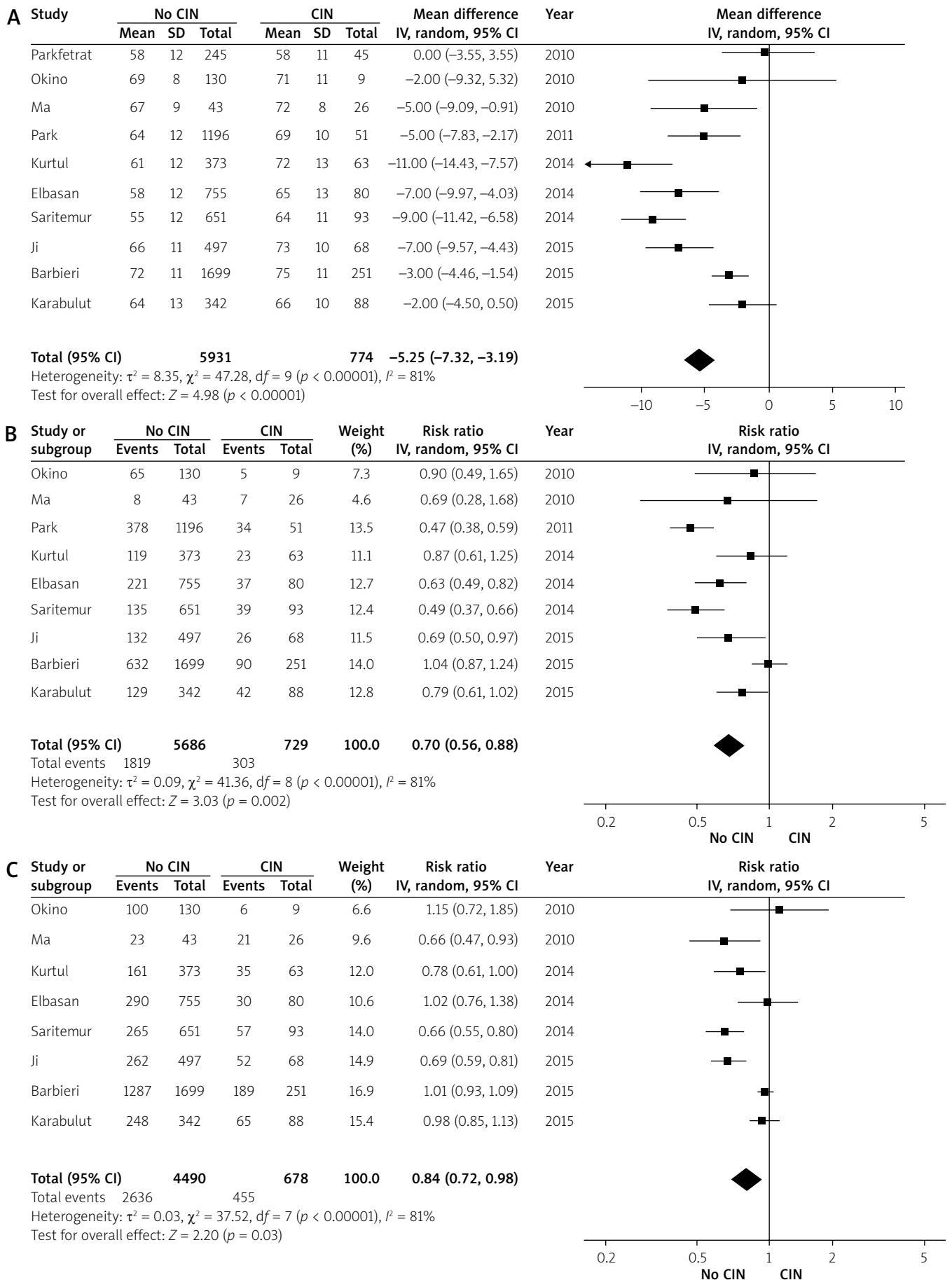


Figure 3. Forest plot of risk ratios for contrast-induced nephropathy according to age (A), diabetes (B) and hypertension (C). Markers represent point estimates of risk ratios, marker size represents study weight. Horizontal bars indicate 95% confidence intervals

Table IV. Laboratory findings at baseline

Author	Hemoglobin [g/l]		Glycemia [mg/dl]		Total cholesterol [mg/dl]		LDL cholesterol [mg/dl]		HDL cholesterol [mg/dl]		Triglyceride [mg/dl]	
	No CIN x̄ (SD)	CIN x̄ (SD)	No CIN x̄ (SD)	CIN x̄ (SD)	No CIN x̄ (SD)	CIN x̄ (SD)	No CIN x̄ (SD)	CIN x̄ (SD)	No CIN x̄ (SD)	CIN x̄ (SD)	No CIN x̄ (SD)	CIN x̄ (SD)
Parkfetrat	NA	NA	125 (63)	131 (54)	186 (48)	189 (30)	111 (37)	110 (25)	39 (11)	42 (14)	184 (106)	155 (79)
Okino	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ma	NA	NA	107 (99–136)	125 (106–143)	195 (40)	203 (50)	NA	NA	NA	NA	NA	NA
Park	13.5 (1.9)	11.9 (2.1)	118 (39)	145 (73)	NA	NA	NA	NA	NA	NA	NA	NA
Kurtul	14.1 (1.9)	12.7 (2.1)	158 (87)	158 (78)	191 (49)	176 (51)	121 (42)	106 (40)	41 (10)	42 (11)	131 (35–815)	112 (39–624)
Elbasan	13.6 (1.9)	12.2 (2.2)	146 (79)	159 (86)	190 (46)	191 (40)	122 (37)	122 (37)	38 (9)	39 (12)	148 (118)	153 (87)
Saritemur	13.6 (1.8)	12.9 (2.2)	NA	NA	NA	NA	113 (36)	116 (42)	39 (12)	41 (12)	139 (93)	123 (64)
Ji	13.3 (1.8)	12.6 (2.2)	NA	NA	158 (43)	158 (50)	95 (37)	94 (42)	NA	NA	180 (12–483)	158 (20–189)
Barbieri	13.2 (NA)	12.7 (NA)	127 (NA)	134 (NA)	159 (NA)	159 (NA)	91 (NA)	92 (NA)	41 (NA)	42 (NA)	140 (NA)	137 (NA)
Karabulut	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Overall	13.6 (0.3) 95% CI: 13.2–13.9	12.5 (0.4) 95% CI: 12.1–12.9	130 (19) 95% CI: 110–149	142 (14) 95% CI: 127–157	180 (17) 95% CI: 162–197	179 (18) 95% CI: 160–198	108 (13) 95% CI: 95–122	106 (12) 95% CI: 94–119	40 (2) 95% CI: 37–41	41 (2) 95% CI: 39–43	153 (22) 95% CI: 130–177	139 (19) 95% CI: 119–159
P-value	< 0.00001		0.239		0.923		0.788		0.092		0.271	

CIN – contrast-induced nephropathy, HDL – high-density lipoprotein, LDL – low-density lipoprotein.

Table V. Pre- and post-procedural findings

Author	Contrast media [ml]		Baseline eGFR		Baseline creatinine [mg/dl]		Post-creatinine [mg/dl]		LV ejection fraction (%)	
	No CIN x̄ (SD)	CIN x̄ (SD)	No CIN x̄ (SD)	CIN x̄ (SD)	No CIN x̄ (SD)	CIN x̄ (SD)	No CIN x̄ (SD)	CIN x̄ (SD)	No CIN n (%)	CIN n (%)
Parkfetrat	62 (45)	84 (73)	82 (36)	67 (16)	0.90 (0.30)	1.10 (0.20)	NA	NA	49 (13)	43 (17)
Okino	177 (131)	148 (74)	40 (13)	32 (11)	1.43 (0.60)	1.67 (0.43)	NA	NA	NA	NA
Ma	160 (46)	181 (53)	NA	NA	NA	NA	NA	NA	56 (10)	47 (10)
Park	306 (132)	359 (159)	86 (33)	45 (26)	0.81 (0.26)	1.52 (0.71)	NA	NA	55 (13)	47 (14)
Kurtul	NA	NA	72 (20)	50 (18)	1.06 (0.27)	1.37 (0.38)	NA	NA	47 (10)	40 (10)
Elbasan	197 (79)	253 (124)	NA	NA	0.91 (0.22)	0.96 (0.26)	0.97 (0.23)	2.29 (1.40)	46 (10)	44 (8)
Saritemur	256 (64)	286 (72)	90 (23)	70 (23)	0.86 (0.20)	1.03 (0.40)	0.93 (NA)	1.71 (NA)	48 (8)	44 (9)
Ji	NA	NA	65 (25)	50 (30)	0.94 (0.37)	1.36 (0.79)	NA	NA	NA	NA
Barbieri	217 (NA)	291 (NA)	NA	NA	1.18 (NA)	1.17 (NA)	1.20 (NA)	1.78 (NA)	NA	NA
Karabulut	NA	NA	69 (21)	64 (23)	1.05 (0.27)	1.13 (0.25)	1.07 (0.27)	1.69 (0.70)	48 (15)	47 (14)
Overall	196 95% CI: 125–267	208 95% CI: 140–316	72 95% CI: 56–87	54 95% CI: 41–66	1.01 95% CI: 0.86–1.16	1.27 95% CI: 1.07–1.43	1.04 95% CI: 0.85–1.23	1.86 95% CI: 1.41–2.31	50 95% CI: 46–53	45 95% CI: 42–47
P-value	0.800		0.053		< 0.0001		0.043		< 0.00001	

CIN – contrast-induced nephropathy, CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate.

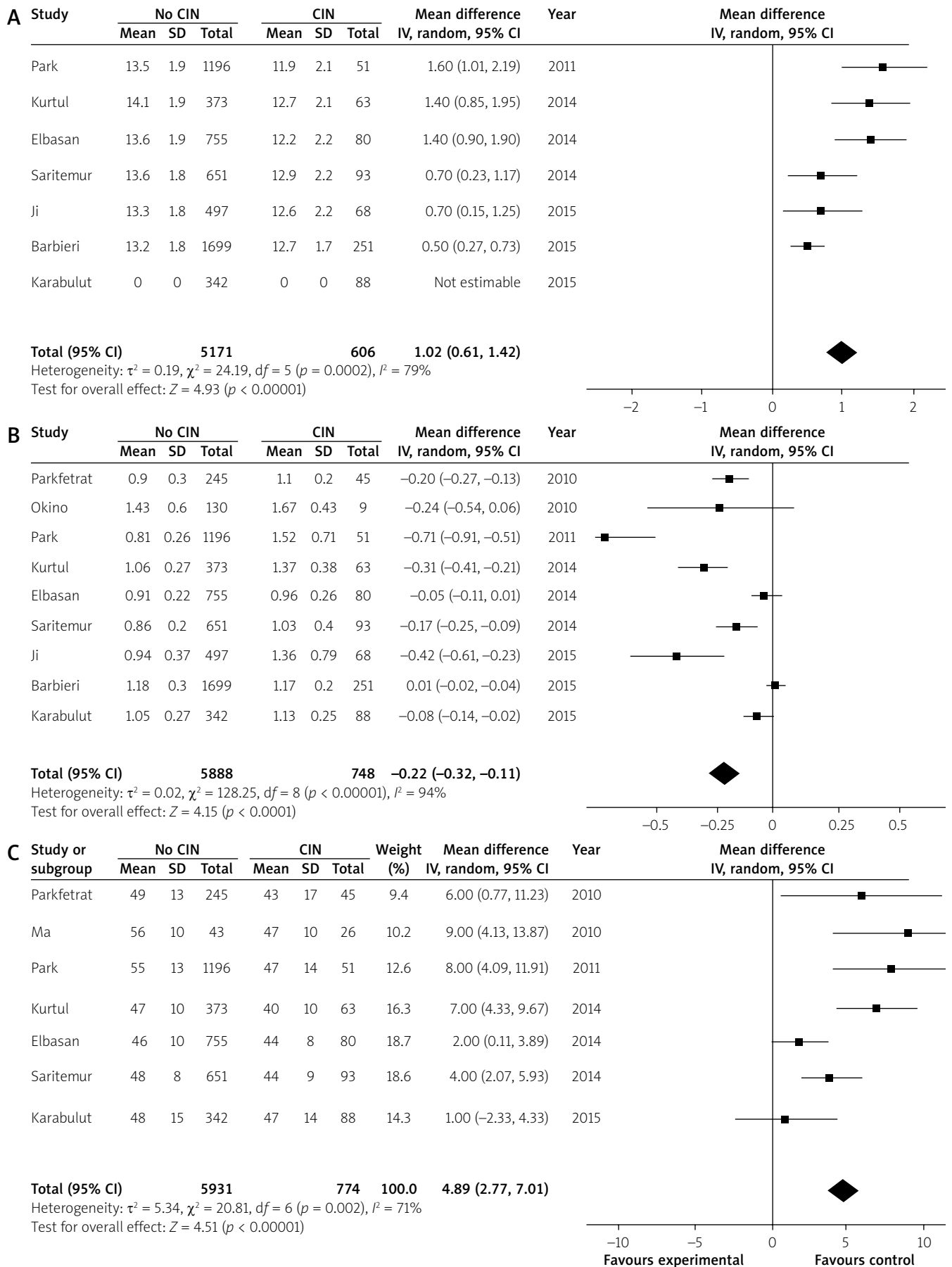


Figure 4. Forest plot of risk ratios for contrast-induced nephropathy according to hemoglobin (A), creatinine (B) and ejection fraction (C). Markers represent point estimates of risk ratios, marker size represents study weight. Horizontal bars indicate 95% confidence intervals

Table VI. Meta-regression weighted by total sample size of studies

Parameter	β	95% CI	P-value
Age	0.13	0.01–0.26	0.03
Hemoglobin	-1.06	-2.10–0.01	0.06
Diabetes	0.04	-0.01–0.08	0.07
Hypertension	0.02	-0.03–0.07	0.40
Creatinine	0.71	-1.78–3.20	0.58
Ejection fraction	-0.06	-0.28–0.16	0.62

tion between uric acid and baseline levels of creatinine, which is the most important single risk factor for CIN [1]. Measuring serum uric acid levels before PCI might be a useful method for assessing the risk of developing CIN and short-term clinical outcomes. The difference in uric acid levels between patients with or without CIN was 0.88 mg/dl, suggesting that even a moderate increase in uric acid levels can be of clinical relevance in this setting. Noteworthy, our findings are in agreement with previous work by Shacham *et al.*, who performed a retrospective analysis of 1,372 consecutive patients with acute myocardial infarction and found that uric acid was an independent predictor of CIN [37]. Interestingly, these authors noted that for every 1-mg/dl increase in the uric

acid concentration, the adjusted risk for CIN increased by 46% [37].

There are some intrinsic limitations of this study as a result of the study design. Major limitations include the case-control design and the relatively small number of studies included in the meta-analysis, which might affect the main results and the results of the meta-regression analysis. Another limitation is the high heterogeneity among the studies. Indeed, studies selected for this meta-analysis differ in multiple aspects (i.e. sample size, definition or frequency of CIN, etc). However, in order to evaluate the stability of the results, we performed a ‘leave-one-out’ sensitivity analysis and were able to show that omission of each study did not change the overall results. We acknowledge the fact that assessment of serum uric acid is affected by the hydration status. Also, the results of the present study should not lead to disregarding the well-recognized role of diabetes, hypertension and renal function, which have been previously demonstrated to be major predictors of CIN. Our review focused only on studies in which contrast was administered for a coronary procedure; therefore, the risk models reviewed might not be applied to other procedures, such as intravenous contrast-enhanced computed tomography, computed tomography angiography, and non-coronary angiography. Publication bias always remains a concern because this investigation could analyze only published data, although funnel

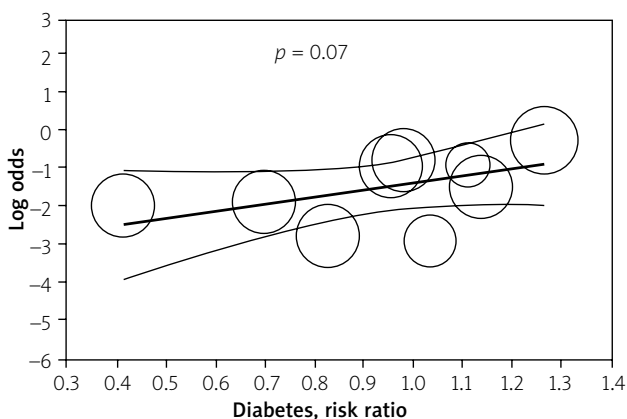
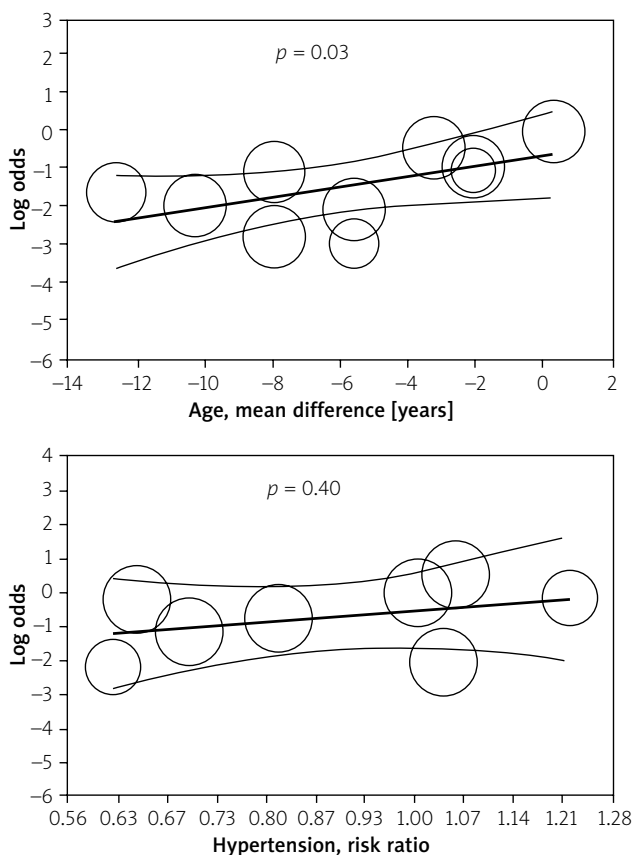


Figure 5. Meta-regression of the effects of age, hypertension and diabetes on baseline uric acid levels. Each circle size represents a study highlighted by its weight in the analysis

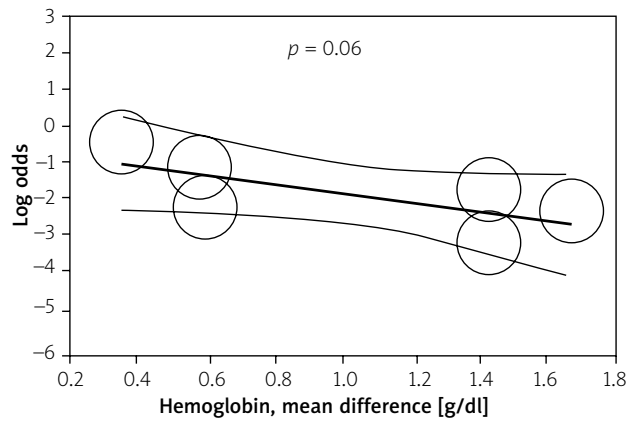
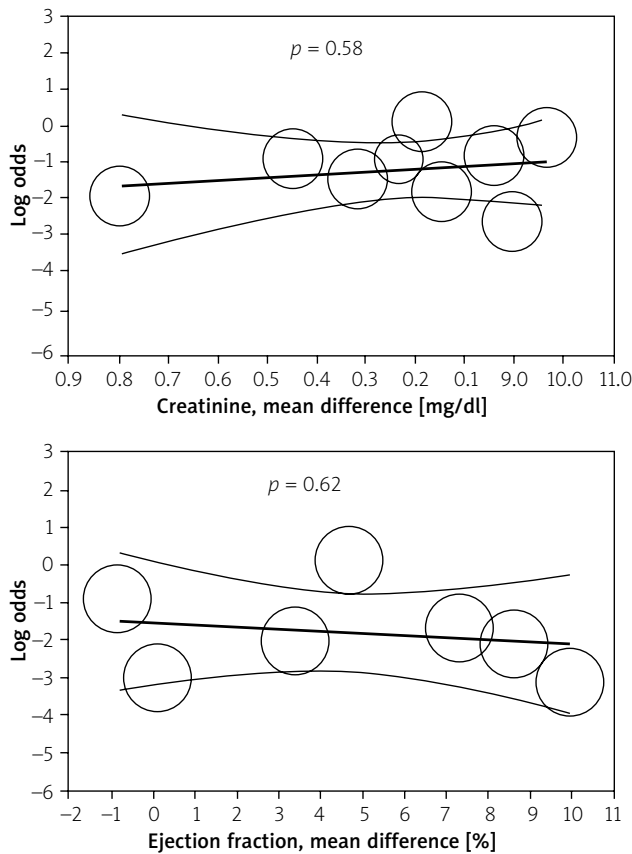


Figure 6. Meta-regression of the effects of creatinine, left ventricular ejection fraction and hemoglobin on baseline uric acid levels. Each circle size represents a study highlighted by its weight in the analysis

plot analysis did not show any evidence of publication bias. A possible drawback lies in the study-level setting, thus lacking the precision and flexibility of a patient-level work, which would have enabled more detailed analyses. Although individual patient data would have provided more detailed information, patient-level and study-level meta-analyses are often in agreement, and thus our findings should be consistent with future prospective studies in individual patients. Although the case control design of selected studies does not allow uric acid to be defined as an independent risk factor, our meta-regression analysis does not suggest a correlation of uric acid with other risk factors, with the exception of age.

Conclusions

This large study-level meta-analysis and meta-regression indicates that uric acid is significantly associated with CIN. Uric acid correlated significantly with age only, but not with other major predictors of CIN. These results should be considered hypothesis-generating findings that may warrant further investigation to verify the potential role of uric acid to improve CIN risk stratification.

Conflict of interest

The authors declare no conflict of interest.

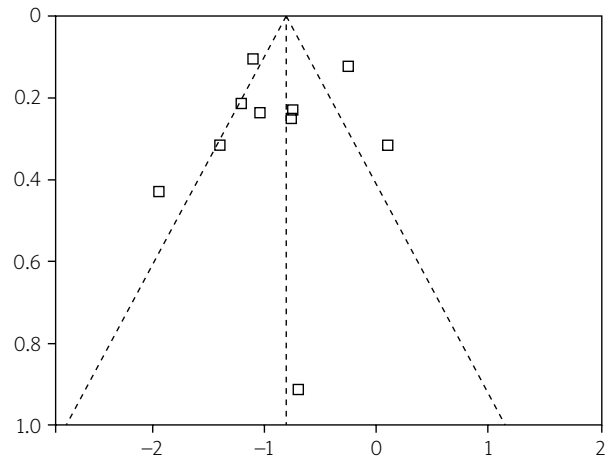


Figure 7. Funnel plot for the occurrence of CIN. The analysis showed no asymmetry suggesting a significant risk of publication bias, and that results did not depend on the size of the studies

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