Risk of Acute Kidney Injury After Intravenous Contrast Media Administration

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Study objective: The study objective was to determine whether intravenous contrast administration for computed tomography (CT) is independently associated with increased risk for acute kidney injury and adverse clinical outcomes.

Methods: This single-center retrospective cohort analysis was performed in a large, urban, academic emergency department with an average census of 62,179 visits per year; 17,934 ED visits for patients who underwent contrast-enhanced, unenhanced, or no CT during a 5-year period (2009 to 2014) were included. The intervention was CT scan with or without intravenous contrast administration. The primary outcome was incidence of acute kidney injury. Secondary outcomes included new chronic kidney disease, dialysis, and renal transplantation at 6 months. Logistic regression modeling and between-groups odds ratios with and without propensity-score matching were used to test for an independent association between contrast administration and primary and secondary outcomes. Treatment decisions, including administration of contrast and intravenous fluids, were examined.

Results: Rates of acute kidney injury were similar among all groups. Contrast administration was not associated with increased incidence of acute kidney injury (contrast-induced nephropathy criteria odds ratio=0.96, 95% confidence interval 0.85 to 1.08; and Acute Kidney Injury Network/Kidney Disease Improving Global Outcomes criteria odds ratio=1.00, 95% confidence interval 0.87 to 1.16). This was true in all subgroup analyses regardless of baseline renal function and whether comparisons were made directly or after propensity matching. Contrast administration was not associated with increased incidence of chronic kidney disease, dialysis, or renal transplant at 6 months. Clinicians were less likely to prescribe contrast to patients with decreased renal function and more likely to prescribe intravenous fluids if contrast was administered.

Conclusion: In the largest well-controlled study of acute kidney injury following contrast administration in the ED to date, intravenous contrast was not associated with an increased frequency of acute kidney injury. [Ann Emerg Med. 2016;■:1-10.]

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INTRODUCTION

Background

Intravenous iodinated contrast media are routinely used to improve the diagnostic accuracy of computed tomography (CT). Although more than 80 million doses of intravenous contrast media are administered annually,[1] clinical decisionmaking in regard to their use is complicated by concerns related to their potential for precipitating renal dysfunction.[2-6] Indeed, contrast media administration is cited as the third most common cause of iatrogenic acute kidney injury[6,7] and has been linked to increased risk of major adverse events, including initiation of dialysis, renal failure, stroke, myocardial infarction, and death.[3,8,9] Recent studies performed in the emergency department (ED), where intravenous administration of contrast media for enhancement of CT imaging is often necessary to diagnose acute critical conditions, have reported an incidence of contrast-induced nephropathy as high as 14% and linked contrast-induced nephropathy to a 2-fold increased risk of major adverse events within 1 year.[3,10-12] Although these reports are concerning, the causal relationship between administration of intravenous contrast media and the development of acute kidney injury has recently been challenged.[13-19]

Importance

Current understanding of contrast-induced nephropathy is complicated by studies that predate widespread use of low- and iso-osmolar contrast media and extrapolation of findings from arterial angiographic studies to the use of

Editor's Capsule Summary

What is already known on this topic

Many providers defer intravenous contrast enhancement with computed tomography (CT) because of concerns about acute kidney injury.

What question this study addressed

How often does acute kidney injury occur after enhanced and nonenhanced emergency department (ED) CT?

What this study adds to our knowledge

Using a propensity-matched case-control design at one site, the frequency of later acute kidney injury in 7,201 patients undergoing contrast-enhanced CT, 5,499 undergoing unenhanced CT, and 5,234 with no imaging did not differ (10.2% to 10.9%).

How this is relevant to clinical practice

This study suggests fear of triggering acute kidney injury after intravenous contrast during ED CT is disproportionate to objective data. A randomized trial is needed to confirm this finding.

intravenous contrast media. Additionally, the majority of studies examining acute kidney injury after contrast media administration, including those performed in ED patients,[3,10-12] were performed without control populations that did not receive contrast media. Indeed, serum creatinine level fluctuations meeting criteria for contrast-induced nephropathy occur in patients undergoing unenhanced CT at rates similar to those published after contrast-enhanced CT,[13] and systematic reviews and meta-analyses of the few existing studies analyzing intravenous contrast media administration with adequate controls found no increased risk of acute kidney injury associated with contrast media.[14,16]

Historically, randomized controlled trials designed to elucidate the true incidence of contrast-induced nephropathy have been perceived as unethical because of the presumption that contrast media administration is a direct cause of acute kidney injury. To date, all controlled studies of contrast-induced nephropathy have been observational, and conclusions from these studies are severely limited by selection bias associated with the clinical decision to administer contrast media. Two research groups have recently used propensity-score analysis to control for this bias, approximating randomization by matching nonrandomized populations from large single-center databases according to their probability of treatment assignment.[18,20] These investigators, however, reached opposite conclusions. McDonald et al[15,17,18] found no increased risk of acute kidney injury, emergency dialysis, or mortality after contrast media administration in any patient group regardless of baseline renal function, whereas Davenport et al[21] reported an increased risk of acute kidney injury after contrast media administration in patients with preexisting renal dysfunction. Potential explanations for these discrepant results include different strategies for propensity matching, variances in institutional contrast-enhanced CT protocols, and widely discordant subgroup sample sizes, especially at the lowest baseline renal function.

Goals of This Investigation

In this study, we sought to clarify the incidence of acute kidney injury attributable to intravenous contrast media administration by testing the hypothesis that such injury occurs at higher rates in patients undergoing contrast-enhanced CT than in those not receiving contrast media. To minimize biases associated with comparison of nonrandomized populations, we used 2 distinct control populations that did not receive contrast media, used propensity-score analysis to minimize bias associated with treatment assignment, and analyzed large numbers of patients in all subgroups of baseline renal function. We also examined selected clinician practice patterns that may affect the incidence of acute kidney injury after contrast media administration.

MATERIALS AND METHODS

Study Design and Setting

This was a single-center retrospective cohort study conducted in a large urban academic ED. During the study period, our mean annual ED census was 62,179 total visits (range 55,955 to 69,249), with a mean annual admission rate of 23.4% (range 22.2% to 25.1%). This study was approved by our university institutional review board.

An experienced data user (E.Y.K.) extracted all clinical information from a relational database that underlies the electronic medical record of our ED. Queries using structured query language were performed separately for patients who did and did not undergo CT. For patients who underwent CT, data were extracted for all encounters that had both an order and result interpretation for at least one CT scan during the study period. Two authors (J.S.H. and M.R.E.) not involved in data extraction classified CT studies as enhanced or unenhanced based on specific and standardized order and result interpretation identifiers. When order and result interpretation identifiers differed

(which occurred in cases in which the radiology team, in consultation with the ordering ED clinician, performed a study that differed from the original order), result interpretation identifiers were used. Any discrepancies were resolved through consensus. For patients who did not undergo CT, data were extracted for all encounters that lacked an order or result for a CT study. All data relating to vital signs, medication administration, and preexisting diagnoses entered in the ED, as well as laboratory results and new procedure or diagnostic codes entered from any point in our hospital system, were extracted with the same structured query language for every patient. Medical diagnoses and procedures were identified with *International Classification of Diseases, Ninth Edition, Clinical Modification* (*ICD-9-CM*) diagnostic and procedure codes.

Selection of Participants

Patients aged 18 years and older who received a CT with or without contrast enhancement in the ED between January 1, 2009, and June 30, 2014, and had both an initial serum creatinine level measured in the 8 hours before CT and a second level measured 48 to 72 hours after CT were included. To minimize bias associated with the decision to obtain imaging, we included a second control group of contrast media-unexposed ED patients aged 18 years and older and treated during the study period who did not undergo CT imaging, and had both an initial serum creatinine level measured in the ED and a second level measured 48 to 72 hours later. Exclusion criteria included initial serum creatinine level less than 0.4 mg/dL (to minimize inclusion of random laboratory error as cases of acute kidney injury) or equal to or greater than 4.0 mg/dL (already meeting partial criteria for severe acute kidney injury), insufficient serum creatinine level data, a history of renal transplant or ongoing or previous dialysis, an ED visit in the 6 months before the study start date, a CT scan performed in the 6 months preceding the index ED visit, and contrast-enhanced CT performed within 72 hours of ED departure. We chose the antecedent 6-month window to minimize potential confounding residual effects of previously administered contrast media and the subsequent 72-hour window to minimize potential group crossover of patients undergoing CT scan after ED departure within the period defined by contrast-induced nephropathy criteria. CT scans were classified as contrast enhanced or unenhanced. Consecutive CT acquisitions at different anatomic locations were treated as a single-scan event, and those performed with and without contrast media were treated as a single contrast-enhanced CT. All eligible patients during a 5-year period were included, resulting in a sample size powered to detect a difference in incidence of acute kidney injury between populations as low as 1.5%.

The primary variable of interest was administration of intravenous contrast media. Control variables included age, sex, race, initial serum creatinine level, initial estimated glomerular filtration rate,[20] and chronic comorbidities and acute illness severity indicators previously shown to predispose to the development of contrast-associated acute kidney injury.[22-24] Chronic comorbidities included diabetes mellitus, hypertension, HIV/AIDS, congestive heart failure, chronic kidney disease, and history of renal transplantation (all identified by *ICD-9-CM* codes[25]). Acute illness severity indicators included hypotension (systolic blood pressure <80 mm Hg), designation by an ED attending physician as a patient requiring critical care, anemia (hematocrit level <39% or <36% for men and women, respectively), and hypoalbuminemia (<3.5 g/dL) during the index ED visit. Additional control variables included ED administration of nephrotoxic or nephroprotective medications (see Figure E1, available online at http://www.annemergmed.com, for full list)[26] and ED administration of intravenous crystalloid fluids in any amount.

All contrast media administration was performed according to institutional protocols, available online at http://www.ctisus.com/protocols. Patients who underwent contrast-enhanced CT were administered either iohexol or iodixanol intravenously, as dictated by radiologic study-specific protocol, and volumes of administration ranged from 80 to 120 mL. According to institutional policy, patients provided consent before administration of intravenous contrast, and for patients with serum creatinine level greater than 1.7 mg/dL, treating clinicians cosigned consent for contrast-enhanced CT.

Outcome Measures

The primary outcome variable was incidence of acute kidney injury. The clinical definition of acute kidney injury has undergone multiple revisions, with published studies of contrast-induced nephropathy using varied equations to calculate its incidence. We estimated the incidence of acute kidney injury for all study participants by using both the most frequently published criteria for contrast-induced nephropathy (absolute increase in serum creatinine level ≥0.5 mg/dL or ≥25% increase over baseline serum creatinine level at 48 to 72 hours after imaging or, for non-CT patients, after initial serum creatinine level measurement)[27] and for acute kidney injury as defined by the Acute Kidney Injury Network/Kidney Disease

Improving Global Outcomes guidelines.[28,29] By Acute Kidney Injury Network/Kidney Disease Improving Global Outcomes creatinine-based criteria, acute kidney injury is staged (stage 1: absolute increase in serum creatinine level $\geq$0.3 mg/dL or a 1.5- to 1.9-fold increase over baseline serum creatinine level; stage 2: 2.0- to 2.9-fold increase over baseline serum creatinine level; stage 3: 3-fold increase over baseline serum creatinine level, increase to serum creatinine level $\geq$4.0 mg/dL, or initiation of dialysis). We classified any patient meeting Acute Kidney Injury Network/Kidney Disease Improving Global Outcomes stage 1 criteria as having acute kidney injury and performed subanalyses to compare patients meeting criteria for stages 2 and 3. Patient-centered outcomes were assessed, including newly diagnosed chronic kidney disease, initiation of dialysis, and renal transplantation (each assessed by *ICD-9-CM* or procedure code documentation in our institutional electronic medical record) within 6 months of the index ED visit.

Primary Data Analysis

Dichotomous variables are displayed as percentages, categorical data as relative frequencies (in percentages), and continuous data as medians with interquartile ranges. A multivariable logistic regression model was used to ascertain how contrast media administration was associated with the risk of acute kidney injury in the entire study population after controlling for demographic variables and medical conditions previously reported to increase risk for developing such injury.[23,24] Incidence of acute kidney injury was calculated as the percentage of visits with occurrence of acute kidney injury.

The association between contrast media and acute kidney injury was first assessed with the test of proportions to compare incidence of acute kidney injury in patients who underwent contrast-enhanced CT with those who underwent unenhanced CT and with all patients who did not receive contrast media. To reduce potential selection bias inherent to administration of contrast media, we also used propensity-score matching to estimate the effect of contrast media on acute kidney injury. The clinical decision to administer contrast media is guided by patient pathology and conditional patient-related factors that might contraindicate contrast media administration. The conditional patient factors included in the estimation of the propensity scores were sex, age, race, initial serum creatinine level or estimated glomerular filtration rate, crystalloid fluid administration, nephrotoxic medication administration, chronic comorbidities (as noted above), and whether the patient was designated as requiring critical care. Propensity-score matching was performed with default parameters (nearest neighbor of one, no caliper restriction, and sampling with replacement), and the average treatment effect was calculated. All comparisons were made for the entire study population and for subgroups stratified by initial serum creatinine level and estimated glomerular filtration rate. Matching for propensity score was performed by group for subgroup analyses. Results are presented as odds ratios (ORs). All analysis, including propensity-score matching, was conducted in Stata (version 14.1; StataCorp, College Station, TX).

RESULTS

During the study period, there were 82,729 patient visits in which a CT was performed among 54,740 unique patients. Of these, 12,700 patient visits by 11,567 patients met all inclusion and no exclusion criteria. Of all CT scans, 56.7% were contrast enhanced. There were 272,961 patient visits during the study period wherein patients did not undergo CT. Of these, 5,234 met all inclusion and no exclusion criteria. Thus, a total of 17,934 patient visits from 16,801 unique patients were included in the final analysis (Figure 1).

All 3 patient groups analyzed (contrast-enhanced CT, unenhanced CT, and non-CT) were demographically similar, although the unenhanced CT group was slightly older (Table 1). Patients in the contrast-enhanced CT group were less likely to have diabetes, congestive heart failure, or chronic kidney disease. Initial serum creatinine values were similar across groups, although the contrast-enhanced CT group had a higher estimated glomerular filtration rate.

Multivariable logistic regression modeling of the entire study population, with inclusion of predictor variables previously reported to affect the incidence of acute kidney injury, revealed no independent effect of contrast media on the probability of developing acute kidney injury (Table 2 and Table E1, available online at http://www.annemergmed.com). Factors associated most strongly with an increased probability of acute kidney injury were increased age, administration of nephrotoxic medication(s), preexisting diagnosis of congestive heart failure or chronic kidney disease, and hypoalbuminemia. Administration of intravenous crystalloids was associated with a lower probability of developing acute kidney injury. When modeling was performed with initial estimated glomerular filtration rate as a predictor variable, the effect of race on acute kidney injury differed by criteria: black ethnicity was associated with higher probability of acute kidney injury by

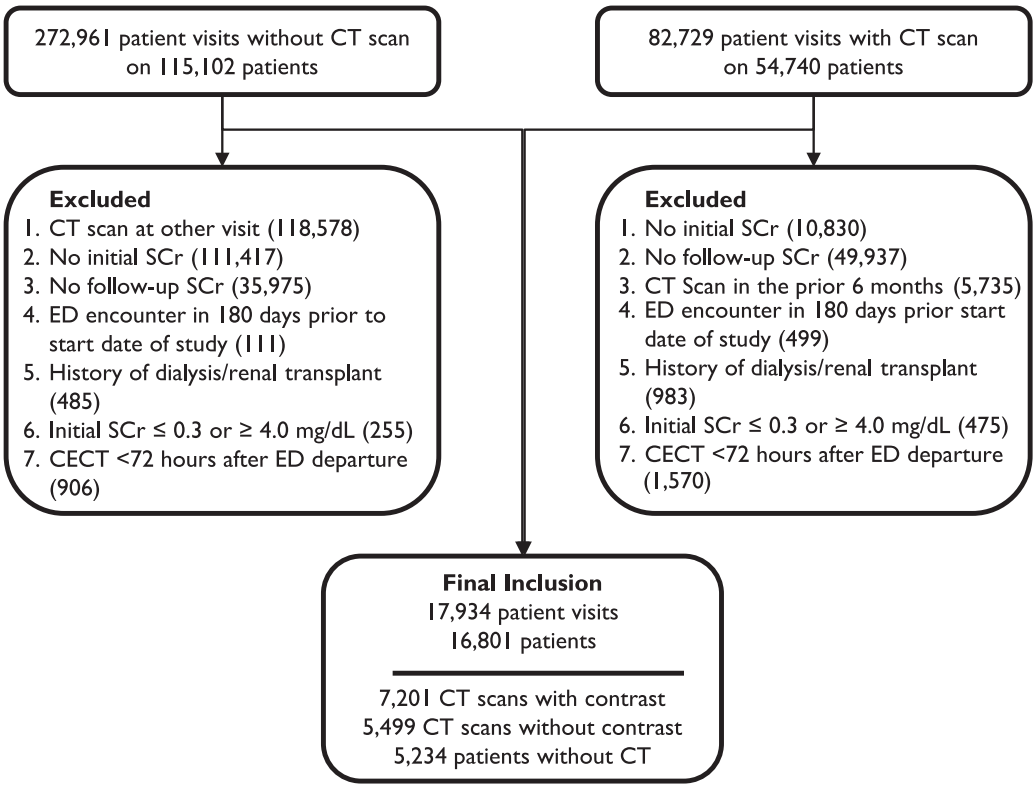

Figure 1. Study inclusion flowchart. *SCr*, Serum creatinine; *CECT*, contrast-enhanced CT.

Acute Kidney Injury Network criteria and a lower probability by traditional contrast-induced nephropathy criteria (Table 2). When initial estimated glomerular filtration rate was replaced by initial serum creatinine level in the model, black ethnicity was associated with higher probability of acute kidney injury under both criteria (Table E1, available online at http://www.annemergmed.com). Similarly, female sex was associated with a higher probability of developing acute kidney injury by all criteria when modeling was performed with initial estimated glomerular filtration rate (Table 2), but that effect was not demonstrated when initial serum creatinine level was used (Table E1, available online at http://www.annemergmed.com).

Using the Acute Kidney Injury Network/Kidney Disease Improving Global Outcomes criteria, the probability of developing acute kidney injury was 6.8%, 8.9%, and 8.1% in the contrast-enhanced CT, unenhanced CT, and non-CT groups, respectively. Contrast media administration was associated with a decreased risk of developing acute kidney injury when directly compared to all patients who did not receive contrast media (OR=0.78; 95% confidence interval [CI] 0.70 to 0.88) and patients who underwent unenhanced CT (OR=0.75; 95% CI 0.66 to 0.85), but this effect was not observed after propensity-score-matching adjustment (OR=1.00, 95% CI 0.99 to 1.01, and OR=1.00, 95% CI 0.99 to 1.01, respectively), and a significant difference was not observed in any subgroup (Table 3 and Table E2, available online at http://www.annemergmed.com). The majority (86.3%) of cases of acute kidney injury were stage 1; the remainder were stage 2 (7.6%) and stage 3 (6.0%). The ORs for developing stage 2 or 3 acute kidney injury after contrast media administration were similar to those for developing acute kidney injury in general.

Under the traditional definition of contrast-induced nephropathy, the probability of developing acute kidney injury was 10.6%, 10.2%, and 10.9% in the contrast-enhanced CT, unenhanced CT, and non-CT groups, respectively. Contrast-enhanced CT patients were no more likely to develop acute kidney injury than all patients who did not receive contrast media (OR=1.01; 95% CI 0.92 to 1.12) or than patients who underwent unenhanced CT (OR=1.05; 95% CI 0.94 to 1.18). These results were consistent even when bias was accounted for in contrast media administration, using propensity-score matching (OR=0.99, 95% CI 0.98 to 1.00, and OR=1.00, 95% CI 0.98 to 1.01, respectively). Analysis of subgroups stratified by initial estimated glomerular filtration rate and serum creatinine level also

Table 1. Patient demographics and clinical characteristics.

Characteristics	Contrast-Enhanced CT	Unenhanced CT	Non-CT
Number of patient visits (%)	7,201 (40.2)	5,499 (30.7)	5,234 (29.2)
Age, y	53 (40–65)	60 (48–73)	55 (41–68)
Women (%)	3,535 (49.1)	2,727 (49.6)	2,637 (50.4)
Race (%)			
Black	3,747 (52.0)	2,951 (53.7)	2,367 (45.2)
White	2,851 (39.6)	2,206 (40.1)	2,415 (46.1)
Other	603 (8.4)	342 (6.2)	452 (8.6)
Initial SCr value (IQR), mg/dL	0.9 (0.7–1.1)	1.0 (0.8–1.6)	1.0 (0.7–1.3)
eGFR (IQR), mL/min per 1.73 m^2	95 (74–114)	77 (44–102)	84 (55–108)
Acute illness severity indicators (%)			
ED critical care designation	763 (10.6)	651 (11.8)	170 (3.2)
Hospital admission	6,749 (93.7)	5,159 (93.8)	4,882 (93.3)
Hypotension*	270 (3.7)	249 (4.5)	196 (3.7)
Anemia*	3,457 (48.0)	2,819 (51.3)	2,658 (50.8)
Hypoalbuminemia*	1,387 (19.3)	1,010 (18.4)	978 (18.7)
Medications administered (%)			
Nephrotoxic†	1,072 (14.9)	596 (10.8)	2,097 (40.1)
Nephroprotective‡	56 (0.8)	17 (0.3)	78 (1.5)
Crystalloid fluids	1,748 (24.3)	783 (14.2)	2,530 (48.3)
Comorbidities (%)§			
Diabetes mellitus	1,373 (19.1)	1,461 (26.6)	1,183 (22.6)
Hypertension	3,050 (42.4)	2,881 (52.4)	2,073 (39.6)
Congestive heart failure	918 (12.7)	979 (17.8)	928 (17.7)
HIV/AIDS	303 (4.2)	331 (6.0)	130 (2.5)
Chronic kidney disease	445 (6.2)	1,112 (20.2)	735 (14.0)

IQR, Interquartile range; *eGFR*, estimated glomerular filtration rate.

*Based on vital signs and laboratory analyses from the index ED visit. Anemia: hematocrit level <39% or <36% for men and women, respectively; hypoalbuminemia (<3.5 g/dL); hypotension (systolic blood pressure <80 mm Hg).

†Medications from the following classes: angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, antimicrobial, loop and thiazide diuretic, nonsteroidal anti-inflammatory, and other (see Figure E1, available online at http://www.annemergmed.com, for more details).

‡Medications from the following classes: acetylcysteine, sodium bicarbonate, and statins.

§Based on *ICD-9-CM* diagnostic codes from index ED visit or previous hospitalizations.

failed to reveal any significant differences in risk for acute kidney injury, although statistical analysis was limited in the lowest renal function subgroups because of sample size (Table 3 and Table E2, available online at http://www.annemergmed.com).

The probability of developing chronic kidney disease within 6 months of the index ED visit was 2.0%, 4.6%, and 3.5% in the contrast-enhanced CT, unenhanced CT, and non-CT groups, respectively. The respective probabilities for initiation of dialysis were 0.4%, 0.9%, and 0.6%, and those for renal transplantation were 0%, 0.1%, and 0.1%. Unadjusted ORs suggested that contrast media administration for contrast-enhanced CT was associated with a decreased risk for new diagnosis of chronic kidney disease, initiation of dialysis, or renal transplantation within 6 months. However, this effect was abrogated after use of propensity-score analysis to control for factors influencing the clinical decision to administer contrast media (Table E3, available online at http://www.annemergmed.com).

Although patients with serum creatinine level greater than or equal to 4.0 mg/dL were excluded from primary analysis, separate analyses were performed for this population and are included as supplemental data. Multivariable logistic regression modeling revealed no independent effect of contrast media on risk for developing acute kidney injury in these patients (Table E4, available online at http://www.annemergmed.com), and no significant differences in risk for acute kidney injury as defined by Acute Kidney Injury Network/Kidney Disease Improving Global Outcomes criteria were observed between patients who underwent contrast-enhanced CT, unenhanced CT, or no CT, even after propensity-score-matching adjustment (Table E2, available online at http://www.annemergmed.com).

Finally, we observed clinical treatment patterns that are relevant to our results. As initial estimated glomerular filtration rate declined, clinicians were less likely to order CT scans with contrast media enhancement (Figure 2) and were nearly twice as likely to administer intravenous crystalloid fluids to patients undergoing contrast-enhanced CT than to patients undergoing unenhanced CT (24.3% and 14.2%, respectively) (Table 1).

Table 2. Association between contrast media administration and acute kidney injury.*

Characteristics	AKI (CIN Criteria†)	AKI (AKIN/KDIGO Criteria‡)
Intravenous contrast administration	0.96 (0.85–1.08)	1.00 (0.87–1.16)
CT	0.97 (0.84–1.11)	1.00 (0.86–1.17)
Female	1.43 (1.30–1.58)	1.12 (1.00–1.26)
Age	1.02 (1.01–1.02)	1.01 (1.00–1.01)
Race		
Black	1 [Reference]	1 [Reference]
White	1.16 (1.05–1.30)	0.80 (0.71–0.91)
Other	1.40 (1.16–1.69)	0.94 (0.74–1.18)
eGFR	1.02 (1.02–1.02)	1.00 (1.00–1.00)
Acute illness severity indicators		
ED critical care designation	0.94 (0.78–1.13)	0.94 (0.76–1.16)
Hypotension§	0.82 (0.61–1.09)	0.74 (0.54–1.00)
Anemia§	1.05 (0.95–1.17)	1.17 (1.04–1.32)
Hypoalbuminemia§	1.35 (1.20–1.53)	1.45 (1.26–1.66)
Medications administered		
Nephrotoxic‖	1.57 (1.38–1.78)	1.63 (1.41–1.89)
Nephroprotective¶	1.05 (0.62–1.81)	1.22 (0.72–2.07)
Crystalloid fluid	0.64 (0.56–0.73)	0.53 (0.46–0.62)
Comorbidities#		
Diabetes mellitus	1.20 (1.06–1.35)	1.28 (1.12–1.46)
Hypertension	1.22 (1.09–1.36)	1.16 (1.02–1.31)
Congestive heart failure	2.23 (1.96–2.55)	2.22 (1.94–2.55)
HIV/AIDS	1.16 (0.91–1.48)	0.93 (0.70–1.24)
Chronic kidney disease	1.85 (1.56–2.20)	1.82 (1.55–2.14)

AKI, Acute kidney injury; *CIN*, contrast-induced nephropathy; *AKIN/KDIGO*, Acute Kidney Injury Network/Kidney Disease Improving Global Outcomes.

*Results are ORs with 95% CIs in parentheses.

†Absolute increase ≥0.5 mg/dL or ≥25% increase over baseline SCr at 48 to 72 hours.

‡Absolute increase ≥0.3 mg/dL or ≥1.5 times increase over baseline SCr at 48 to 72 hours.

§Based on vital signs and laboratory analyses from the index ED visit. Anemia: hematocrit level <39% or <36% for men and women, respectively; hypoalbuminemia (<3.5 g/dL); hypotension (systolic blood pressure <80 mm Hg).

‖Medications from the following classes: angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, antimicrobial, loop and thiazide diuretic, nonsteroidal anti-inflammatory, and other (see Figure E1, available online at http://www.annemergmed.com, for more details).

¶Medications from the following classes: acetylcysteine, sodium bicarbonate, and statins.

#Based on *ICD-9-CM* diagnostic codes from the index ED visit or previous hospitalizations.

LIMITATIONS

Although our study population was large, all patients were treated in a single academic medical center ED with advanced radiology protocols and clinician practice patterns that may affect the overall incidence of acute kidney injury. Additionally, the majority of patients studied were admitted to the hospital. Because patients requiring inpatient admission are more ill—and thus at potentially higher risk for developing acute kidney injury—than those discharged from the ED, our results may overestimate the incidence of acute kidney injury in the general ED population. Furthermore, our retrospective observational approach limited our examination of comorbidities and outcomes to those recorded in our institutional electronic medical record, although electronic records for the study cohort were analyzed from 1993 through the end of 2014. Although it is possible that patients included in our study sought treatment at other medical institutions for renal complications that were not recorded in our electronic medical record, it is unlikely that this would occur in any particular patient cohort more than the others. Additionally, our analysis of clinical practice patterns was limited to the ED. Consequently, our analysis would not capture nephroprotective or nephrotoxic interventions performed after patients departed the ED, although we specifically excluded patients who received contrast-enhanced CT up to 72 hours after their ED departure. Finally, although we attempted to minimize the bias associated with treatment assignment by using propensity-score matching, this approach is limited by the inability to include all factors that might conceivably influence the clinical decision to administer contrast media.

DISCUSSION

Historically, studies of contrast-induced nephropathy have inferred causality from a temporal relationship between iodinated contrast media administration and occurrence of acute kidney injury. The very definition of contrast-induced nephropathy, which relies on changes in renal function at an interval after contrast media administration, is based on this supposition. As discussed above, the majority of contrast-induced nephropathy studies have focused on patients undergoing arterial angiography, were performed before the routine use of low- and iso-osmolar contrast media agents, or have not included adequate control populations. For these reasons, the assumption of causality between intravenous contrast media administration and acute kidney injury has been challenged in multiple recent publications.[13,15-19]

In this ED-based retrospective single-center study, we demonstrate that for patients who present with serum creatinine levels less than 4.0 mg/dL, administration of intravenous contrast media for CT enhancement is not associated with the development of acute kidney injury, nor is it associated with the diagnosis of chronic kidney disease, need for dialysis, or renal transplantation at 6 months. Although our primary analysis did not include patients with a serum creatinine level of 4.0 mg/dL or greater at presentation, comparisons made with the test of proportions with and without propensity matching in this group (Table E2, available online at http://www.annemergmed.com) and supplemental logistic regression analyses (Table E4, available online at http://www.annemergmed.com) suggest a similar lack of relationship between contrast media administration and development of

Table 3. Risk of acute kidney injury after intravenous contrast administration with subgroup analysis stratified by initial estimated glomerular filtration rate.

eGFR subgroup, mL/min per 1.73 m^2	CECT	Unenhanced CT	No CT	Contrast vs No Contrast	CECT vs Unenhanced CT*	Contrast vs No Contrast (Propensity-Score Matched)†	CECT vs Unenhanced CT (Propensity-Score Matched)*
	Rate of AKI by CIN Criteria (%)‡			ORs of AKI by CIN Criteria (95% CI)‡			
Overall	766/7,201 (10.6)	559/5,499 (10.2)	569/5,234 (10.9)	1.01 (0.92–1.12)	1.05 (0.94–1.18)	0.99 (0.98–1.00)	1.00 (0.98–1.01)
≥90	510/4,127 (12.4)	261/2,039 (12.8)	304/2,360 (12.9)	0.96 (0.84–1.09)	0.96 (0.82–1.13)	1.00 (0.98–1.02)	1.00 (0.98–1.02)
60–89	179/2,176 (8.2)	111/1,337 (8.3)	133/1,374 (9.7)	0.91 (0.74–1.11)	0.99 (0.77–1.27)	1.01 (0.99–1.03)	1.01 (0.98–1.03)
45–59	59/575 (10.3)	68/714 (9.5)	59/589 (10.0)	1.06 (0.76–1.47)	1.09 (0.75–1.57)	1.02 (0.99–1.06)	1.02 (0.98–1.06)
30–44	12/241 (5.0)	57/768 (7.4)	44/550 (8.0)	0.63 (0.34–1.17)	0.65 (0.34–1.24)	1.00 (0.95–1.04)	0.96 (0.90–1.01)
15–29	6/78 (7.7)	53/599 (8.8)	27/345 (7.8)	0.90 (0.38–2.13)	0.86 (0.36–2.07)	0.99 (0.91–1.07)	1.03 (0.95–1.11)
<15	0/4	9/42 (21.4)	2/16 (12.5)				
	Rate of AKI by AKIN/KDIGO Criteria (%)§			ORs of AKI by AKIN/KDIGO Criteria§ (95% CI)			
Overall	488/7,201 (6.8)	488/5,499 (8.9)	426/5,234 (8.1)	0.78 (0.70–0.88)	0.75 (0.66–0.85)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
≥90	225/4,127 (5.5)	115/2,039 (5.6)	115/2,360 (4.9)	1.05 (0.87–1.26)	0.96 (0.77–1.22)	1.00 (0.98–1.01)	1.00 (0.99–1.02)
60–89	161/2,176 (7.4)	98/1,337 (7.3)	112/1,374 (8.2)	0.95 (0.77–1.18)	1.01 (0.78–1.31)	1.00 (0.98–1.02)	1.01 (0.98–1.03)
45–59	71/575 (12.3)	88/714 (12.3)	73/589 (12.4)	1.00 (0.74–1.35)	1.00 (0.72–1.40)	1.02 (0.97–1.06)	1.03 (0.99–1.08)
30–44	22/241 (9.1)	91/768 (11.8)	73/550 (13.3)	0.71 (0.44–1.13)	0.75 (0.46–1.22)	1.01 (0.96–1.06)	0.97 (0.91–1.04)
15–29	8/78 (10.3)	86/599 (14.4)	50/345 (14.5)	0.68 (0.32–1.44)	0.68 (0.32–1.47)	0.97 (0.89–1.07)	0.96 (0.86–1.08)
<15	1/4 (25.0)	10/42 (23.8)	3/16 (18.8)	1.15 (0.11–12.05)	1.07 (0.10–11.43)		

*Absolute increase ≥0.5 mg/dL or ≥25% increase over baseline SCr at 48 to 72 hours.
†OR of developing AKI in patients who underwent CECT versus patients who underwent CT without contrast enhancement.
‡OR of developing AKI in patients who underwent CECT versus all patients who did not receive contrast.
§Absolute increase ≥0.3 mg/dL or ≥1.5 times increase over baseline SCr at 48 to 72 hours.

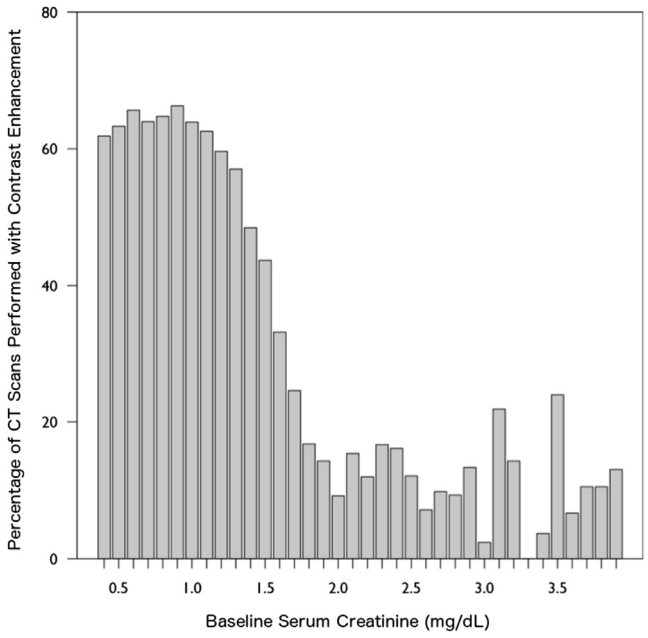

Figure 2. Nephroprotective strategic choices in contrast administration. The frequency of intravenous contrast administration decreases as initial serum creatinine level increases, representing the current clinical context that favors nephroprotection and reduction of contrast exposure for patients at perceived increased risk of acute kidney injury.

acute kidney injury. However, conclusions in regard to these patients are limited by small sample size (493 total patients, 53 of whom underwent contrast-enhanced CT) and a wide range of serum creatinine levels at presentation (4.0 mg/dL to 21.1 mg/dL). Further study of this specific population is warranted.

To our knowledge, this is the largest controlled study of acute kidney injury after contrast media administration in the ED, a setting in which diagnostic burden is high and patients often present with acute pathologies that independently affect the risk for developing acute kidney injury. Indeed, this is one of very few studies to compare the incidence of acute kidney injury in patients who did and did not receive contrast media in any setting, and to our knowledge is the only study to date that compares the incidence of acute kidney injury in patients receiving contrast media for contrast-enhanced CT directly with both patients undergoing unenhanced CT and those who did not undergo CT at all. Inclusion of 2 distinct control populations, in addition to the use of propensity-score-matching analysis, considerably strengthens the findings of our study by minimizing selection bias inherent to retrospective analysis.

Nevertheless, our findings could lead to inappropriate conclusions about the overall safety of intravenous contrast media administration. It is likely that nephroprotective treatment patterns are at least partially responsible for the observed lack of increased acute kidney injury incidence after contrast media administration. Indeed, we found that clinicians were less likely to administer contrast media to patients with decreased baseline renal function and comorbid conditions associated with acute kidney injury and were more likely to administer intravenous fluids. Although we have attempted to control for as many of these behaviors as possible, a limitation of our statistical approach and retrospective research in general is inability to account for all conceivable confounders, including clinician gestalt. If one concludes that there is no risk associated with contrast media administration, and the collective conscience shifts to remove these nephroprotective behaviors from practice, an increased incidence of acute kidney injury after contrast-enhanced CT may result.

Although a well-controlled randomized prospective study is required to fully determine the contribution of intravenous contrast media to the development of acute kidney injury, our results clearly demonstrate that in current clinical context, contrast media administration is not associated with an increased incidence of acute kidney injury. Indeed, our findings, along with those of several other retrospective studies performed in other contexts, support the notion that randomization of patients to receive intravenous contrast, once considered ethically infeasible, is very likely safe (at least in patients with serum creatinine level <4.0 mg/dL) and will be necessary to fully understand the role of contrast media in precipitation of renal dysfunction. Our data also suggest that in cases in which contrast-enhanced CT is indicated to avoid delayed or missed diagnosis, the potential morbidity and mortality resulting from a failure to diagnose possibly life-threatening conditions outweigh any potential risk of contrast-induced nephropathy in patients with serum creatinine levels up to 4.0 mg/dL. Therefore, in light of our findings, the weight attributed to potential for contrast-precipitated renal dysfunction in the decisionmaking process of clinicians should be adjusted.

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was performed primarily by EYK. JSH and MRE drafted the manuscript, and all authors contributed substantially to its revision. JSH takes responsibility for the paper as a whole.

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Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers

Benazepril
Captopril
Enalapril
Enalaprilat
Lisinopril
Losartan
Ramipril
Valsartan

Antimicrobials

Acyclovir
Amoxicillin/clavulanic acid
Amphotericin
Ampicillin
Ampicillin/sulbactam
Aztreonam
Cefazolin
Cefepime
Cefotaxime
Cefotetan
Cefoxitin
Cefpodoxime
Ceftazidime
Ceftriaxone
Cefuroxime
Cephalexin
Chloramphenicol
Ciprofloxacin
Cyclosporine
Dicloxacillin
Doxycycline
Fluconazole
Flucytosine
Ganciclovir
Gentamicin
Itraconazole
Oxacillin
Penicillin
Piperacillin
Piperacillin/tazobactam
Quinine
Rifampin
Tenofovir
Tobramycin
Trimethoprim/sulfamethoxazole
Vancomycin
Voriconazole

Loop and Thiazide Diuretics

Furosemide
Torsemide
Chlorothiazide
Chlorthalidone
Hydrochlorothiazide

Nonsteroidal Anti-inflammatory Drugs

Celecoxib
Ibuprofen
Indomethacin
Ketorolac
Naproxen

Other

Hydralazine
Lithium
Pantoprazole
Phenytoin
Ranitidine
Terbutaline

Figure E1. Medications designated as nephrotoxic.[26]

Table E1. Association between contrast media administration and likelihood of acute kidney injury (serum creatinine level as main comparator).*

Characteristics	AKI* (CIN Criteria†)	AKI* (AKIN Criteria‡)
Intravenous contrast administration	0.97 (0.85–1.09)	1.00 (0.87–1.16)
CT	0.95 (0.83–1.09)	1.00 (0.86–1.17)
Women	0.97 (0.87–1.08)	1.12 (1.00–1.26)
Age	1.00 (1.00–1.01)	1.01 (1.00–1.01)
Race		
Black	1 [Reference]	1 [Reference]
White	0.86 (0.77–0.96)	0.81 (0.71–0.92)
Other	1.01 (0.84–1.22)	0.94 (0.74–1.19)
Initial SCr value, mg/dL	0.03 (0.02–0.04)	0.87 (0.60–1.28)
Initial SCr value squared	2.15 (1.97–2.36)	1.05 (0.95–1.15)
Acute illness severity indicators		
ED critical care designation	0.94 (0.78–1.14)	0.95 (0.77–1.16)
Hypotension§	0.78 (0.59–1.04)	0.73 (0.54–1.00)
Anemia§	1.05 (0.95–1.17)	1.17 (1.04–1.32)
Hypoalbuminemia§	1.31 (1.15–1.48)	1.44 (1.26–1.65)
Medications administered		
Nephrotoxic‖	1.58 (1.39–1.80)	1.63 (1.41–1.89)
Nephroprotective¶	1.01 (0.59–1.74)	1.22 (0.71–2.07)
Crystalloid fluids	0.64 (0.56–0.72)	0.53 (0.45–0.62)
Comorbidities#		
Diabetes mellitus	1.18 (1.05–1.33)	1.28 (1.12–1.46)
Hypertension	1.20 (1.07–1.34)	1.16 (1.02–1.32)
Congestive heart failure	2.30 (2.01–2.62)	2.24 (1.95–2.57)
HIV/AIDS	1.14 (0.89–1.45)	0.93 (0.70–1.24)
Chronic kidney disease	1.96 (1.64–2.34)	1.84 (1.56–2.18)

*Results are ORs with 95% CIs in parentheses.
†Absolute increase ≥0.5 mg/dL or ≥25% increase over baseline SCr at 48 to 72 hours.
‡Absolute increase ≥0.3 mg/dL or ≥1.5 times increase over baseline SCr at 48 to 72 hours.
§Based on vital signs and laboratory analyses from the index ED visit. Anemia: hematocrit level <39% or <36% for men and women, respectively; hypoalbuminemia (<3.5 g/dL); hypotension (systolic blood pressure <80 mm Hg).
‖Medications from the following classes: angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, antimicrobial, loop and thiazide diuretic, nonsteroidal anti-inflammatory, and other (see Figure E1 for more details).
¶Medications from the following classes: acetylcysteine, sodium bicarbonate, and statins.
#Based on *ICD-9-CM* diagnostic codes from the index ED visit or previous hospitalizations.

Table E2. Risk of acute kidney injury after intravenous contrast administration with subgroup analysis stratified by initial serum creatinine level.

Initial SCr	CECT	Unenhanced CT	No CT	Contrast vs No Contrast	CECT vs Unenhanced CT*	Contrast vs No Contrast (Propensity-Score Matched)†	CECT vs Unenhanced CT (Propensity-Score Matched)*
	Rate of AKI by CIN Criteria (%)‡			ORs of AKI by CIN Criteria‡ (95% CI)			
0.4–0.9	578/4,415 (13.1)	307/2,391 (12.8)	365/2,598 (14.0)	0.97 (0.86–1.09)	1.02 (0.88–1.19)	1.00 (0.98–1.02)	1.01 (0.99–1.03)
1.0–1.4	165/2,380 (6.9)	124/1,571 (7.9)	126/1,642 (7.7)	0.88 (0.72–1.08)	0.87 (0.68–1.11)	1.01 (0.99–1.03)	1.00 (0.97–1.02)
1.5–1.9	16/294 (5.4)	42/700 (6.0)	45/514 (8.8)	0.75 (0.43–1.29)	0.90 (0.50–1.63)	0.96 (0.92–1.01)	1.01 (0.96–1.06)
2.0–2.9	6/85 (7.1)	58/610 (9.5)	23/341 (6.7)	0.82 (0.34–1.93)	0.72 (0.30–1.73)	0.98 (0.91–1.05)	1.00 (0.93–1.08)
3.0–4.0	1/27 (3.7)	28/227 (12.3)	10/139 (7.2)	0.33 (0.04–2.52)	0.27 (0.04–2.09)	0.96 (0.86–1.08)	1.00 (0.92–1.08)
≥4.0	7/53 (13.2)	24/255 (9.4)	25/185 (13.5)	1.21 (0.52–2.84)	1.67 (0.74–3.79)	1.04 (0.93–1.16)	1.00 (0.87–1.15)
	Rate of AKI by AKIN/KDIGO Criteria§			ORs of AKI by AKIN/KDIGO Criteria§ (95% CI)			
0.4–0.9	269/4,415 (6.1)	144/2,391 (6.0)	152/2,598 (5.9)	1.03 (0.87–1.22)	1.01 (0.82–1.25)	1.00 (0.99–1.02)	1.01 (1.00–1.02)
1.0–1.4	178/2,380 (7.5)	141/1,571 (9.0)	141/1,642 (8.6)	0.84 (0.69–1.02)	0.82 (0.65–1.03)	1.00 (0.99–1.02)	1.00 (0.98–1.02)
1.5–1.9	29/294 (9.9)	80/700 (11.4)	66/514 (12.8)	0.80 (0.53–1.22)	0.85 (0.54–1.33)	0.98 (0.93–1.04)	1.01 (0.95–1.07)
2.0–2.9	9/85 (10.6)	85/610 (13.9)	51/341 (15.0)	0.71 (0.35–1.45)	0.73 (0.35–1.51)	0.98 (0.90–1.07)	1.01 (0.96–1.07)
3.0–4.0	3/27 (11.1)	38/227 (16.7)	16/139 (11.5)	0.72 (0.21–2.48)	0.62 (0.18–2.17)	0.96 (0.83–1.12)	1.04 (0.92–1.17)
≥4.0	7/53 (13.2)	31/255 (12.2)	30/185 (16.2)	0.95 (0.41–2.19)	1.27 (0.57–2.81)	1.02 (0.90–1.15)	0.96 (0.83–1.11)

*OR of developing AKI in patients who underwent CECT versus patients who underwent CT without contrast enhancement.
†OR of developing AKI in patients who underwent CECT versus all patients who did not receive contrast.
‡Absolute increase ≥0.5 mg/dL or ≥25% increase over baseline SCr at 48 to 72 hours.
§Absolute increase ≥0.3 mg/dL or ≥1.5 times increase over baseline SCr at 48 to 72 hours.

Table E3. Risk of chronic kidney disease, dialysis, or renal transplant in the 6 months after contrast.

Diagnosis	CECT (%)	Unenhanced CT (%)	No CT (%)	OR CM vs No CM (95% CI)*	OR CECT vs Unenhanced CT (95% CI)†	Propensity-Score-Adjusted OR CM vs No CM (95% CI)*	Propensity-Score-Adjusted OR CECT vs Unenhanced CT (95% CI)†
Chronic kidney disease	146/7,201 (2.0)	255/5,499 (4.6)	185/5,234 (3.5)	0.48 (0.40–0.59)	0.43 (0.35–0.52)	0.99 (0.98–1.00)	0.99 (0.98–0.99)
Dialysis	27/7,201 (0.4)	49/5,499 (0.9)	32/5,234 (0.6)	0.49 (0.32–0.77)	0.42 (0.26–0.67)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Renal transplant	1/7,201 (0)	7/5,499 (0.1)	7/5,234 (0.1)	0.11 (0.01–0.81)	0.11 (0.01–0.89)	1.00 (1.00–1.00)	1.00 (1.00–1.00)

CM, Contrast media.

*OR of a new diagnosis of chronic kidney disease, dialysis, or renal transplant for patients who received CM compared with all patients who did not receive CM regardless of whether they received a CT scan.

†OR of a new diagnosis of dialysis, renal failure, or renal transplant for patients who received CM compared with patients who received an unenhanced CT.

Table E4. Association between contrast media administration and acute kidney injury for patients with initial serum creatinine level greater than or equal to 4.0 mg/dL.*

Characteristics	AKI (CIN Criteria†)	AKI (AKIN/KDIGO Criteria†)
Intravenous contrast administration	1.56 (0.59–4.15)	1.15 (0.44–3.00)
CT	0.44 (0.21–0.91)	0.50 (0.26–0.96)
Women	1.14 (0.60–2.19)	1.35 (0.74–2.46)
Age	1.01 (0.99–1.03)	1.00 (0.98–1.02)
Race		
Black	1 [Reference]	1 [Reference]
White	0.70 (0.33–1.51)	0.74 (0.36–1.50)
Other	0.50 (0.11–2.34)	0.59 (0.16–2.17)
eGFR	0.99 (0.91–1.07)	1.01 (0.94–1.09)
Acute illness severity indicators		
ED critical care designation	1.64 (0.56–4.78)	1.22 (0.42–3.51)
Hypotension§	0.29 (0.07–1.29)	0.24 (0.05–1.03)
Anemia§	1.11 (0.53–2.34)	1.42 (0.69–2.92)
Hypoalbuminemia§	1.09 (0.57–2.07)	1.37 (0.77–2.44)
Medications administered		
Nephrotoxic‖	0.50 (0.19–1.30)	0.67 (0.29–1.53)
Nephroprotective¶	1.54 (0.29–8.30)	1.14 (0.22–5.93)
Crystalloid fluids	0.29 (0.13–0.63)	0.32 (0.16–0.66)
Comorbidities#		
Diabetes mellitus	1.00 (0.48–2.08)	1.37 (0.71–2.62)
Hypertension	0.47 (0.23–0.95)	0.47 (0.24–0.89)
Congestive heart failure	1.14 (0.50–2.61)	0.98 (0.46–2.10)
HIV/AIDS	0.17 (0.02–1.36)	0.13 (0.02–1.00)
Chronic kidney disease	0.60 (0.31–1.17)	0.67 (0.36–1.22)

*Results are ORs with 95% CIs in parentheses.

†Absolute increase ≥0.5 mg/dL or ≥25% increase over baseline SCr at 48 to 72 hours.

‡Absolute increase ≥0.3 mg/dL or ≥1.5 times increase over baseline SCr at 48 to 72 hours.

§Based on vital signs and laboratory analyses from the index ED visit. Anemia: hematocrit level <39% or <36% for men and women, respectively; hypoalbuminemia (<3.5 g/dL); hypotension (systolic blood pressure <80 mm Hg).

‖Medications from the following classes: angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, antimicrobial, loop and thiazide diuretic, nonsteroidal anti-inflammatory, and other (see Figure E1 for more details).

¶Medications from the following classes: acetylcysteine, sodium bicarbonate, and statins.

#Based on *ICD-9-CM* diagnostic codes from the index ED visit or previous hospitalizations.