ORIGINAL RESEARCH

Incidence and risk of developing contrast-induced acute kidney injury following intravascular contrast administration in elderly patients

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Background: The purpose of this meta-analysis was to evaluate the epidemiology of contrast-induced acute kidney injury (CI-AKI) in the elderly.

Methods: A literature review was undertaken to determine the incidence of CI-AKI in individuals receiving intravascular contrast medium in the hospital setting.

Results: Twenty-two studies with 186,455 patients were identified. The pooled incidence of CI-AKI was 13.6% in 67,831 patients older than 65 years of age (95% confidence interval [CI] 10.1–18.2, I^2=0.496). The pooled odds ratio of CI-AKI in the elderly was 2.55 (95% CI 1.85–3.52, I^2=0.34). The high incidence of CI-AKI in the elderly was consistent across different administration route subgroups (intracoronary contrast medium group, 15.5% [95% CI 10.3–22.6]; intravenous contrast medium group, 12.4% [95% CI 8.0–18.8]).

Conclusion: Elderly patients are at greater risk for developing CI-AKI.

Keywords: contrast-induced acute kidney injury, angiography, enhanced computed tomography, epidemiology, meta-analysis

Introduction

Contrast-induced acute kidney injury (CI-AKI) following administration of intravascular contrast media (CM) is currently the third leading cause of hospital-acquired acute kidney injury and occurs in approximately 7% of unselected patients.[1,2] Advanced age has been identified as an important risk factor for CI-AKI.[3] However, limited data exist to determine the actual epidemiology of CI-AKI in elderly patients. To address this issue, we performed a meta-analysis on currently available clinical studies to evaluate the incidence and risk of CI-AKI developing in the elderly.

Materials and methods
Search strategy

We performed a MEDLINE literature search from 1966 to June 2013. We derived three comprehensive search themes that were combined by the Boolean operator "AND" (see Supplementary material). For the theme "CI-AKI", 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 "radio-contrast induced nephropathy". For the theme "elderly", the terms "elderly", "aged", "geriatric", "older", "senior", "age group", "old persons", "65 years", "75 years", and

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"80 years" were used. For the theme "clinical study", we used a previously published search strategy.[4]

Study selection and data extraction

We included cohort studies and randomized controlled trials that reported the incidence or adjusted odds ratios (ORs) of CI-AKI following intravascular CM administration in elderly patients. An elderly patient was defined as a patient ≥65 years of age. There were no restrictions regarding patient inclusion criteria or administration route of CM. The exclusion criterion was a duplicate report. The studies were reviewed by two independent investigators (WS and TZ) to determine whether the studies met the inclusion criteria. Discrepancies were resolved by consensus between the two review authors when the discrepancy was due to simple oversight by one of these authors. Otherwise, a third author was consulted when the discrepancy was due to a difference in interpretation. Data from included studies were recorded using a standardized form, including the source and design of the studies, inclusion/exclusion criteria, baseline characteristics of participants, and outcomes.

Endpoints, data synthesis, and analysis

The endpoint was the incidence of CI-AKI, which was defined as an increase in serum creatinine levels of more than 25% or 0.5 mg/dL following intravascular CM administration.[2] If data for this definition were unavailable, the endpoint of CI-AKI reported in the original study was chosen. The overall incidence of CI-AKI in the elderly was estimated with 95% confidence intervals (CIs) by pooling the reported incidences of CI-AKI from individual studies according to the DerSimonian-Laird random-effect model using MetaAnalyst software (version Beta3.13; Tufts Medical Center, Boston, MA, USA).[5] The incidence of CI-AKI in prespecified subgroups was also analyzed, including patients aged ≥75 years and ≥80 years of age, with intracoronary CM administration, intra-arterial CM administration other than via the coronary artery, intravenous CM administration, and administration route other than via coronary artery. Pooled ORs of CI-AKI in elderly patients versus younger patients were estimated according to the inverse-variance random-effect model using Review Manager software (Rev-Man Analyses version 5.1.4; Copenhagen, Denmark; The Nordic Cochrane Center, The Cochrane Collaboration, 2011) by pooling the calculated ORs based on the incidence of CI-AKI in the two groups and the reported adjusted ORs from individual studies. Heterogeneity between studies was analyzed by the I^2 statistic. An I^2 less than 50% indicated that the magnitude of heterogeneity may not be important. To explore sources of heterogeneity, metaregression in incidence of CI-AKI was performed using the restricted maximum likelihood method by Stata version 12.0 (Stata Corporation, College Station, TX, USA). Definition of elderly (≥65 years or ≥75 years), definition of CI-AKI (serum creatinine increase ≥25% or 0.5 mg/dL, or others), and route of CM administration (intravenous or intra-arterial) were used as covariates in the regression model. Sensitivity analysis was performed by sequentially excluding a single study. *P*-values less than 0.05 in two-tailed tests were considered to be statistically significant.

Results

We retrieved 159 unique articles. Among these, 32 were excluded based on the abstract alone. The remaining 127 articles included a full-text review, and 105 were excluded for the reasons listed in Figure 1. Consequently, 22 studies (21 cohort studies and one randomized controlled trial) with 186,455 patients were identified using our search criteria.

The routes of CM administration were coronary arteries for coronary angiography or intervention in 14 studies;[3,6–18] periphery arteries other than the coronary artery in two studies;[19,20] veins for enhanced computed tomography in five studies;[21–25] and both periphery arteries and veins in one study.[26] The main characteristics of the study design and participants in the included studies are listed in Table 1.

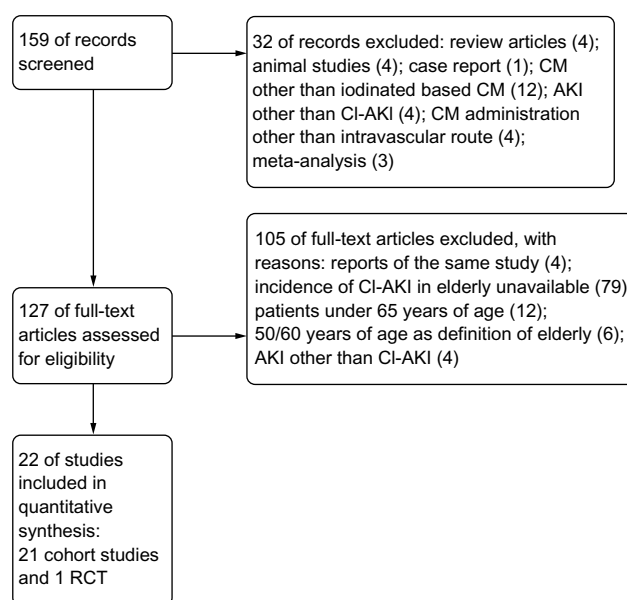Among the included 67,831 participants ≥65 years of age, the overall incidence of CI-AKI was 13.6%

Figure 1 Search flow diagram.
Abbreviations: AKI, acute kidney injury; CI-AKI, contrast-induced acute kidney injury; CM, contrast medium; RCT, randomized controlled trial.

Table I General characteristics of the included studies

Year	Reference	Study location	Recruitment period	Design	Patients (n)	Definition of elderly (years)	Definition of CI-AKI	Patient characteristics
Intravenous								
2007	Cheruvu et al[21]	NY, USA	November 2003 to June 2005	Retrospective	568	≥70	SCr ≥0.5 mg/dL or 25%	Patients undergoing contrast-enhanced CT and receiving iodixanol
2008	Hipp et al[22]	NY, USA	January 2004 to August 2005	Retrospective	235	≥75	SCr ≥0.5 mg/dL or 25%	Trauma patients undergoing contrast-enhanced CT
2011	Matsushima et al[25]	PA and TX, USA	January 2007 to December 2007	Retrospective	1,184	≥65	SCr ≥0.5 mg/dL or 25%	Trauma patients undergoing contrast-enhanced CT
2012	Finigan et al[24]	CA, USA	2010	Retrospective	118	≥65	SCr ≥0.5 mg/dL or 25%	Elderly trauma patients undergoing contrast-enhanced CT
2012	Huang et al[23]	Taiwan	January 2007 to June 2007	Retrospective	594	≥65	SCr ≥0.5 mg/dL	Elderly patients undergoing contrast-enhanced CT in emergency department
IA								
2011	Plaisance et al[20]	MI, USA	January 2001 to December 2008	Prospective	7,764	≥70	SCr ≥0.5 mg/dL	Patients undergoing percutaneous lower extremity peripheral vascular intervention
2012	Zhao et al[19]	Beijing, People's Republic of China	January 2003 to January 2010	Retrospective	81	≥65	SCr ≥0.5 mg/dL or 25%	Elderly patients undergoing percutaneous transluminal renal angioplasty with stent implantation
IV and IA								
2013	Ray et al[26]	TX, USA	July 2010 to June 2011	Retrospective	75	≥75	SCr ≥0.3mg/dL or 50% or oligurine	Patients with subarachnoid hemorrhage undergoing cerebral angiography or contrast-enhanced CT
IC								
1990	Rich and Crecelius[6]	WA, USA	July 1987 to May 1988	Prospective	183	≥70	SCr ≥0.5 mg/dL	Elderly patients undergoing coronary angiography
2004	Mehran et al[3]	NY, USA	NA	Prospective	4,898	≥75	SCr ≥0.5 mg/dL or 25%	Patients undergoing PCI
2004	Marenzi et al[7]	Milan, Italy	January 2001 to June 2003	Prospective	208	≥75	SCr ≥0.5 mg/dL	AMI patients undergoing primary PCI
2006	Toprak et al[8]	Turkey	September 2002 to January 2005	Prospective	219	≥70	SCr ≥25%	Patients with reduced kidney function undergoing nonemergent coronary angiography
2007	Miranda Malpica et al[9]	Mexico	January 1997 to November 2004	Retrospective	73	≥80	SCr ≥0.5 mg/dL or 25%	Elderly patients undergoing PCI
2007	Sosnowski et al[10]	Poland	NA	Retrospective	63	≥80	NA	Elderly AMI patients undergoing PCI
2008	Morikawa et al[12]	Japan	NA	RCT	254	≥70	SCr ≥0.5 mg/dL or 25%	Patients with SCr ≥1.3 mg/dL undergoing coronary angiography received either ANP or Ringer solution alone
2008	Sidhu et al[11]	NY, USA	January 1998 to July 2006	Prospective	13,127	≥65	SCr ≥0.5 mg/dL or 25%	Patients undergoing coronary angiography

(*Continued*)

Table I (Continued)

Year	Reference	Study location	Recruitment period	Design	Patients (n)	Definition of elderly (years)	Definition of CI-AKI	Patient characteristics
2010	Chong et al[13]	Singapore	May 1996 to March 2007	Prospective	3,036	≥70	SCr ≥0.5 mg/dL or 25%	Patients with SCr <1.5 mg/dL undergoing PCI
2011	Thomas et al[14]	MI, USA	2003 to 2008	Prospective	149,347	≥70	SCr ≥0.5 mg/dL	Patients undergoing PCI
2012	Fu et al[15]	Tianjin, People's Republic of China	January 2008 to December 2010	Retrospective	945	≥65	SCr ≥0.5 mg/dL or 25%	Elderly patients undergoing PCI
2012	Maioli et al[16]	Prato, Italy	June 2003 to March 2008	Prospective	1,477	≥75	SCr ≥0.5 mg/dL	Patients undergoing coronary angiography
2012	Murphy et al[17]	Australia	September 2005 to July 2011	Prospective	1,218	≥80	SCr ≥50%	Elderly AMI patients undergoing PCI
2013	Liu et al[18]	Guangdong, People's Republic of China	February 2010 to January 2011	Prospective	788	≥75	SCr ≥0.5 mg/dL	Patients with SCr <1.5 mg/dL undergoing PCI

Abbreviations: AMI, acute myocardial infarction; ANP, atrial natriuretic peptide; CI-AKI, contrast-induced acute kidney injury; CT, computed tomography; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SCr, serum creatinine; IA, intra-arterial; IC, intracoronary; IV, intravenous; NA, not available.

(95% CI 10.1–18.2, I^2=0.496, Figure 2). The incidence of CI-AKI in six prespecified subgroups is listed in Table 2. In 12 studies for which the incidence of CI-AKI in both the elderly and younger groups was reported, the pooled OR of CI-AKI in the elderly was 2.10 (95% CI 1.77–2.48, I^2=0.77, Figure 3A). The risk of CI-AKI in the elderly was consistent across the subsets of the different CM administration routes. In six studies for which adjusted ORs of CI-AKI in the elderly were reported, the pooled OR of CI-AKI in the elderly was 2.55 (95% CI 1.85–3.52, I^2=0.34, Figure 3B).

The metaregression showed that the regression model explained 65.33% of total between-study variance in incidence of CI-AKI. Definition of elderly was associated with and explained a statistically significant degree of variability (P=0.002). The metaregression model is presented in Table 3. The sensitivity analysis suggested that no single study strongly influenced the overall results, because sequentially excluding one individual study at a time did not affect the movement of the point estimate outside the 95% CI (data not shown).

Discussion

In the present study, we report the results of a meta-analysis that pooled the incidence and ORs of CI-AKI in the elderly, categorized into different subsets. To the best of our knowledge, this is the first meta-analysis on this issue.

CI-AKI is an important potential complication following CM-based procedures, including noninvasive enhanced computed tomography or invasive angiography. CI-AKI generally resolves spontaneously in most instances, but patients with CI-AKI tend to experience prolonged hospital stays, increased risk of in-hospital death, and long-term adverse cardiac and renal events.[27–30] Except for continued volume expansion and minimized CM volume, no pharmacologic prophylaxes have been shown to offer benefit in CI-AKI prevention.[31] Iodixanol, a new iso-osmolar CM, is not associated with less CI-AKI when compared with low-osmolar CM.[32,33] Prophylactic hemodialysis as an adjunct to angiography has been shown to be harmful.[34] Therefore, current practice guidelines for CI-AKI management emphasize risk factor assessment and balancing the relative benefits and risks before any CM-based procedure is performed.[31,34,35]

Advanced age has been recognized for years as an important independent risk factor for the development of CI-AKI.[3,6] As the population ages, the number of elderly patients referred for CM-based procedures is increasing steadily.[14,20] On the other hand, limited data regarding the true

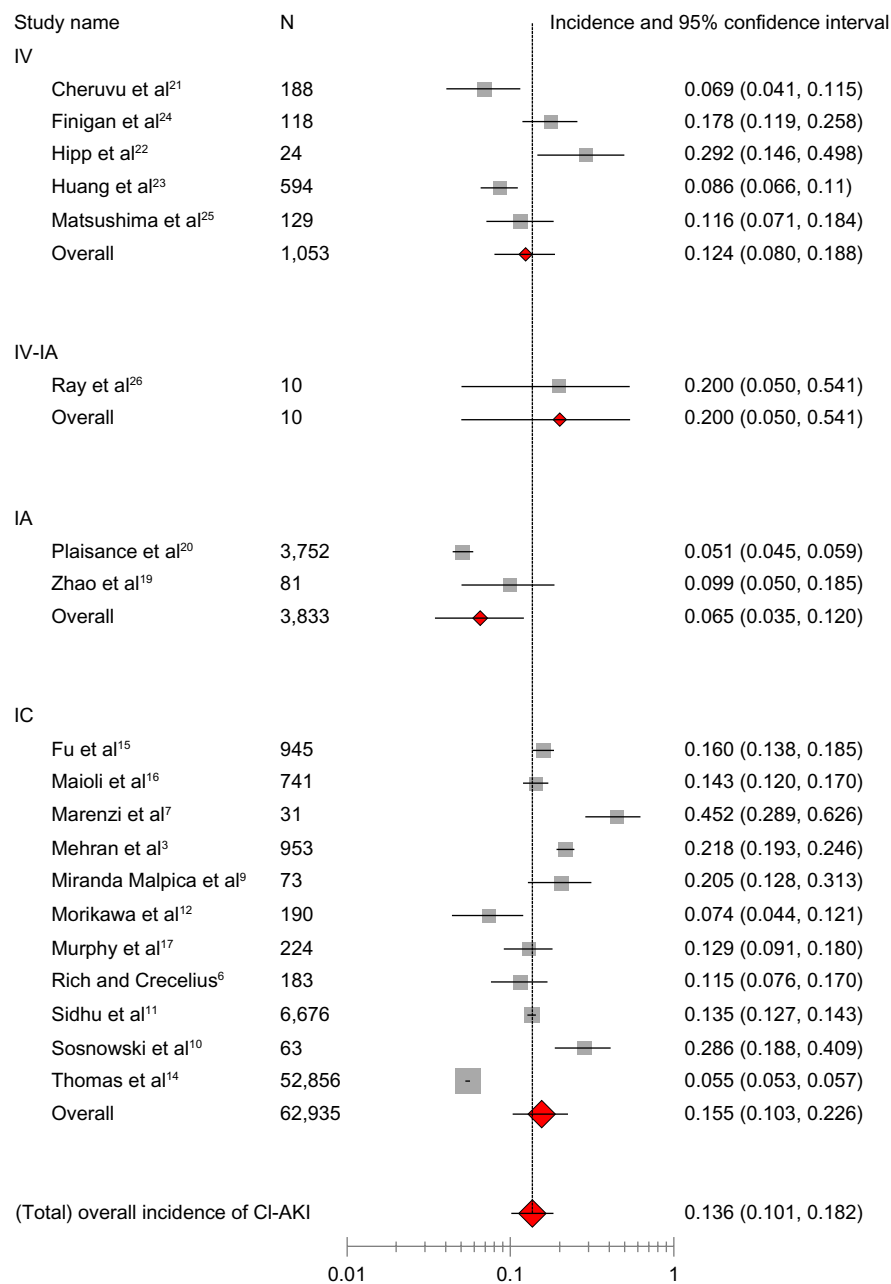| Study name	N	Incidence and 95% confidence interval
IV		
Cheruvu et al[21]	188	0.069 (0.041, 0.115)
Finigan et al[24]	118	0.178 (0.119, 0.258)
Hipp et al[22]	24	0.292 (0.146, 0.498)
Huang et al[23]	594	0.086 (0.066, 0.11)
Matsushima et al[25]	129	0.116 (0.071, 0.184)
Overall	1,053	0.124 (0.080, 0.188)
IV-IA		
Ray et al[26]	10	0.200 (0.050, 0.541)
Overall	10	0.200 (0.050, 0.541)
IA		
Plaisance et al[20]	3,752	0.051 (0.045, 0.059)
Zhao et al[19]	81	0.099 (0.050, 0.185)
Overall	3,833	0.065 (0.035, 0.120)
IC		
Fu et al[15]	945	0.160 (0.138, 0.185)
Maioli et al[16]	741	0.143 (0.120, 0.170)
Marenzi et al[7]	31	0.452 (0.289, 0.626)
Mehran et al[3]	953	0.218 (0.193, 0.246)
Miranda Malpica et al[9]	73	0.205 (0.128, 0.313)
Morikawa et al[12]	190	0.074 (0.044, 0.121)
Murphy et al[17]	224	0.129 (0.091, 0.180)
Rich and Crecelius[6]	183	0.115 (0.076, 0.170)
Sidhu et al[11]	6,676	0.135 (0.127, 0.143)
Sosnowski et al[10]	63	0.286 (0.188, 0.409)
Thomas et al[14]	52,856	0.055 (0.053, 0.057)
Overall	62,935	0.155 (0.103, 0.226)
(Total) overall incidence of CI-AKI		0.136 (0.101, 0.182)

0.01   0.1   1

Figure 2 Overall incidence of CI-AKI in elderly patients (age ≥65 years). Meta-analysis of administration route stratified by pooling the reported incidences of CI-AKI from individual studies.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; IA, intra-arterial; IC, intracoronary; IV, intravenous; n, number of participants.

Table 2 Incidence of CI-AKI in prespecified subgroups

Subgroup	Studies (n)	Patients (n)	Estimated incidence (%)	95% CI	I^2 statistic
Age (years)					
≥75	12	23,007	16.5	11.7–22.7	0.494
≥80	6	20,778	13.5	8.6–20.6	0.495
CM administration routes					
IC	11	62,935	15.5	10.3–22.6	0.498
IA, other than via coronary artery	2	3,833	6.5	3.5–12.0	0.416
IV	5	1,053	12.4	8.0–18.8	0.442
Other than via coronary artery	8	4,896	11	7.1–16.5	0.471

Abbreviations: CI-AKI, contrast-induced acute kidney injury; CI, confidence interval; CM, contrast medium; IA, intra-arterial; IC, intracoronary; IV, intravenous.
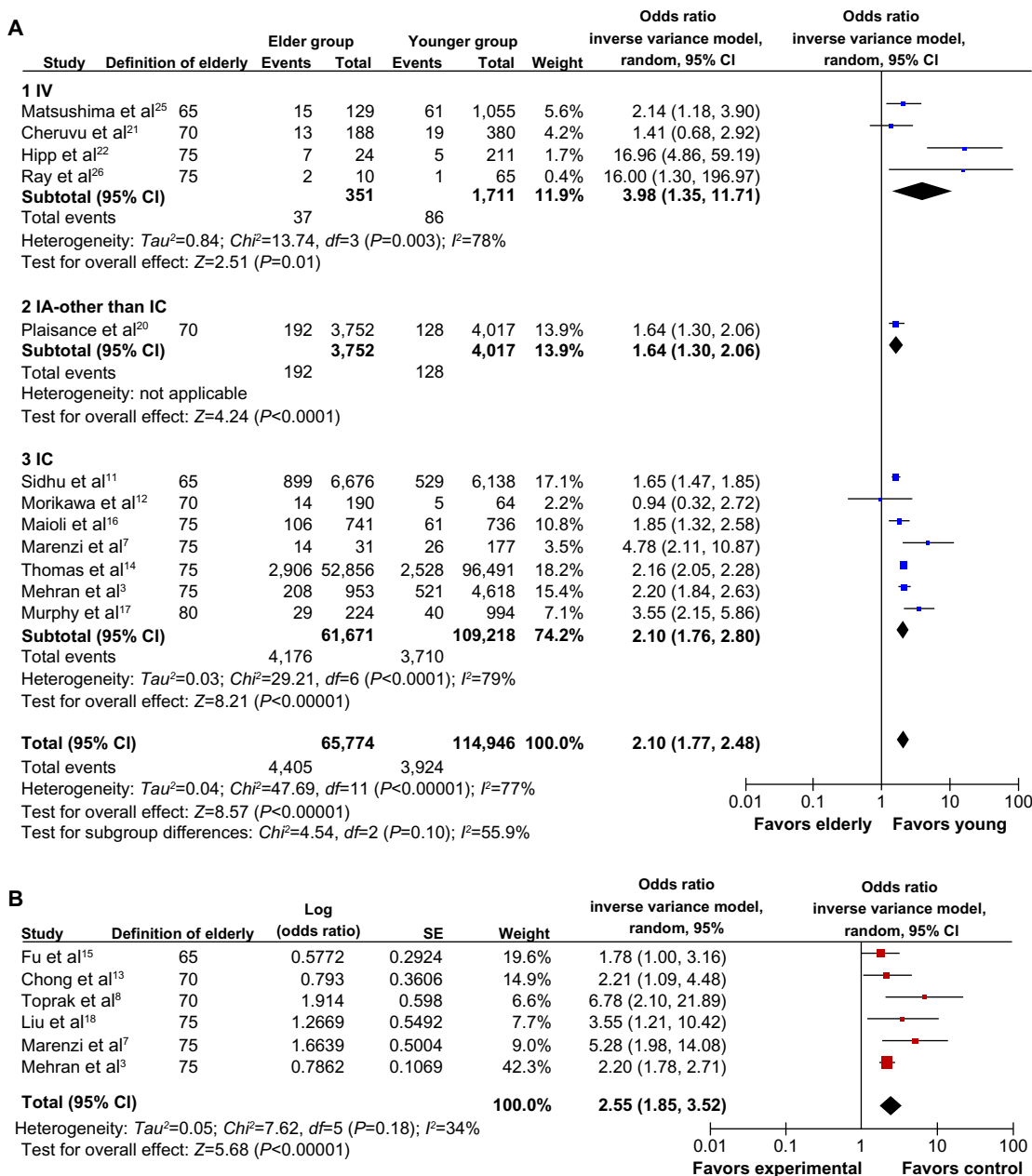
A

Study	Definition of elderly	Elder group Events	Elder group Total	Younger group Events	Younger group Total	Weight	Odds ratio inverse variance model, random, 95% CI
1 IV							
Matsushima et al[25]	65	15	129	61	1,055	5.6%	2.14 (1.18, 3.90)
Cheruvu et al[21]	70	13	188	19	380	4.2%	1.41 (0.68, 2.92)
Hipp et al[22]	75	7	24	5	211	1.7%	16.96 (4.86, 59.19)
Ray et al[26]	75	2	10	1	65	0.4%	16.00 (1.30, 196.97)
Subtotal (95% CI)			**351**		**1,711**	**11.9%**	**3.98 (1.35, 11.71)**
Total events		37		86			

Heterogeneity: Tau^2=0.84; Chi^2=13.74, df=3 (P=0.003); I^2=78%
Test for overall effect: Z=2.51 (P=0.01)

2 IA-other than IC							
Plaisance et al[20]	70	192	3,752	128	4,017	13.9%	1.64 (1.30, 2.06)
Subtotal (95% CI)			**3,752**		**4,017**	**13.9%**	**1.64 (1.30, 2.06)**
Total events		192		128			

Heterogeneity: not applicable
Test for overall effect: Z=4.24 (P<0.0001)

3 IC							
Sidhu et al[11]	65	899	6,676	529	6,138	17.1%	1.65 (1.47, 1.85)
Morikawa et al[12]	70	14	190	5	64	2.2%	0.94 (0.32, 2.72)
Maioli et al[16]	75	106	741	61	736	10.8%	1.85 (1.32, 2.58)
Marenzi et al[7]	75	14	31	26	177	3.5%	4.78 (2.11, 10.87)
Thomas et al[14]	75	2,906	52,856	2,528	96,491	18.2%	2.16 (2.05, 2.28)
Mehran et al[3]	75	208	953	521	4,618	15.4%	2.20 (1.84, 2.63)
Murphy et al[17]	80	29	224	40	994	7.1%	3.55 (2.15, 5.86)
Subtotal (95% CI)			**61,671**		**109,218**	**74.2%**	**2.10 (1.76, 2.80)**
Total events		4,176		3,710			

Heterogeneity: Tau^2=0.03; Chi^2=29.21, df=6 (P<0.0001); I^2=79%
Test for overall effect: Z=8.21 (P<0.00001)

Total (95% CI)			**65,774**		**114,946**	**100.0%**	**2.10 (1.77, 2.48)**
Total events		4,405		3,924			

Heterogeneity: Tau^2=0.04; Chi^2=47.69, df=11 (P<0.00001); I^2=77%
Test for overall effect: Z=8.57 (P<0.00001)
Test for subgroup differences: Chi^2=4.54, df=2 (P=0.10); I^2=55.9%

Odds ratio inverse variance model, random, 95% CI
0.01 0.1 1 10 100
Favors elderly   Favors young

B

Study	Definition of elderly	Log (odds ratio)	SE	Weight	Odds ratio inverse variance model, random, 95% CI
Fu et al[15]	65	0.5772	0.2924	19.6%	1.78 (1.00, 3.16)
Chong et al[13]	70	0.793	0.3606	14.9%	2.21 (1.09, 4.48)
Toprak et al[8]	70	1.914	0.598	6.6%	6.78 (2.10, 21.89)
Liu et al[18]	75	1.2669	0.5492	7.7%	3.55 (1.21, 10.42)
Marenzi et al[7]	75	1.6639	0.5004	9.0%	5.28 (1.98, 14.08)
Mehran et al[3]	75	0.7862	0.1069	42.3%	2.20 (1.78, 2.71)
Total (95% CI)				**100.0%**	**2.55 (1.85, 3.52)**

Heterogeneity: Tau^2=0.05; Chi^2=7.62, df=5 (P=0.18); I^2=34%
Test for overall effect: Z=5.68 (P<0.00001)

Odds ratio inverse variance model, random, 95% CI
0.01 0.1 1 10 100
Favors experimental   Favors control

Figure 3 Odds ratios of CI-AKI in the elderly. (**A**) Meta-analysis of administration route stratified by pooling the calculated odds ratios based on the incidence of CI-AKI in the elderly and younger groups. (**B**) Meta-analysis by pooling the reported adjusted odds ratios from individual studies.
Abbreviations: AKI, acute kidney injury; CI-AKI, contrast-induced acute kidney injury; CM, contrast medium; RCT, randomized controlled trial; Chi, Chi-square test; CI, confidence interval; df, degrees of freedom; IA, intra-arterial; IC, intracoronary; IV, intravenous; SD, standard deviation; SE, standard error.

Table 3 Metaregression model in incidence of CI-AKI

Covariates	B^a (95% CI)	P-values	Adjusted R^{2,b}
Definition of elderly	0.107 (0.047–0.168)	0.002	65.33%
Definition of CI-AKI	−0.042 (−0.096–0.011)	0.109	
Route of CM administration	−0.006 (−0.070–0.058)	0.844	

Notes: ^{a}Coefficient of covariation; ^{b}reflects proportion of variability in between-study variance explained by the metaregression model.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; CI, confidence interval; CM, contrast medium.

incidence and risk of developing CI-AKI in the elderly affect decision-making. Based on our meta-analysis, we found that: the risk of developing CI-AKI in the elderly is over two times higher than in younger patients, even after adjustment for other risk factors; the estimated overall incidence of CI-AKI following intravascular CM administration is 13.6% in the elderly, which is higher than the previously reported incidence in an unselected population;[2] and the trend of a high incidence of CI-AKI in the elderly is consistent across different administration route subgroups. Thus, advanced age

should be given serious consideration when referring elderly patients for any CM-based procedure.

Limitations

First, the prevalence of other known risk factors of CI-AKI, such as chronic kidney disease, diabetes, dehydration, and concurrent nephrotoxic medication is high in the elderly. These comorbidities might also play important roles in the development of CI-AKI in the elderly.[36] A metaregression with these risk factors as covariates would investigate the extent of these comorbidities contributing to the onset of CI-AKI in the elderly. However, due to incomplete information of these factors from the original studies, we could not add these factors into our regression model. On the other hand, we had pooled the ORs adjusted by risk factors in our meta-analysis, which might help us to evaluate the sole role of advanced age in the development of CI-AKI. Second, definitions of elderly and CI-AKI varied among the included studies, which brought heterogeneity into our meta-analysis. Metaregression indicated that different definitions of elderly could partially explain the heterogeneity. The age-stratified subgroup analysis we performed would be helpful to reduce the heterogeneity. Although definition of CI-AKI was not shown to be associated with a significant degree of variability by metaregression, the incidence of CI-AKI could have been underestimated in studies using only the absolute increase in serum creatinine as the definition of CI-AKI. Meanwhile, the recently published KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommended the definition of CI-AKI should be based on both urinary output and changes in serum creatinine, and the severity of CI-AKI should be graded the same as the definition of acute kidney injury.[34] This criteria was not used in our meta-analysis because the vast majority of clinical trials on CI-AKI used the definition based on serum creatinine alone and without grading. Third, we used just PubMed as a search engine. Although we identified 186,455 patients from 22 studies for the present study, using other search engines might yield more information on the incidence and risk of developing CI-AKI following intravascular contrast administration in elderly patients. Finally, no data regarding the impact of CI-AKI on a patient's clinical course and prognosis, and no conclusive management strategy for the elderly are available. Further studies are needed to address these issues.

Conclusion

Elderly patients are at greater risk for the development of CI-AKI. The overall incidence of CI-AKI in patients ≥65 years of age is up to 13.6%.

Acknowledgments

Author contributions

WS and BH developed the study protocol; WS and TZ performed the literature search; WS, TZ, and JP analyzed the data; WS, LS, and BH interpreted data and prepared the manuscript; and WS, TZ, JP, LS and BH revised the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material
Search strategy in MEDLINE (from 1966 to June 2013)

For the theme of "CI-AKI": "contrast induced nephropathy" [All Fields] OR "contrast associated nephropathy" [All Fields] OR "radiocontrast induced nephropathy" [All Fields] OR "contrast nephropathy" [All Fields] OR "contrast nephrotoxicity" [All Fields] OR "contrast induced nephrotoxicity" [All Fields] OR "contrast associated nephrotoxicity" [All Fields] OR "contrast induced acute renal failure" [All Fields] OR "contrast induced acute kidney injury" [All Fields].

For the theme of "Elderly": "Aged" [Majr] OR "Aged, 80 and over" [MESH] OR "Frail Elderly" [MESH] OR "aged" [Title/Abstract] OR "age group" [Title/Abstract] OR "age groups" [Title/Abstract] OR "elderly" [Title/Abstract] OR "elder population" [Title/Abstract] OR "geriatric" [Title/Abstract] OR "senior" [Title/Abstract] OR "seniors" [Title/Abstract] OR "old persons" [Title/Abstract] OR "older adult" [Title/Abstract] OR "older adults" [Title/Abstract] OR "older patient" [Title/Abstract] OR "older patients" [Title/Abstract] OR "65 years" [All Fields] OR "75 years" [All Fields] OR "80 years" [All Fields].

For the theme of "clinical study": (randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab]) OR "Clinical Trial" [Publication Type] OR "Comparative Study" [Publication Type] OR "Clinical Trials as Topic" [MESH] OR "Epidemiologic Studies" [MESH] OR "Registries" [MESH] OR longitud*[tiab] OR prospectiv*[tiab] OR retrospectiv*[tiab] OR observation*[tiab] OR cohort*[tiab] OR registry[tiab] OR "clinical trial" [tiab] OR "case control" [tiab] OR "cross section" [tiab]) NOT (animals[mh] NOT humans[mh]).

Three comprehensive search themes were combined by the Boolean operator "AND."