

# Intravenous Contrast Material–induced Nephropathy: Causal or Coincident Phenomenon?<sup>1</sup>

Robert J. McDonald, MD, PhD  
Jennifer S. McDonald, PhD  
John P. Bida, PhD  
Rickey E. Carter, PhD  
Chad J. Fleming, MD  
Sanjay Misra, MD  
Eric E. Williamson, MD  
David F. Kallmes, MD

## Purpose:

To determine the causal association and effect of intravenous iodinated contrast material exposure on the incidence of acute kidney injury (AKI), also known as contrast material–induced nephropathy (CIN).

## Materials and Methods:

This retrospective study was approved by an institutional review board and was HIPAA compliant. Informed consent was waived. All contrast material–enhanced (contrast group) and unenhanced (noncontrast group) abdominal, pelvic, and thoracic CT scans from 2000 to 2010 were identified at a single facility. Scan recipients were sorted into low- (<1.5 mg/dL), medium- (1.5–2.0 mg/dL), and high-risk (>2.0 mg/dL) subgroups of presumed risk for CIN by using baseline serum creatinine (SCr) level. The incidence of AKI (SCr  $\geq$  0.5 mg/dL above baseline) was compared between contrast and noncontrast groups after propensity score adjustment by stratification, 1:1 matching, inverse weighting, and weighting by the odds methods to reduce intergroup selection bias. Counterfactual analysis was used to evaluate the causal relation between contrast material exposure and AKI by evaluating patients who underwent contrast-enhanced and unenhanced CT scans during the study period with the McNemar test.

## Results:

A total of 157 140 scans among 53 439 unique patients associated with 1510 001 SCr values were identified. AKI risk was not significantly different between contrast and noncontrast groups in any risk subgroup after propensity score adjustment by using reported risk factors of CIN (low risk: odds ratio [OR], 0.93; 95% confidence interval [CI]: 0.76, 1.13;  $P = .47$ ; medium risk: odds ratio, 0.97; 95% CI: 0.81, 1.16;  $P = .76$ ; high risk: OR, 0.91; 95% CI: 0.66, 1.24;  $P = .58$ ). Counterfactual analysis revealed no significant difference in AKI incidence between enhanced and unenhanced CT scans in the same patient (McNemar test:  $\chi^2 = 0.63$ ,  $P = .43$ ) (OR = 0.92; 95% CI: 0.75, 1.13;  $P = .46$ ).

## Conclusion:

Following adjustment for presumed risk factors, the incidence of CIN was not significantly different from contrast material–independent AKI. These two phenomena were clinically indistinguishable with established SCr-defined criteria, suggesting that intravenous iodinated contrast media may not be the causative agent in diminished renal function after contrast material administration.

© RSNA, 2013

Supplemental material: <http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.12121823/-/DC1>

<sup>1</sup>From the Clinician Investigator Training Program (R.J.M.), Department of Radiology (R.J.M., J.S.M., C.J.F., S.M., E.E.W., D.F.K.), Department of Health Sciences Research (R.E.C.), and Department of Neurosurgery (D.F.K.), College of Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905; and Department of Biochemistry, Stanford University School of Medicine, Stanford, Calif (J.P.B.). From the 2012 RSNA Annual Meeting. Received August 12, 2012; revision requested October 1; revision received October 16; accepted October 25; final version accepted October 31.

Address correspondence to R.J.M. (e-mail: [mcdonald.robert@mayo.edu](mailto:mcdonald.robert@mayo.edu)).

The nephrotoxic potential of iodinated contrast media is widely accepted in the medical literature (1–5). Such injury, termed *contrast material–induced nephropathy* (CIN), is typically defined as an absolute or percentage increase in serum creatinine (SCr) level over baseline. Recently, however, the causal link between intravenous iodinated contrast material and nephrotoxicity has come under scrutiny based on several observations (6,7). First, the presumed nephrotoxicity of intravenous contrast material has been largely extrapolated from more invasive angiographic studies of intraarterial contrast material administration (6). Second, because these intraarterial studies inherently lack control groups where contrast material was not administered, they cannot extricate the true incidence of CIN from iatrogenic and physiologic confounders that also elevate SCr (8,9). Third, only a small fraction of CIN studies were directly focused on intravenous contrast material use, and of those, only 13 included control groups where contrast material was not administered (10–22). Collectively, these 13 controlled studies paradoxically

demonstrated that acute kidney injury (AKI) is as common if not more common in patients not exposed to contrast material compared with contrast material–exposed patients (23).

Although these controlled studies add value to prior uncontrolled case series regarding the true incidence of CIN, important knowledge gaps remain. Most of these studies examined small numbers of focused patient populations not randomly assigned as to whether they were administered contrast material. Thus, it remains possible that the lack of evidence for CIN in these controlled studies simply reflects selection bias where clinicians were able to triage at-risk patients away from contrast material exposure. The effect of this potential bias on the incidence of AKI remains undefined in these prior controlled studies.

The ideal mechanism for determining the nephrotoxic potential of contrast material would be a prospective randomized trial. As no such trial exists at present, important advances in our understanding of CIN could be gained through large, retrospective, controlled studies with adjustment for presumed risk factors for CIN between contrast material–exposed and unexposed cohorts (23). In our study, we therefore sought to compare the incidence of AKI between recipients of contrast material–enhanced and those of unenhanced CT scans after adjustment for potentially confounding variables with

propensity score and counterfactual analysis to determine the causal effect of intravenous contrast material administration on AKI.

## Materials and Methods

Investigator-initiated grant support for our study was provided to authors (J.S.M. and E.E.W.) by GE Healthcare (Princeton, NJ). No author of our study is a consultant to this company, and the authors had control of all data and information presented herein.

## Study Design

Design and execution of this single-center retrospective study was subject to institutional review board oversight and Health Insurance Portability and Accountability Act privacy guidelines. Informed consent was waived. All authors participated in study design. All clinical data were extracted from our electronic medical record with relational database software (DDQB; IBM, Armonk, New York) by authors (J.S.M. and R.J.M.) and were parsed on a shared-resource multinode Beowulf-style supercomputing cluster (R.J.M. and J.P.B.). Current procedural terminology coding was used to identify procedural data, and *International Classification of Diseases, Ninth Edition, Clinical Modification*


## Advances in Knowledge

- After propensity score adjustment for differences in presumed risk factors of contrast material–induced nephropathy (CIN), recipients of unenhanced CT scans are at equivalent risk of serum creatinine (SCr)–defined acute kidney injury (AKI) compared with recipients of contrast-enhanced CT scans.
- Counterfactual analysis of a large subset of patients who underwent both a contrast-enhanced and unenhanced CT scan demonstrates an equivalent likelihood of AKI after either scan.
- These results question both the utility of SCr level as a marker for kidney injury in this setting and the long-held causal relation between intravenous contrast material exposure and SCr–defined AKI.

## Implications for Patient Care

- Our study indicates that SCr–defined AKI after intravenous contrast material administration is clinically indistinguishable from contrast material–independent AKI.
- These findings suggest that CIN is either a diagnosis of misattribution or represents a condition obscured by other factors contributing to AKI.
- Prospective randomized studies are needed to define the true nephrotoxic risks of intravenous contrast material.

## Published online before print

10.1148/radiol.12121823 **Content code:** 

**Radiology 2013;** 267:106–118

## Abbreviations:

AKI = acute kidney injury

CI = confidence interval

CIN = contrast material–induced nephropathy

ICD-9 = *International Classification of Diseases, Ninth Edition, Clinical Modification*

IQR = interquartile range

SCr = serum creatinine

## Author contributions:

Guarantors of integrity of entire study, R.J.M., J.S.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, R.J.M., J.S.M., C.J.F., S.M., E.E.W., D.F.K.; clinical studies, R.J.M., S.M.; statistical analysis, R.J.M., J.S.M., J.P.B., R.E.C.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

See also articles by McDonald et al and Davenport et al and the editorial by Newhouse and RoyChoudhury in this issue.

(ICD-9) diagnostic codes were used to identify specific medical diagnoses within the electronic medical record. Additional details of the data retrieval from the electronic medical record, propensity score analysis, and counterfactual analysis are provided in Appendix E1 (online).

**Study Population**

Inclusion criteria, as shown in Figure 1, were as follows: (a) all patients who underwent an unenhanced (noncontrast group) or intravenous contrast-enhanced (contrast group) abdominal, pelvic, and/or thoracic CT scan from January 1, 2000, to December 31, 2010, at our institution; (b) who had one or more postscan SCr results during the time period of expected development of CIN (24–72 hours after CT scanning) (24); and (c) who also had at least one

baseline SCr result in the 24-hour window prior to scanning. Exclusion criteria included patients who had preexisting renal dialysis requirements; did not have sufficient SCr data to permit detection of AKI; or who underwent multiple distinct CT scans or percutaneous cardiac interventions with iodinated contrast material within a 14-day period. This 14-day threshold was selected on the basis of published contrast material use guidelines as a means to avoid the transient acute renal effects from prior contrast material exposure at the subsequent examination (24). Consecutive CT acquisitions at different anatomic locations were treated as a single-scan event.

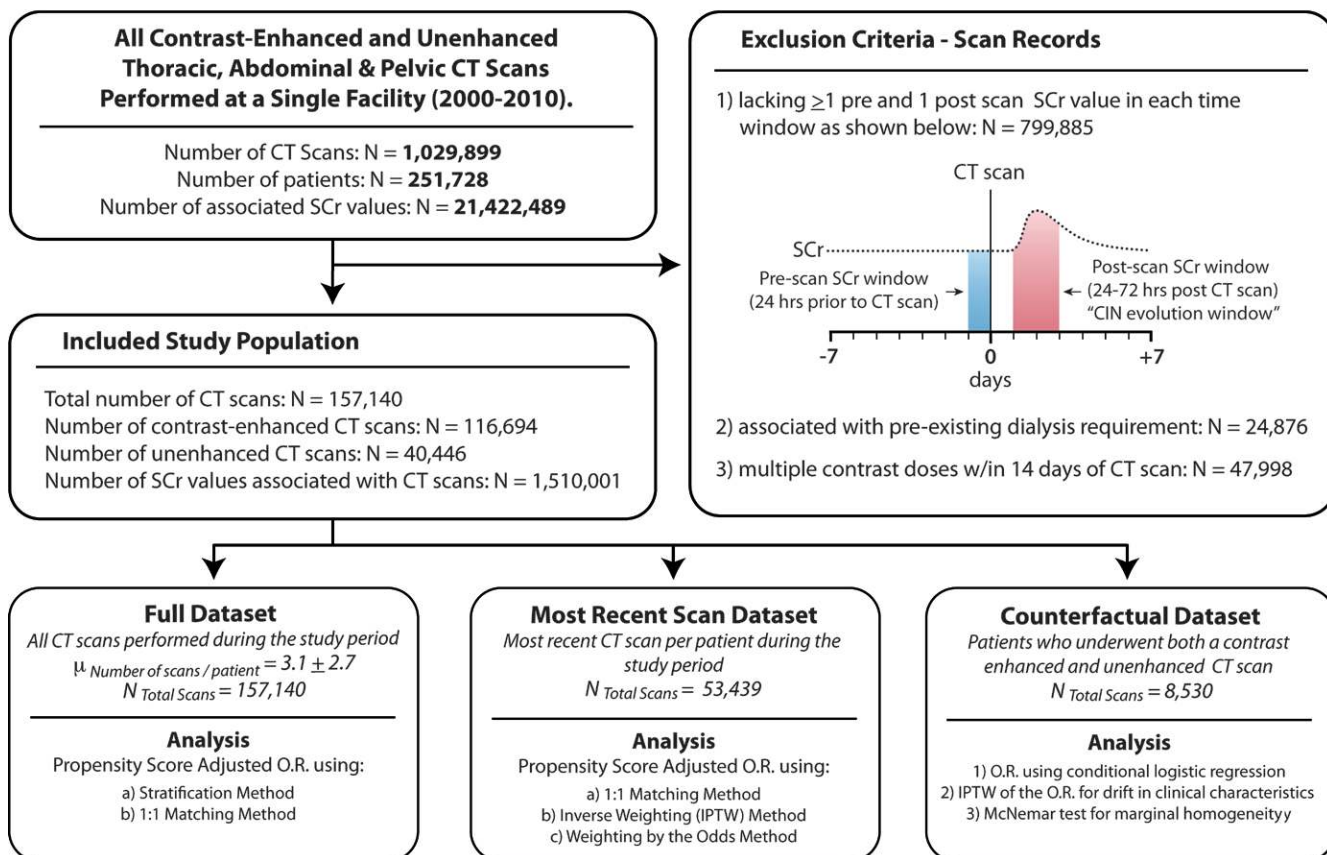
In addition to the “complete data set” representing all scan records meeting inclusion and exclusion criteria described previously, two smaller subgroups of

this data set were created for additional analyses. First, in an effort to minimize potential bias from patients who underwent multiple scans over the course of the 11-year study window, a “single-scan data set” was generated that included only the most recent scan performed per patient. Second, a “counterfactual data set” was generated that included only patients who underwent both a contrast-enhanced and unenhanced CT scan during the study time frame to assess the causal relation between intravenous contrast material administration and subsequent development of AKI as described below.

**Predictor Variables**

The exposure of interest was intravenous contrast material administration during CT scanning. Demographic information, including age, inpatient status

**Figure 1**



**Figure 1:** Study inclusion flowchart. *IPTW* = inverse probability of treatment weighting, *O.R.* = odds ratio, *w/in* = within.  $\mu$  = mean.

at the time of scan, sex, and race, were extracted from the electronic medical record. Predisposing medical conditions reportedly associated with development of AKI after contrast material administration, including diabetes, diabetic nephropathy, congestive heart failure, chronic renal failure, chronic renal pathophysiology, and acute renal failure, were also identified (25–27). Charlson comorbidity scores, a validated measure of comorbidity severity and mortality probability based on 19 unique chronic medical conditions, were calculated for each patient by using ICD-9 codes as previously described (28). All SCr data associated with each scan record were extracted from the electronic medical record and temporally sorted with respect to the date of each unique scan record with a supercomputing cluster. Scan recipients were stratified with respect to their presumptive risk for AKI by baseline SCr level as follows: low risk, SCr < 1.5 mg/dL; medium risk, SCr 1.5–2.0 mg/dL; high risk, SCr  $\geq$  2.0 mg/dL. (To convert SCr level to International System of Units [ $\mu\text{mol/L}$ ], multiply by 88.4.) These SCr-defined risk subgroups were derived from institutional practice guidelines and prior literature that have used similar thresholds to stratify the presumed risk of CIN (3,29,30).

### Outcome Variables

For our study, AKI was defined as a rise in maximal observed SCr level of 0.5 mg/dL or greater over baseline in the 24–72 hours after the time of CT scan. This definition and terminology was applied to both contrast material-dependent renal injury after contrast-enhanced CT, colloquially termed *CIN*, and contrast material-independent renal injury after unenhanced CT to provide a uniform and commonly used definition of AKI (31). This definition of AKI was chosen over the more recently proposed lower threshold for CIN/AKI of 0.3 mg/dL by the Acute Kidney Injury Network because the former is potentially more specific, less likely to yield false-positive results from cumulative biologic and assay variability, represents the definition of CIN during the

time period of our study, and remains a more commonly used definition in current medical practice (30,32–34).

### Contrast Material Use

At our institution, patients with a baseline SCr level greater than 2.0 mg/dL who warrant a contrast-enhanced CT examination received the iso-osmolar contrast agent Visipaque (iodixanol, GE Healthcare), while all others received the low-osmolar agent Omnipaque 300 (iohexol, GE Healthcare). Contrast material dosing at our institution is protocol-specific but based on a standardized dosing nomogram adjusted for patient weight and baseline renal function. Typical intravenous iodinated contrast material doses ranged between 80 and 200 mL and were followed by a 50-mL saline flush.

### Propensity Score Analysis

Propensity score adjustment represents a means to account for the potential selection bias that arises from nonrandomized distributions of covariates between treated and control groups in observational studies. Accounting for risk factors reported to be associated with the outcome of interest, a propensity score model can be generated that represents the probability of treatment in both treated and control groups (35,36). This method replicates the process in which prospective randomization controls for known confounding variables, permitting the comparison of patients with similar characteristics, thereby minimizing selection bias.

Propensity score estimates, representing the probability of intravenous contrast material administration for patients in both the contrast and noncontrast groups, were generated for each AKI risk subgroup by authors (R.J.M., J.S.M., and R.E.C.) using a logistic regression model derived from 160 unique ICD-9 codes and seven additional clinical variables (Appendix E1 [online]) (35). Covariates included in these models are shown in Table 1. The risk of AKI was analyzed after several well-established propensity score adjustment methods including stratification (37,38), 1:1 matching (39), weighting

by the odds (36,40), and inverse probability of treatment weighting (36,41,42). Matching methods were performed without replacement. Stratification and 1:1 matching were initially performed on the complete data set, representing scan records from one or more scans for each unique patient (Fig 1). Additional propensity score adjustment (1:1 matching, weighting by the odds, and inverse probability of treatment weighting) was performed on the single-scan data set to minimize potential bias (Fig 1) (43).

### Counterfactual Causal Effect Analysis

Counterfactual analysis represents an experiment whereby a single patient cohort is subjected, simultaneously, to both arms of a two-arm study (eg, treated and control arms) (44). Such an experiment nullifies the potential effect of confounding bias from unbalanced covariates, as each individual serves as his or her own internal control (Fig E1 [online]). Counterfactual analysis represents the ideal means to elucidate causality, yet because it is impossible to subject patients to both study arms simultaneously, it remains largely theoretical. However, because CIN is reported to be a transient self-limited phenomenon, the conditions of counterfactual analysis can be approximated in this study, and separate contrast-enhanced and unenhanced CT scans performed in the same individual can be treated as unique unrelated events (45).

Accordingly, we identified the subset of patients who underwent both a contrast-enhanced and unenhanced CT scan at least 14 days apart during the study time frame (counterfactual data set) (Figs 1, E1 [online]). Propensity scores were generated (R.J.M., J.S.M., and R.E.C.) for each paired scan event by using the same logistic model noted previously. Approximated counterfactual conditions were simulated with inverse probability weighting adjustment of the propensity score to account for small changes in baseline clinical characteristics and demographics (eg, age, new comorbidities) that might occur between the initial and subsequent scan in the same patient. After adjustment,

**Table 1**

**Patient Demographics and Clinical Characteristics of Unadjusted Complete and Matched Single-Scan Data Sets**

Variable and Risk Subgroup	Complete Data Set*				1:1 Matched Single-Scan Data Set†			
	Contrast Group	Noncontrast Group	Unadjusted P Value	Adjusted P Value‡	Contrast Group	Noncontrast Group	Unadjusted P Value	Adjusted P Value§
<b>No. of patients</b>								
Low	102 590	22 692	...	...	7 281	7 281	...	...
Medium	11 357	8 294	...	...	2 447	2 447	...	...
High	2 747	9 460	...	...	958	958	...	...
<b>Age (y)<sup>  </sup></b>								
Low	60 (45–72)	60 (46–72)	<.001	.81	62 (49–74)	63 (48–74)	.21	.76
Medium	69 (57–78)	68 (57–78)	.75	.91	71 (59–79)	71 (59–80)	.25	.92
High	67 (56–77)	68 (56–78)	.09	.28	69 (58–77)	68 (56–77)	.58	.43
<b>Female sex</b>								
Low	51 026 (50)	11 658 (51)	<.001	.83	3 783 (52)	3 745 (51)	.53	.68
Medium	3 770 (33)	3 098 (37)	<.001	.72	849 (35)	869 (36)	.55	.80
High	1 023 (37)	3 427 (36)	.33	.74	352 (37)	346 (36)	.77	.78
<b>Race</b>								
<b>White</b>								
Low	85 078 (83)	18 887 (83)	.27	.95	5 985 (82)	6 080 (84)	.04	.87
Medium	9 564 (84)	7 262 (88)	<.001	.90	1 950 (80)	2 034 (83)	.002	.64
High	2 268 (82)	8 053 (85)	<.001	.33	786 (82)	785 (82)	.95	.41
<b>Black</b>								
Low	1 217 (1)	295 (1)	.16	.91	84 (1)	119 (2)	.01	.28
Medium	134 (1)	88 (1)	.44	.92	28 (1)	29 (1)	.89	.65
High	38 (1)	147 (2)	.52	.96	10 (1)	12 (1)	.67	.45
<b>Asian</b>								
Low	715 (1)	199 (1)	.004	.81	57 (1)	63 (1)	.58	.92
Medium	66 (1)	50 (1)	.84	.91	16 (1)	12 (0)	.45	.42
High	21 (1)	44 (0)	.06	.79	4 (0)	3 (0)	.71	.96
<b>Other or not specified</b>								
Low	15 580 (15)	3 311 (15)	.023	.96	1 120 (15)	1 054 (14)	.13	.81
Medium	1 593 (14)	894 (11)	<.001	.90	453 (19)	372 (15)	.002	.60
High	425 (15)	1 217 (13)	<.001	.28	158 (16)	158 (16)	.99	.46
<b>Inpatient versus outpatient</b>								
Low	92 741 (90)	20 337 (90)	<.001	.84	6 657 (91)	6 543 (90)	<.001	.34
Medium	10 360 (91)	7 436 (90)	<.001	.92	2 203 (90)	2 202 (90)	.96	.54
High	2 508 (91)	8 611 (91)	.66	.85	874 (91)	863 (90)	.39	.41
<b>Baseline SCr level<sup>  </sup></b>								
Low	1.0 (0.8–1.1)	1.0 (0.2–1.2)	<.001	.36	0.9 (0.8–1.1)	1.0 (0.8–1.2)	<.001	.24
Medium	1.6 (1.5–1.8)	1.7 (1.6–1.9)	<.001	.55	1.7 (1.5–1.8)	1.7 (1.5–1.8)	<.001	.41
High	2.4 (2.1–2.9)	2.6 (2.3–3.4)	<.001	.50	2.4 (2.1–3.0)	2.5 (2.2–3.0)	<.001	.68
<b>Charlson score<sup>  #</sup></b>								
Low	2 (1–3)	2 (1–3)	.49	.03	2 (1–3)	2 (1–3)	<.001	.92
Medium	2 (1–3)	2 (2–4)	<.001	.93	2 (1–3)	2 (1–4)	<.001	.42
High	2 (2–4)	2 (2–4)	<.001	.92	2 (2–4)	2 (2–4)	.44	.65
<b>Diabetes mellitus</b>								
Low	15 338 (15)	3 731 (16)	<.001	.94	1 345 (18)	1 170 (16)	<.001	.70
Medium	2 585 (23)	2 172 (26)	<.001	.79	639 (26)	620 (25)	.53	.85
High	694 (25)	2 543 (27)	.09	.20	250 (26)	247 (26)	.88	.52
<b>Diabetic nephropathy</b>								
Low	161 (0.2)	101 (0.4)	<.001	.05	23 (0)	23 (0)	.48	.39
Medium	128 (1.5)	83 (0.7)	<.001	.79	27 (1)	27 (1)	.99	.87
High	40 (1)	250 (3)	<.001	.82	13 (1)	17 (2)	.88	.42

Table 1 (continues)

Table 1 (continued)

## Patient Demographics and Clinical Characteristics of Unadjusted Complete and Matched Single-Scan Data Sets

Variable and Risk Subgroup	Complete Data Set*				1:1 Matched Single-Scan Data Set†			
	Contrast Group	Noncontrast Group	Unadjusted P Value	Adjusted P Value‡	Contrast Group	Noncontrast Group	Unadjusted P Value	Adjusted P Value§
<b>Chronic renal disease</b>								
Low	2099 (2)	984 (4)	<.001	<.001	259 (4)	299 (4)	.08	.44
Medium	1205 (11)	1526 (18)	<.001	.69	379 (15)	400 (16)	.41	.96
High	504 (18)	2782 (29)	<.001	.93	181 (19)	180 (19)	.95	.43
<b>Chronic renal pathophysiology</b>								
Low	658 (1)	339 (1)	<.001	.008	99 (1)	105 (1)	.67	.64
Medium	295 (3)	480 (6)	<.001	.62	98 (4)	102 (4)	.77	.43
High	106 (4)	770 (8)	<.001	.42	42 (4)	46 (5)	.66	.89
<b>Acute renal disease</b>								
Low	8619 (8)	2821 (12)	<.001	.66	695 (10)	779 (11)	.02	.33
Medium	3472 (31)	3384 (41)	<.001	.64	934 (38)	958 (39)	.48	.57
High	1444 (53)	5565 (59)	<.001	.17	524 (55)	540 (56)	.46	.64
<b>Congestive heart failure</b>								
Low	8209 (8)	2508 (11)	<.001	.27	802 (11)	888 (12)	.03	.45
Medium	1954 (17)	1621 (20)	<.001	.97	511 (21)	542 (22)	.28	.73
High	469 (17)	1752 (19)	.08	.21	192 (20)	169 (18)	.18	.73

Note.—Unless otherwise indicated, data are numbers of scans, with percentages in parentheses.

\* Full data set represents all recipients with and without contrast enhancement meeting inclusion and exclusion criteria as outlined in Figure 1 and in the Materials and Methods section.

† One-to-one propensity score matching on the single-scan data set was generated from full data set by using nearest neighbor (greedy-type) 1:1 matching methods utilized in the R software package MatchIt (R Foundation for Statistical Computing, Vienna, Austria). Each scan in this data set represents data from the most recent scan during the study period (2000–2010).

‡ Adjusted differences between contrast and noncontrast groups in the full data set were determined by conditional logistic regression, controlling for decile-stratified results through conditional estimation.

§ Adjusted differences between contrast and noncontrast groups in the 1:1 propensity score matched data derived from the single-scan data set were determined by conditional logistic regression, controlling for matched strata through conditional estimation.

|| Data are medians, with interquartile ranges in parentheses.

# For Charlson score, see Appendix E1 (online) and reference 28.

the incidence of AKI was compared between the paired scans (eg, contrast-enhanced and unenhanced CT scans) of the counterfactual data set.

### Statistical Analysis

Statistical analyses were performed by four authors (R.J.M., J.S.M., J.P.B., R.E.C.) by using R software (version 2.15, R Foundation for Statistical Computing, Vienna, Austria) (46). Dichotomous variables were displayed as counts with percentages, categorical data were displayed as relative frequencies (in percentages), and continuous data were presented as medians with interquartile ranges (IQRs). The effects of contrast material exposure on the incidence of AKI within risk subgroups were assessed with the Fisher exact test. The collective risk of AKI across risk subgroups was

assessed with Cochran-Mantel-Haenszel estimates. Propensity score adjustment by stratification and 1:1 matching methods was performed with the MatchIt package, whereas weighting by the odds and inverse propensity score weighting were performed by using the IPTW and Twang packages (42,47,48). Conditional logistic regression was used to re-estimate covariate balance after propensity score generation. The risk of AKI after contrast material exposure in the counterfactual data set was determined by conditional logistic regression, controlling for paired data with conditional estimation. Counterfactual estimates of marginal homogeneity to test the causal relationship between intravenous contrast material exposure and subsequent AKI were assessed with the McNemar test (49,50).

## Results

### Patient Population

A total of 1029899 scan records from 251728 unique patients were initially identified. Of these, 157140 scan records among 53439 unique patients associated with 1510001 SCr values met all inclusion and exclusion criteria (Fig 1). The median number of SCr values collected per patient was two (IQR = one to five) prior to scanning and five (IQR = three to nine) after scanning. The majority of excluded scan records ( $n = 799885$ , 78%) represented an enriched population of outpatients who lacked sufficient postscan SCr data as a direct result of absent outpatient follow-up. As such, a majority of the patients included in our study represented inpatients who, as expected, were more likely to

Table 2

## Propensity Score–adjusted Risk of AKI after CT Scan

Subgroup and Adjustment Method	AKI after Contrast-enhanced CT Scan (Contrast Group)	AKI after Unenhanced CT Scan (Noncontrast Group)	Odds Ratio*	P Value
<b>Low risk (SCr &lt; 1.5 mg/dL)</b>				
Unadjusted (complete data set)	2615/102 590 (3)	804/22 692 (4)	0.71 (0.66, 0.77)	<.0001
Stratified (complete data set) <sup>†</sup>	2615/102 590 (3)	804/22 692 (4)	0.88 (0.78, 0.99)	.02
1:1 matched (complete data set) <sup>‡</sup>	741/22 467 (3)	787/22 467 (4)	0.94 (0.85, 1.04)	.24
1:1 matched (single-scan data set) <sup>§</sup>	210/7281 (3)	226/7281 (3)	0.93 (0.76, 1.13)	.47
Inverse weighting (single-scan data set) <sup>§</sup>	950/35 751 (3)	228/7292 (3)	0.98 (0.96, 1.01)	.61
Odds weighting (single-scan data set) <sup>§</sup>	950/35 751 (3)	228/7292 (3)	0.97 (0.83, 1.13)	.33
<b>Medium risk (1.5 ≤ SCr &lt; 2.0 mg/dL)</b>				
Unadjusted (complete data set)	776/11 357 (7)	764/8294 (9)	0.72 (0.65, 0.80)	<.0001
Stratified (complete data set) <sup>†</sup>	776/11 357 (7)	764/8294 (9)	1.02 (0.91, 1.13)	.80
1:1 matched (complete data set) <sup>‡</sup>	609/7408 (8)	624/7408 (8)	0.97 (0.87, 1.09)	.68
1:1 matched (single-scan data set) <sup>§</sup>	209/2447 (9)	215/2447 (9)	0.97 (0.81, 1.16)	.76
Inverse weighting (single-scan data set) <sup>§</sup>	300/4023 (8)	221/2509 (9)	1.01 (0.99, 1.02)	.57
Odds weighting (single-scan data set) <sup>§</sup>	300/4023 (8)	221/2509 (9)	0.91 (0.76, 1.10)	.12
<b>High risk (SCr ≥ 2.0 mg/dL)</b>				
Unadjusted (complete data set)	238/2747 (9)	1198/9460 (13)	0.65 (0.56, 0.76)	<.0001
Stratified (complete data set) <sup>†</sup>	238/2747 (9)	1198/9460 (13)	0.71 (0.61, 0.82)	<.0001
1:1 matched (complete data set) <sup>‡</sup>	238/2736 (9)	293/2736 (11)	0.79 (0.66, 0.95)	.01
1:1 matched (single-scan data set) <sup>§</sup>	96/958 (10)	103/958 (11)	0.91 (0.66, 1.24)	.58
Inverse weighting (single-scan data set) <sup>§</sup>	108/959 (11)	346/2905 (12)	0.99 (0.97, 1.01)	.59
Odds weighting (single-scan data set) <sup>§</sup>	108/959 (11)	346/2905 (12)	0.90 (0.72, 1.14)	.56

Note.—Unless otherwise indicated, data are number of scans, with percentages in parentheses.

\* Data in parentheses are 95% CIs.

<sup>†</sup> After propensity score generation, patients in each risk subgroup of the full data set of 157 140 patient scan records were stratified into deciles of the propensity score. The summed odds ratio was calculated as discussed in Appendix E1 (online).

<sup>‡</sup> One-to-one matching on the propensity score was performed on the full data set of 157 140 patient scan records as discussed in the Materials and Methods.

<sup>§</sup> One-to-one matching on the propensity score and weighting methods, including weighting by the odds and inverse weighting of the propensity score, were performed on the subset of data representing the most recent scan performed in each patient in the full data set, representing 53 439 patient scan records, as discussed in Materials and Methods.

receive postscan SCr monitoring as part of their routine medical care (Table 1). Additional exclusions included patients with preexisting dialysis requirements ( $n = 24876$ , 2%) and patients exposed to multiple intravenous or intraarterial contrast material doses within 14 days ( $n = 47998$ , 5%).

### Baseline Demographic Characteristics

The demographic and clinical characteristics of included patients, sorted by contrast material exposure and presumed AKI risk, are shown in Table 1. The frequency of contrast material exposure diminished among patients in the medium- and high-risk subgroups compared with low-risk patients. In general, patients exposed to contrast material were younger, were less likely to have comorbidities, and had lower

baseline SCr levels than those not exposed to contrast material in each risk subgroup.

### Unadjusted Effect of Contrast Material Exposure on AKI Incidence

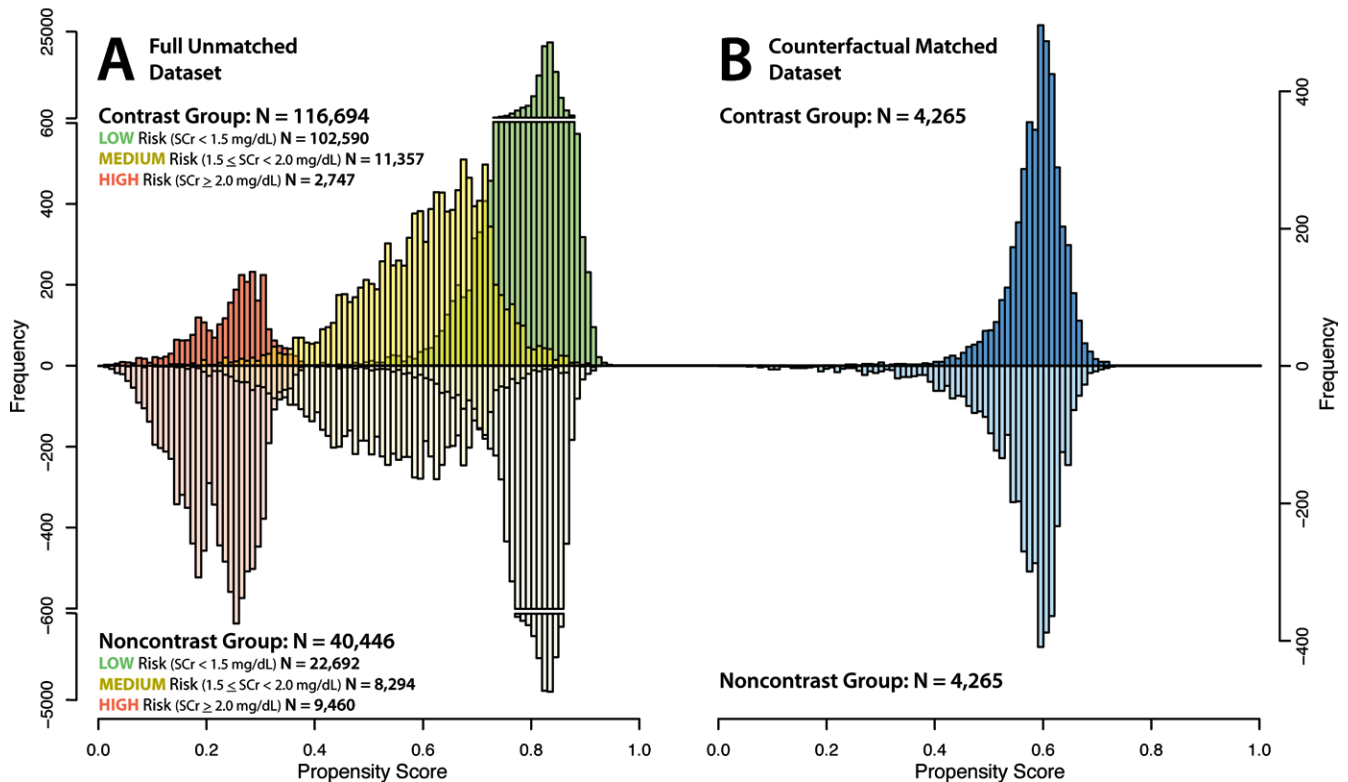
The unadjusted effect of contrast material exposure on the incidence of SCr-defined AKI, sorted by presumed AKI risk, is shown in Table 2. Adjusting for baseline AKI risk alone, individuals in the noncontrast group were significantly more likely than individuals in the contrast group to develop AKI (Cochran-Mantel-Haenszel  $\chi^2 = 52$ ;  $P < .0001$ ; pooled odds ratio = 0.70; 95% confidence interval [CI]: 0.61, 0.82). Similar findings were seen after adjustment by estimated glomerular filtration rate–defined Kidney Disease Outcomes Quality Initiative stages of

chronic renal failure (Table E1 [online]) (Cochran-Mantel-Haenszel  $\chi^2 = 257$ ;  $P < .0001$ ; pooled odds ratio = 0.41; 95% CI: 0.39, 0.43) (51).

### Propensity Score Analysis

Propensity score distributions of the unadjusted complete data set, sorted by risk subgroup and scan type, are shown in Figure 2, A. Distributions were very similar between contrast and noncontrast groups in all risk strata. Propensity score adjustment significantly improved covariate balance in all data subsets (Table 1). The relative influence of the covariates on the estimated propensity score, sorted by baseline risk, is shown in Figure 3. In all logistic models, age and baseline SCr level were the major determinants of propensity score.

Figure 2



**Figure 2:** Chart shows distribution of propensity scores in study population. Patients who underwent contrast-enhanced CT scan (contrast group) are shown above the x-axis and patients who underwent unenhanced CT scan (noncontrast group) are shown below the x-axis. *A*, Distribution of the full unadjusted data set ( $n = 157\,140$ ) and low-, medium-, and high-risk subgroups. *B*, Distribution of the subset of scans included in the counterfactual analysis ( $n = 8530$ ).

After propensity score adjustment by stratification (Table E2 [online]), the excess incidence of AKI in the noncontrast group relative to the contrast group was significantly reduced for individuals in the medium-risk subgroup (Table 2) (odds ratio = 1.02; 95% CI: 0.91, 1.13;  $P = .80$ ). Noncontrast group patients in the low- and high-risk subgroups retained a significantly elevated likelihood of AKI compared with contrast group members (low-risk group: odds ratio = 0.88; 95% CI: 0.78, 0.99;  $P = .02$ ; high-risk group: odds ratio = 0.71; 95% CI: 0.61, 0.82;  $P < .0001$ ).

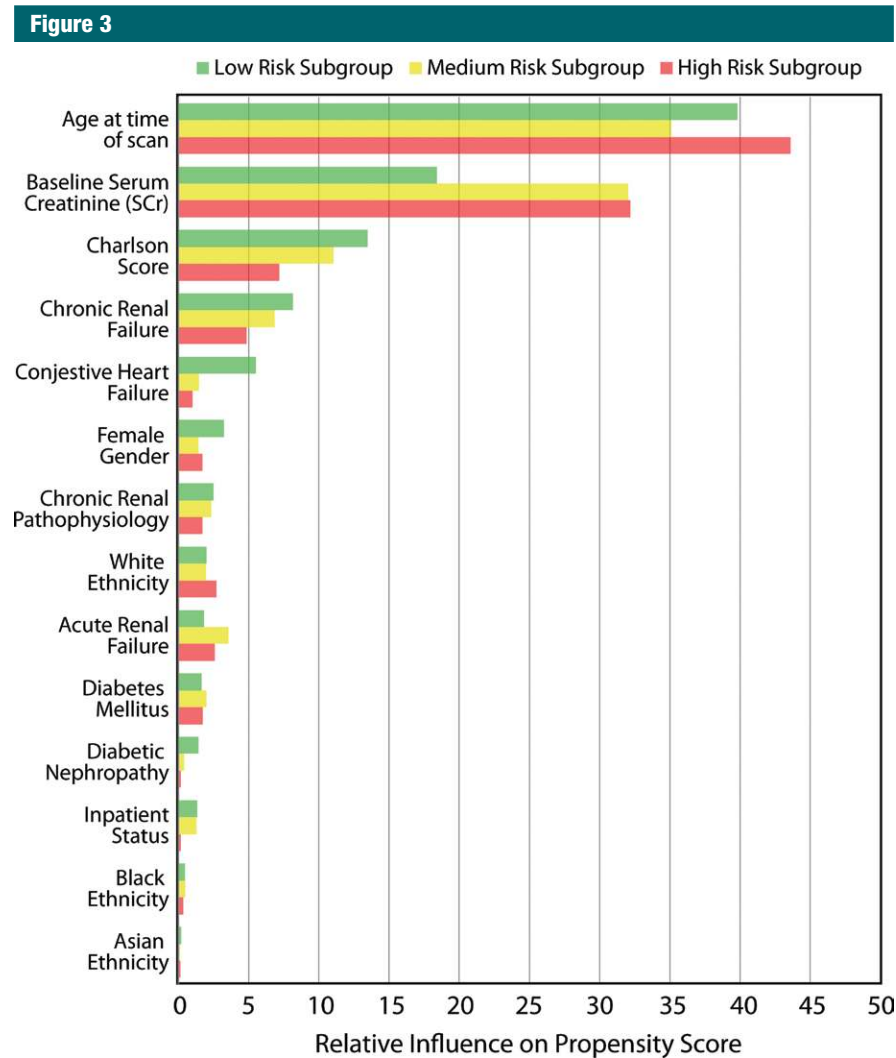
Heterogeneity in the stratified odds ratio trends (Table E2 [online]) prompted additional propensity score adjustment to further eliminate confounding bias. One-to-one matching of the complete data set, representing 65 222 scan events, further reduced the excess AKI

incidence in the noncontrast group, relative to the contrast group, for individuals at low and medium, but not high, risk of AKI (Tables 2, E3 [online]). Propensity score adjustment of the single-scan data set with 1:1 matching, representing 21 372 scan records (Table 1), completely eliminated the excess significant risk of AKI in the noncontrast group, relative to the contrast group, for all risk subgroups (Table 2) (low-risk group: odds ratio = 0.93; 95% CI: 0.76, 1.13;  $P = .47$ ; medium-risk group: odds ratio = 0.97; 95% CI: 0.81, 1.16;  $P = .76$ ; high-risk group: odds ratio = 0.91; 95% CI: 0.66, 1.24;  $P = .58$ ). Weighting by the odds and inverse probability of treatment also resulted in nonsignificant differences in the risk of AKI between recipients of contrast-enhanced and unenhanced imaging in all risk subgroups (Tables 2, E4 [online]).

### Counterfactual Analysis

A total of 4265 patients were identified in the counterfactual data set who met all inclusion and exclusion criteria and underwent both a contrast-enhanced and unenhanced CT scan during the study period (Table 3). The median duration in time between the first and second scan was 141 days (IQR, 41–653 days). The propensity score distribution of this subset of patients is shown in Figure 2, *B*. In this group of patients, the risk of AKI was not significantly different between contrast-enhanced and unenhanced scans within the same patient (Table 4) (odds ratio = 0.92; 95% CI: 0.75, 1.13;  $P = .46$ ). Propensity score adjustment of the counterfactual data set resulted in similar findings (odds ratio = 0.97; 95% CI: 0.79, 1.18;  $P = .65$ ) and improved covariate balance (Table 3). The McNemar test of association of





**Figure 3:** Chart shows the relative influence of the covariates on the estimated propensity score for each risk subpopulation.

the off-diagonal matched-pair observations resulted in nonsignificant results (Fig 4) ( $\chi^2 = 0.63$ ,  $df = 1$ ,  $P = .43$ ), demonstrating the presence of marginal homogeneity (50). Notably, these findings were insensitive to the order of contrast material exposure.

### Discussion

The results of our large, single-center, retrospective study revealed that, after propensity score adjustment for differences in presumed risk factors of CIN, recipients of unenhanced CT scans were at equivalent risk of SCr-defined

AKI compared with recipients of contrast-enhanced CT scans, regardless of baseline renal function. Counterfactual analysis of patients who underwent both contrast-enhanced and unenhanced CT scans suggested a coincidental rather than a causal relationship between intravenous contrast material exposure and AKI. These results question both the utility of SCr as a marker for kidney injury and the long-held causal relation between intravenous contrast material exposure and SCr-defined AKI. Our study did not identify CIN as being a distinct phenomenon that can be

accurately determined by SCr-derived tests of renal function, as the incidence of contrast material-independent renal injury obfuscates diagnosis of contrast material-dependent renal injury. If CIN occurs at all, it appears to occur at a rate low enough to be obscured by other causes of renal injury.

While previous studies have compared patients undergoing contrast-enhanced CT to those undergoing unenhanced CT, most have focused on specific patient subgroups, including those with acute trauma, advanced age, acute stroke, and intracranial

Table 3

## Patient Demographics and Clinical Characteristics of the Counterfactual Data Set

Variable	Contrast-enhanced Scans	Unenhanced Scans	Unadjusted P Value*	Adjusted P Value†
No. of patients	4265	4265	...	...
Age (y)‡	62 (48–72)	62 (49–72)	.84	.95
Female sex	1980 (46)	1980 (46)	.99	.83
Race				
White	3692 (87)	3692 (87)	.99	.62
Black	53 (1)	53 (1)	.99	.94
Asian	34 (1)	34 (1)	.99	.90
Other or not specified	486 (11)	486 (11)	.99	.69
Inpatient versus outpatient	4135 (97)	4109 (96)	.40	.85
Baseline SCr level‡	1.0 (0.8–1.3)	1.1 (0.9–1.6)	<.001	.04
Charlson score‡	2 (1–3)	2 (1–4)	<.001	.85
Diabetes mellitus	981 (23)	1065 (25)	.03	.88
Diabetic nephropathy	16 (0)	16 (0)	.99	.84
Chronic renal disease	298 (7)	391 (9)	<.001	.76
Chronic renal pathophysiology	171 (4)	215 (5)	.02	.52
Acute renal disease	682 (16)	856 (20)	<.001	.59
Congestive heart failure	851 (20)	897 (21)	.17	.73

Note.—Unless otherwise indicated, data are numbers of scans, with percentages in parentheses.

\* Unadjusted P values were derived from the Student *t* test for the differences between the contrast-enhanced and unenhanced subgroups.

† Adjusted P values were derived from conditional logistic regression, conditioned on the pair identification of each matched enhanced-unenhanced scan performed.

‡ Data are medians, with interquartile ranges in parentheses.

hemorrhage (10,17–21). Our study offers several advances over these previous studies. First, compared with these previous studies, the large sample size of our study permitted inclusion of multiple risk factors and comorbidities reported to increase the risk of CIN. Second, our study utilized rigorous propensity score adjustment techniques to minimize the effects of selection bias resulting from unequal distributions of demographic variables between contrast material-exposed and unexposed individuals that may causally influence the incidence of AKI. Third, we performed a counterfactual analysis to study the causal association of contrast material on AKI among patients who underwent both a contrast-enhanced and unenhanced CT scan, essentially eliminating the intrinsic selection bias present in retrospective studies.

The causes of the unadjusted excess AKI in the noncontrast group compared with the contrast group are likely a result of several factors. First, patients

not exposed to contrast material were more likely to have an elevated SCr level and comorbidities associated with acute and chronic renal dysfunction. This observation is likely a manifestation of the underlying selection bias present in the consideration of contrast material use and reflects the ability of clinicians to identify at-risk individuals. If the incidence of AKI is at least partially unrelated to contrast material administration as our propensity score adjusted data suggest, the excess AKI in the noncontrast group may be a manifestation of greater frequency of comorbidities in that group that can independently elevate SCr levels. Indeed, the majority of prior CIN studies demonstrated slightly higher rates of AKI in the noncontrast groups, similar to our unadjusted results. Second, it has been hypothesized that contrast material administration, as a partial result of the additional fluid administration from the contrast material itself and from additional prophylactic intravenous fluid doses, may

Table 4

## Risk of AKI after CT Scan in the Counterfactual Data Set

Variable	AKI
Group	
Contrast enhanced*	194/4265 (4.5)
Unenhanced*	209/4265 (4.9)
Unadjusted analysis†	
Odds ratio‡	0.92 (0.75, 1.13)
P value	.46
Adjusted analysis§	
Odds ratio‡	0.97 (0.79, 1.18)
P value	.65

\* Data are numbers of scans, with percentages in parentheses.

† Unadjusted analysis represents the odds ratio derived from conditional logistic regression, controlling for paired patient data with conditional estimation.

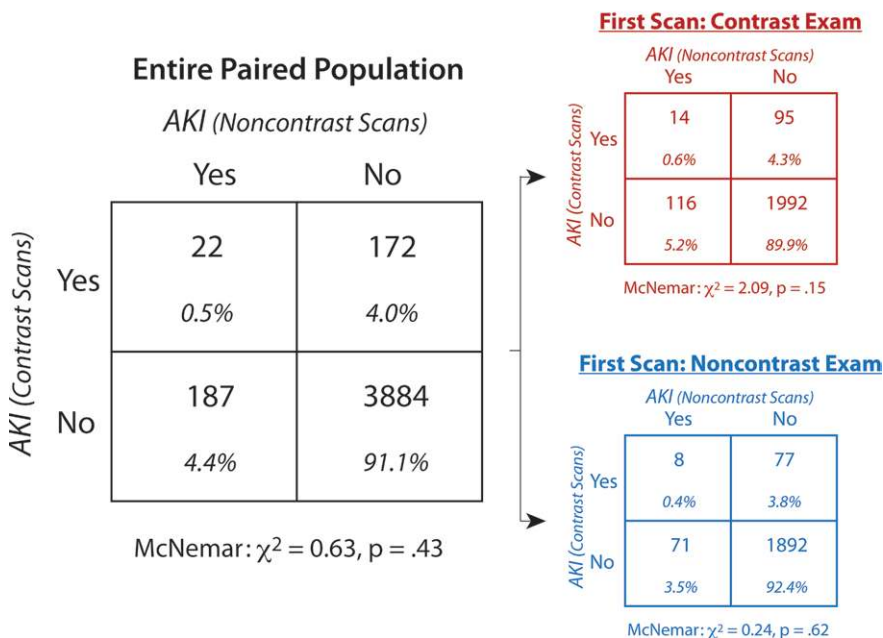
‡ Odds ratios are reported with 95% CIs in parentheses.

§ Adjusted analysis represents the odds ratio derived from propensity score adjustment by using the inverse propensity score weighting method to account for minor changes in propensity score, within the same patient, that took place over time between the first and subsequent scan.

actually have a paradoxical renal protective effect (45). However, our adjusted analyses argue against this hypothesis.

After propensity score adjustment, we could not detect a statistically significant difference in the AKI rate between recipients of contrast-enhanced and unenhanced CT scans. The ability to discriminate clinically significant differences in these rates can be determined from the precision (width) of the CIs. These widths define the range of values considered to be statistically compatible with the point estimate of the odds ratio (52–54). Values greater than the upper bound of the 95% CI, relative to the point estimate, are considered significantly different. Thus, for a given probability of AKI, the largest observed upper confidence limit represents a conservative estimate of the smallest significant difference between contrast and noncontrast groups detectable by the study (53). Among low-risk individuals, significant differences as small as 0.5% in AKI can be detected (assuming AKI rate = 4%; upper CI limit = 1.13). Even among the high-risk group, where the

**Figure 4**



**Figure 4:** Incidence of AKI within the paired counterfactual data set. Contingency tables compare the incidence of AKI after contrast-enhanced scans with the incidence of AKI after unenhanced CT scans for the entire counterfactual data set (black), the subset of patients within the counterfactual data set where the contrast-enhanced examination was performed first (red), and the subset of patients within the counterfactual data set where the unenhanced examination was performed first (blue).

smaller sample size diminished some precision of the estimated odds ratios, the CIs were sufficiently narrow to detect AKI rate differences as small as 2.6% (assuming AKI rate = 13%; upper CI limit = 1.24). The magnitude of these differences is smaller than reported rates of contrast material–dependent AKI (1,3–6). Thus, the precision of the odds ratio estimates in our study was not adversely affected by sample size limitations and was sufficient to make meaningful interpretations.

The observation of similar AKI incidence rates after contrast-enhanced and unenhanced scans has several clinical implications. First, our findings demonstrate that SCr-defined AKI after intravenous contrast material administration is clinically indistinguishable from contrast material–independent AKI. This observation suggests either that CIN is a diagnosis of misattribution or represents a condition obscured by other factors contributing to AKI. These causes

notwithstanding, our results demonstrate the true incidence of CIN remains indeterminate using accepted SCr-based definitions. Second, while such findings may be interpreted as evidence for more liberalized use of intravenous contrast material, further studies, including randomized prospective studies, are needed to extricate contrast material–dependent from contrast material–independent effects on renal function. Ideally, our study will provide additional evidence to justify these future studies. If our findings are recapitulated in future prospective studies, the benefits of enhanced tissue conspicuity could potentially improve diagnostic accuracy among individuals who, at present, undergo unenhanced CT imaging studies because of concern over compromised preexisting renal function.

Selection bias is an inherent concern for any observational nonrandomized study. This selection bias was clearly evident in our unadjusted data

set and likely arises from the ability of clinicians to identify at-risk individuals for AKI. The use of propensity score adjustment and subsequent counterfactual analysis permits the comparison of individuals between contrast and noncontrast groups with similar demographics, comorbidities, and risk for AKI. To that end, our propensity score model accounted for the major variables thought to be associated with subsequent development of CIN. However, other potential variables, including hydration status, prophylactic treatments, nephrotoxic medications, prescan fluctuations in SCr level, and other comorbidities, were not included in our model. These variables were not easily retrievable from the medical record (nephrotoxic medications), were a subject of some debate with respect to their efficacy (prophylactic treatments), were not present in sufficient numbers (trends in prescan SCr data), or involved difficulty in identifying the timing of the administration before or after the CT scan (intravenous fluid administration). Finally, propensity score adjustment cannot account for unknown variables that may confound the incidence of AKI.

In addition to the potential selection bias mentioned previously, our study had several additional limitations. First, large numbers of patients were excluded because of insufficient SCr data, predominantly representing an outpatient population that did not receive follow-up SCr testing. As such, our data were enriched with inpatients and were favorably biased toward individuals with greater comorbidity and propensity toward AKI. Our results are therefore not generalizable to the outpatient population. Second, our study used SCr to diagnose AKI, even though it is known to be a less sensitive marker for renal function compared with measured glomerular filtration rate. The decision to use a SCr-based definition of AKI/CIN was influenced by the fact that measured glomerular filtration rate assays are rarely used in the clinical setting, have not been validated in the setting of AKI/CIN, and are still limited by numerous laboratory assay issues (55). Third, as the majority of high-risk patients

received iso-osmolar contrast material per our institutional guidelines, the incidence of CIN in this risk group may have been reduced compared with if they had been administered low-osmolar contrast material. However, the efficacy of iso-osmolar agents in reducing AKI compared with that of low osmolar agents has been debated (56–59). Fourth, the reasons physicians chose to administer intravenous contrast material, whether because of concern for AKI or because of the scan indication, were beyond the scope of our study. Finally, our analysis relied on use of electronic medical record ICD-9 coding to identify patients with AKI-predisposing comorbidities. This method of identifying comorbidities can be less sensitive and specific compared with medical chart review. Although coding errors are common among electronic medical record data, they have been shown to occur in a random pattern (60). As such, it is unlikely that coding errors would manifest in a manner that would bias one of the two groups in our study.

In conclusion, our findings directly question the causal relationship between intravenous contrast material administration and AKI. While our data cannot directly refute the existence of intravenous CIN, they indicate that accepted SCr-based definitions of CIN cannot identify this phenomenon as a distinct clinical entity. The current clinical definition of contrast material-dependent AKI is confounded by a sufficiently high false-positive rate of contrast material-independent AKI so as to make detection of CIN impossible, even among patients with the most compromised renal function. Additional studies are necessary to further evaluate the incidence and clinical importance of CIN.

**Acknowledgments:** The authors thank Richard W. Katzberg, MD, Patrick W. Eiken, MD, Robert P. Hartman, MD, Claire E. Bender, MD, and Bernard F. King, Jr, MD, for their input and critical analysis of this manuscript.

**Disclosures of Conflicts of Interest:** R.J.M. No relevant conflicts of interest to disclose. J.S.M. Financial activities related to the present article: institution receives investigator-initiated research grant for CIN studies. Financial activities not related to the present article: none to

disclose. Other relationships: none to disclose. J.P.B. No relevant conflicts of interest to disclose. R.E.C. No relevant conflicts of interest to disclose. C.J.F. No relevant conflicts of interest to disclose. S.M. No relevant conflicts of interest to disclose. E.E.W. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution receives grant from GE Medical. Other relationships: none to disclose. D.E.K. Financial activities related to the present article: institution receives grant from GE Healthcare for support for research associated for CIN research. Financial activities not related to the present article: institution is consultant for eV3 (PI for clinical trials); institution has grants from MicroVention, eV3, Sequent Medical, Micrus, and Benue for support for preclinical or clinical studies of aneurysms; author receives royalties from UVA Patent Foundation for spine fusion patent; institution receives payment for development of educational presentations from eV3; institution receives travel, accommodations, and/or meeting expenses from MicroVention and Codman. Other relationships: none to disclose.

## References

- Barrett BJ, Parfrey PS. Clinical practice: preventing nephropathy induced by contrast medium. *N Engl J Med* 2006;354(4):379–386.
- Gleeson TG, Bulugahapitiya S. Contrast-induced nephropathy. *AJR Am J Roentgenol* 2004;183(6):1673–1689.
- Solomon R, Dumouchel W. Contrast media and nephropathy: findings from systematic analysis and Food and Drug Administration reports of adverse effects. *Invest Radiol* 2006; 41(8):651–660.
- Tepel M, Aspelin P, Lameire N. Contrast-induced nephropathy: a clinical and evidence-based approach. *Circulation* 2006;113(14): 1799–1806.
- Tublin ME, Murphy ME, Tessler FN. Current concepts in contrast media-induced nephropathy. *AJR Am J Roentgenol* 1998;171(4): 933–939.
- Katzberg RW, Newhouse JH. Intravenous contrast medium-induced nephrotoxicity: is the medical risk really as great as we have come to believe? *Radiology* 2010;256(1):21–28.
- Rao QA, Newhouse JH. Risk of nephropathy after intravenous administration of contrast material: a critical literature analysis. *Radiology* 2006;239(2):392–397.
- Baumgarten DA, Ellis JH. Contrast-induced nephropathy: contrast material not required? *AJR Am J Roentgenol* 2008;191(2):383–386.
- Katzberg RW, Barrett BJ. Risk of iodinated contrast material-induced nephropathy with intravenous administration. *Radiology* 2007;243(3):622–628.
- Bansal GJ, Darby M. Measurement of change in estimated glomerular filtration rate in patients with renal insufficiency after contrast-enhanced computed tomography: a case-control study. *J Comput Assist Tomogr* 2009;33(3):455–459.
- Cramer BC, Parfrey PS, Hutchinson TA, et al. Renal function following infusion of radiologic contrast material: a prospective controlled study. *Arch Intern Med* 1985; 145(1):87–89.
- Heller CA, Knapp J, Halliday J, O'Connell D, Heller RF. Failure to demonstrate contrast nephrotoxicity. *Med J Aust* 1991;155(5): 329–332.
- Heller M, Husk G, Bowers W, et al. Contrast CT scans in the emergency department: is there really an increased risk of adverse clinical outcomes? *Acad Emerg Med* 2011; 18(Supplement s1):S4–S249.
- Ng CS, Shaw AD, Bell CS, Samuels JA. Effect of IV contrast medium on renal function in oncologic patients undergoing CT in ICU. *AJR Am J Roentgenol* 2010;195(2):414–422.
- Polena S, Yang S, Alam R, et al. Nephropathy in critically ill patients without preexisting renal disease. *Proc West Pharmacol Soc* 2005; 48:134–135.
- Aulicky P, Mikulík R, Goldemund D, Reif M, Dufek M, Kubelka T. Safety of performing CT angiography in stroke patients treated with intravenous thrombolysis. *J Neurol Neurosurg Psychiatry* 2010;81(7):783–787.
- Langner S, Stumpe S, Kirsch M, Petrik M, Hosten N. No increased risk for contrast-induced nephropathy after multiple CT perfusion studies of the brain with a nonionic, dimeric, iso-osmolal contrast medium. *AJNR Am J Neuroradiol* 2008;29(8):1525–1529.
- Lima FO, Lev MH, Levy RA, et al. Functional contrast-enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy. *AJNR Am J Neuroradiol* 2010;31(5):817–821.
- McGillicuddy EA, Schuster KM, Kaplan LJ, et al. Contrast-induced nephropathy in elderly trauma patients. *J Trauma* 2010;68(2): 294–297.
- Oleinik A, Romero JM, Schwab K, et al. CT angiography for intracerebral hemorrhage does not increase risk of acute nephropathy. *Stroke* 2009;40(7):2393–2397.
- Tremblay LN, Tien H, Hamilton P, et al. Risk and benefit of intravenous contrast in trauma patients with an elevated serum creatinine. *J Trauma* 2005;59(5):1162–1166; discussion 1166–1167.
- Bruce RJ, Djmal A, Shinki K, Michel SJ, Fine JP, Pozniak MA. Background fluctuation of kidney function versus contrast-induced nephrotoxicity. *AJR Am J Roentgenol* 2009;192(3):711–718.
- McDonald JS, McDonald RJ, Comin J, et al. Frequency of acute kidney injury following intravenous contrast administration: a systematic review and meta-analysis. *Radiology* (in press).

24. Stacul F, van der Molen AJ, Reimer P, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol* 2011;21(12):2527–2541.
25. Kern EF, Maney M, Miller DR, et al. Failure of ICD-9-CM codes to identify patients with comorbid chronic kidney disease in diabetes. *Health Serv Res* 2006;41(2):564–580.
26. Quach S, Blais C, Quan H. Administrative data have high variation in validity for recording heart failure. *Can J Cardiol* 2010;26(8):306–312.
27. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. *Diabetes Res Clin Pract* 2010;89(2):189–195.
28. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43(11):1130–1139.
29. McCullough PA, Bertrand ME, Brinker JA, Stacul F. A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. *J Am Coll Cardiol* 2006;48(4):692–699.
30. Elicker BM, Cypel YS, Weinreb JC. IV contrast administration for CT: a survey of practices for the screening and prevention of contrast nephropathy. *AJR Am J Roentgenol* 2006;186(6):1651–1658.
31. Waikar SS, Liu KD, Chertow GM. Diagnosis, epidemiology and outcomes of acute kidney injury. *Clin J Am Soc Nephrol* 2008;3(3):844–861.
32. Davidson C, Stacul F, McCullough PA, et al. Contrast medium use. *Am J Cardiol* 2006;98(6A):42K–58K.
33. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J Am Soc Nephrol* 2009;20(3):672–679.
34. Molitoris BA, Levin A, Warnock DG, et al. Improving outcomes from acute kidney injury. *J Am Soc Nephrol* 2007;18(7):1992–1994.
35. Blackstone EH. Comparing apples and oranges. *J Thorac Cardiovasc Surg* 2002;123(1):8–15.
36. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci* 2010;25(1):1–21.
37. Cochran WG. The effectiveness of adjustment by subclassification in removing bias in observational studies. *Biometrics* 1968;24(2):295–313.
38. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. *Stat Med* 2004;23(19):2937–2960.
39. Stuart EA, Rubin DB. Matching methods for causal inference: designing observational studies. In: Osborne J, ed. *Best practices in quantitative methods*. Thousand Oaks, Calif: Sage, 2007; 155–176.
40. Hirano K, Imbens GW, Ridder G. Efficient estimation of average treatment effects using the estimated propensity score. *Econometrica* 2003;71(4):1161–1189.
41. Stürmer T, Schneeweiss S, Brookhart MA, Rothman KJ, Avorn J, Glynn RJ. Analytic strategies to adjust confounding using exposure propensity scores and disease risk scores: nonsteroidal antiinflammatory drugs and short-term mortality in the elderly. *Am J Epidemiol* 2005;161(9):891–898.
42. van der Wal WM, Geskus RB. IPW: an R package for inverse probability weighting. *J Stat Softw* 2011;43(13):1–23.
43. Horwitz RI, Feinstein AR. Improved observational method for studying therapeutic efficacy: suggestive evidence that lidocaine prophylaxis prevents death in acute myocardial infarction. *JAMA* 1981;246(21):2455–2459.
44. Luo Z, Gardiner JC, Bradley CJ. Applying propensity score methods in medical research: pitfalls and prospects. *Med Care Res Rev* 2010;67(5):528–554.
45. Newhouse JH, Kho D, Rao QA, Starren J. Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity. *AJR Am J Roentgenol* 2008;191(2):376–382.
46. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2012.
47. Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. R package version 2.2-11. <http://gking.harvard.edu/matchit>. Accessed March 26, 2012.
48. Ridgeway G, McCaffrey D, Morral A, Burgette L, Griffin BA. Toolkit for weighting and analysis of nonequivalent groups: a tutorial for the twang package. [Santa Monica, Calif]: RAND. <http://cran.r-project.org/web/packages/twang/vignettes/twang.pdf>. Accessed February 6, 2012.
49. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika* 1947;12(2):153–157.
50. Moussa MA. Testing marginal homogeneity in square tables; with emphasis on matched data. *Comput Programs Biomed* 1985;19(2-3):239–247.
51. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 Suppl 1):S1–S266.
52. Pocock SJ, Ware JH. Translating statistical findings into plain English. *Lancet* 2009;373(9679):1926–1928.
53. Goodman SN, Berlin JA. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. *Ann Intern Med* 1994;121(3):200–206.
54. Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. *Br Med J (Clin Res Ed)* 1986;292(6522):746–750.
55. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function: measured and estimated glomerular filtration rate. *N Engl J Med* 2006;354(23):2473–2483.
56. Barrett BJ, Katzberg RW, Thomsen HS, et al. Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol. *Invest Radiol* 2006;41(11):815–821.
57. Carraro M, Malalan F, Antonione R, et al. Effects of a dimeric vs a monomeric nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. *Eur Radiol* 1998;8(1):144–147.
58. Heinrich MC, Häberle L, Müller V, Bautz W, Uder M. Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. *Radiology* 2009;250(1):68–86.
59. Kuhn MJ, Chen N, Sahani DV, et al. The PREDICT study: a randomized double-blind comparison of contrast-induced nephropathy after low- or isoosmolar contrast agent exposure. *AJR Am J Roentgenol* 2008;191(1):151–157.
60. Berthelsen CL. Evaluation of coding data quality of the HCUP National Inpatient Sample. *Top Health Inf Manage* 2000;21(2):10–23.

cently published European Association for the Study of the Liver–Asociación Latinoamericana para el Estudio del Hígado guidelines (8).

**Disclosures of Conflicts of Interest:** L.E. disclosed no relevant relationships. P.E.R. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: receives personal fees from Gilead. Other relationships: disclosed no relevant relationships. L.C. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: receives lecture fees from Echoscans. Other relationships: disclosed no relevant relationships.

### References

1. Elkrief L, Rautou PE, Ronot M, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. *Radiology* 2015;275(2):589–598.
2. Procopet B, Berzigotti A, Abraldes JG, et al. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. *J Hepatol* 2015;62(5):1068–1075.
3. Stefanescu H, Grigorescu M, Lupsor M, Procopet B, Maniu A, Badea R. Spleen stiffness measurement using Fibroscan for the non-invasive assessment of esophageal varices in liver cirrhosis patients. *J Gastroenterol Hepatol* 2011;26(1):164–170.
4. Colecchia A, Montrone L, Scaiola E, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology* 2012;143(3):646–654.
5. Sharma P, Kirnake V, Tyagi P, et al. Spleen stiffness in patients with cirrhosis in predicting esophageal varices. *Am J Gastroenterol* 2013;108(7):1101–1107.
6. Takuma Y, Nouse K, Morimoto Y, et al. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. *Gastroenterology* 2012;144(1):92–101.e2.
7. Castera L, Garcia-Tsao G. When the spleen gets tough, the varices get going. *Gastroenterology* 2013;144(1):19–22.
8. EASL-ALEH clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015;63(1):237–264.

### Errata

#### Originally published in:

*Radiology* 2013;267(1):106–118  
DOI: 10.1148/radiol.12121823  
Intravenous Contrast Material–induced Nephropathy: Causal or Coincident Phenomenon?  
Robert J. McDonald, Jennifer S. McDonald, John P. Bida, Rickey E. Carter, Chad J. Fleming, Sanjay Misra, Eric E. Williamson, and David F. Kallmes

#### Erratum in:

*Radiology* 2016;278(1):306  
DOI:10.1148/radiol.2015154044

Table E2, under the category “Medium-Risk Subgroup,” the odds ratio data for strata row 1 should read as follows: 1.68 (1.35, 2.10).

#### Originally published in:

*Radiology* 2015;275(1):177–187  
DOI:10.1148/radiol.14141282  
Targeted Screening of Individuals at High Risk for Pancreatic Cancer: Results of a Simulation Model  
Pari V. Pandharipande, Curtis Heberle, Emily C. Dowling, Chung Yin Kong, Angela Tramontano, Katherine E. Perzan, William Brugge, and Chin Hur

#### Erratum in:

*Radiology* 2016;278(1):306  
DOI:10.1148/radiol.2015154045

In the first paragraph of “Implementation of PDAC Screening in the Model,” fourth sentence, the authors wish to make the following clarification: “**Without more granular data available to inform this type of misidentification, we applied the same false-negative rate to patients with a low-risk cystic lesion, a high-risk cystic lesion, or PDAC.**”