Acute Kidney Injury After Computed Tomography: A Meta-analysis

Ryan D. Aycock, MD, MS*; Lauren M. Westafer, DO, MPH; Jennifer L. Boxen, MLS, MA; Nima Majlesi, DO; Elizabeth M. Schoenfeld, MD, MS; Raveendhara R. Bannuru, MD, PhD

*Corresponding Author. E-mail: ryanaycock@gmail.com.

Study objective: Computed tomography (CT) is an important imaging modality used in the diagnosis of a variety of disorders. Imaging quality may be improved if intravenous contrast is added, but there is a concern for potential renal injury. Our goal is to perform a meta-analysis to compare the risk of acute kidney injury, need for renal replacement, and total mortality after contrast-enhanced CT versus noncontrast CT.

Methods: We searched MEDLINE (PubMed), the Cochrane Library, CINAHL, Web of Science, ProQuest, and Academic Search Premier for relevant articles. Included articles specifically compared rates of renal insufficiency, need for renal replacement therapy, or mortality in patients who received intravenous contrast versus those who received no contrast.

Results: The database search returned 14,691 articles, inclusive of duplicates. Twenty-six unique articles met our inclusion criteria, with an additional 2 articles found through hand searching. In total, 28 studies involving 107,335 participants were included in the final analysis, all of which were observational. Meta-analysis demonstrated that, compared with noncontrast CT, contrast-enhanced CT was not significantly associated with either acute kidney injury (odds ratio [OR] 0.94; 95% confidence interval [CI] 0.83 to 1.07), need for renal replacement therapy (OR 0.83; 95% CI 0.59 to 1.16), or all-cause mortality (OR 1.0; 95% CI 0.73 to 1.36).

Conclusion: We found no significant differences in our principal study outcomes between patients receiving contrast-enhanced CT versus those receiving noncontrast CT. Given similar frequencies of acute kidney injury in patients receiving noncontrast CT, other patient- and illness-level factors, rather than the use of contrast material, likely contribute to the development of acute kidney injury. [Ann Emerg Med. 2017;■:1-10.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2017.06.041

INTRODUCTION

Background

Computed tomography (CT) is an important imaging modality used for the analysis of a variety of disorders, with more than 75.6 million CT scans performed in the United States in 2013 alone.[1] Intravenous contrast is required for certain scans, including CT angiograms to diagnose aortic dissection or pulmonary embolism, and may improve imaging quality in other cases.[2]

The concern over postcontrast acute kidney injury, historically referred to as contrast-induced nephropathy, has caused many institutions to adopt guidelines requiring measurement of renal function before contrast administration or restricting the use of intravenous contrast in patients with possible renal insufficiency. Postcontrast acute kidney injury is loosely understood as an increase in creatinine level or decrease in glomerular filtration rate after contrast administration. However, there is no consistent definition of postcontrast acute kidney injury that has been used across studies. The most common descriptions include an increase in creatinine level by 25% after contrast administration or an absolute increase of 0.3 to 0.5 mg/dL within 3 days.[3,4] Because postcontrast acute kidney injury is a laboratory-based diagnosis, its potentially adverse effects on various patient-centered outcomes are less clear.

Importance

The incidence of postcontrast acute kidney injury is imprecise, with one meta-analysis reporting occurrences ranging from 1% to greater than 20%.[5] Possible explanations include heterogeneous definitions of postcontrast acute kidney injury, differences in rates of postcontrast acute kidney injury after procedures versus CT scans, and differing characteristics of the patient populations. Recent recommendations from the American

Editor's Capsule Summary

What is already known about this topic

Recent literature suggests that patients receiving contrast for computed tomography (CT) imaging may be at less risk for postcontrast acute kidney injury than previously feared.

What question this study addressed

What is the risk of acute kidney injury, renal replacement therapy, and mortality after CT with intravenous contrast compared with noncontrast CT?

What this study adds to our knowledge

This meta-analysis of 28 observational studies including more than 100,000 patients found no significant association between contrast CT and examined outcomes.

How this is relevant to clinical practice

There are various definitions of postcontrast acute kidney injury, potential selection bias, and differing populations, exposures, and comorbidities in published studies. Clinicians should continue to follow current practices, which appear to be effective in avoiding postcontrast acute kidney injury.

College of Radiology attribute much of the incidence of postcontrast acute kidney injury to the patient's underlying comorbidities rather than to the contrast material, but the studies reporting postcontrast acute kidney injury after CT scans vary in quality and association with intravenous contrast.[2]

Goals of This Investigation

We performed a systematic review and meta-analysis of the available published literature to compare the rates of acute kidney injury, the receipt of renal replacement therapy, and mortality in adult populations receiving contrast-enhanced CT versus those receiving noncontrast CT.

MATERIALS AND METHODS

This meta-analysis was registered on the PROSPERO registry and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses and the Meta-analysis of Observational Studies in Epidemiology guidelines.[6]

Literature Search and Selection of Studies

Our goal was to identify all adult human studies that compared the incidence of renal insufficiency in patients who underwent contrast-enhanced CT scans with patients who received noncontrast CT scans. With the aid of a medical librarian (J.L.B.), we searched MEDLINE (PubMed), the Cochrane Library, CINAHL, Web of Science, ProQuest, and Academic Search Premier up to December 2016 for relevant published studies, using a search strategy that included variations of the terms "contrast media," "computed tomography," and "nephropathy." The search strategy is included in Figure E1, available online at http://www.annemergmed.com. The authors hand searched the references of systematic reviews and meta-analyses for additional original articles. Conference abstracts between 2009 and 2016 from the American Society of Nephrology, the American College of Radiology, and the Society for Academic Emergency Medicine were hand searched for abstracts meeting inclusion criteria. This search was conducted iteratively until no new potential citations were found. One author (E.M.S.) subscribed to PubMed alerts and articles-in-press feeds of high-impact emergency medicine, radiology, and nephrology journals to identify new articles through the end of the abstract screening process. The final articles included in this meta-analysis were then searched in Google Scholar for any additional prospectively discovered citations. Two authors (R.D.A. and L.M.W.) independently screened all titles and abstracts for our predefined inclusion and exclusion criteria. The same 2 authors independently read the retained full-text articles for fulfillment of inclusion criteria, which included noninterventional, adult studies assessing renal insufficiency with contrast-enhanced CT and noncontrast CT arms. There were no language restrictions. Because we aimed to assess the risk of postcontrast acute kidney injury after CT scan in the acute care setting, we excluded articles on pediatrics and intra-arterial procedures (including percutaneous coronary angiography), studies on prevention strategies (eg, *N*-acetylcysteine, sodium bicarbonate drips), case reports, review articles, clinical guidelines, and other meta-analyses.

Data Extraction

Data were extracted independently from articles with a piloted, standardized data collection form (CTCIA; Tufts Medical Center, Boston, MA). Discordances at all stages were resolved through discussion. When data were unclear, we contacted authors of potentially includable articles by e-mail and social media (LinkedIn, Twitter, and ResearchGate) to clarify our questions. Extracted information included body area scanned, study setting, total

patient population, type of contrast used, comorbidities, timing of follow-up creatinine level measurement, definition of postcontrast acute kidney injury, analytic techniques, and the outcomes of incidence of nephropathy, need for renal replacement therapy, and mortality.

Outcome Measures

The primary study outcome was the development of acute kidney injury in individuals receiving contrast-enhanced CT compared with those who had a noncontrast CT. The authors of the individual studies defined acute kidney injury. Secondary outcomes included differences in need for renal replacement therapy and all-cause mortality between these 2 comparison groups. Subgroup analyses were specified a priori to assess the effect of emergency department (ED) setting, timing of follow-up creatinine-level measurement, and use of matching methods on the incidence of acute kidney injury. We also planned an analysis of the effect of class of contrast media on acute kidney injury because it is believed that osmolarity may affect the risk of nephrotoxicity.[7]

Assessment of Risk of Bias in Included Studies

To assess the quality of abstracted information, including the clarity of reporting study methods, error, and bias, 2 authors (R.D.A. and L.M.W.) independently assessed the methodological quality of all included studies, using the Tool to Assess Risk of Bias in Cohort Studies, developed by the CLARITY Group (McMaster University).[8] Studies were judged to have high or low risk of bias for each domain according to composite assessment. Discrepant quality assessments were adjudicated by discussion.

Primary Data Analysis

Meta-analysis estimates were computed with OpenMetaAnalyst software, using a DerSimonian-Laird random effects model because of heterogeneity between study populations.[9-11] Statistical heterogeneity was assessed with the index of inconsistency (I^2), which describes the percentage of variation among studies because of heterogeneity instead of chance.[12] Pooled estimates were reported as odds ratios (ORs).

A funnel plot was generated and inspected for visual evidence of publication bias. We mathematically assessed for bias with the Harbord-Egger method in StatsDirect (version 3.1.0; StatsDirect Ltd, Cheshire, UK).[13]

RESULTS

Figure 1 demonstrates details of the search strategy and study selection. A total of 14,691 citations, inclusive of duplicates, were initially found through the search strategy. Of these, 26 were included in the final analysis after screening for our inclusion and exclusion criteria.[14-39] Three additional full-text articles were discovered by searching references, one of which met the inclusion criteria.[40] One more was located through a subscription feed to emergency medicine articles in press.[41]

Table 1 summarizes the study design characteristics. Six studies included only ED patients,[16,23,33,38,39,41] 7 assessed ICU patients,[17,22,25,26,28,36,40] and the remainder included multiple settings or were not specified. Low or iso-osmolar contrast was most frequently used, with only one study reporting use of high-osmolar contrast.[15] Patients with chronic kidney disease were included in 82% of studies, and the mean baseline creatinine level between groups was not statistically significant (P=.10).

All of the included studies were observational, and the majority were retrospective chart reviews of patients treated in the ED, inpatient medical ward, or ICU. Five of the articles were prospective observational studies.[14,18,28,33,35] Although most articles captured data from all patients who met the individual studies' inclusion criteria, 7 studies used matching techniques.[22,28,30,31,37,40,41]

Of the 28 studies involving 107,335 participants included in the final analyses, 26 evaluated and defined acute kidney injury, 13 measured the need for renal replacement therapy, and 9 measured all-cause mortality at various points, with all but 1 including only inhospital mortality. Meta-analysis demonstrated that, compared with noncontrast CT, contrast-enhanced CT was not significantly associated with acute kidney injury (OR 0.94; 95% confidence interval [CI] 0.83 to 1.07), need for renal replacement therapy (OR 0.83; 95% CI 0.59 to 1.16), or mortality (OR 1.0; 95% CI 0.73 to 1.36). The forest plots in Figure 2 summarize these findings. The I^2 index for assessing heterogeneity among nephropathy studies was 65.1%, indicating moderate heterogeneity.[12] Heterogeneity was less in studies reporting renal replacement therapy and mortality data, with an I^2 of 19.9% and 35.8%, respectively.

Seven studies used matching techniques, one of which did not measure nephropathy and instead focused only on progression to end-stage renal disease.[7] Of the 6 remaining matched studies involving 54,820 participants, contrast-enhanced CT was not associated with nephropathy (OR 0.98; 95% CI 0.92 to 1.05). No statistical heterogeneity was detected (I^2=0%).

We examined the potential effect of sources of clinical heterogeneity and confounding through subgroup analyses including assessment of type of contrast used, population setting, study definition of acute kidney injury, and timing

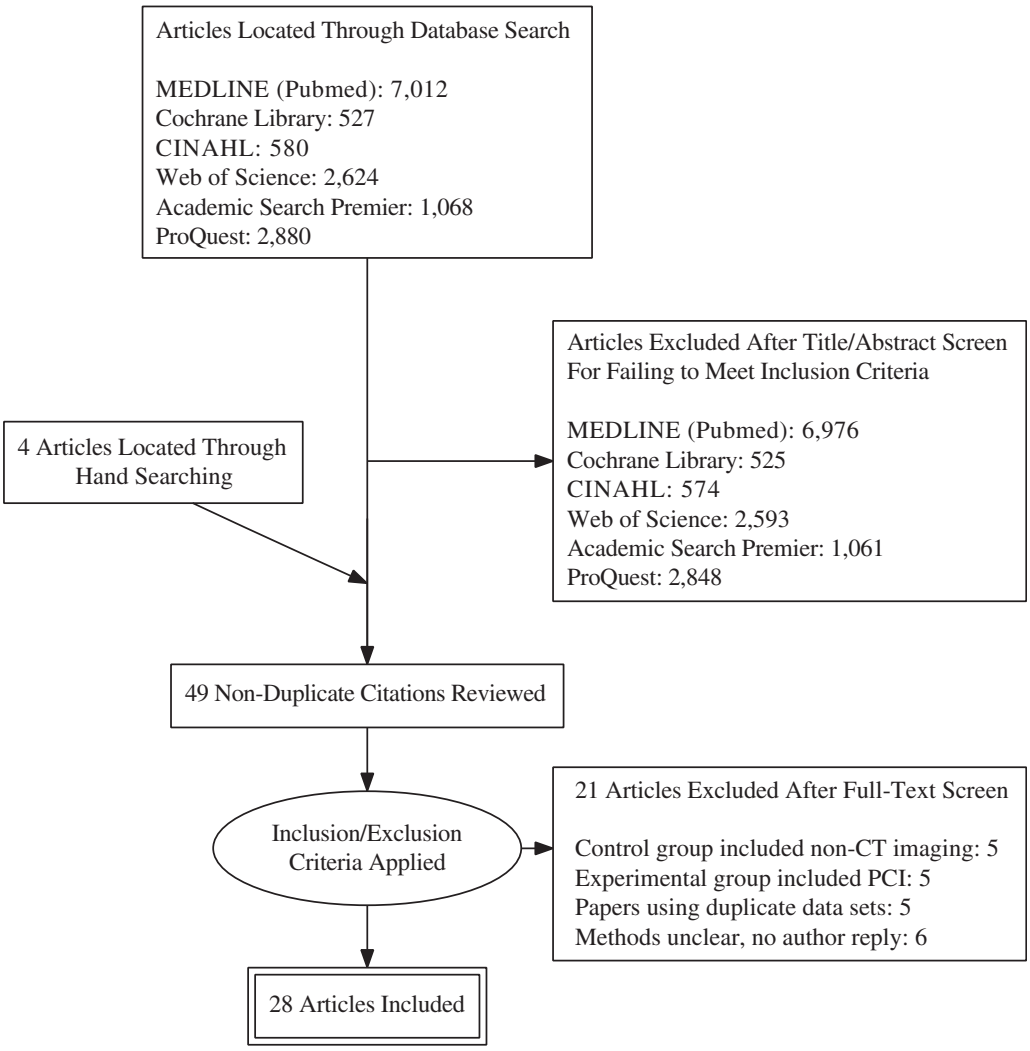


Figure 1. Flow diagram of study selection. *PCI*, Percutaneous coronary intervention.

of follow-up creatinine level. The results of these analyses are displayed in Table 2.

Figure E2 (available online at http://www.annemergmed.com) provides a funnel plot of publications, with an equal distribution of studies demonstrated visually. The Harbord-Egger test of bias was calculated to be –0.18 (P=.70), indicating a low likelihood of publication bias.[13] Table E1 (available online at http://www.annemergmed.com) summarizes the assessment of bias.

LIMITATIONS

This meta-analysis has several limitations. First, these data are entirely observational and largely retrospective. Because of the differing indications for contrast-enhanced CT and the unethical nature of performing a randomized controlled trial solely assessing harms of intravenous contrast, no randomized trials have been conducted.[42,43] There is an inherent selection bias that comes from these studies as a result. Because none of the studies randomized patients to either contrast or noncontrast material, the type of CT scan ordered would have been prompted by indication for the scan or baseline renal function because of physician fear of postcontrast acute kidney injury. Further selection bias resulted from the requirement for a follow-up creatinine-level measurement, including a sicker cohort more likely to be hospitalized at laboratory marker follow-up and who may have had a greater baseline risk of acute kidney injury.

Second, heterogeneity from multiple sources exists, including type of contrast media used, setting from which the CT scan was obtained, and differing patient populations, including trauma, inpatients, ED, various settings, and critical care units. However, exploration of an effect in subgroup analyses found no difference between these populations. Furthermore, the sizes of studies varied from as few as 95 patients to greater than

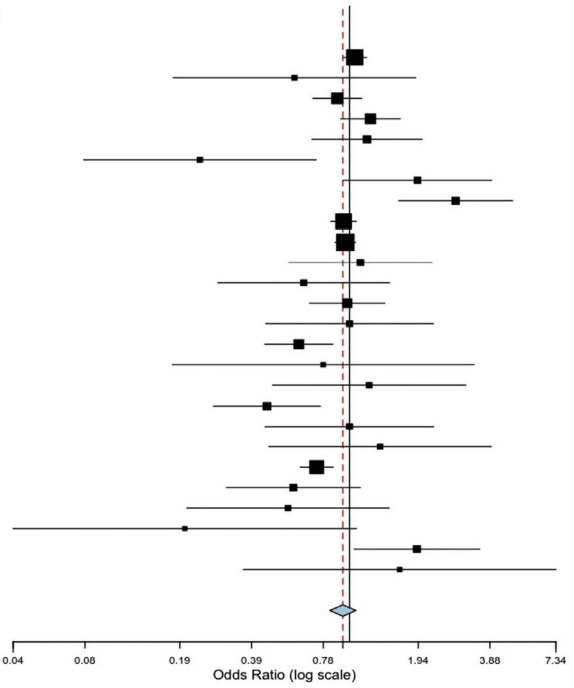
Table 1. Study characteristics.

Reference	Design	Patients (n)	Setting	Definition of Nephropathy	Contrast Agent	Body Area of CT	Incidence of AKI in CECT	Incidence of AKI in Non-CECT, %
Hinson, 2017	Retrospective matched	12,700	ED	0.5 mg/dL or 25% ↑ in creatinine in 48-72 h	Ioxhexol, iodixanol	Any	10.6	10.2
Ehrlich, 2016	Retrospective	289	ED	25% ↑ in creatinine in 24-48 h	Iohexol	Brain	3.2	5.3
Heller, 2016	Retrospective	7,863	ED	25% ↑ in creatinine by at 96 h	NR	Any	8.6	9.6
Hsieh, 2016	Retrospective	14,200	NR	N/A - evaluated ESRD	NR	Any	NR	NR
Gao, 2015	Retrospective	2,370	ICU	0.3 mg/dL or 25% ↑ in creatinine in 24-48 h	NR	Brain	14.8	12.4
Hemmet, 2015	Prospective observational	600	Multiple	0.3 mg/dL ↑ in creatinine in 7 days	NR	Any	11	9.5
Paliwal, 2015	Retrospective matched	296	NR	NR	NR	Any	2.5	9.7
Sonhaye, 2015	Prospective observational	1,292	ED	0.5 mg/dL ↑ in creatinine during inpatient stay	Iomeprol	Chest, brain, abd/pelvis	3.4	1.8
Alsafi, 2014	Retrospective	1,164	Inpatient	0.5 mg/dL or 25% ↑ in creatinine	Iohexol	Any	9.2	3.5
McDonald, 2014	Retrospective matched	21,346	Multiple	0.5 mg/dL↑ in creatinine in 24-72 h	Iohexol, iodixanol	Any	4.8	5.1
Davenport, 2013	Retrospective matched	20,242	Inpatient	0.5 mg/dL or 1.5 X ↑ in creatinine	Iohexol, iopamidol, iopromide, iodixanol	Any	8.3	8.6
Kidoh, 2013	Retrospective	470	Multiple	25% ↑ in creatinine	Iohexol, iopamidol	Abd/pelvis	9.1	8.3
Cely, 2012	Prospective observational matched	106	ICU	↓ 33% in mCrCl in 72 h	Iopromide, iodixanol	Any	26.4	35.8
Murakami, 2012	Retrospective	2,034	NR	0.5 mg/dL or 25% ↑ in creatinine in 72 h	Iopamidol, iomeprol	Chest, brain, abd/pelvis	6.1	6.2%
Silcock, 2012	Retrospective matched	264	ICU	0.5 mg/dL or 25% ↑ in creatinine or need for RRT in 72 h	NR	Abd/pelvis, chest	9.8	9.
Sinert, 2012	Retrospective	3,729	ICU	0.5 mg/dL or 25% ↑ in creatinine in 48–72 h	Iohexol, iodixanol	Any	5.7	9.0
Aulicky, 2010	Retrospective	241	ICU	0.5 mg/dL in 24–72 h ↑ in creatinine	Iomeprol, iohexol, iopamidol, iopromide, iodixanol, iobitridol	Brain	3.0	3.9
McGillicuddy, 2010	Retrospective	1,152	Trauma	0.5 mg/dL or 25% ↑ in creatinine in 72 h	Iohexol, iomeprol, iopamidol, iopromide	Brain	2.2	1.8
Lima, 2010	Retrospective	918	ED	25% ↑ in creatinine in 72 h	Iopamidol	Chest, brain, abd/pelvis	4.9	10.2
Ng, 2010	Retrospective matched	162	ICU, oncology	0.3 mg/dL or 50% creatinine ↑ in creatinine 24–72 h	Ioversol	Any	17.3	17.3
Bansal, 2009	Retrospective	139	CKD patients	0.5 mg/dL or 25% ↑ increase in creatinine	Iopromide, iodixanol	Any	12.3	9.5
Bruce, 2009	Retrospective	13,274	Multiple	0.5 mg/dL ↑ in creatinine or 25% ↓ in glomerular filtration rate in 3 days	Iohexol, iodixanol	Any	4.4	5.9
Oleinik, 2009	Retrospective	539	Inpatient	0.5 mg/dL or 25% ↑ in creatinine in 5 days	NR	Brain	6.0	9.9
Langner, 2008	Prospective observational	200	Inpatient stroke	25% ↑ in creatinine in 72 h	Iodixanol	Brain	7.0	12.0
Haveman, 2006	Retrospective	340	ICU	0.5 or 50% ↑ in creatinine in 5 days	Iohexol, iodixanol	Abd/pelvis	2.2	NR
Tremblay, 2005	Retrospective	95	ED, trauma	25% ↑ in creatinine in 48 h	Iohexol	Any	3.6	15.4
Heller, 1991	Case control	884	Inpatient	0.5 mg/dL or 50% ↑ in creatinine in 5 days	Iopamidol, diatrizoate	Any	7.3	4.0
Cramer, 1985	Prospective observational	426	Inpatient	50% ↑ in creatinine at 48 h	NR	Brain	2.1	1.3

AKI, Acute kidney injury; *abd/pelvis*, abdomen/pelvis; *CECT*, contrast-enhanced CT; *NR*, not reported; *RRT*, renal replacement therapy; *CKD*, chronic kidney disease.

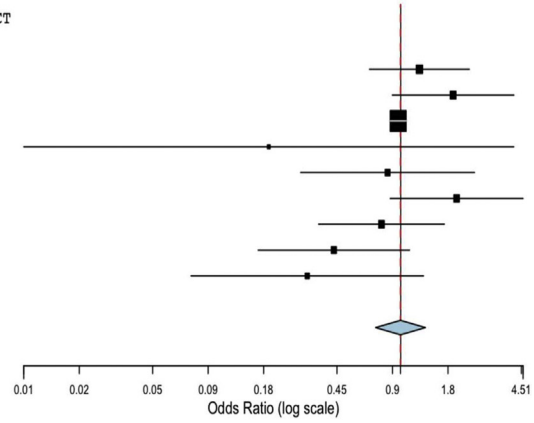
Acute Kidney Injury

Studies	Estimate (95% C.I.)	#AKI/Total CECT	#AKI/Total non-CECT
Hinson 2017	1.052 (0.938, 1.180)	766/7201	559/5499
Ehrlich 2016	0.587 (0.182, 1.896)	5/157	7/132
Heller 2016	0.889 (0.702, 1.126)	598/6954	87/909
Gao 2015	1.225 (0.918, 1.634)	70/474	235/1896
Hemmet 2015	1.184 (0.695, 2.016)	36/326	26/274
Paliwal 2015	0.236 (0.077, 0.724)	5/203	9/93
Sonhaye 2015	1.928 (0.941, 3.953)	21/620	12/672
Alsafi 2014	2.787 (1.608, 4.830)	62/677	17/487
McDonald 2014	0.944 (0.834, 1.068)	515/10673	544/10673
Davenport 2013	0.960 (0.869, 1.060)	835/10121	867/10121
Kidoh 2013	1.111 (0.556, 2.222)	13/143	27/327
Cely 2012	0.642 (0.280, 1.472)	14/53	19/53
Murakami 2012	0.978 (0.680, 1.407)	57/938	68/1096
Silcock 2012	1.000 (0.445, 2.247)	13/132	13/132
Sinert 2012	0.613 (0.441, 0.852)	44/773	265/2956
Aulicky 2010	0.776 (0.181, 3.332)	5/164	3/77
McGillicuddy 2010	1.209 (0.476, 3.073)	18/822	6/330
Lima 2010	0.450 (0.269, 0.755)	28/575	35/343
Ng 2010	1.000 (0.443, 2.258)	14/81	14/81
Bansal 2009	1.343 (0.459, 3.932)	8/65	7/74
Bruce 2009	0.728 (0.622, 0.854)	252/5790	440/7484
Oleinik 2009	0.581 (0.304, 1.111)	21/348	19/191
Langner 2008	0.552 (0.208, 1.466)	7/100	12/100
Tremblay 2005	0.204 (0.039, 1.069)	2/56	6/39
Heller 1991	1.917 (1.045, 3.516)	35/479	16/405
Cramer 1985	1.623 (0.359, 7.340)	4/193	3/233
Overall (I^2=6513 %, P< 0.001)	**0.938 (0.825, 1.065)**	**3448/48118**	**3316/44677**



Mortality

Studies	Estimate (95% C.I.)	# Deaths/Total CECT	# Deaths/Total non-CECT
Heller 2016	1.264 (0.677, 2.360)	106/6954	11/909
Gao 2015	1.924 (0.900, 4.114)	10/474	21/1896
McDonald 2014	0.969 (0.878, 1.069)	850/10673	875/10673
Cely 2012	0.193 (0.009, 4.108)	0/53	2/53
Sinert 2012	0.849 (0.287, 2.516)	4/773	18/2956
Aulicky 2010	2.010 (0.877, 4.610)	31/164	8/77
Ng 2010	0.787 (0.358, 1.726)	14/81	17/81
Haveman 2006	0.434 (0.168, 1.118)	77/321	8/19
Tremblay 2005	0.311 (0.073, 1.330)	3/56	6/39
Overall (I^2=3979 %, P=0.102)	**0.998 (0.730, 1.362)**	**1095/19549**	**966/16703**



Renal Replacement Therapy

Studies	Estimate (95% C.I.)	# RRT/Total CECT	# RRT/Total non-CECT
Hinson 2017	0.419 (0.261, 0.670)	27/7201	49/5499
Ehrlich 2016	0.841 (0.017, 42.687)	0/157	0/132
Heller 2016	4.326 (0.259, 72.161)	16/6954	0/909
Hsieh 2016	1.044 (0.807, 1.350)	121/7100	116/7100
Sonhaye 2015	1.084 (0.021, 54.703)	0/620	0/672
McDonald 2014	0.926 (0.537, 1.596)	25/10673	27/10673
Cely 2012	1.000 (0.061, 16.417)	1/53	1/53
Sinert 2012	3.822 (0.076, 192.783)	0/773	0/2956
Aulicky 2010	0.471 (0.009, 23.965)	0/164	0/77
McGillicuddy 2010	2.014 (0.096, 42.063)	2/822	0/330
Ng 2010	2.025 (0.180, 22.788)	2/81	1/81
Oleinik 2009	0.182 (0.007, 4.495)	0/348	1/191
Tremblay 2005	1.407 (0.123, 16.084)	2/56	1/39
Overall (I^2=1989 %, P=0.243)	**0.825 (0.587, 1.160)**	**196/35002**	**196/28712**

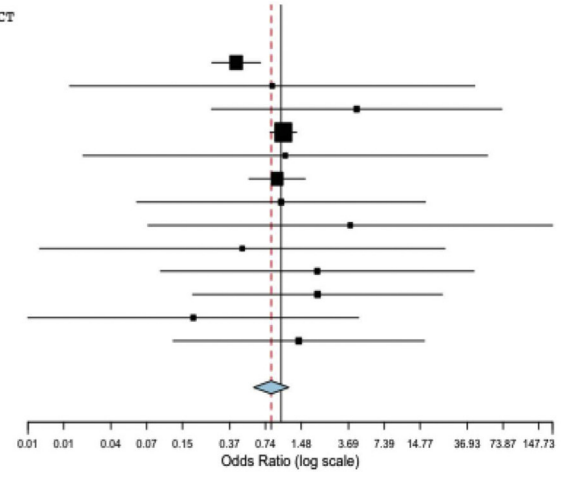


Figure 2. Main study results.

Table 2. Subgroup analysis results.

Subgroup	AKI in CECT Arm	AKI in Non-CECT Arm	OR (95% CI)
Class of contrast			
Nonionic iso-osmolar	7/100	12/100	0.55 (0.21–1.47)
Nonionic low osmolar	207/3,926	165/3,180	1.00 (0.59–1.65)
Nonionic low and iso-osmolar	2,452/34,983	2,731/37,264	0.89 (0.78–1.01)
Mixed osmolality	35/479	16/405	1.92 (1.05–3.52)
Not reported	747/8,630	392/3,728	0.92 (0.68–1.23)
Matching			
Matched	2,157/28,261	2,016/26,559	0.98 (0.92–1.05)
Unmatched	1,291/19,857	1,300/18,118	0.93 (0.75–1.15)
AKI definition			
0.5 mg/dL or 25% increase in creatinine	1,241/16,746	1,394/18,249	0.96 (0.74–1.24)
25% increase in creatinine	653/7,985	174/1,850	0.67 (0.46–0.99)
0.3 mg/dL increase in creatinine	106/800	261/2,170	1.22 (0.94–1.57)
0.5 mg/dL increase in creatinine	541/11,457	559/11,422	1.13 (0.69–1.85)
Other	67/806	52/772	1.19 (0.69–2.04)
Timing of follow-up creatinine level, h			
≤72	3,329/46,344	3,232/43,078	0.90 (0.79–1.02)
>72	98/1,154	72/927	1.04 (0.59–1.83)
Not reported	21/620	12/672	1.93 (0.94–3.95)
Population setting			
ED	1,464/16,336	971/10,550	0.79 (0.58–1.08)
ICU	116/904	284/2,239	1.10 (0.87–1.41)
Inpatient	964/11,918	934/11,537	1.19 (0.73–1.94)
Trauma	18/822	6/330	1.21 (0.48–3.09)
Multiple settings	824/16,997	1,044/18,832	0.90 (0.74–1.10)

21,000. Differing definitions of acute kidney injury and timing of renal function measurements were also used among studies, with only 18.5% of studies reporting renal function measurements greater than 72 hours after CT scan, which may have resulted in measurement bias. However, subgroup analysis found no difference in risk of acute kidney injury in studies using different follow-up creatinine-level times and only one significant association in risk of acute kidney injury in subgroups assessing definitions of acute kidney injury (Table 2). This analysis demonstrated a lower risk of acute kidney injury when it was defined as a 25% increase in creatinine level without an absolute creatinine level value, and, although this achieved statistical significance, clinical significance is doubtful. Additionally, use of nephrotoxic agents, prophylactic medications, and intravenous hydration was reported in several articles, but could introduce additional confounding. The best available evidence fails to demonstrate the efficacy of hydration and prophylactic medications in reducing postcontrast acute kidney injury, making this source of confounding less influential.[2,44]

Many of the included articles focused on a particular theme (eg, stroke patients) yet used all comers without considering various potentially confounding factors such as sex, age, or other comorbid conditions. However, 7 studies used matching techniques to mitigate these confounders.[45]

All included studies are observational and many are subject to selection bias and measurement bias, yet this meta-analysis's strength is that it was inclusive of large data sets and evaluated subgroups that may have produced different results as a result of population, setting, renal function measurement, or definition, and the results supported the conclusion that postcontrast acute kidney injury is not associated with contrast-enhanced CT. Furthermore, randomized controlled trials on postcontrast acute kidney injury are improbable, and this demonstrates the synthesis of the best available evidence to guide clinicians.

DISCUSSION

This meta-analysis demonstrated no difference in the rates of renal insufficiency, need for dialysis, or mortality between patients receiving contrast-enhanced CT versus those receiving noncontrast CT. These findings contradict years of dogma that intravenous radiocontrast causes nephropathy but are in line with the recent literature questioning the validity of earlier studies.[5] This difference may be partially due to the select group we evaluated in this study—patients undergoing CT scan—instead of patients receiving contrast for procedures.

Additionally, early studies linking contrast-enhanced CT to postcontrast acute kidney injury failed to use noncontrast CT control groups and may have attributed the increase in creatinine level to intravenous contrast,

failing to account for the patients' other risk factors for development of acute kidney injury, including sepsis, dehydration, end-organ dysfunction, or administration of nephrotoxic medications.[2,46,47] We were unable to analyze these patient-level factors. However, the majority of studies included in this review were ED patients admitted to the hospital or were inpatient and ICU patients, creating a selection bias toward a sicker patient population, which should overestimate the incidence of acute kidney injury, need for renal replacement therapy, and mortality compared with an unselected ED or outpatient population.

Although the data are observational, our analyses did not identify significant associations between contrast-enhanced CT and postcontrast acute kidney injury. This finding was maintained even in the studies that attempted to adjust for factors that may influence a provider's decision to obtain a contrast-enhanced CT compared with a noncontrast CT. Because the risk of postcontrast acute kidney injury has been tied to high-osmolar contrast agents that have largely been replaced by low-osmolar and iso-osmolar ones, we performed a subgroup analysis by class of contrast agent. We found no association between postcontrast acute kidney injury and nonionic low osmolar contrast, nonionic low and iso-osmolar contrast, and iso-osmolar contrast (Table 2). There was also no association in the studies that did not report the contrast agent used. There was an association between acute kidney injury and use of a high-osmolar contrast agent; however, congruent with current practices avoiding the use of high-contrast media, this article from 1991 was the only study to use a high-osmolar contrast agent.[15]

We also found no association between contrast exposure and postcontrast acute kidney injury in studies using matching techniques to address the confounding by indication that may complicate these cohorts. Propensity score matching has gained popularity in mitigating systematic differences in baseline characteristics between subjects and estimating treatment effects by accounting for covariates in observational studies.[48] However, propensity score matching does not replace randomization because it cannot account for unmeasured confounders.[49] Yet, without randomized trials of postcontrast acute kidney injury after contrast-enhanced CT, this subgroup with minimal heterogeneity provides the best available evidence that postcontrast acute kidney injury is not associated with contrast-enhanced CT.

Last, using increases in serum creatinine levels to assess renal insufficiency is of questionable utility because creatinine level can naturally fluctuate during a 5-day period and may depend on sex, body mass, and other patient factors.[50,51] Further prospective studies are needed to make a definitive conclusion about a causal relationship between intravenous contrast and clinically significant patient-oriented outcomes because, ultimately, a transient fluctuation in renal function may not be clinically relevant.

In conclusion, our study found a lack of association between acute kidney injury and contrast-enhanced CT and no association with important patient-oriented and clinical outcomes, including the need for renal replacement therapy and mortality. The American College of Radiology *ACR Manual on Contrast Media*[2] underscores this point and argues for a shift in language from contrast-induced nephropathy to postcontrast acute kidney injury, with the understanding that the acute kidney injury may be incidental rather than caused by the contrast. These findings are limited by the quality of included studies and by significant selection bias, including provider selection for contrast-enhanced CT. These observational data demonstrate that physician selection of patients to receive contrast-enhanced CT seems to add no additional risk of acute kidney injury, need for renal replacement therapy, or mortality. These findings are congruent with current assertions from the American College of Radiology.[2]

Supervising editor: Allan B. Wolfson, MD

Author affiliations: From Emergency Services, Eglin Air Force Base Hospital, Eglin Air Force Base, FL (Aycock); the Department of Emergency Medicine, Baystate Medical Center/UMMS, Springfield, MA (Westafer, Schoenfeld); the Health Sciences Library, Hofstra Northwell School of Medicine, Hempstead, NY (Boxen); the Department of Emergency Medicine, Staten Island University Hospital, Staten Island, NY (Majlesi); and the Center for Treatment Comparison and Integrative Analysis, Tufts Medical Center, Boston, MA (Bannuru).

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Publication dates: Received for publication May 20, 2017. Revisions received June 18, 2017, and June 24, 2017. Accepted for publication June 27, 2017.

Trial registration number: CRD42017056195

REFERENCES

1. OECD. Health at a glance 2015. OECD health statistics 2015. Available at: http://dx.doi.org/10.1787/health-data-en. Accessed June 13, 2017.
2. American College of Radiology. *ACR Manual on Contrast Media v10.2*. Reston, VA: American College of Radiology; 2016.
3. Morcos SK, Thomsen HS, Webb JA. Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). *Eur Radiol*. 1999;9:1602-1613.
4. Mitchell AM, Jones AE, Tumlin JA, et al. Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting. *Clin J Am Soc Nephrol*. 2010;5:4-9.
5. Kooiman J, Pasha SM, Zondag W, et al. Meta-analysis: serum creatinine changes following contrast enhanced CT imaging. *Eur J Radiol*. 2012;81:2554-2561.
6. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264-269; W264.
7. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology*. 1993;188:171-178.
8. CLARITY Group. Tool to assess risk of bias in cohort studies. Available at: http://methods.cochrane.org/sites/methods.cochrane.org.bias/files/public/uploads/Tool%20to%20Assess%20Risk%20of%20Bias%20in%20Cohort%20Studies.pdf. Accessed May 9, 2017.
9. Wallace BC, Dahabreh IJ, Trikalinos TA, et al. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw*. 2012;49:1-15.
10. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Software*. 2010;36:1-48.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
12. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
13. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006;25:3443-3457.
14. Cramer BC, Parfrey PS, Hutchinson TA, et al. Renal function following infusion of radiologic contrast material. A prospective controlled study. *Arch Intern Med*. 1985;145:87-89.
15. Heller CA, Knapp J, Halliday J, et al. Failure to demonstrate contrast nephrotoxicity. *Med J Aust*. 1991;155:329-332.
16. Tremblay LN, Tien H, Hamilton P, et al. Risk and benefit of intravenous contrast in trauma patients with an elevated serum creatinine. *J Trauma*. 2005;59:1162-1166; discussion 1166-1167.
17. Haveman JWGR, Bongaerts AHH, Nijsten MWN. Low incidence of nephropathy in surgical ICU patients receiving intravenous contrast: a retrospective analysis. *Intensive Care Med*. 2006;32:1199-1205.
18. Langner S, Stumpe S, Kirsch M, et al. No increased risk for contrast-induced nephropathy after multiple CT perfusion studies of the brain with a nonionic, dimeric, iso-osmolal contrast medium. *AJNR Am J Neuroradiol*. 2008;29:1525-1529.
19. Oleinik A, Romero JM, Schwab K, et al. CT angiography for intracerebral hemorrhage does not increase risk of acute nephropathy. *Stroke*. 2009;40:2393-2397.
20. Bruce RJ, Djamali A, Shinki K, et al. Background fluctuation of kidney function versus contrast-induced nephrotoxicity. *AJR Am J Roentgenol*. 2009;192:711-718.
21. Bansal GJ, Darby M. Measurement of change in estimated glomerular filtration rate in patients with renal insufficiency after contrast-enhanced computed tomography: a case-control study. *J Comput Assist Tomogr*. 2009;33:455-459.
22. Ng CS, Shaw AD, Bell CS, et al. Effect of IV contrast medium on renal function in oncologic patients undergoing CT in ICU. *AJR Am J Roentgenol*. 2010;195:414-422.
23. Lima FO, Lev MH, Levy RA, et al. Functional contrast-enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy. *AJNR Am J Neuroradiol*. 2010;31:817-821.
24. McGillicuddy EA, Schuster KM, Kaplan LJ, et al. Contrast-induced nephropathy in elderly trauma patients. *J Trauma*. 2010;68:294-297.
25. Aulicky P, Mikulik R, Goldemund D, et al. Safety of performing CT angiography in stroke patients treated with intravenous thrombolysis. *J Neurol Neurosurg Psychiatry*. 2010;81:783-787.
26. Sinert R, Brandler E, Subramanian RA, et al. Does the current definition of contrast-induced acute kidney injury reflect a true clinical entity? *Acad Emerg Med*. 2012;19:1261-1267.
27. Murakami R, Hayashi H, Sugizaki K, et al. Contrast-induced nephropathy in patients with renal insufficiency undergoing contrast-enhanced MDCT. *Eur Radiol*. 2012;22:2147-2152.
28. Cely CM, Schein RM, Quartin AA. Risk of contrast induced nephropathy in the critically ill: a prospective, case matched study. *Crit Care*. 2012;16:R67.
29. Kidoh M, Nakaura T, Awai K, et al. Low-contrast dose protection protocol for diagnostic computed tomography in patients at high-risk for contrast-induced nephropathy. *J Comput Assist Tomogr*. 2013;37:289-296.
30. Davenport MS, Khalatbari S, Dillman JR, et al. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. *Radiology*. 2013;267:94-105.
31. McDonald RJ, McDonald JS, Carter RE, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. *Radiology*. 2014;273:714-725.
32. Alsafi A, Alsafi Z, Lakhani A, et al. Changes in renal function in elderly patients following intravenous iodinated contrast administration: a retrospective study. *Radiol Res Pract*. 2014;2014:1-4.
33. Sonhaye L, Kolou B, Tchaou M, et al. Intravenous contrast medium administration for computed tomography scan in emergency: a possible cause of contrast-induced nephropathy. *Radiol Res Pract*. 2015;2015:1-4.
34. Paliwal P, Chua H, Yeo L, et al. Risk of contrast induced nephropathy and persistent renal impairment from CT angiography in acute stroke. *Cerebrovasc Dis*. 2015;40(suppl 1):67.
35. Hemmett J, Er L, Chiu HH, et al. Time to revisit the problem of CIN? the low incidence of acute kidney injury with and without contrast in hospitalized patients: an observational cohort study. *Can J Kidney Health Disease*. 2015;2:38.
36. Gao J, Zhang M, Fang G, et al. [Risk and harm of contrast induced nephropathy in critically ill patients]. *Chin Crit Care Med*. 2015;27:366-370.
37. Hsieh MS, Chiu CS, How CK, et al. Contrast medium exposure during computed tomography and risk of development of end-stage renal disease in patients with chronic kidney disease: a nationwide population-based, propensity score-matched, longitudinal follow-up study. *Medicine*. 2016;95:e3388.
38. Heller M, Krieger P, Finefrock D, et al. Contrast CT scans in the emergency department do not increase risk of adverse renal outcomes. *West J Emerg Med*. 2016;17:404-408.
39. Ehrlich MTH, Currie L, Wintermark M, et al. Safety of computed tomographic angiography in the evaluation of patients with acute stroke: a single-center experience. *Stroke*. 2016;47:2045-2050.
40. Silcock DJ, Sundaram R, Koteeswaran S, et al. Evaluating the effect of intravenous contrast on renal function in critically ill patients undergoing radiological investigations: a retrospective cohort study. *Intensive Care Med*. 2012;38(suppl 1):S45.
41. Hinson JS, Ehmann MR, Fine DM, et al. Risk of acute kidney injury after intravenous contrast media administration. *Ann Emerg Med*. 2017;69:577-586.e574.

42. Norris S, Atkins D, Bruening W, et al. *Selecting Observational Studies for Comparing Medical Interventions: Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville, MD: Agency for Healthcare Research & Quality; 2008.
43. O'Neil M, Berkman N, Hartling L, et al. *Observational Evidence and Strength of Evidence Domains: Case Examples*. Rockville, MD: Agency for Healthcare Research & Quality; 2014.
44. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic Hydration to Protect Renal Function From Intravascular Iodinated Contrast Material in Patients at High Risk of Contrast-Induced Nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet*. 2017;389:1312-1322.
45. Baek S, Park SH, Won E, et al. Propensity score matching: a conceptual review for radiology researchers. *Korean J Radiol*. 2015;16:286-296.
46. Katzberg RW, Lamba R. Contrast-induced nephropathy after intravenous administration: fact or fiction? *Radiol Clin North Am*. 2009;47:789-800, v.
47. Rao QA, Newhouse JH. Risk of nephropathy after intravenous administration of contrast material: a critical literature analysis. *Radiology*. 2006;239:392-397.
48. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399-424.
49. Luo Z, Gardiner JC, Bradley CJ. Applying propensity score methods in medical research: pitfalls and prospects. *Med Care Res Rev*. 2010;67:528-554.
50. Newhouse JH, Kho D, Rao QA, et al. Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity. *AJR Am J Roentgenol*. 2008;191:376-382.
51. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care*. 2016;20:299.

Table E1. Assessment of bias of included studies.

Author	Was Selection of Exposed and Nonexposed Cohorts Drawn From the Same Population?	Can We Be Confident of the Assessment of Exposure?	Can We Be Confident That the Outcome of Interest Was Not Present at the Start of the Study?	Did the Study Match Exposed and Unexposed for All Variables That Are Associated With the Outcome of Interest?	Can We Be Confident in the Assessment of the Presence or Absence of Prognostic Factors?	Can We Be Confident in the Assessment of Outcome?	Was the Follow-up of Cohorts Adequate?	Were Cointerventions Similar Between Groups?	Bias Because of Missing Data	Overall Risk of Bias
Hinson, 2017	Definitely yes	Probably yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably no	Low
Ehrlich, 2016	Probably yes	Probably yes	Probably yes	Probably no	Probably yes	Definitely yes	Probably yes	Probably yes	Probably yes	Moderate
Heller, 2016	Probably yes	Probably yes	Probably yes	Probably no	Probably no	Probably yes	Probably yes	Probably no	Definitely yes	Serious
Hsieh, 2016	Definitely yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Definitely yes	Probably yes	Probably yes	Moderate
Gao, 2015	Probably yes	Probably yes	Probably yes	Probably no	Probably yes	Definitely yes	Probably yes	Probably no	Definitely yes	Serious
Hemmett, 2015	Probably yes	Definitely yes	Definitely yes	Probably no	Probably no	Probably yes	Definitely yes	Probably no	Probably yes	Serious
Paliwal, 2015	Probably yes	Probably yes	Probably yes	Definitely no	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	Moderate
Sonhaye, 2015	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Definitely yes	Probably yes	Moderate
Alsafi, 2014	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	Low
McDonald, 2014	Definitely yes	Definitely yes	Probably yes	Definitely yes	Probably yes	Definitely yes	Probably yes	Probably yes	Probably no	Low
Davenport, 2013	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Probably yes	Probably yes	Probably no	Low
Kidoh, 2013	Probably yes	Probably yes	Probably yes	Probably no	Probably no	Probably yes	Probably yes	Probably no	Definitely yes	Serious
Cely, 2012	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably no	Low
Murakami, 2012	Probably yes	Probably yes	Probably yes	Probably no	Probably no	Probably yes	Probably yes	Probably no	Definitely yes	Serious
Silcock, 2012	Probably yes	Probably yes	Probably no	Probably yes	Probably no	Probably no	Probably yes	Probably no	Definitely yes	Critical
Sinert, 2012	Probably yes	Definitely yes	Definitely yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably no	Probably yes	Moderate
Aulicky, 2010	Definitely yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Definitely yes	Moderate
McGillicuddy, 2010	Probably yes	Probably yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes	Definitely yes	Serious
Lima, 2010	Probably yes	Probably yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably no	Probably no	Moderate
Ng, 2010	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Low
Bansal, 2009	Probably yes	Probably yes	Probably yes	Definitely no	Probably no	Probably yes	Probably yes	Probably yes	Definitely yes	Critical
Bruce, 2009	Probably yes	Probably yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably no	Probably yes	Serious
Oleinik, 2009	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably yes	Probably yes	Definitely yes	Probably yes	Probably yes	Moderate
Langner, 2008	Definitely no	Definitely Yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably no	Definitely yes	Serious
Haveman, 2006	Probably yes	Definitely yes	Definitely yes	Probably no	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	Serious
Tremblay, 2005	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably yes	Probably yes	Definitely yes	Probably yes	Probably no	Low
Heller, 1991	Probably yes	Probably yes	Probably yes	Probably no	Probably no	Probably yes	Probably yes	Probably yes	Definitely yes	Serious
Cramer, 1985	Probably yes	Definitely yes	Definitely yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	Definitely yes	Moderate

(contrast OR "Accupaque" OR "Acid, Amidotricoic"[Mesh] OR "Acide iotalamique" OR "Acido iotalamico" OR "Acidum Iotalamicum" OR "Agent, Radiocontrast"[Mesh] OR "Agents, Contrast"[Mesh] OR "Agents, Radiocontrast"[Mesh] OR "Amidol" OR "Amidotrezoate" OR "Amidotricoic Acid" OR "Amidotrizoate" OR "Amidotrizoate, Meglumine"[Mesh] OR "Amidotrizoic Acid" OR "Angiografin" OR "B 15000" OR "Bystage" OR "C.I. Fluorescent Brightening Agent 28" OR "Cholografin" OR "Clarograf"[Mesh] OR "Conray" OR "contrast" OR "Contrast Agents" OR "Contrast Materials" OR "Contrast media" OR "Contrast Media"[Mesh] OR "Cysto-Conray" OR "Diatrizoate" OR "Diatrizoate"[Mesh] OR "Diatrizoate meglumine" OR "Diatrizoate Meglumine"[Mesh] OR "Diatrizoate Methylglucamine" OR "Diatrizoate sodium" OR "Diatrizoate, Methylglucamine" OR "Diatrizoic Acid Methylglucamine"[Mesh] OR "Exypaque" OR "Gastromiro" OR "Hemoray" OR "Hexabrix" OR "Hypaque" OR "Hypaque 50" OR "Imagenil" OR "Imeron" OR "Iobitridol" OR "Iobrix" OR "iocarmate meglumine" OR "Iodamide"[Mesh] OR "Iodinated contrast medium" OR "Iodipamide"[Mesh] OR "iodixanol" OR "Iodixanolum" OR "Iodized Oil"[Mesh] OR "Iodopyracet"[Mesh] OR "iohexol" OR "Iohexol"[Mesh] OR "Iohexolum" OR "iomeprol" OR "iomeron" OR "Iopamed" OR "Iopamidol" OR "Iopamidol"[Mesh] OR "Iopamidolo" OR "Iopamidolum" OR "Iopamigita" OR "Iopamiro" OR "Iopamiron" OR "Iopanoic Acid"[Mesh] OR "Iopaque" OR "Iopasen" OR "Iopathek" OR "iopentol" OR "Iopromid" OR "Iopromida" OR "Iopromide" OR "Iopromidum" OR "iosimenol" OR "iosmin" OR "Iotalamic Acid" OR "Iotalaminsäure" OR "Iotalamique" OR "iothalamate" OR "Iothalamate Meglumine"[Mesh] OR "Iothalamate Sodium" OR "Iothalamate Sodium"[Mesh] OR "Iothalamic Acid" OR "Iothalamic Acid"[Mesh] OR "iotrolan" OR "Ioverin" OR "ioversol" OR "Ioversolum" OR "IOX" OR "ioxaglate" OR "Ioxaglate Meglumine" OR "Ioxaglate Sodium" OR "Ioxaglate, Methylglucamine"[Mesh] OR "Ioxaglic Acid" OR "Ioxaglic Acid"[Mesh] OR "Ioxaglic Acid Monosodium Salt"[Mesh] OR "Ioxaglic Acid, Calcium Salt"[Mesh] OR "Ioxaglic Acid"[Mesh] OR "Ioxeol" OR "Ioxeol"[Mesh] OR "Ioxilan" OR "Ioxilane" OR "ioxitalamic acid" OR "Ioxitol" OR "Isopaque" OR "Isovue" OR "Jopamidol" OR "Jopamiro" OR "Kopaq" OR "lopromid" OR "Magnetite Nanoparticles"[Mesh] OR "Materials, Contrast"[Mesh] OR "MD-76" OR "Media, Contrast"[Mesh] OR "Media, Radiocontrast"[Mesh] OR "Media, Radiopaque"[Mesh] OR "Medixol" OR "Meglumine"[Mesh] OR "Meglumine Amidotrizoate" OR "Meglumine Diatrizoate" OR "meglumine iodipamide" OR "Meglumine Iotalamate"[Mesh] OR "Meglumine Iothalamate"[Mesh] OR "meglumine iotroxinate" OR "meglumine ioxithalamate" OR "Meglumine sodium" OR "Meglumine, Diatrizoate"[Mesh] OR "Meglumine, Ioxaglate"[Mesh] OR "Methylglucamine Diatrizoate" OR "Methylglucamine Ioxaglate" OR "Methylglucamine, Diatrizoate"[Mesh] OR "Methylglucamine, Diatrizoic Acid"[Mesh] OR "metrizoate" OR "Metrizoate"[Mesh] OR "MI 216" OR "Moiopamin" OR "Moiopaque" OR "MP 328" OR "Natrium iotalamat" OR "Niopam" OR "Nycodenz" OR "Omnipaque" OR "Omnitrast" OR "Optiject" OR "Optiray" OR "Ou Su" OR "Oxilan" OR "oxilanum" OR "Oypalomin" OR "Pamiray" OR "Pamiray-300" OR "Pamiray-370" OR "Pamitra" OR "postcontrast" OR "post-contrast" OR "Proscope" OR "radiocontrast" OR "Radiocontrast Agent" OR "Radiocontrast Agents" OR "Radiocontrast Media" OR "Radiomiron" OR "Radiopaque Media" OR "Radoso" OR "Reno 60" OR "Reno M Dip" OR "Reno MDip"[Mesh] OR "Reno M-Dip" OR "Renograffin" OR "Renografin" OR "Renografin M 76" OR "Renografin M76"[Mesh] OR "Renografin M-76" OR "Scanlux" OR "Shuang Bei" OR "Sinografin" OR "Sodium Diatrizoate" OR "Sodium Iotalamate" OR "Sodium Iotalamate Injection" OR "Sodium Iothalamate" OR "Sodium Magnesium Diatrizoate"[Mesh] OR "Sodium-Magnesium Diatrizoate" OR "Solutrast" OR "SQ 13396"[Mesh] OR "Telebrix" OR "Triombrast" OR "Triombrin" OR "Triosil" OR "Ultravist" OR "Unilux" OR "Urografin" OR "Urografin 76" OR "Urogranoic Acid" OR "Urovist" OR "Verografin" OR "Visipaque" OR "Win 39424" OR "Xenetix" OR "ZK 35760") AND ("Beam Tomography, Electron"[Mesh] OR "CAT scan" OR "CAT Scan, Spiral"[Mesh] OR "CAT Scan, X Ray"[Mesh] OR "CAT Scan, X-Ray"[Mesh] OR "CAT Scans, Spiral"[Mesh] OR "CAT Scans, X-Ray"[Mesh] OR "Cine CT" OR "Cine-CT" OR "computed tomography" OR "Computed Tomography, Helical"[Mesh] OR "Computed Tomography, Spiral"[Mesh] OR "Computed Tomography, Transmission"[Mesh] OR "Computed Tomography, X Ray"[Mesh] OR "Computed Tomography, Xray"[Mesh] OR "Computed Tomography, X-Ray"[Mesh] OR "Computed X Ray Tomography"[Mesh] OR "Computed X-Ray Tomography"[Mesh] OR "Computer Assisted Tomography, Spiral"[Mesh] OR "Computer-Assisted Tomography, Spiral"[Mesh] OR "Computerized Tomography, Spiral"[Mesh] OR "Computerized Tomography, X Ray"[Mesh]

Figure E1. PubMed search strategy.

OR "Computerized Tomography, X-Ray"[Mesh] OR "CT" OR "CT Angiography" OR "CT Scan, Spiral"[Mesh] OR "CT Scan, X Ray"[Mesh] OR "CT Scan, X-Ray"[Mesh] OR "CT Scans, Spiral"[Mesh] OR "CT Scans, X-Ray"[Mesh] OR "CT X Ray" OR "CT X Rays" OR "CT, Helical"[Mesh] OR "CT, Spiral"[Mesh] OR "CTs, Helical"[Mesh] OR "CTs, Spiral"[Mesh] OR "Electron Beam Computed Tomography"[Mesh] OR "Electron Beam Tomography"[Mesh] OR "Helical Computed Tomography" OR "Helical CT" OR "Helical CTs" OR "Multidetector Computed Tomography"[Mesh] OR "Scan, Spiral CAT"[Mesh] OR "Scan, Spiral CT"[Mesh] OR "Scan, X-Ray CAT"[Mesh] OR "Scan, X-Ray CT"[Mesh] OR "Scans, Spiral CAT"[Mesh] OR "Scans, Spiral CT"[Mesh] OR "Scans, X-Ray CAT"[Mesh] OR "Scans, X-Ray CT"[Mesh] OR "Spiral CAT Scan" OR "Spiral CAT Scans" OR "Spiral Computed Tomography" OR "Spiral Computer-Assisted Tomography" OR "Spiral Computerized Tomography" OR "Spiral CT" OR "Spiral CT Scan" OR "Spiral CT Scans" OR "Spiral CTs" OR "Tomographies, Computed X-Ray"[Mesh] OR "Tomography, Computed X-Ray"[Mesh] OR "Tomography, Electron Beam"[Mesh] OR "Tomography, Helical Computed"[Mesh] OR "Tomography, Spiral Computed"[Mesh] OR "Tomography, Spiral Computer-Assisted"[Mesh] OR "Tomography, Spiral Computerized"[Mesh] OR "Tomography, Transmission Computed"[Mesh] OR "Tomography, X Ray Computed"[Mesh] OR "Tomography, X Ray Computer Assisted"[Mesh] OR "Tomography, X Ray Computerized"[Mesh] OR "Tomography, X Ray Computerized Axial"[Mesh] OR "Tomography, Xray Computed"[Mesh] OR "Tomography, X-Ray Computed"[Mesh] OR "Tomography, X-Ray Computer Assisted"[Mesh] OR "Tomography, X-Ray Computer*" OR "Tomography, X-Ray Computerized"[Mesh] OR "Tomography, X-Ray Computerized Axial"[Mesh] OR "Transmission Computed Tomography" OR "X Ray Computer Assisted Tomography" OR "X Ray Computerized Axial Tomography"[Mesh] OR "X Ray Computerized Tomography" OR "X Ray Tomography, Computed"[Mesh] OR "X Ray, CT"[Mesh] OR "X Rays, CT"[Mesh] OR "X-Ray CAT Scan"[Mesh] OR "X-Ray CAT Scans"[Mesh] OR "Xray Computed Tomography" OR "X-Ray Computed Tomography" OR "X-Ray Computer Assisted Tomography" OR "X-Ray Computerized Axial Tomography"[Mesh] OR "X-Ray Computerized Tomography" OR "X-Ray CT Scan" OR "X-Ray CT Scans" OR "X-Ray Tomography, Computed"[Mesh]) AND (((Kidney OR Renal) AND (injur* OR injury OR injuries OR failure OR disease OR diseases OR insufficiency OR dysfunction OR impair* OR damag* OR reduc*)) OR "Acute kidney injury"[Mesh] OR "Acute kidney injury" OR "Acute Kidney Injury/chemically induced*" OR "Acute Kidney Injury/classification" OR "Acute Kidney Injury/mortality" OR "AKIN system" OR "CIN" OR "Contrast Induced Nephrotoxicity" OR "Contrast Media/adverse effects*" OR "Contrast Media/diagnostic use" OR "Contrast-induced Nephrotoxicity" OR "Coronary Angiography/adverse effects*" OR "Coronary Angiography/methods" OR "Creatinine"[Mesh] OR "Creatinine/blood" OR "Deterioration of renal function" OR "Glomerular Filtration Rate" OR "Glomerular Filtration Rate/drug effects" OR "Hemofiltration" OR "Iodine/adverse effects" OR "Iodine/diagnostic use" OR "Kidney Diseases/blood" OR "Kidney Diseases/chemically induced" OR "Kidney Diseases/diagnosis" OR "Kidney Diseases/epidemiology" OR "Kidney Diseases/mortality" OR "Kidney Diseases/physiopathology" OR "Kidney Diseases/prevention and control" OR "Kidney Function Tests" OR "nephropath*" OR "Nephrotox*" OR "Renal Insufficiency"[Mesh] OR "Renal Dialysis" OR "Renal Insufficiency, Chronic/chemically induced*" OR "Renal Insufficiency, Chronic/mortality" OR "RIFLE system")

Figure E1. Continued.

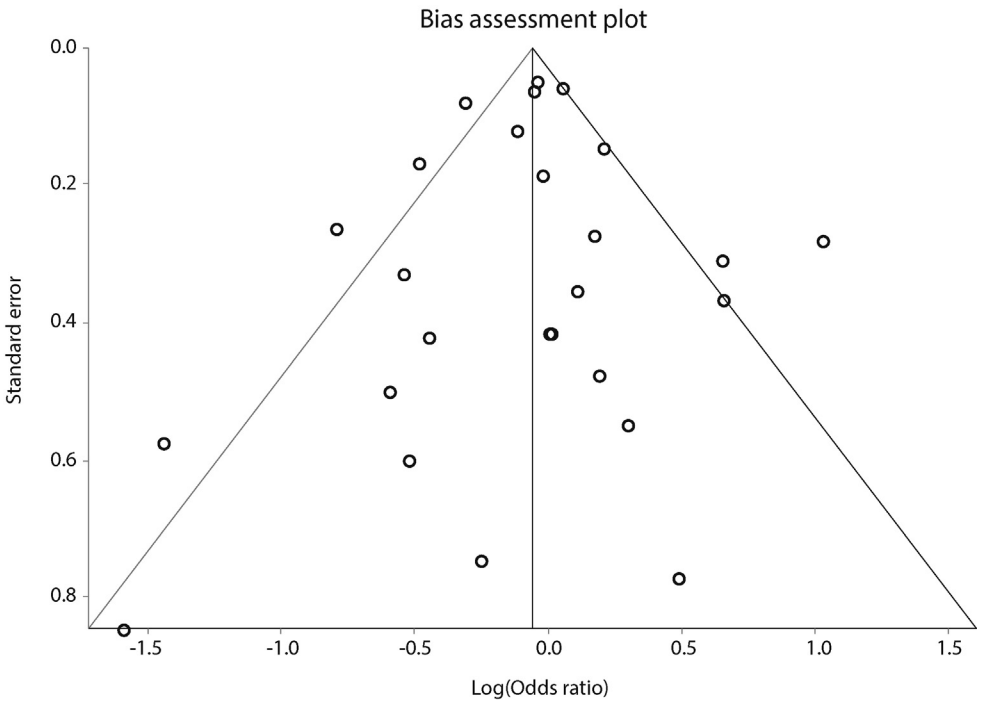


Figure E2. Funnel plot of studies included in the meta-analysis for acute kidney injury, demonstrating a lack of publication bias.