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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Nephrotoxicity of gadolinium-based contrast in the setting of renal artery intervention: retrospective analysis with 10-year follow-up

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PURPOSE
We aimed to determine the incidence rate and potential risk factors for postcontrast acute kidney injury (PC-AKI) as well as the long-term clinical implications on dialysis and mortality in patients with chronic kidney disease (CKD) who underwent renal artery stent placement exclusively with gadolinium-based contrast agents.

METHODS
This retrospective study reviewed 412 patients with CKD who underwent renal artery stent placement. Sixty-eight patients underwent intervention exclusively with gadolinium-based contrast agents and were analyzed. Criteria for PC-AKI included either an absolute serum creatinine increase >0.3 mg/dL or percentage increase in serum creatinine >50% within 48 hours of intervention. Logistic regression analysis was performed to identify risk factors for PC-AKI. The cumulative proportion of patients who died or went on to hemodialysis was determined using Kaplan-Meier survival analysis.

RESULTS
The incidence of PC-AKI was 14.7%. The rate of AKI decreased for every 1 unit increase in glomerular filtration rate (GFR, odds ratio [OR]=0.91, $P = 0.047$). Prehydration was associated with a lower PC-AKI rate (OR=0.17; $P = 0.015$). Acute kidney injury after intervention was associated with an increased rate of dialysis (Hazard ratio [HR]=4.51, $P = 0.002$) and mortality (HR=2.52; $P = 0.027$).

CONCLUSION
Gadolinium-based contrast agents are potentially nephrotoxic when used for endovascular intervention in patients with CKD. The risk of PC-AKI increased with lower GFR and decreased with prehydration. Dialysis and mortality risk were increased in patients who developed PC-AKI.

Gadolinium-based contrast agents (GBCA) are widely used in magnetic resonance imaging (MRI) to improve image contrast and diagnostic accuracy. In 2006, the association between GBCA and nephrogenic systemic fibrosis (NSF) was identified (1–3). As a result, these contrast agents became contraindicated in patients with renal dysfunction. Prior to the recognition of gadolinium-associated NSF, GBCA was used as an alternative to iodinated contrast for patients with chronic kidney disease (CKD) undergoing fluoroscopic procedures. Several studies prior 2006 looked at the potential nephrotoxicity of GBCA (4–6). However, the quantity of data in the literature pales in comparison to that of iodinated contrast.

A few cases of postcontrast acute kidney injury (PC-AKI) after GBCA administration have been reported (6, 7). The majority of these studies were published prior to 2006 and data on gadolinium nephrotoxicity remains limited (8). While GBCA is no longer used as a substitute for iodinated contrast in patients with CKD, it is occasionally used in patients with severe iodinated contrast allergies who require fluoroscopically-guided intervention (9, 10). Furthermore, patients with predialysis CKD continue to receive GBCA routinely for MRI scans. The present study aimed to identify the incidence rate and potential contributing factors for PC-AKI as well as the long-term clinical implications on dialysis and mortality in patients with CKD who underwent renal artery stent placement exclusively with GBCA.

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Methods

Institutional review board approval was obtained for this single-institution retrospective longitudinal follow-up study. A consent waiver was obtained. All patients who underwent endovascular renal artery stent placement from 1996 through 2006 were identified. No patient was administered GBCA for renal artery intervention after 2006 due to the emergence of data which showed gadolinium was linked to NSF. Of the 412 patients identified, 340 were excluded due to the use of iodinated contrast agents. An additional 4 patients were excluded due to incomplete follow-up data. The remaining 68 patients, all of whom underwent renal artery intervention exclusively with GBCA, were analyzed. CO_2 was not used in any patient. Baseline patient characteristics are summarized in Table 1.

Laboratory data were obtained within one month prior to intervention. Information on the need for dialysis for chronic end-stage renal disease was obtained by querying the USRDS database. Dialysis events for acute non-PC-AKI indications were not recorded. Mortality information was obtained by querying death data in the United States Social Security Death Index and health system medical record.

Procedure

Patients were referred to the Intervention Radiology Division for renal artery stent placement if they demonstrated medically refractory hypertension with Doppler ultrasound measuring a peak systolic velocity >180 cm/s or a renal-to-aortic ratio >3.5. All procedures were performed by three board-certified interventional radiologists. Antihypertensive and statin medications were continued until the day of the procedure in all patients. Intravascular access was obtained from the common femoral artery. Renal artery angiograms were obtained. Stenosis >50% of the luminal diameter was considered significant and was treated with balloon-mounted bare-metal stent. Embolic protection devices were not used in any of the cases.

Two contrast agents were used, Omniscan (Gadodiamide, GE Healthcare) and ProHance (Gadoteridol, Bracco Diagnostics). Contrast agent choice was based on operator preference. Fifty patients (73.5%) were admitted up to 24 hours before the procedure and pretreated with intravenous isotonic fluids at a rate of 1 mL/kg/h. Bicarbonate and N-acetylcysteine (NAC) administration were not recorded for this study.

Measured outcomes

The primary outcome was the incidence of PC-AKI within 48 hours of renal stent placement. Secondary endpoints included incidence of hemodialysis and death. Estimated glomerular filtration rate (GFR), 24-hour proteinuria, medications and comorbidities including chronic kidney disease (CKD), cardiac disease, metabolic disease, and smoking history were analyzed as possible contributing factors for PC-AKI.

GFR was calculated based on preintervention serum creatinine levels and patient demographic information using the Modification of Diet in Renal Disease equation (11). Chronic kidney disease stages were determined based on the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group classification (12).

Acute kidney injury was defined as an absolute serum creatinine increase ≥0.3 mg/dL or a relative increase in serum creatinine ≥50% within 48 hours of intervention based on the Acute Kidney Injury Network (AKIN) criteria, which is the standard criteria adopted by the American College of Radiology (13). A reduction in urine output ≤0.5 mL/kg/hr for at least 6 hours within 48 hours of a nephrotoxic event is also considered criteria for PC-AKI; however, this metric was not available for analysis.

Table 1. Baseline characteristics of patients who underwent renal artery stent placement

	PC-AKI (n=10)	No PC-AKI (n=58)	Total (n=68)
Gender, n (%)			
Female	2 (20.0)	30 (51.7)	32
Male	8 (80.0)	28 (48.3)	36
Age (years), mean±SD	73.2±12.2	73.6±8.4	
Bilateral renal artery stenosis, n (%)	2 (80)	15 (25.9)	17
GFR (mL/min per 1.73 m^2), mean±SD	18.2±7.9	25.0±10.0	
Proteinuria (mg/24 h), mean±SD	1970.1±3174.3	1221.9±2216.1	
CKD stage, n (%)			
1/2	0 (0)	0 (0)	0
3A	0 (0)	3 (5.2)	3
3B	1 (10.0)	11 (19.0)	12
4	5 (50.0)	34 (58.6)	39
5	4 (40.0)	10 (17.2)	14
Current smoker, n (%)	2 (20.0)	13 (22.4)	15
Diabetes, n (%)	5 (50.0)	24 (41.4)	29
Coronary artery disease, n (%)	8 (80.0)	47 (81.0)	55
Hyperlipidemia, n (%)	8 (80.0)	53 (91.4)	61
Hypertension, n (%)	9 (90.0)	56 (96.6)	65

PC-AKI, postcontrast acute kidney injury; SD, standard deviation; GFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Main points

- Gadolinium-based contrast agents (GBCAs) are potentially nephrotoxic in patients with CKD, with a postcontrast acute kidney injury (PC-AKI) rate of 14.7% after renal artery stenting exclusively using GBCAs.
- Renal prophylaxis with intravenous hydration prior to renal stenting decreased the risk for PC-AKI ($P = 0.015$).
- Patients who developed PC-AKI had increased risk of chronic dialysis and mortality ($P = 0.002$ and $P = 0.027$, respectively).

Statistical analysis

Statistical analysis was performed with SAS version 9.4 (SAS Institute). Logistic regression analysis was performed to identify risk factors for PC-AKI. Kaplan-Meier analyses and Cox proportional hazard models were used to assess hemodialysis, mortality and associated risk factors after PC-AKI. Statistical significance was defined as $P < 0.05$.

Results

Of the 68 patients who underwent renal artery stent placement with GBCA, 10 (14.7%) developed PC-AKI within 48 hours after intervention. Potential factors associated with PC-AKI are demonstrated in Table 2. Patients who had normal postintervention renal function had an average baseline GFR of 25.0±10.0 mL/min per 1.73 m^2 compared with 18.2±7.9 mL/min per 1.73 m^2 among patients with PC-AKI. The rate of PC-AKI decreased for every 1 unit increase in GFR (odds ratio [OR]=0.91; 95% Confidence interval [CI], 0.82–0.99; P = 0.047). Other renal function parameters including stage 4 CKD (OR=2.06; 95% CI, 0.22–19.24; P = 0.86), stage 5 CKD (OR=5.60, 95% CI, 0.54–57.92; P = 0.098), baseline creatinine (OR=1.87; 95% CI, 0.97–3.60; P = 0.063) and proteinuria (OR=1.11; 95% CI, 0.88–1.41; P = 0.37) were not significantly associated with PC-AKI. Prehydration was associated with a lower PC-AKI rate (OR=0.17; 95% CI, 0.04–0.72; P = 0.015). Contrast volume was not significantly associated with PC-AKI (OR=1.02; 95% CI, 0.83–1.24; P = 0.86).

No patient was on dialysis at the time of intervention and no patient required emergent dialysis for PC-AKI. Twenty-seven patients (39.7%) went on hemodialysis for end-stage renal disease. Of the patients who had PC-AKI, six (60%) eventually went on long-term hemodialysis. Kaplan-Meier analysis of dialysis-free survival is demonstrated in Fig. 1. Acute kidney injury after intervention was associated with an increased rate of dialysis (hazard ratio [HR]=4.51; 95% CI, 1.71–11.73; P = 0.002) (Table 3). For every 1 unit increase in GFR, the risk of dialysis significantly decreased (HR=0.90; 95% CI, 0.84–0.95; P < 0.001). Other factors significantly associated with increased incidence of dialysis included elevated creatinine (HR=2.89; 95% CI, 1.88–4.46; P < 0.001), and stage 5 CKD (HR=11.2; 95% CI, 3.29–50.08; P < 0.001).

A total of 49 patients (72.1%) died over the follow-up period (Fig. 2). Factors associated with mortality are summarized in Table 2. Similar to patients who went on dialysis, PC-AKI (HR=2.51; 95% CI, 1.11–5.66; P = 0.027) and elevated creatinine (HR=1.37; 95% CI, 1.02–1.86; P = 0.039) were significantly associated with mortality (Table 4). Diabetes was also associated with higher rates of death (HR=2.92; 95% CI, 1.58–5.39; P = 0.001). For every 1 unit increase in GFR, the risk of death significantly decreased (HR 0.96; 95% CI, 0.93–0.99; P < 0.020). Patients taking statin medications had lower mortality (HR=0.36; 95% CI, 0.14–0.92; P = 0.034).

Table 2. Logistic regression analysis for predictors of postcontrast acute kidney injury following renal artery stent placement

	OR[a]	Lower 95% CI	Upper 95% CI	*P*
Male sex	4.29	0.84	21.94	0.08
Proteinuria[b]	1.11	0.88	1.41	0.37
Creatinine	1.87	0.97	3.60	0.06
GFR	0.91	0.82	0.99	0.047
CKD stage				
3A/3B	1.00			
4	2.06	0.22	19.24	0.86
5	5.60	0.54	57.92	0.098
Current smoker	0.79	0.15	4.19	0.78
Diabetes	1.42	0.37	5.44	0.61
Coronary artery disease	0.85	0.16	4.63	0.85
Hypertension	0.32	0.03	3.92	0.37
Hyperlipidemia	0.38	0.06	2.28	0.29
Statin medication	0.38	0.06	2.28	0.29
Antihypertensive medication				
ACEI/ARB	0.94	0.17	5.04	0.94
Beta blocker	0.85	0.09	8.14	0.89
Bilateral intervention	0.72	0.14	3.76	0.68
Prehydration	0.17	0.04	0.72	0.015
Contrast volume	1.02	0.83	1.24	0.86
Contrast type				
ProHance	1.00			
Omniscan	1.39	0.27	7.30	0.69

OR, odds ratio; CI, confidence interval; GFR, glomerular filtration rate; CKD, chronic kidney disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]Odds ratios for continuous variables are all per 1 unit increase unless otherwise specified.
[b]Per 1000 unit increase.

Discussion

In this study, the incidence of PC-AKI after renal artery stent placement using exclusively GBCA was 14.7%. The rates of PC-AKI increased as preprocedure renal function decreased. Also, patients who developed PC-AKI were found to have higher rates of going on to chronic dialysis for end-stage renal disease as well as mortality. These finding suggest a need for caution when considering the use of GBCA as a substitute for iodinated contrast in endovascular procedures.

All patients who developed PC-AKI after renal artery stent placement had stage 3B CKD or greater. Acute kidney injury after GBCA exposure has been previously de-

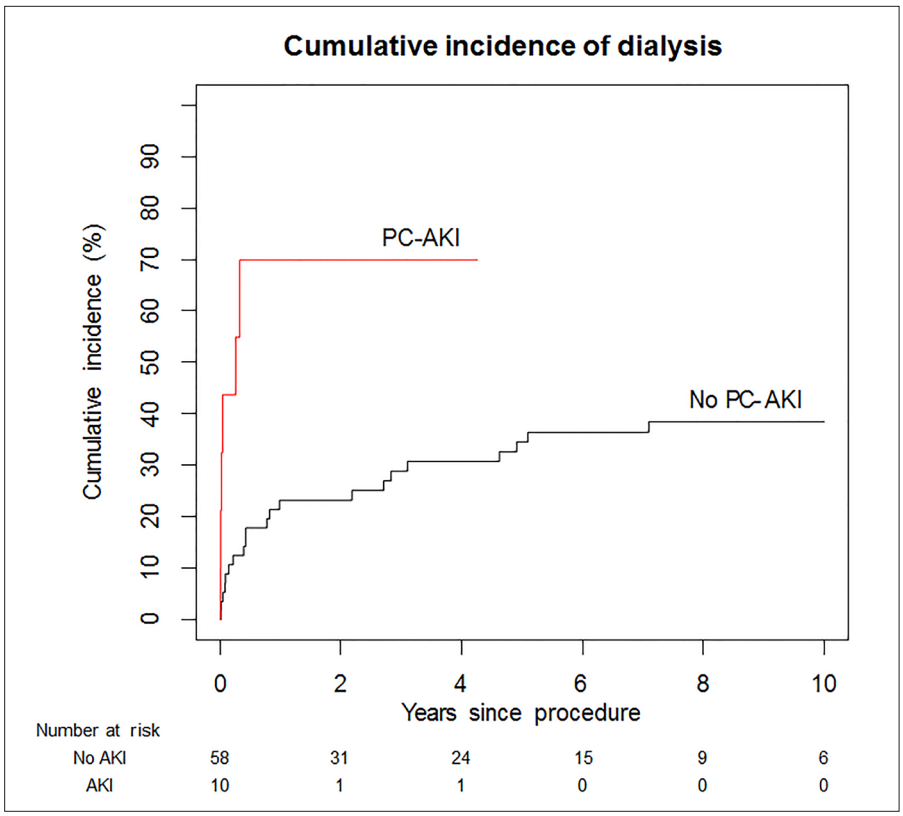

Figure 1. Kaplan-Meier hemodialysis-free survival curves show that patients with postcontrast acute kidney injury (PC-AKI) had higher rates of eventually requiring dialysis.

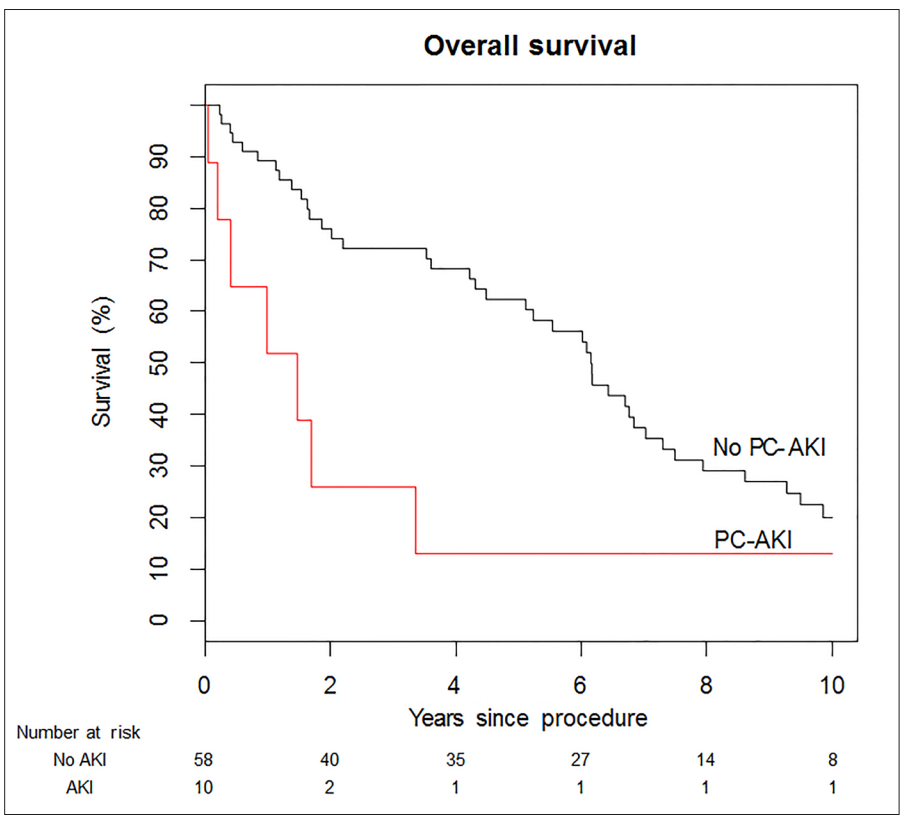

Figure 2. Kaplan-Meier overall survival curves demonstrate that patients with postcontrast acute kidney injury (PC-AKI) had higher morality.

scribed in the setting of contrast-enhanced MRI studies. Chien et al. (14) reported a PC-AKI rate of 16.5% among 158 patients with renal impairment, similar to the current study. Sepsis was determined to be a significant risk factor for PC-AKI in that study. Additionally, Ergun et al. (15) demonstrated a PC-AKI rate of 12.1% among 91 patients with stage 3 and 4 CKD (15). No prior studies on GBCA-associated PC-AKI after renal artery stent placement were available for comparison. However, the previously published PC-AKI rate after renal artery stent placement with iodinated contrast was 5.9% (16). In that study, the rates for kidney injury in patients with Stage 3B, 4, and 5 CKD were 5.9%, 3.5%, and 25%, respectively, which were lower than the rates observed in the current study of 8.3%, 12.8%, and 28.6%, respectively. Although a positive trend between PC-AKI incidence and CKD stage was observed, this association was not statistically significant. Similar to the present study, no embolic protection was used. The mean iodinated contrast volume in that study was 135.2±72.2 mL. Spinosa et al. (4) reported only 1 out of 18 patients developed PC-AKI after lower extremity endovascular intervention using a mean GBCA volume of 55 mL. The mean GBCA volume in this study was 75.8±32.4 mL. Although this was higher than the prior study, no significant difference in contrast volume was found between the PC-AKI and non-PC-AKI groups in the current study.

In 2002, the Contrast Media Safety Committee of the European Society of Urogenital Radiology concluded that according to experimental animal data, GBCA was more nephrotoxic than iodinated contrast at equivalent x-ray attenuating doses (17). Other retrospective studies found that GBCA was less nephrotoxic than iodinated contrast in the setting of both angiographic procedures with intra-arterial contrast and MRI studies with intravenous contrast (5, 18). Studies on PC-AKI with iodinated contrast have found intra-arterial contrast administration to be more nephrotoxic than intravenously administered contrast (19). However, similar studies have not been performed on GBCAs. Moreover, studies using intra-arterial GBCA focused primarily on lower extremity intervention for peripheral arterial disease, which would result in contrast bypassing the kidneys on first pass and may be a less optimal model for PC-AKI than direct renal artery injections of contrast. The findings of the present study sug-

Table 3. Cox proportional hazard model assessment for dialysis risk factors after PC-AKI

	HR[a]	Lower 95% CI	Upper 95% CI	*P*
Age	1.12	0.71	1.77	0.64
Male sex	0.83	0.39	1.77	0.63
Proteinuria[b]	1.28	1.07	1.53	0.007
Creatinine	2.89	1.88	4.46	<0.001
GFR	0.90	0.84	0.95	<0.001
CKD stage				
3A/3B	1.0			
4	2.70	0.77	9.46	0.12
5	12.84	3.29	50.08	<0.001
Statin medication	0.66	0.20	2.21	0.50
Antihypertensive medication				
ACEI/ARB	0.51	0.20	1.27	0.15
Beta blocker	0.53	0.18	1.55	0.25
Current smoker	0.58	0.20	1.69	0.32
Diabetes	1.48	0.69	3.19	0.32
Coronary artery disease	2.90	0.87	9.70	0.08
Hypertension	0.26	0.08	0.87	0.03
Hyperlipidemia	0.55	0.19	1.59	0.27
Bilateral intervention	0.39	0.13	1.14	0.09
Prehydration	0.65	0.29	1.50	0.31
PC-AKI	4.51	1.71	11.73	0.002

PC-AKI, postcontrast acute kidney injury; HR, hazard ratio; CI,confidence interval; GFR, glomerular filtration rate; CKD, chronic kidney disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]Odds ratios for continuous variables are all per 1 unit increase unless otherwise specified.
[b]Per 1000 unit increase.

gest that gadolinium-based contrast is potentially nephrotoxic although the contrast doses were higher than what is routinely used in MRI (20, 21).

The rate of dialysis-free survival was lower among patients with PC-AKI. The data on dialysis after GBCA-induced kidney injury in the literature is limited. Sam et al. (5) reported that 2 of 7 (29%) patients with CKD who developed AKI after gadolinium exposure went on to long-term dialysis, fewer than the 60% observed in the current study. A prior study on PC-AKI after renal artery stent placement using iodinated contrast found no significant risk for long-term dialysis after PC-AKI (16). Similarly, McDonald et al. (22) reported PC-AKI after CT did not increase dialysis risk. Our findings suggest PC-AKI after GBCA may have greater implications on long-term renal function compared with iodinated contrast.

Patients who developed PC-AKI after renal artery stenting using gadolinium had higher rates of mortality. This is the first study to demonstrate increased mortality risk from PC-AKI related to GBCA exposure. Previous studies on iodinated contrast demonstrated increased mortality among patients with PC-AKI (23–26). For example, Abe et al. (23) reported that mortality after PC-AKI increased with a hazard ratio of 2.26 ($P < 0.0001$) among 4371 patients who underwent coronary intervention. This mortality risk may be greater in patients with persistent creatinine elevation for at least one year after intervention compared with patients who had transient elevations that resolved within one year (27). Takahashi et al. (16) reported that mortality risk was not significantly associated with PC-AKI after renal artery stenting with iodinated contrast, with a hazard ratio of 1.44 ($P = 0.17$) (16).

No significant difference in PC-AKI rate was observed between Omniscan and ProHance contrast. Both contrast agents are nonionic. Omniscan possesses a linear molecular structure, which is less stable and has greater gadolinium dissociation. Consequently, patients who receive Omniscan may have higher risk for NSF and cerebral tissue deposition. ProHance has a macrocyclic structure that encompasses the gadolinium ion resulting in less dissociation. The role of the gadolinium ion in PC-AKI is unclear, but higher GBCA volume is associated with nephrotoxicity (28). Iodinated contrast viscosity is correlated with renal parenchyma tissue hypoxia suggesting that the physical properties of the contrast medium have significant effect on renal function (29). The risk for NSF may increase with higher total and cumulative GBCA exposure (30). Nevertheless, GBCA-associated skin disease has been reported to occur after exposure to volumes ranging from 20 mL to 160 mL suggesting that the correlation between contrast volume and NSF is weak (31, 32). Advanced CKD remains the most important risk factor for NSF. No patient in the present study developed NSF, confirming data showing that gadolinium-associated skin disease, despite being catastrophic, is relatively uncommon (33). This was despite relatively high volumes of GBCAs.

This study was limited by its retrospective design as well as nonstandardized medical therapy and follow-up. Short-term follow-up for patients with PC-AKI was inconsistent, limiting the evaluation of the impact of PC-AKI. Specific indications for stent placement, in addition to medically refractory hypertension in the setting of renal artery stenosis, such as rapidly declining renal function, were not recorded, which could have an impact on outcomes. Also, correlation between PC-AKI and of mortality was limited because the cause of death was unavailable. The lack of a control group prevents the true incidence of GBCA-associated PC-AKI to be delineated from iatrogenic and physiologic confound-

Table 4. Cox proportional hazard model assessment for mortality risk factors after PC-AKI

	Hazard Ratio	Lower 95% CI	Upper 95% CI	*P*
Age	1.42	0.99	2.03	0.052
Male sex	1.08	0.62	1.90	0.79
Proteinuria[a]	0.94	0.80	1.75	0.38
Creatinine	1.37	1.02	1.86	0.04
GFR	0.96	0.93	0.99	0.02
CKD stage				
3A/3B	1.00			
4	1.60	0.78	3.30	0.20
5	2.37	0.98	5.78	0.06
Statin medication	0.36	0.14	0.92	0.03
Antihypertensive medication				
ACEI/ARB	0.96	0.45	2.05	0.91
Beta blocker	0.74	0.27	2.09	0.57
Current smoker	0.88	0.45	1.74	0.72
Diabetes	2.92	1.58	5.39	0.001
Coronary artery disease	1.55	0.70	3.47	0.28
Hypertension	0.35	0.11	1.14	0.08
Hyperlipidemia	1.10	0.39	3.05	0.86
Bilateral intervention	1.16	0.62	2.17	0.65
Prehydration	0.99	0.52	1.88	0.96
PC-AKI	2.51	1.11	5.66	0.03

Hazard ratios for continuous variables are all per 1 unit increase unless otherwise specified.
PC-AKI, postcontrast acute kidney injury; HR, hazard ratio; CI,confidence interval; GFR, glomerular filtration rate; CKD, chronic kidney disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]Per 1000 unit increase.

ers. However, a prospective trial involving the administration of GBCA to patients with CKD is not feasible due to the risk of NSF. Furthermore, the interventions in this study occurred prior to the availability of embolic protection devices; other studies on PC-AKI after renal artery intervention do not account for such variables, permitting similar comparisons to those studies (16). The definition of PC-AKI in this study was based on the AKIN criteria, which are used by the American College of Radiology. Prior studies have used other definitions for PC-AKI with time to diagnosis up to 72 hours after contrast administration; also, the risk for kidney injury may increase in proportion to the number of comorbidities (34–36). This variability in PC-AKI definition and the heterogeneity of patients in this study's population may affect the final interpretation of outcomes.

In conclusion, GBCA is potentially nephrotoxic when used for endovascular intervention in patients with CKD. The risk of PC-AKI increased with lower GFR and decreased with intravenous prehydration. Dialysis and mortality risk were increased in patients who developed PC-AKI.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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