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, I²=0.496). The pooled odds ratio of CI-AKI in the elderly was 2.55 (95% CI 1.85–3.52, I²=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. Advanced age has been identified as an important risk factor for CI-AKI. 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 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 “radiocontrast 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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analyzed by the
of CI-AKI in the two groups and the reported adjusted ORs
random-effect model using Review Manager software
sus younger patients were estimated according to the inverse-
coronary artery. Pooled ORs of CI-AKI in elderly patients ver
administration other than via the coronary artery, intravenous
administered, including patients aged 65 years or 75 years,
incidence of CI-AKI in elderly unavailable (79); patients under 65 years of age (12);
other than CI-AKI (4); CM administration other than intravascular route (4); meta-analysis (3)
then 0.5 mg/dL, or others), and route of CM adminis-
(18); periphery arteries other than the coronary artery in two
veseasts for enhanced computed tomography in
results included in Figure 1. Consequently, 22 studies (21 cohort
study (1); CM other than iodinated based CM (12); AKI other than CI-AKI (4); CM administra-
tion route other than via the coronary artery, intra-arterial CM were used as covariates in the regression model. Sensitivity analysis was performed by sequentially excluding a single study. P-values less than
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;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%
Table 1 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                                                                 |
|------|--------------------|----------------------|----------------------------------------|--------------|--------------|------------------------------|---------------------|----------------------------------------------------------------------------------------|
| 2007 | Cheruvu et al²¹     | NY, USA              | November 2003 to June 2005             | Retrospective| 568          | ≥70                          | SCr ≥0.5 mg/dL or 25%                      | Patients undergoing contrast-enhanced CT and receiving ioxanol                       |
| 2008 | Hipp et al²²        | 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 al²³  | 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 al²⁴     | CA, USA              | 2010                                  | Retrospective| 118          | ≥65                          | SCr ≥0.5 mg/dL or 25%                      | Elderly trauma patients undergoing contrast-enhanced CT                            |
| 2008 | Huang et al²³       | Taiwan               | January 2007 to June 2007             | Retrospective| 594          | ≥65                          | SCr ≥0.5 mg/dL                            | Elderly patients undergoing contrast-enhanced CT in emergency department            |
| 2011 | Plaisance et al²⁰   | 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 al¹⁹        | 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 |
| 2013 | Ray et al²⁶         | TX, USA              | July 2010 to June 2011               | Retrospective| 75           | ≥75                          | SCr ≥0.3 mg/dL or 50% or oligurine        | Patients with subarachnoid hemorrhage undergoing cerebral angiography or contrast-enhanced CT |
| 1990 | Rich and Crecelius² | WA, USA              | July 1987 to May 1988                 | Prospective  | 183          | ≥70                          | SCr ≥0.5 mg/dL                            | Elderly patients undergoing coronary angiography                                  |
| 2004 | Mehran et al²¹      | NY, USA              | NA                                    | Prospective  | 4,898        | ≥75                          | SCr ≥0.5 mg/dL or 25%                      | Patients undergoing PCI                                                            |
| 2004 | Marenzi et al²⁷     | Milan, Italy         | January 2001 to June 2003             | Prospective  | 208          | ≥75                          | SCr ≥0.5 mg/dL                            | AMI patients undergoing primary PCI                                                |
| 2006 | Toprak et al²⁸      | Turkey               | September 2002 to January 2005        | Prospective  | 219          | ≥70                          | SCr ≥0.25%                                | Patients with reduced kidney function undergoing nonemergent coronary angiography  |
| 2007 | Miranda et al²⁹     | Mexico               | January 1997 to November 2004         | Retrospective| 73           | ≥80                          | SCr ≥0.5 mg/dL or 25%                      | Elderly patients undergoing PCI                                                   |
| 2007 | Sosnowski et al³⁰   | Poland               | NA                                    | Retrospective| 63           | ≥80                          | NA                                        | Elderly AMI patients undergoing PCI                                                |
| 2008 | Morikawa et al²¹    | 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 al¹¹       | NY, USA              | January 1998 to July 2006             | Prospective  | 13,127       | ≥65                          | SCr ≥0.5 mg/dL or 25%                      | Patients undergoing coronary angiography                                           |

(Continued)
(95% CI 10.1–18.2, $F=0.496$, 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, $F=0.77$, 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, $F=0.34$, 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.34,20 On the other hand, limited data regarding the true
Contrast-induced acute kidney injury in elderly

Table 2 Incidence of CI-AKI in prespecified subgroups

| Subgroup                                           | Studies (n) | Patients (n) | Estimated incidence (%) | 95% CI       | P 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.
### Table 3: Metaregression model in incidence of CI-AKI

| Covariates                  | B* (95% CI) | P-values | Adjusted R²a |
|-----------------------------|-------------|----------|--------------|
| 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: *Coefficient of covariation; †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; 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. 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. 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%.

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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” [Major] 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 longitudinal[tiab] OR prospective[tiab] OR retrospective[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.”