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Renal outcomes following intravenous contrast administration in patients with acute kidney injury: a multi-site retrospective propensity-adjusted analysis

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Abstract

Purpose: Evidence of an association between intravenous contrast media (CM) and persistent renal dysfunction is lacking for patients with pre-existing acute kidney injury (AKI). This study was designed to determine the association between intravenous CM administration and persistent AKI in patients with pre-existing AKI.

Methods: A retrospective propensity-weighted and entropy-balanced observational cohort analysis of consecutive hospitalized patients ≥ 18 years old meeting Kidney Disease Improving Global Outcomes (KDIGO) creatinine-based criteria for AKI at time of arrival to one of three emergency departments between 7/1/2017 and 6/30/2021 who did or did not receive intravenous CM. Outcomes included persistent AKI at hospital discharge and initiation of dialysis within 180 days of index encounter.

Results: Our analysis included 14,449 patient encounters, with 12.8% admitted to the intensive care unit (ICU). CM was administered in 18.4% of all encounters. AKI resolved prior to hospital discharge for 69.1%. No association between intravenous CM administration and persistent AKI was observed after unadjusted multivariable logistic regression modeling (OR 1; 95% CI 0.89–1.11), propensity weighting (OR 0.93; 95% CI 0.83–1.05), and entropy balancing (OR 0.94; 95% CI 0.83–1.05). Sub-group analysis in those admitted to the ICU yielded similar results. Initiation of dialysis within 180 days was observed in 5.4% of the cohort. An association between CM administration and increased risk of dialysis within 180 days was not observed.

Conclusion: Among patients with pre-existing AKI, contrast administration was not associated with either persistent AKI at hospital discharge or initiation of dialysis within 180 days. Current consensus recommendations for use of intravenous CM in patients with stable renal disease may also be applied to patients with pre-existing AKI.

Keywords: Acute kidney injury, Contrast media, Contrast-induced nephropathy, Contrast-associated nephropathy

Introduction

Acute kidney injury (AKI) is common and associated with major patient-centered adverse events [1–3]. Among hospitalized patients, AKI that persists beyond 72 h is associated with an increased likelihood of incident or progressive chronic kidney disease (CKD), long-term

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dialysis, and all-cause mortality within 3 months of hospital discharge [4]. Regardless of AKI severity, reversal of an AKI episode within 48–72 h of onset is associated with better outcomes than longer durations of AKI [5].

Historically, intravenous (IV) iodinated contrast media (CM) for computed tomography has been identified as a leading cause of iatrogenic AKI, termed contrast-induced acute kidney injury (CI-AKI) [6]. More recently, multiple large and well-controlled retrospective studies and meta-analyses have challenged the CI-AKI paradigm by finding no independent association between IV CM administration and AKI in both unselected and selected patient populations, including the critically ill [7–15].

In 2020, the American College of Radiology and National Kidney Foundation published a consensus statement that reviewed the updated evidence on CI-AKI and contrast-associated AKI (CA-AKI) and downgraded the recommended level of caution around IV CM administration in patients with stable pre-existing kidney disease [16, 17]. The consensus states that stable estimated glomerular filtration rate (eGFR) is the best indicator of risk for CI-AKI and that clinicians should exercise increased caution around CM administration to patients not on dialysis with a stable eGFR below 30 mL/min/1.73 m^2 or with unstable renal function, including pre-existing AKI. However, for the latter population, the authors acknowledge that current understanding of a potential association between IV CM and exacerbation of pre-existing AKI is limited. While this evidence-based consensus has been welcomed, its applicability has been limited in the acute care environment because, in this setting, many patients have unstable renal function, including AKI [18–24].

In the current study, we sought to fill a gap in current evidence by clarifying the risk for adverse renal outcomes attributable to IV CM administration to patients with pre-existing AKI. We evaluated whether, among patients who presented to the emergency department (ED) with community-acquired acute kidney injury, AKI would persist at a higher rate in those who receive IV CM than in those who do not. We also measured the association between IV CM administration and initiation of dialysis within 180 days for patients in this population.

Take-home message

Evidence of an association between intravenous contrast and persistent renal dysfunction has been lacking for patients with unstable renal function, including those with pre-existing acute kidney injury. This study demonstrates that, among patients with pre-existing AKI, contrast administration was not associated with either persistent AKI at hospital discharge or an increased risk of dialysis initiation within 180 days.

Methods

Study design and setting

This multi-site retrospective analysis was performed in a cohort of patient visits to the EDs of three hospitals within a university-based health system between July 1, 2017 and June 30, 2021. Study sites included an urban academic hospital (site 1), an urban community–academic hybrid hospital (site 2), and a suburban community hospital (site 3). Two experienced data users (AS and EYK) extracted all clinical information from a relational database that underlies the common electronic health record (EHR) (Epic, Verona, Wisconsin, USA) used at all sites. This study was approved by the Johns Hopkins Medicine Institutional Review Board (IRB00125114) and was performed in accordance with STROBE guidelines for observational research [25].

Study population

Visits by adult patients (≥ 18 years old) who met Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine (sCr)-based criteria for AKI stage 1 or greater (an absolute increase in sCr of at least 0.3 mg/dL or relative increase of at least 1.5 times over baseline sCr) at the time of ED arrival were included [26]. Urine output-based criteria were not included in our definition of AKI because this variable was not reliably recorded in the EHR. Baseline sCr was defined for each patient as the median of all sCr levels measured in any setting within our integrated health system 0–180 days prior to the index ED visit; if only a single sCr was available from this interval it was used as baseline [27]. Patients who did not meet criteria for AKI on ED arrival, who did not have at least one sCr recorded in our integrated health system EHR 0–180 days prior to the index visit (precluding reliable identification of AKI), patients with pre-existing dialysis dependence or whose baseline sCr was greater than 4 mg/dL, and patients who were discharged to the community after their ED encounter (precluding serial sCr measurement) were excluded. Separate sub-groups of those presenting to the ED with an eGFR < 30 mL/min/1.73 m^2 and those admitted to the intensive care unit (ICU) were defined for analysis.

Variables

The independent variable of interest was administration of IV CM during the index ED encounter, identified using EHR medication administration data. Patients who received CM were administered 70–120 cc of iohexol or iodixanol intravenously according to institutional protocols. Control variables included age, sex, race, hospital site, hospital length of stay, eGFR calculated using the

CKD-EPI creatinine formula, chronic comorbidities and acute illness severity indicators previously shown to predispose patients for development of contrast-associated AKI, and administration of nephrotoxic medications or IV crystalloid fluids in the ED [28–32]. Chronic comorbidities included diabetes mellitus, hypertension, human immunodeficiency virus/Acquired ImmunoDeficiency Syndrome (HIV/AIDS), congestive heart failure (CHF) and chronic kidney disease; all were identified using the International Classification of Diseases 10th Revision (ICD-10) codes from active medical problem fields within the EHR. Acute illness severity indicators included the Sequential Organ Failure Assessment (SOFA) score (derived from the lowest calculated PaO_2/FiO_2 ratio, lowest platelet count, highest bilirubin, lowest mean arterial pressure with the highest recorded rate of infusion of adrenergic agents, lowest Glasgow Coma Scale (GCS) score, and highest sCr [33–35]), hypotension (systolic blood pressure < 80 mmHg) on arrival, critical care designation (patients triaged to ED acuity levels 1 or 2), anemia (hemoglobin < 13 g/dL or < 12 g/dL for males and females, respectively), and hypoalbuminemia (< 3.5 g/dL) during the index ED visit.

Outcomes

Our primary outcome variable was persistent AKI. Persistent AKI was differentiated from AKI that resolved during the hospital encounter with AKI resolution defined as recovery of renal function to a degree that patients no longer met KDIGO sCr-based criteria for AKI. Determination of AKI resolution was made by comparing the last sCr measured during the encounter with pre-encounter baseline. A key secondary outcome of interest was initiation of dialysis within 180 days of the ED encounter, identified by entry of ICD-10 diagnostic and procedure codes associated with renal dialysis.

Analysis

Dichotomous variables are displayed as percentages, categorical data as relative frequencies (in percentages), and continuous data as means with 95% confidence intervals (CI). Rates of AKI and AKI-related outcomes were calculated as the percentage of visits with occurrence.

The association between CM and each outcome was assessed using separate unweighted multivariable logistic regression models to ascertain whether, and to what degree, CM administration was independently associated with incidence of each outcome in the entire study population after controlling for demographic variables and medical conditions previously reported to increase risk for AKI [29–32].

Selection of diagnostic imaging modality (contrast-enhanced computed tomography (CT) versus unenhanced CT versus no CT) is guided by institutional protocols, patient acuity, specific pathology, and patient-related factors that are perceived to predispose patients to adverse clinical outcomes following CM administration. Inverse probability of treatment weighting (IPTW) is a common method to reduce bias in observational studies and improve the accuracy of results [36]. Application of IPTW uses a set of patient-specific variables to generate the probability of treatment such that the distribution of the baseline covariates is similar between treatment and control groups. Entropy balancing similarly constructs weights for patients to balance covariates, but unlike propensity scores which typically use a logistic or probit model to construct weights, employs non-linear equations to generate weights that are as close as possible to base weights but exactly balance the covariates between groups. The resulting weights from both methods can then be utilized in statistical analyses. In this study, because the cohort is highly biased, we employed both IPTW and entropy balancing analyses to evaluate the effect of CM more robustly.

Treatment (CM administration) propensity score weights and entropy balance weights were generated for all patients based on initial eGFR, gender, race, age, hospital, chronic comorbidities commonly associated with CA-AKI (diabetes, CHF, HIV/AIDS, and CKD—all identified using ICD-10 CM codes for active medical problems), acute illness severity indicators (SOFA score, hypotension, anemia, and hypoalbuminemia as defined above) and ED critical care designation. The last of these was included because the threshold for ordering a contrast-enhanced CT may be lower in critically ill patients than in the general ED population. The weights were then used to adjust multivariable logistic regression models for the entire study population. *E*-values were calculated to measure the potential effect of unmeasured confounders [37]. The primary outcome variable was defined as occurring in hospital and all patients were admitted, limiting missing outcomes data. The secondary outcome variable was captured by diagnosis and procedure codes. In the unlikely case where dialysis was performed but not recorded in the EHR, the encounter would have been counted as outcome negative. If comorbidities were not recorded in the active medical problems list, they were assumed to be absent. For all other variables included in our multivariate regression, if no value was recorded in the EHR that met criteria for inclusion, they were assumed to be absent. All analyses were done in Stata version 17 (StataCorp LP, College Station, TX). Propensity scores were generated using PSMATCH2; entropy balancing utilized ebalance [38, 39].

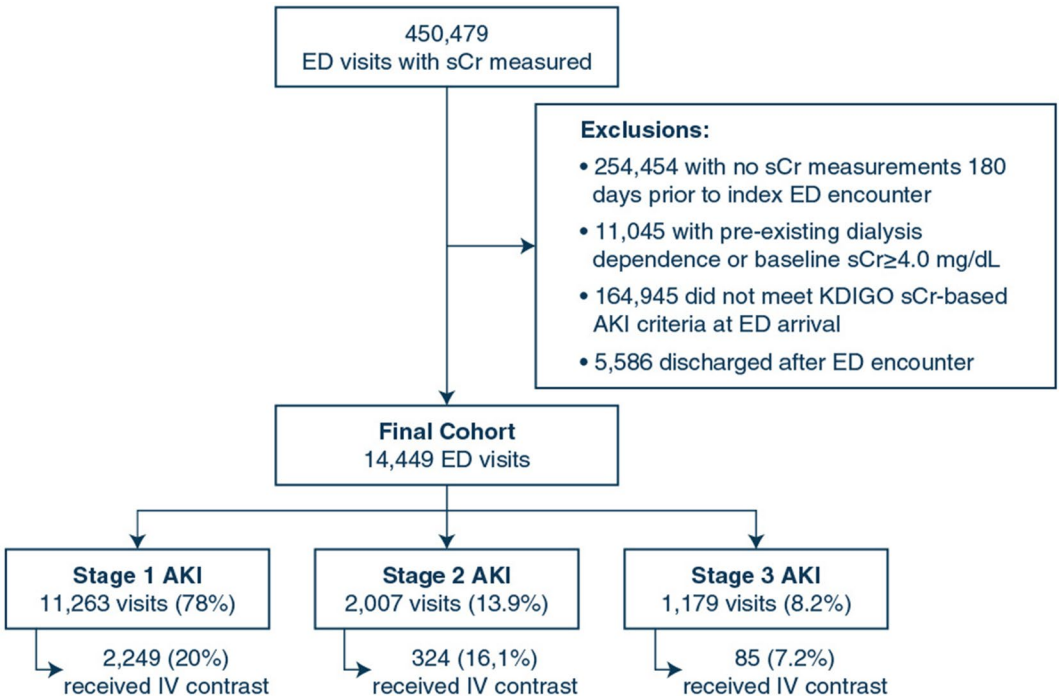

Fig. 1 Study inclusion flowchart

Role of the funding source

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Results

During the study period, sCr was measured in 450,479 encounters, of which 14,449 met all inclusion and no exclusion criteria (Fig. 1). Within the cohort, 78% ($n=11,263$) of patient encounters met KDIGO criteria for stage 1 AKI, 13.9% ($n=2007$) met criteria for stage 2 AKI, and 8.2% ($n=1179$) met criteria for stage 3 AKI.

Intravenous CM was administered during 18.4% ($n=2658$) of all encounters in the cohort (Table 1). CM was administered during 21.5% ($n=1194$) of encounters at site 1; 19.9% ($n=1014$) at site 2; and 11.9% ($n=450$) at site 3. CM was administered to 20% ($n=2,249$) of patients with stage 1 AKI; to 16.1% ($n=324$) of patients with stage 2 AKI; and to 7.2% ($n=85$) of patients with stage 3 AKI (Fig. 1). Patients who received CM were demographically similar to those who did not receive CM, but comparatively younger and more likely to be female (Table 1). Patients who received CM had lower mean sCr values, higher mean eGFR values, were more likely to receive both nephrotoxic medications and crystalloid fluids, and were less likely to have comorbid diabetes, hypertension, CHF, or CKD. Acute illness severity markers were similar between groups (Table 1).

Propensity score weighting for IPTW achieved high degrees of balance across treatment groups for demographics, burden of comorbid diseases, and acute illness severity indicators (Supplemental Fig. 1 and Supplemental Table 1). Balance of mean initial eGFR across treatment and control groups was improved after IPTW, but some imbalance remained (raw standardized difference 0.84 versus −0.04 after weighting) (Supplemental Table 1). For entropy balancing, balance across treatment groups for all variables was nearly exact (Supplemental Table 2).

For most encounters (69.1%, $n=9983$), AKI resolved prior to hospital discharge (Table 1). Persistent AKI was more common in patients who did not receive IV CM (32.7%, 95% CI 32.1–33.6%) than in those who did (22.9%, 95% CI 22–24.5%) (Table 1). Unadjusted multivariable logistic regression modeling revealed no independent association between intravenous (IV) CM administration and persistent AKI (OR 1, 95% CI 0.89–1.11) (Table 2 and Supplemental Fig. 2). This result was robust to confounding, with *E*-values of 1.23, 1.54 and 1.79 at respective risk ratios of 1, 1.1 and 1.2; to generate a positive association between CM administration

Table 1 Patient demographics and clinical characteristics

Characteristics	Contrast	No contrast
Number of patient encounters (%)	2658 (18.4)	11,791 (81.6)
Women, *n* (%)	1355 (51)	5491 (46.6)
Age in years, *n* (%)		
18–44	489 (18.4)	1601 (13.6)
45–64	1066 (40.1)	4260 (36.1)
65–84	945 (35.6)	4765 (40.4)
85+	158 (5.9)	1165 (9.9)
Race, *n* (%)		
Black	1094 (41.2)	5026 (42.6)
White	1381 (52)	5939 (50.4)
Other	183 (6.9)	826 (7)
Location[a], *n* (%)		
Hospital 1	1194 (44.9)	4359 (37)
Hospital 2	1014 (38.1)	4091 (34.7)
Hospital 3	450 (16.9)	3341 (28.3)
Median length of hospital stay, days (IQR)	4.7 (2.7–8)	4.3 (2.5–8)
Medications administered, *n* (%)		
Nephrotoxic[b]	1753 (66)	6558 (55.6)
Crystalloid fluids	2176 (81.9)	7507 (63.7)
Acute illness severity indicators[c]		
Admitted to intensive care unit, *n* (%)	406 (15.3)	1447 (12.3)
Mean SOFA score (95% CI)	2.6 (2.5–2.7)	3.1 (3.1–3.2)
Hypotension, *n* (%)	142 (5.3)	429 (3.6)
Anemia, *n* (%)	1628 (61.2)	8030 (68.1)
Hypoalbuminemia, *n* (%)	1124 (42.3)	4717 (40)
Comorbidities[d], *n* (%)		
Diabetes mellitus	599 (22.5)	3911 (33.2)
Hypertension	1050 (39.5)	5416 (45.9)
Congestive heart failure	316 (11.9)	2695 (22.9)
HIV/AIDS	5 (0.2)	44 (0.4)
Chronic kidney disease	354 (13.3)	3954 (33.5)
Initial kidney function at ED arrival		
Mean sCr (95% CI), mg/dL	1.5 (1.5–1.5)	2.4 (2.4–2.4)
Mean eGFR (95% CI), mL/min/1.73 m^2	54.1 (53.3–54.9)	36.1 (35.7–36.5)
Post-AKI kidney function[e]		
AKI persisted at discharge	609 (22.9)	3857 (32.7)
AKI resolved at discharge	2049 (77.1)	7934 (67.3)
New dialysis initiated within 180 days	55 (2.1)	723 (6.1)

[a] Hospital 1, urban academic; hospital 2, urban academic–community hybrid; hospital 3, suburban community

[b] Medications from the following classes: angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, antimicrobial, loop and thiazide diuretic, nonsteroidal anti-inflammatory, and other

[c] Based on vital signs and laboratory analyses from the index ED visit: Sequential Organ Failure Assessment (SOFA) score (derived from the lowest calculated PaO_2/FiO_2 ratio, lowest platelet count, highest bilirubin, lowest mean arterial pressure with the highest recorded rate of infusion of adrenergic agents, lowest Glasgow Coma Score, and highest sCr), hypotension (systolic blood pressure < 80 mm Hg), anemia (hemoglobin < 13 g/dL or < 12 g/dL for men and women, respectively), hypoalbuminemia (albumin < 3.5 g/dL)

[d] Based on ICD-10-CM diagnostic codes for chronic medical problems present during index ED visit

Table 1 (continued)

[e] Acute kidney injury (AKI) defined using Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine (sCr)-based criteria as an absolute increase of 0.3 mg/dL or 1.5 times increase over pre-encounter baseline; AKI resolution defined as recovery of renal function to a degree that patients no longer met KDIGO sCr-based criteria for AKI

and persistent AKI, an unidentified confounder would need to have a greater strength of association with our primary outcome than any variable included in our analysis. This was further supported by multivariable logistic regression performed with both propensity-weighted analysis and entropy balancing, neither of which revealed an independent association between these two variables (OR 0.93, 95% CI 0.83–1.05; and OR 0.94; 95% CI 0.83–1.05, respectively) (Table 2). While no independent association between IV CM administration and persistent AKI was observed, independent associations with this outcome were observed for age, site of care, hospital length of stay, initial kidney function, crystalloid fluid administration, SOFA score, hypotension, hypoalbuminemia, CHF and HIV/AIDS (Table 2).

Importantly, similar results were found when analyses were restricted to patients with severely impaired renal function and those admitted to the ICU. Among the 5544 patients with an initial eGFR < 30 ml/min/1.73 m^2 at ED presentation, no independent association between IV CM administration and persistent AKI was observed after unadjusted multivariable logistic regression modeling (OR 0.97, 95% CI 0.73–1.29), propensity weighting (OR 0.88, 95% CI 0.66–1.18), and entropy balancing (OR 0.88, 95% CI 0.66–1.19) (Supplemental Table 3). Among the 1,853 patients admitted to the ICU from the ED, no independent association between IV CM administration and persistent AKI was observed after unadjusted multivariable logistic regression modeling (OR 0.90, 95% CI 0.68–1.20), propensity weighting (OR 0.81, 95% CI 0.60–1.10), and entropy balancing (OR 0.81, 95% CI 0.60–1.10) (Supplemental Table 4).

Initiation of dialysis within 180 days of the index encounter was observed for 5.4% ($n = 778$) of patients in the cohort (Table 1). Like persistent AKI, dialysis initiation was observed more frequently in patients who did not receive IV CM (6.1%, 95% CI 5.7–6.6%) than in those who did (2.1%, 95% CI 1.5–2.8%) (Table 1). Unadjusted multivariable logistic regression modeling, propensity-weighted analysis, and entropy balancing did not reveal an increased risk of dialysis initiation within 180 days in patients who received IV CM (OR 0.90, 95% CI 0.65–1.24; OR 0.67, 95% CI 0.47–0.96; and 0.69, 95% CI 0.48–0.98, respectively) (Table 3).

Table 2 Association between contrast exposure and persistent AKI at hospital discharge

Characteristics	Persistent AKI, OR (95% CI) unmatched	Persistent AKI, OR (95% CI) propensity weighted	Persistent AKI, OR (95% CI) entropy balanced
Intravenous contrast administration	1 (0.89–1.11)	0.93 (0.83–1.05)	0.94 (0.83–1.05)
Female	0.94 (0.87–1.02)	1.1 (0.98–1.24)	1.09 (0.97–1.23)
Age in years			
18–44	Ref	Ref	Ref
45–64	0.84 (0.74–0.95)	0.96 (0.81–1.15)	0.96 (0.81–1.14)
65–84	0.7 (0.62–0.8)	0.81 (0.67–0.99)	0.81 (0.66–0.98)
85+	0.72 (0.61–0.85)	0.91 (0.7–1.19)	0.91 (0.69–1.18)
Race			
White	Ref	Ref	Ref
Black	0.98 (0.9–1.06)	1.07 (0.94–1.21)	1.07 (0.94–1.21)
Other	1.15 (0.99–1.33)	1.02 (0.81–1.28)	1.02 (0.81–1.28)
Location[a]			
Hospital 1	Ref	Ref	Ref
Hospital 2	0.62 (0.56–0.68)	0.57 (0.49–0.66)	0.57 (0.49–0.65)
Hospital 3	1.29 (1.17–1.42)	1.47 (1.25–1.72)	1.47 (1.26–1.71)
Hospital length of stay	0.98 (0.98–0.99)	0.98 (0.97–0.99)	0.98 (0.97–0.99)
Initial kidney function			
Initial eGFR value	0.95 (0.94–0.95)	0.97 (0.96–0.98)	0.97 (0.96–0.98)
Initial eGFR value square	1 (1–1)	1 (1–1)	1 (1–1)
Medications administered			
Nephrotoxic[b]	1.03 (0.96–1.12)	0.96 (0.85–1.08)	0.96 (0.85–1.08)
Crystalloid fluids	0.55 (0.51–0.6)	0.6 (0.52–0.68)	0.59 (0.52–0.67)
Acute illness severity indicators[c]			
SOFA score	1.08 (1.06–1.11)	1.11 (1.07–1.14)	1.11 (1.07–1.14)
Hypotension	0.72 (0.59–0.87)	0.73 (0.56–0.96)	0.73 (0.56–0.96)
Anemia	1.14 (1.05–1.24)	1.07 (0.94–1.21)	1.07 (0.95–1.21)
Hypoalbuminemia	1.5 (1.38–1.63)	1.43 (1.26–1.63)	1.43 (1.26–1.63)
Comorbidities[d]			
Diabetes mellitus	1.03 (0.95–1.13)	1.04 (0.9–1.19)	1.04 (0.91–1.19)
Hypertension	0.99 (0.91–1.08)	0.99 (0.87–1.12)	0.98 (0.87–1.12)
Congestive heart failure	1.09 (1–1.2)	1.23 (1.04–1.45)	1.23 (1.05–1.45)
HIV/AIDS	0.49 (0.24–1.01)	0.18 (0.06–0.56)	0.18 (0.06–0.55)
Chronic kidney disease	0.85 (0.77–0.93)	0.9 (0.77–1.05)	0.9 (0.77–1.05)
Number of observations	14,449	14,449	14,449

Results are odds ratios with 95% confidence intervals in parentheses. Acute kidney injury (AKI) defined using Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine (sCr)-based criteria as an absolute increase of 0.3 mg/dL or 1.5 times increase over pre-encounter baseline

[a] Hospital 1, urban academic; hospital 2, urban academic–community hybrid; hospital 3, suburban community

[b] Medications from the following classes: angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, antimicrobial, loop and thiazide diuretic, nonsteroidal anti-inflammatory, and other

[c] Based on vital signs and laboratory analyses from the index ED visit: Sequential Organ Failure Assessment (SOFA) score (derived from the lowest calculated PaO_2/FiO_2 ratio, lowest platelet count, highest bilirubin, lowest mean arterial pressure with the highest recorded rate of infusion of adrenergic agents, lowest Glasgow Coma Score, and highest sCr), hypotension (systolic blood pressure < 80 mm Hg), anemia (hemoglobin < 13 g/dL or < 12 g/dL for men and women, respectively), hypoalbuminemia (albumin < 3.5 g/dL)

[d] Based on ICD-10-CM diagnostic codes for chronic medical problems present during index ED visit

Table 3 Association between contrast exposure and new dialysis within 180 days

Characteristics	Dialysis, OR (95% CI) unmatched	Dialysis, OR (95% CI) propensity weighted	Dialysis, OR (95% CI) entropy balanced
Intravenous contrast administration	0.9 (0.65–1.24)	0.67 (0.47–0.96)	0.69 (0.48–0.98)
Female	0.94 (0.8–1.11)	1.12 (0.8–1.57)	1.09 (0.79–1.52)
Age in years			
18–44	Ref	Ref	Ref
45–64	0.72 (0.55–0.93)	1.19 (0.68–2.1)	1.18 (0.68–2.03)
65–84	0.54 (0.41–0.71)	0.95 (0.51–1.79)	0.94 (0.51–1.72)
85+	0.17 (0.11–0.27)	0.18 (0.05–0.63)	0.18 (0.05–0.62)
Race			
White	Ref	Ref	Ref
Black	0.88 (0.74–1.05)	1.03 (0.72–1.46)	1.03 (0.73–1.45)
Other	1.35 (1.01–1.81)	1.6 (0.87–2.97)	1.6 (0.87–2.92)
Location[a]			
Hospital 1	Ref	Ref	Ref
Hospital 2	0.57 (0.46–0.69)	0.5 (0.33–0.77)	0.52 (0.34–0.79)
Hospital 3	0.79 (0.64–0.99)	0.67 (0.39–1.16)	0.69 (0.41–1.18)
Hospital length of stay	1.04 (1.03–1.04)	1.03 (1.02–1.03)	1.03 (1.02–1.03)
Initial kidney function			
Initial eGFR value	0.91 (0.9–0.92)	0.93 (0.91–0.95)	0.93 (0.91–0.95)
Initial eGFR value square	1 (1–1)	1 (1–1)	1 (1–1)
Medications administered			
Nephrotoxic[b]	1.46 (1.22–1.74)	1.5 (1.01–2.22)	1.5 (1.02–2.21)
Crystalloid fluids	0.45 (0.38–0.54)	0.66 (0.47–0.94)	0.65 (0.46–0.91)
Acute illness severity indicators[c]			
SOFA score	1.17 (1.12–1.22)	1.2 (1.12–1.29)	1.19 (1.11–1.28)
Hypotension	0.69 (0.46–1.02)	0.52 (0.29–0.92)	0.53 (0.3–0.94)
Anemia	1.99 (1.58–2.52)	1.9 (1.16–3.12)	1.94 (1.21–3.1)
Hypoalbuminemia	1.79 (1.5–2.13)	2.69 (1.85–3.9)	2.62 (1.82–3.77)
Comorbidities[d]			
Diabetes mellitus	1.1 (0.92–1.31)	1.06 (0.74–1.52)	1.05 (0.74–1.49)
Hypertension	1.03 (0.87–1.23)	0.69 (0.49–0.97)	0.7 (0.5–0.97)
Congestive heart failure	1.33 (1.11–1.6)	1.19 (0.84–1.69)	1.2 (0.85–1.69)
HIV/AIDS	1.01 (0.31–3.28)	2.19 (0.32–15.17)	1.91 (0.29–12.62)
Chronic kidney disease	1.2 (1.01–1.43)	1.19 (0.86–1.63)	1.17 (0.86–1.6)
Number of observations	14,449	14,449	14,449

Results are odds ratios with 95% confidence intervals in parentheses

[a] Hospital 1, urban academic; hospital 2, urban academic–community hybrid; hospital 3, suburban community

[b] Medications from the following classes: angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, antimicrobial, loop and thiazide diuretic, nonsteroidal anti-inflammatory, and other

[c] Based on vital signs and laboratory analyses from the index ED visit: Sequential Organ Failure Assessment (SOFA) score (derived from the lowest calculated PaO_2/FiO_2 ratio, lowest platelet count, highest bilirubin, lowest mean arterial pressure with the highest recorded rate of infusion of adrenergic agents, lowest Glasgow Coma Score, and highest sCr), hypotension (systolic blood pressure < 80 mm Hg), anemia (hemoglobin < 13 g/dL or < 12 g/dL for men and women, respectively), hypoalbuminemia (albumin < 3.5 g/dL)

[d] Based on ICD-10-CM diagnostic codes for chronic medical problems present during index ED visit

Discussion

Among patients with pre-existing AKI, contrast administration was not associated with persistent AKI at hospital discharge or an increased risk of dialysis initiation within 180 days. These results were consistent when analyses were performed for all ED patients, for the subset with lowest eGFR, and for those who required ICU admission.

For nearly 70 years, cases of AKI that followed CM administration were assumed to be caused by CM [40, 41]. Over the past decade, numerous high-quality

studies performed in a wide range of populations and practice settings have failed to support this causal relationship [9–15]. Collectively, these data strongly suggest that the risk for AKI historically attributed to CM has been overestimated. Consequently, in 2020, the American College of Radiology (ACR) and National Kidney Foundation (NKF) reduced the recommended level of caution for administering CM to patients with stable pre-existing kidney disease [16, 17]. Although the ACR-NKF consensus statement represents an evidence-driven paradigm shift among the nephrology and radiology communities, it identifies a paucity of evidence analyzing the association between CM administration and worsening kidney function among patients with unstable renal function, including those with pre-existing AKI [18].

This large multi-center study fills this research gap for patients with AKI on arrival to the acute care setting by demonstrating no significant association between the administration of contrast and AKI persistence during the index hospitalization or initiation of dialysis within 180 days of the index encounter. To our knowledge, this is the first well-controlled study to test for an association between IV CM administration and subsequent renal dysfunction among patients with community-acquired AKI preceding CM exposure.

This finding has important clinical implications since persistent AKI among hospitalized patients is associated with an increased likelihood of numerous adverse events, including incident or progressive chronic kidney disease, long-term dialysis, and all-cause mortality [4]. During the early stages of acute care episodes, patients who present with a pre-existing AKI are at an unknown position on their renal dysfunction trajectory (i.e., potentially improving, plateauing, or worsening). Initiation of nephroprotective strategies and avoidance of nephrotoxins during this early portion of the hospital encounter is important to clinicians for whom the administration of CM can be a vital tool to confirm or exclude potentially life-threatening diagnoses among undifferentiated patients [3, 24]. A dogmatic belief that CM is a leading cause of iatrogenic AKI leads many to withhold CM in scenarios where risk for adverse kidney outcomes is perceived to be high, an observation supported by our finding that CM was more commonly administered to patients with less severe stages of AKI and a higher initial eGFR (Fig. 1 and Table 1). However, other nephrotoxic medications are often administered to these same patients (Table 1) [9, 11, 42]. This study demonstrates that, while certain identifiable conditions such as hypoalbuminemia and an elevated SOFA score are associated with AKI persistence at hospital discharge and the patient-centered outcome of dialysis initiation within 6 months of an index AKI encounter, administration of CM is not [31, 32, 43].

Our finding that CM administration was not associated with persistent AKI for patients with community-acquired AKI and severe renal impairment (eGFR < 30 mL/min/1.73 m^2) at the time of ED arrival (38% of our cohort) is important (Supplemental Table 3). This observation is consistent with many recent studies that have measured the association between CM administration and subsequent AKI in patients with CKD and found none, even among patients with eGFR < 30 mL/min/1.73 m^2 [9, 11, 12]. Other studies have observed some risk of AKI associated with CM administration in those with severely impaired kidney function [10, 44]. Consequently, in the absence of randomized trials differentiating CA-AKI from CI-AKI in patients with eGFR < 30 mL/min/1.73 m^2, uncertainty remains as to the true relationship between CM and adverse renal outcomes for these patients. Nevertheless, the results reported here add to a growing body of evidence suggesting that, among even those with severe renal impairment, the risk for adverse kidney outcomes attributable to CM is substantially lower than historically believed.

Furthermore, our finding that CM administration was not associated with persistent AKI among patients with community-acquired AKI admitted from the ED to the ICU (12.8% of our cohort) is notable (Supplemental Table 4). Intensivists frequently manage critically ill patients with community-acquired AKI and this study strengthens the existing evidence demonstrating no association between CM administration and subsequent renal dysfunction among ICU patients [14]. As intensivists rely on IV CM as an invaluable tool for the evaluation of disease, when its administration is denied or delayed due to perceived risks of CI-AKI, patients are potentially exposed to indirect harm related to delayed and missed diagnosis [8, 16, 17]. Within the limitations of a sub-group analysis, the results of this study suggest that, when indicated, CM may be safely administered to ICU patients with pre-existing AKI.

Perhaps most importantly, for the patient-centered outcome of new dialysis initiation, we observed that patients who receive CM are not more likely to require kidney replacement therapy than those who do not receive CM. After propensity weighting and entropy balancing, these patients appear to be at lower risk for this outcome within 180 days of the index encounter (Table 3). This counterintuitive finding (i.e., the suggestion that CM is nephroprotective against dialysis) is likely a result of the retrospective nature of our study which does not allow for measurement of subsequent renal injury that may have occurred in the 180 days following the index encounter. It is further exacerbated by

our observational dataset being drawn from a clinical environment in which CM is withheld from patients perceived to be at increased risk for adverse kidney outcomes from other causes (e.g., sepsis, decompensated CHF, hypovolemia). Further study is warranted to better understand clinician behaviors and decision-making regarding CM administration in these patients.

This study is strengthened by its large sample size, highly granular clinical dataset, and propensity weighting and entropy balancing analyses, but does have important limitations. First, clinical data from a single university-based health system were analyzed and results could reflect treatment decisions specific to this system. However, three discrete hospitals within this system—each representing a different practice environment (academic, community, and academic–community hybrid) with distinct clinical patterns and institutional protocols—were included to strengthen the generalizability of our results. Second, the retrospective nature of the study limits analysis to events recorded in this health system's EHR. This includes our secondary outcome of dialysis initiation, which was captured by ICD-10 codes and may have missed patients started on dialysis in other health systems though the likelihood that such an unmeasured outcome would have occurred disproportionately in either study group is low. Third, all included encounters were from patients admitted to the hospital so it is possible that important trends were missed in patients with AKI discharged from the ED. However, admitted patients tend to be sicker than those discharged from the ED and thus at higher risk for AKI persistence or progression [45]. Fourth, many patients were excluded from this analysis because they did not have sCr measured in the 180 days preceding the index encounter, precluding calculation of baseline renal function; this is a potential source of selection bias. In keeping with consensus recommendations, we excluded these patients rather than impute a baseline to avoid including patients whose sCr was elevated due to CKD rather than AKI, since our objective was to assess the association between CM and renal dysfunction in patients with community-acquired AKI and there is abundant literature on the association between CM and adverse renal outcomes in patients with CKD [5, 16, 17]. Finally, while propensity weighting and entropy balancing were used to mitigate the selection bias associated with treatment assignment and adjust for factors contributing to the clinical decision to administer CM, this approach is limited by an inability to include all factors that could influence this decision. However, the calculated E values of 1.23, 1.54 and 1.79 at respective risk ratios of 1.0, 1.1 and 1.2 suggest that our analysis was robust to unmeasured confounding [37].

Despite the numerous large and well-controlled retrospective analyses in both unselected and selected patient populations that have found no independent association between IV CM administration and AKI, the concept of CI-AKI persists in both clinical care and research [46, 47]. Over 2300 studies on contrast-induced nephropathy have been published in the past two decades, alone. Although this current study adds to the now substantial body of observational evidence that suggests no association between CM and subsequent renal dysfunction, no randomized controlled trial has been performed to definitively answer this question. Consequently, a prospective randomized controlled trial is warranted to overcome the inherent limitations of retrospective observational research and to fully determine the contribution of intravenous contrast media to the development, or persistence, of AKI.

Conclusions

Among nearly 14,500 patients who met KDIGO sCr-based criteria for AKI on arrival to the ED, we found no independent association between the administration of CM and persistence of AKI or an increased risk of dialysis initiation within 180 days. Our findings suggest that the recent ACR-NKF consensus recommendations for use of IV CM in patients with stable renal disease may also be applied to patients with pre-existing AKI [16, 17].

Supplementary Information
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Data availability
The clinical data used in this study are from the Johns Hopkins Health System (JHHS). These individual-level patient data are protected for privacy. Qualified researchers affiliated with Johns Hopkins University (JHU) may apply for access through the Johns Hopkins Institutional Review Board (IRB) (https://www.hopkinsmedicine.org/institutional_review_board/). Those not affiliated with JHU seeking to collaborate may contact the corresponding author. Access to

these data for research collaboration with JHU must comply with IRB and data sharing protocols (https://ictrweb.johnshopkins.edu/ictr/dmig/Best_Practice/c8058e22-0a7e-4888-aecc-16e06aabc052.pdf).

Declarations

Conflicts of interest
The authors declare that they do not have any conflicts of interest.

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