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Incidence of acute kidney injury in patients with acute ischaemic stroke undergoing CT angiography (CTA) and CT perfusion (CTP): a systematic review and meta-analysis

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ABSTRACT

Background and purpose We conducted a systematic review and meta-analysis to assess the incidence of acute kidney injury (AKI) in patients undergoing CT angiography (CTA) and CT perfusion (CTP) for acute ischaemic stroke (AIS). Concerns over contrast-induced nephropathy (CIN) often lead medical centres to mandate pre-imaging serum creatinine level assessments, causing unnecessary delays. We aim to confirm further the practice of conducting CTA/CTP without first testing creatinine.

Methods We searched PubMed, Cochrane Central and Scopus from inception until March 2023 for studies reporting on AKI in patients with AIS receiving CTA/CTP. Outcomes of interest were (1) the odds of AKI in patients receiving CTA/CTP versus non-contrast CT and (2) the overall incidence of AKI and haemodialysis in patients with AIS undergoing CTA/CTP.

Results Results were pooled using a random effects model. 13 studies were included (5 cohort and 8 single-arm studies) with 5104 patients in total, out of which 4347 patients received CTA/CTP and 757 patients received no contrast. In case–control studies, 4.8% (OR=0.66, 95% CI 0.35 to 1.22, Z=1.32, p=0.19) of patients who received CTA/CTP developed AKI, compared with 7.7% of patients in the control group. Temporary haemodialysis was required for two patients in the analysed studies.

Conclusions Non-randomised evidence suggests that CTA/CTP is not associated with a statistically significant increase in the risk of AKI in patients with stroke. Further well-designed prospective studies are required to explore potential risk factors of CIN in specific patient populations such as diabetes mellitus and chronic kidney disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is apprehension regarding the potential for contrast-induced nephropathy in the use of CT angiography/CT perfusion (CTA/CTP) for the diagnosis of acute ischaemic stroke (AIS). Existing literature does not provide a comprehensive analysis of the incidence of acute kidney injury (AKI) related to this procedure.

WHAT THIS STUDY ADDS

⇒ We found no association between the use of CTA/CTP and the development of AKI in patients specifically with AIS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It may not be necessary to obtain baseline serum creatinine levels for every patient who exhibits symptoms of AIS before proceeding with diagnostic imaging.

INTRODUCTION

Acute ischaemic stroke (AIS) is a significant cerebrovascular disease characterised by impaired blood flow to the brain, resulting in cell death. Common stroke symptoms include paralysis, paresthesia, aphasia and memory loss.[1] AIS is a major global health concern and is ranked as the second leading cause of death, with over 2.7 million deaths attributed to it annually.[2] However, prompt diagnosis and treatment can lead to improved functional outcomes in patients with AIS, as evidence suggests that every minute from CT administration to reperfusion is associated with a significant drop in functionally independent outcomes.[3] For the diagnosis of AIS, according to the American Heart Association and American Stroke Association guidelines,[4] CT angiography (CTA) and CT perfusion (CTP) are commonly used contrast-enhanced vascular imaging techniques to diagnose AIS.[4] However, before CTA/CTP can be done, many healthcare facilities require that a baseline serum creatinine level should be done to evaluate the risk of acute kidney injury (AKI), and the delay in obtaining these results can

significantly impact the expected mortality.[3] Therefore, the necessity of serum creatinine levels in this context needs to be re-evaluated.

Due to the dearth of reliable evidence, we aim to systematically review and analyse the existing literature covering AKI in patients with AIS receiving CTA/CTP in this meta-analysis. The objectives of our review are to (1) determine whether patients with AIS receiving CTA/CTP have higher rates of AKI than patients with AIS undergoing non-contrast CT (NCCT) alone and (2) determine the rate of AKI among patients with AIS undergoing CTA/CTP.

METHODS

Data sources and search strategy

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) and Cochrane Collaboration guidelines.[5 6] A comprehensive literature search was conducted from inception to March 2023 to identify the relevant studies. Electronic databases such as PubMed, Cochrane Central and Scopus were searched using Medical Subject Heading terms related to stroke, neuroimaging, AKI and contrast-induced nephropathy (CIN). The complete search strategies are available in online supplemental table 1. The references list of the retrieved articles and previous meta-analyses were manually reviewed for the studies that might be relevant.

Study selection and eligibility criteria

All articles were exported to EndNote Reference Library where duplicates were found and excluded. Two reviewers (FA and AK) independently screened the articles based on title and abstract, followed by a full-text review, and any disagreements were resolved by consulting a third reviewer (NSP). We considered original articles for inclusion if they either: (1) investigated the incidence of AKI in patients with AIS who underwent screening with CTA/CTP, or (2) compared AKI rates between patients undergoing CTA/CTP and those undergoing NCCT. We excluded studies that did not meet these criteria or had the following limitations: studies written in non-English languages, insufficient data to perform analysis or studies that were review articles, case reports or conference abstracts. We also excluded studies with less than 50 patients in either treatment arm because small sample sizes might not have the statistical power to accurately identify significant differences or estimate treatment effects.

Data extraction and quality assessment

Primary outcomes of interest were rates of AKI and percentage changes in creatinine. The following data was also extracted: (1) Study details, including the first author, year of publication, study design and geographical location of study. (2) Patient characteristics, encompassing sample size and demographic information such as age, sex and baseline creatinine levels and prevalence of chronic kidney disease (CKD) and diabetes mellitus (DM) in the patient populations. (3) Intervention details, including contrast agent used, dosage and follow-up duration. The details of the study characteristics are included in table 1.

The Newcastle–Ottawa quality assessment scale was used to assess the risk of bias. With an overall quality score of 9 stars, cohort studies were classed as having a low (7 stars), moderate (5–6 stars) and high (4 stars) risk of bias.[7]

Data extraction and quality assessment of the included studies were conducted independently by two reviewers (NFS and JK). Disagreements were resolved through discussion or consultation with a third reviewer (NSP).

Statistical analysis

Statistical analysis was conducted using Review Manager (RevMan) (V.5.4.1). Pooled estimates of AKI rates, ORs and 95% CIs were derived using a random-effects model. Heterogeneity was assessed using the Higgins I^2 statistic, and in the case of moderate-to-high heterogeneity (>50%), a leave-one-out sensitivity analysis was conducted to understand the study causing heterogeneity. A p value of 0.05 or less was considered significant in every case.

RESULTS

Literature search results

Our initial search of the databases yielded a total of 2980 articles. After the removal of duplicate studies and screening of the titles, we evaluated the full text of 44 articles, of which 22 met our initial inclusion criteria. Four articles were excluded from the final analysis. Two articles were excluded due to their unavailability in the English language. Three articles, that compared the effects of a single dose versus multiple doses of CTA/CTP, did not align with the objectives of our study and were, therefore, excluded. Out of the 13 included studies, there were 5 cohorts and 8 single-arm studies.[8–20] The PRISMA flow chart (figure 1) summarises the results of our literature search.

Study characteristics and quality assessment

A total of 5104 patients were included, of which 4347 received CTA/CTP. The definition of AKI varied only slightly among the studies, with most defining AKI as a >25% increase in baseline creatinine. A total of 12 studies reported the incidence of AKI following CTA/CTP administration. Nine studies included patients who had a history of DM. The amount of contrast used ranged from 70 mL to 150 mL across the studies. Among studies reporting rates of haemodialysis following CTA/CTP, we noted that two patients underwent haemodialysis temporarily. A detailed quality assessment of each study is given in online supplemental table 2. All included studies, both controlled and uncontrolled, demonstrated a fair level of quality.

Table 1 Baseline characteristics of included studies

Study	Study design	n CTA/ CTP: n NCCT	AKI definition	Standard contrast load, cc	Mean baseline Cr, mg/dL CTA/ CTP: NCCT	Follow-up duration	Baseline CKD CTA/ CTP: NCCT	Baseline DM CTA/ CTP: NCCT
Lim *et al*[8]	Uncontrolled	238:NA	≥44 µmol/L or 25% rise in serum Cr	50–150	1.1:NA	>30 days	NA	62:NA
Brito *et al*[9]	Retrospective cohort	161:105	>0.5 mg/dL or 25% rise in serum Cr	90	0.9:0.8	NA	4:1	39:35
Ehrlich *et al*[10]	Retrospective cohort	157:132	>25% rise in serum Cr	70–100	1.1:1.4	24–48 hours	24:52	66:61
Hall *et al*[11]	Uncontrolled	84:NA	>0.5 mg/dL rise in serum Cr	130	NA	NA	NA	NA
Luitse *et al*[12]	Uncontrolled	731:NA	>44 µmol/L or 25% rise in serum Cr within 3 days	NA	NA	3 days	155:NA	NA
Ang *et al*[13]	Uncontrolled	623:NA	NA	100–150	1.1:NA	90 days	258:NA	112:NA
Lima *et al*[14]	Prospective cohort	575:343	>25% rise in serum Cr	100–140	1.0:1.2	24 hours, 48 hours, 72 hours	NA	98:82
Aulicky *et al*[15]	Retrospective cohort	164:77	≥44 µmol/L rise in serum Cr within 24–72 hours	139	1.2:1.2	24–74 hours	8:4	66:25
Langner *et al*[16]	Prospective cohort	100:100	>0.5 mg/dL or 25% rise in serum Cr	120	0.1:1.1	7–13 days	7:13	41:46
Krol *et al*[17]	Uncontrolled	224: NA	>25% rise in serum Cr within 5 d	75–100	NA	5 days (>30 days when data was available)	2:NA	85:NA
Dittrich *et al*[18]	Uncontrolled	162:NA	>0.5 mg/dL or 25% rise in serum Cr	140	1.1:NA	7 days	40:NA	34:NA
Josephson *et al*[19]	Uncontrolled	1075:NA	>0.5 mg/dL rise in serum Cr	150	NA	NA	72:NA	NA
Smith *et al*[20]	Uncontrolled	53:NA	NA	400	1.1:NA	NA	2:NA	NA

AKI, acute kidney injury; CKD, chronic kidney disease; Cr, creatinine; CTA, CT angiography; CTP, CT perfusion; DM, diabetes mellitus; NCCT, non-contrast CT.

Results of meta-analysis

Our study included 4347 patients who received CTA/CTP. From the five case–control studies, 4.8% (55 out of 1157) (OR=0.66, 95% CI 0.35 to 1.22, Z=1.32, p=0.19) of patients who received CTA/CTP developed AKI, compared with 7.7% (58 out of 757) of patients in the control group. Among the case controls (figure 2), there was no significant change in the odds of developing AKI among those receiving CTA/CTP versus the patients who did not receive contrast.

A single-arm analysis conducted for the 1390 patients in the CTA/CTP group (figure 3), demonstrated that 79 (2.5%) developed AKI. The overall rate of AKI was 2.7% (0.012–0.048); p = <0.001). We included eight single-arm studies which showed a heterogeneity of I^2=87.97% and p<0.001. In order to reduce heterogeneity, we performed a sensitivity analysis using the leave-one-out method and removed Josephson *et al*[19] and Lim *et al*[8] which lowered the heterogeneity to I^2=0% and p=0.49 (figure 4).

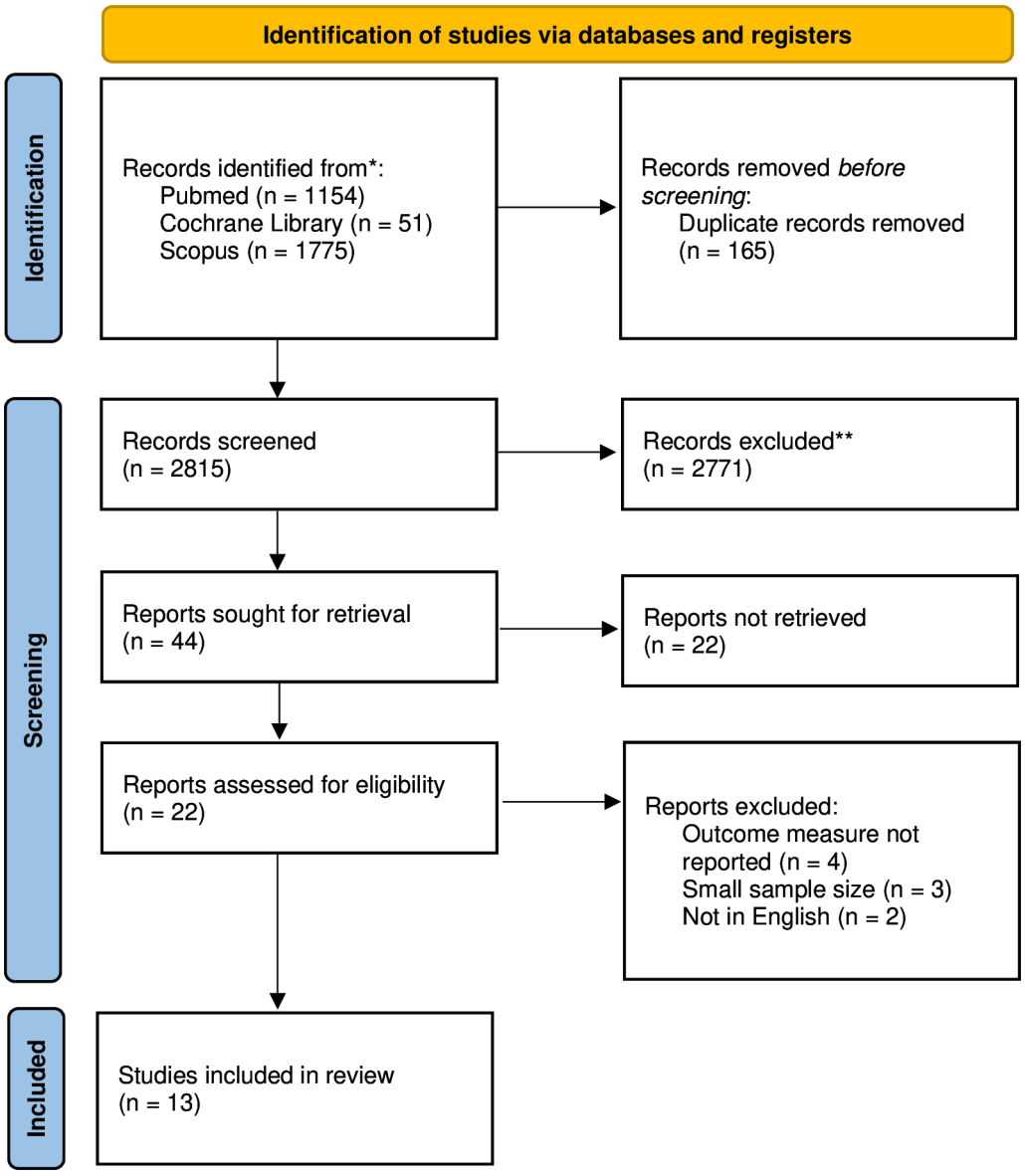

Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analysis flow chart.

DISCUSSION

In cases of stroke, CTA is recommended to assess occlusion severity and guide potential endovascular interventions, such as mechanical thrombectomy. However, the administration of contrast during CTA and then again during subsequent thrombectomy raises legitimate concerns regarding its safety in patients with AIS, specifically the risk of developing CIN. The predicament, therefore, lies in finding the balance between obtaining necessary diagnostic information and mitigating potential complications of the procedure, ensuring safety and the best possible outcome for the patient either way.

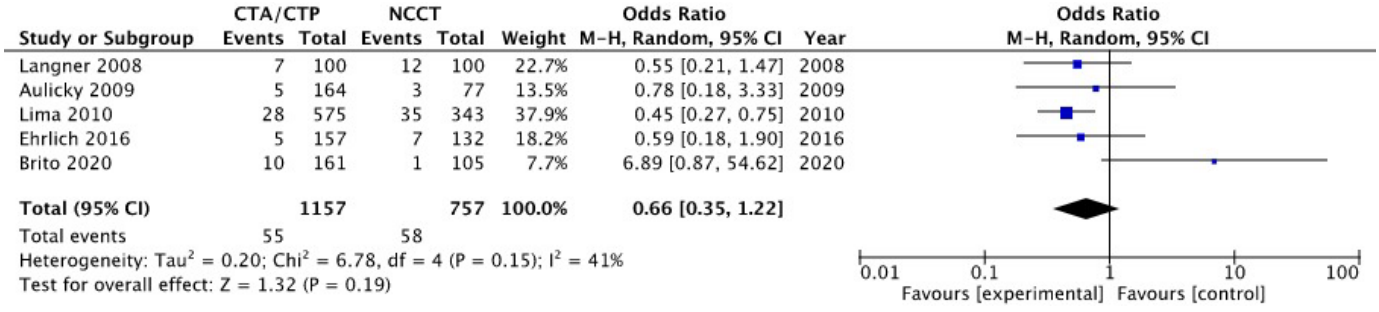

Figure 2 Rate of acute kidney injury cohort studies comparing patients with acute ischaemic stroke receiving CTA/CTP versus control. CTA, CT angiography; CTP, CT perfusion; NCCT, non-contrast CT.

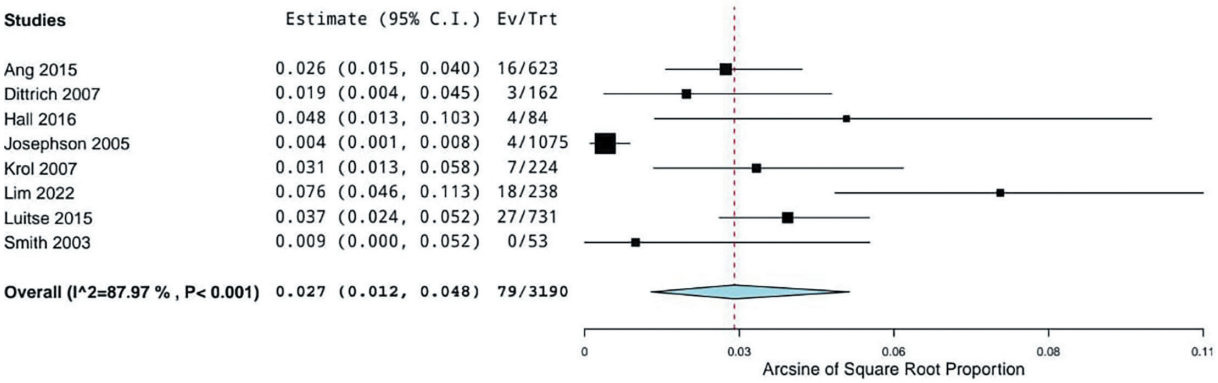

Figure 3 Incidence of acute kidney injury uncontrolled studies in patients with acute ischaemic stroke.
Abbreviations: CI, confidence interval; Ev/Trt, event/treated

Based on our systematic review and meta-analysis of data, we found that there was no significant change in the odds of developing AKI among those receiving CTA/CTP versus the patients who did not receive contrast (p=0.19). These findings challenge CIN concerns in patients with AIS undergoing CTP/CTA, suggesting that such fears may be unfounded. Moreover, waiting for serum creatinine values before initiating intervention unnecessarily delays timely and potentially life-saving measures in a clinical context where every minute counts.

A meta-analysis on the association between CTA/CTP administration in patients with AIS and AKI was conducted in 2017, showing that contrast administration was not linked with the development of AKI in patients with AIS.[21] Since then, other studies have been published with small sample sizes, warranting a comprehensive meta-analysis to synthesise the available evidence on this topic and accurately guide clinical practices for the management of AIS. We included two recent studies from recent years, Brito *et al* and Lim *et al*, both of which administered similar concentrations of contrast and showed no significant incidence of AKI in the studied population.

Brito *et al* encompass patients with a history of DM and baseline CKD, even including a patient in the control group requiring haemodialysis.[9] The study compared the occurrence of AKI contrast exposed group versus contrast unexposed group using the Kidney Disease Improvement Global Outcome criteria. It showed a 6.2% incidence in the contrast exposed group, compared with 1.0% in the contrast unexposed group. However, correction for continuity was applied and showed no statistical difference between the two groups (p=0.073). Overall, the study concluded that contrast is not an independent variable for the occurrence of AKI in patients with AIS.

Lim *et al* evaluated the long-term renal outcome in patients with AIS. In contrast to most of the included studies, which evaluated the renal outcome within 48–72 hours of contrast administration, this study monitored the serum creatinine levels after 5 days post-contrast to up to >30 days post-contrast.[8] A prolonged monitoring period provides insights into the occurrence of AKI over the long term. Although the initial rate of AKI was 7.6% of the population (95% CI 4.2 to 11.0), most cases showed no new or persistent AKI cases, and that serum creatinine levels returned to normal within 14 days. Their findings further support the absence of any AKI cases solely attributable to CIN and shed light on various renal confounders contributing to AKI events. To further evaluate this, future studies could focus on using MicroRNAs as a specific biomarker for predicting the prognosis of CIN, building on the findings of the study conducted by Toruan *et al*.[22]

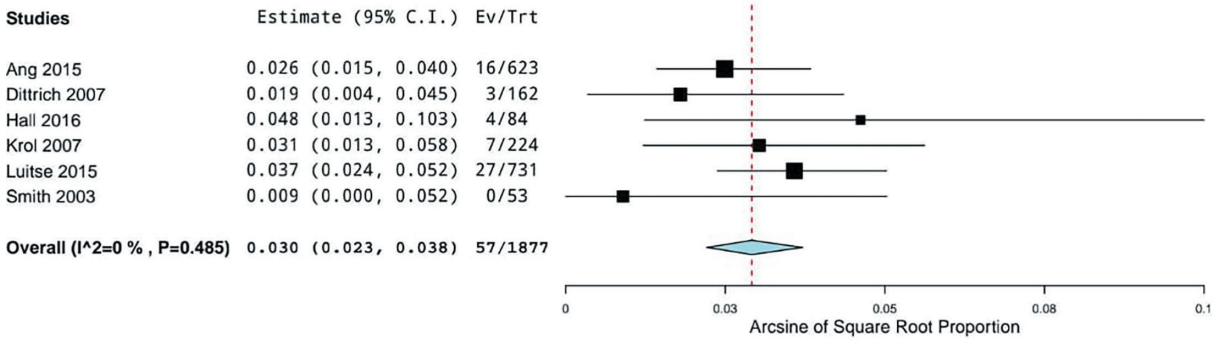

Figure 4 Sensitivity analysis of incidence of acute kidney injury uncontrolled studies in patient with acute ischaemic stroke. CI, confidence interval; Ev/Trt, event/treated.

The initial analysis of single-arm studies yielded a high heterogeneity (87.97%) which was subsequently addressed by a sensitivity analysis that involved the removal of two studies, Josephson *et al*[19] and Lim *et al*.[8] A reduction in heterogeneity to zero was observed. Josephson and colleagues assessed patients who received a specific stroke CT protocol whereas Lim and colleagues reported on long-term renal outcomes after the CT procedures. It is possible that variation in the study approach introduced heterogeneity into the meta-analysis.

The added evidence supporting the absence of an increased likelihood of AKI after contrast exposure holds significant importance within the selected population of patients with AIS. This is because impaired kidney function is known to be associated with worse outcomes in stroke.[23–25] Therefore, the evidence proving the lack of association between contrast exposure and AKI carries dual implications. First, it provides valuable guidance for clinical practices, ensuring physicians can make informed decisions. Second, it helps mitigate the impact of comorbid factors that are known to be linked with increased mortality in AIS. These promising findings relieve physicians from concerns about CTA/CTP posing a risk of poorer outcomes in AIS. Consequently, it becomes clear that CTA/CTP is a safe and uncomplicated choice, eliminating the need for excessive deliberation.

This meta-analysis has a few limitations. First, all studies included are retrospective, not prospective, with no randomised controlled trials being conducted. As a result of the observational nature, all the studies will be affected by a selection bias, as patients with significantly known elevated creatinine levels would generally avoid contrast exposure as a precaution. As no recommendation can be made that could knowingly increase mortality, as is the case here, this bias is unlikely to be eliminated in practicality. However, when comparing patients with CKD to those without, there was still no link between increased baseline creatinine and AKI in the selected population group. There is also heterogeneity in the type and dose of contrast medium used among the studies. There is also variation in the definition of AKI across studies. However, the critical point is that most studies defined it as an increase in creatinine value of 25% from baseline. As there is no established specific test or biomarker to eliminate alternative causes of AKI from CIN, it is difficult to reliably separate when exactly AKI is caused by contrast compared with other risk factors.[26]

CONCLUSION

In conclusion, our systematic review and meta-analysis show no significant association between contrast administration in CTA/CTP and the incidence of AKI in patients with AIS. This shows that the delay in waiting for serum creatinine levels is unnecessary and takes crucial minutes from onset to treatment.

Contributors AK and NSP conceived of the presented idea. NFS and JK performed the analysis. FA and JH verified the analytical methods. SM encouraged SSL to investigate the sensitivity analysis and supervised the findings of this work. SM was also responsible for the overall content as the guarantor. All authors discussed the results and contributed to the final manuscript.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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