Risk of Intravenous Contrast Material–mediated Acute Kidney Injury: A Propensity Score–matched Study Stratified by Baseline-estimated Glomerular Filtration Rate[1]

Jennifer S. McDonald, PhD
Robert J. McDonald, MD, PhD
Rickey E. Carter, PhD
Richard W. Katzberg, MD
David F. Kallmes, MD
Eric E. Williamson, MD

Purpose: To determine the effect of baseline estimated glomerular filtration rate (eGFR) on the causal association between intravenous iodinated contrast material exposure and subsequent development of acute kidney injury (AKI) in propensity score–matched groups of patients who underwent contrast material–enhanced or unenhanced computed tomography (CT).

Materials and Methods: This retrospective study was HIPAA compliant and institutional review board approved. All patients who underwent contrast-enhanced (contrast material group) or unenhanced (non–contrast material group) CT between 2000 and 2010 were identified and stratified according to baseline eGFR by using Kidney Disease Outcomes Quality Initiative cutoffs for chronic kidney disease into subgroups with eGFR of 90 or greater, 60–89, 30–59, and less than 30 mL/min/1.73 m^2. Propensity score generation and 1:1 matching of patients were performed in each eGFR subgroup. Incidence of AKI (serum creatinine [SCr] increase of ≥0.5 mg/dL [≥44.2 μmol/L] above baseline) was compared in the matched subgroups by using the Fisher exact test.

Results: A total of 12 508 propensity score–matched patients with contrast-enhanced and unenhanced scans met all inclusion criteria. In this predominantly inpatient cohort, the incidence of AKI significantly increased with decreasing baseline eGFR ($P < .0001$). However, this incidence was not significantly different between contrast material and non–contrast material groups in any eGFR subgroup; for the subgroup with eGFR of 90 or greater ($n = 1642$), odds ratio (OR) was 0.91 (95% confidence interval [CI]: 0.38, 2.15), $P = .82$; for the subgroup with eGFR of 60–89 ($n = 3870$), OR was 1.03 (95% CI: 0.66, 1.60), $P = .99$; for the subgroup with eGFR of 30–59 ($n = 5510$), OR was 0.94 (95% CI: 0.76, 1.18), $P = .65$; and for the subgroup with eGFR of less than 30 mL/min/1.73 m^2 ($n = 1486$), OR was 0.97 (95% CI: 0.72, 1.30), $P = .89$.

Conclusion: Diminished eGFR is associated with an increased risk of SCr-defined AKI following CT examinations. However, the risk of AKI is independent of contrast material exposure, even in patients with eGFR of less than 30 mL/min/1.73 m^2.

[1] From the Departments of Radiology (J.S.M., R.J.M., D.F.K., E.E.W.), Health Sciences Research (R.E.C.), and Neurosurgery (D.F.K.), College of Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905; and Department of Radiology, Medical University of South Carolina, Charleston, SC (R.W.K.). Received April 1, 2013; revision requested June 12; final revision received September 30; accepted October 16; final version accepted October 22. **Address correspondence to** J.S.M. (e-mail: *mcdonald.jennifer@mayo.edu*).

Intravenous contrast material exposure has long been held to be a common cause of acute kidney injury (AKI), otherwise known as contrast material–induced nephropathy (CIN). Concern in regard to the development of CIN has had a dramatic effect on clinical practice for decades (1–3), where intravenous contrast material is commonly withheld among "high-risk" individuals, often at the expense of diagnostic accuracy. These concerns notwithstanding, the true incidence of contrast material–mediated AKI remains relatively undefined because of the scarcity of properly controlled retrospective and prospective studies. However, a recent meta-analysis of 13 retrospective controlled studies of intravenous contrast material administration demonstrated a similar likelihood of AKI between patients who received intravenous contrast material and patients who did not (4). Further, a recent, large controlled retrospective study of patients who underwent computed tomography (CT) also demonstrated similar rates of AKI between propensity score–matched patients who underwent contrast material–enhanced CT and patients who underwent unenhanced CT (5). These findings suggest that the true incidence of CIN following intravenous contrast material exposure is much lower than what has been estimated (6–8).

Equations to calculate the estimated glomerular filtration rate (GFR) (eGFR) from the serum creatinine (SCr) level demonstrate superior correlation with actual GFR, as compared with SCr measurements alone (9,10), and because of this finding, some authorities speculate that calculation of the eGFR may provide a better assessment of AKI risk prior to administration of potentially nephrotoxic agents (1,2,11,12). The purpose of the current study was to determine the effect of baseline eGFR on the causal association between intravenous iodinated contrast material exposure and subsequent development of AKI in propensity score–matched groups of patients who underwent contrast-enhanced or unenhanced CT.

Advances in Knowledge

- The incidence of serum creatinine–defined acute kidney injury (AKI) following CT scanning, with or without intravenous iodinated contrast material infusion, is inversely related to baseline estimated glomerular filtration rate (eGFR) (for subgroup with baseline eGFR of ≥90 mL/min/1.73 m^2, 1.2%; for subgroup with baseline eGFR of <30 mL/min/1.73 m^2, 14%; $P <$ .0001).
- Following stratification according to baseline eGFR and propensity score adjustment to balance risk factors associated with the development of AKI, patients who underwent contrast-enhanced CT and unenhanced CT were at a similar risk of AKI, even in the patient subgroup with baseline eGFR of lower than 30 mL/min/1.73 m^2; for the subgroup with eGFR of ≥90 mL/min/1.73 m^2, odds ratio (OR) = 0.91 (95% confidence interval [CI]: 0.38, 2.15), P = .82; for the subgroup with eGFR of 60–89 mL/min/1.73 m^2, OR = 1.03 (95% CI: 0.66, 1.60), P = .99; for the subgroup with eGFR of 30–59 mL/min/1.73 m^2, OR = 0.94 (95% CI: 0.76, 1.18), P = .65; for the subgroup with eGFR of <30 mL/min/1.73 m^2, OR = 0.97 (95% CI: 0.72, 1.30), P = .89.

Materials and Methods

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

Implication for Patient Care

- Contrast material–induced nephropathy cannot be differentiated from contrast material–independent causes of AKI, in a predominantly inpatient cohort, even in patients with severely compromised renal function.

Study Design

Study design and implementation for this retrospective study were overseen by the institutional review board of the Mayo Clinic (Rochester, Minn) and conformed to Health Insurance Portability and Accountability Act guidelines on patient data integrity. Clinical data were extracted from our institutional electronic medical record, as previously described (5). Clinical diagnoses and procedures were identified from the electronic medical record by using *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes and *Current Procedural Terminology* procedure codes. The SCr data were extracted from our institutional laboratory information system and were associated with the date and time of CT, as previously described (5).

Study Population

All patients in the current study were included in a previous study (5) in which

Published online before print
10.1148/radiol.13130775 **Content codes:** CT OT

Radiology 2014; 271:65–73

Abbreviations:
AKI = acute kidney injury
CI = confidence interval
CIN = contrast material–induced nephropathy
eGFR = estimated GFR
GFR = glomerular filtration rate
ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification
IQR = interquartile range
KDOQI = Kidney Disease Outcome Quality Initiative
MDRD = Modification of Diet in Renal Disease
OR = odds ratio
SCr = serum creatinine

Author contributions:
Guarantor of integrity of entire study, 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; approval of final version of submitted manuscript, all authors; literature research, R.E.C., R.W.K., E.E.W.; clinical studies, R.J.M., E.E.W.; statistical analysis, J.S.M., R.J.M.; and manuscript editing, all authors

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

the incidence of AKI in patients who underwent contrast-enhanced or unenhanced CT was examined. In that prior study, the incidence of AKI was examined in an unadjusted cohort of patients stratified according to baseline eGFR. However, propensity score adjustment and subsequent analysis were performed only in patients who were stratified according to baseline SCr level, and not in those who were stratified according to eGFR. In a similar fashion to that in the previous study, patients were included in the current study if they *(a)* underwent contrast-enhanced or unenhanced abdominal, pelvic, or thoracic CT between January 1, 2000, and December 31, 2010; *(b)* had sufficient pre- and postscanning SCr data during expected development of AKI (24 hours prior to and 24–72 hours following CT); and *(c)* had the necessary demographic variables for the Modification of Diet in Renal Disease (MDRD) eGFR equation. Patients were excluded if they *(a)* had preexisting dialysis requirements prior to or on the day of the scanning or *(b)* underwent additional contrast-enhanced procedures within a 14-day period of the scanning. Patients were also excluded if they had a diagnosis of acute renal failure in the 14 days prior to their scanning, as determined by the date of the acute renal failure *ICD-9-CM* diagnostic code. Only the most recent scan obtained per patient was examined in patients in whom multiple scans were obtained during the study time frame (13). Patients were classified into groups of those who underwent contrast-enhanced CT (contrast material group) or those who underwent unenhanced CT (non–contrast material group).

Baseline Renal Function Stratification

Baseline eGFR was calculated for each patient from the SCr results obtained 24 hours prior to CT by using the MDRD equation on the basis of the Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations of the National Kidney Foundation (9,11). At our institution, SCr assays were traceable to isotope dilution mass spectrometry starting in September 2006. Accordingly, eGFR results prior to this date were calculated by using the original MDRD equation, and results after this date were calculated by using the revised, isotope dilution mass spectrometry–traceable MDRD equation. In cases where multiple SCr results existed in this 24-hour period, the average SCr level was used. Patients were stratified into subgroups according to baseline eGFR of 90 or higher, 60–89, 30–59, and lower than 30 mL/min/1.73 m^2 to mirror KDOQI guidelines to classify chronic kidney disease (11). An analysis of the subgroup with eGFR of lower than 15 mL/min/1.73 m^2 was not performed because of insufficient sample size (< 100 contrast-enhanced scans).

Clinical and Outcome Variables

Demographic variables (age, sex, race), pre- and postscanning SCr results, and predisposing comorbidities reportedly associated with development of AKI following contrast material administration (diabetes mellitus, diabetic nephropathy, chronic renal failure, acute renal failure, and congestive heart failure) were extracted from the electronic medical record, as previously described. A Charlson comorbidity score was calculated for each patient by using 160 *ICD-9-CM* codes for relevant comorbidities, as previously described (5).

Postscanning AKI was defined as a maximum increase in SCr level of 0.5 mg/dL or greater (≥44.2 μmol/L) over baseline (mean SCr level 24 hours prior to scanning) in the 24–72 hours following CT. An SCr level–defined cutoff of AKI was chosen for this study because eGFR cutoffs have not yet been thoroughly validated or standardized in the setting of contrast material–mediated AKI.

Propensity Score Analysis

Propensity score generation and matching were performed, as previously described, by using the R package MatchIt (R Foundation for Statistical Computing, Vienna, Austria) (5,14). Briefly, propensity score estimates representing the probability of intravenous contrast material administration were generated separately for each eGFR subgroup for patients in both the contrast material and non–contrast material groups by using a logistic regression model derived from 13 clinical variables (Table 1). Following propensity score generation, patients were matched within each eGFR subgroup by using 1:1 nearest neighbor (Greedy-type) matching and a caliper width of a 0.15 standard deviation of the propensity score logit. Matching was performed without replacement, and nonmatched results were discarded. Improvement in covariate balance following matching was measured by using conditional logistic regression, conditioned on the specific pair identification assigned to each match. Relative influence of propensity score model covariates was determined by using the R package Twang (R Foundation for Statistical Computing) (15).

Statistical Analysis

All statistical analyses were performed by using R (version 2.15; R Foundation for Statistical Computing) (16) and JMP (version 9; SAS Institute, Cary, NC). Continuous data were displayed as median scores with IQRs because of nonnormal distributions and were compared by using the Wilcoxon signed-rank test. Categorical data were displayed as relative frequencies (percentages) and were compared by using χ^2 tests of significance. The incidence of AKI was compared between contrast material and non–contrast material groups following propensity score matching by using the Fisher exact test. Significance was assigned to differences with $P \leq .05$.

Results

Study Population and Propensity Score Adjustment

Inclusion and exclusion criteria of this study population have been described previously (5). Among 1 029 899 scan records examined between 2000 and 2010, 41 249 scan records from 41 249 patients met all inclusion criteria for propensity score matching. Propensity score distributions for each eGFR

subgroup, sorted according to contrast material exposure, are shown in Figure 1. The subgroups for eGFR of 90 mL/min/1.73 m^2 or higher and 60–89 mL/min/1.73 m^2 had a similar range of propensity scores, representing a high likelihood that the patients received contrast material. In comparison, the subgroups for eGFR of 30–59 mL/min/1.73 m^2 and of lower than 30 mL/min/1.73 m^2 had much lower ranges of propensity scores and had less overlap with each other than did the subgroups for eGFR of 90 mL/min/1.73 m^2 or higher and 60–89 mL/min/1.73 m^2. The relative influence of all covariates on the propensity score model of each eGFR subgroup is shown in Figure 2. Covariate influence varied according to eGFR subgroup. Patient age was the most influential covariate for the subgroups with eGFR of 90 mL/min/1.73 m^2 or higher, 60–89 mL/min/1.73 m^2, and lower than 30 mL/min/1.73 m^2. Conversely, patient baseline renal function was the most influential covariate for the subgroup with eGFR of 30–59 mL/min/1.73 m^2. Small differences in the influence of other covariates were also noted among eGFR subgroups.

One-to-one matching on the propensity score yielded a cohort of 12508 matched patients in whom contrast-enhanced and unenhanced CT scans were obtained (821 patients in the contrast material group and 821 patients in the non–contrast material group for the subgroup with eGFR of ≥90 mL/min/1.73 m^2, 1935 patients in the contrast material group and 1935 patients in the non–contrast material group for the subgroup with eGFR of 60–89 mL/min/1.73 m^2, 2755 patients in the contrast material group and 2755 patients in the non–contrast material group for the subgroup with eGFR of 30–59 mL/min/1.73 m^2, and 743 patients in the contrast material group and 743 patients in the non–contrast material group for the subgroup with eGFR of <30 mL/min/1.73 m^2) (Table 1). Propensity score adjustment improved covariate balance in all matched eGFR subgroups. Increasing patient age and incidence of diabetes mellitus, diabetic nephropathy, chronic and acute renal failure, and congestive

Table 1

Patient Demographics and Clinical Characteristics of Propensity Score–matched eGFR Subgroups

Variable and Subgroup*	Contrast-enhanced Scans	Unenhanced Scans	*P* Value†
No. of patients			
≥90	821	821	. . .
60–89	1935	1935	. . .
30–59	2755	2755	. . .
<30	743	743	. . .
Age (y)‡			
≥90	47 (27–60)	47 (30–62)	.58
60–89	60 (48–71)	59 (46–71)	.94
30–59	70 (59–79)	70 (60–78)	.29
<30	71 (60–79)	72 (61–80)	.41
Female sex§			
≥90	304 (37)	367 (45)	.58
60–89	910 (47)	993 (51)	.68
30–59	1270 (46)	1145 (42)	.45
<30	480 (65)	463 (62)	.66
Race			
White§			
≥90	631 (77)	653 (80)	.41
60–89	1575 (81)	1607 (83)	.87
30–59	2349 (85)	2398 (87)	.83
<30	630 (85)	628 (85)	.89
Black§			
≥90	24 (3)	28 (3)	.79
60–89	21 (1)	26 (1)	.91
30–59	22 (1)	22 (1)	.74
<30	4 (1)	4 (1)	.99
Asian§			
≥90	3 (0)	6 (1)	.9
60–89	1 (0)	9 (0)	.86
30–59	11 (0)	11 (0)	.78
<30	0	0	. . .
Other§			
≥90	163 (20)	134 (16)	.33
60–89	327 (17)	293 (15)	.86
30–59	373 (14)	324 (12)	.95
<30	109 (15)	111 (15)	.88
Inpatient vs outpatient§			
≥90	746 (91)	760 (93)	.79
60–89	1733 (90)	1757 (91)	.33
30–59	2502 (91)	2513 (91)	.5
<30	686 (92)	687 (92)	.57
Baseline eGFR‖			
≥90	107 (97–127)	105 (96–121)	.52
60–89	73 (66–80)	72 (66–79)	.34
30–59	44 (37–52)	43 (36–51)	.5
<30	25 (19–27)	24 (20–27)	.59
Baseline SCr level#			
≥90	0.7 (0.6–0.8)	0.7 (0.6–0.8)	.7
60–89	1.0 (0.9–1.1)	1.0 (0.9–1.1)	.77
30–59	1.5 (1.3–1.7)	1.5 (1.3–1.8)	.13

Table 1 (continues)

Table 1 (continued)

Patient Demographics and Clinical Characteristics of Propensity Score–matched eGFR Subgroups

Variable and Subgroup*	Contrast-enhanced Scans	Unenhanced Scans	*P* Value†
<30	2.4 (2.0–2.9)	2.4 (2.0–2.9)	.57
Charlson score‡			
≥90	2 (1–3)	2 (1–2)	.87
60–89	2 (1–2)	2 (1–3)	.39
30–59	2 (1–4)	2 (1–3)	.88
<30	2 (2–4)	2 (2–4)	.64
Diabetes mellitus§			
≥90	104 (13)	93 (11)	.39
60–89	284 (15)	277 (14)	.63
30–59	660 (24)	700 (25)	.43
<30	194 (26)	194 (26)	.62
Diabetic nephropathy§			
≥90	1 (0)	1 (0)	.57
60–89	2 (0)	7 (0)	.14
30–59	32 (1)	30 (1)	.61
<30	7 (1)	6 (1)	.63
Chronic renal failure§			
≥90	9 (1)	9 (1)	.5
60–89	61 (3)	55 (3)	.22
30–59	361 (13)	357 (13)	.03
<30	138 (19)	132 (18)	.98
Chronic renal pathophysiologic findings§			
≥90	5 (1)	4 (0)	.9
60–89	20 (1)	27 (1)	.4
30–59	110 (4)	109 (4)	.33
<30	29 (4)	31 (4)	.99
Acute renal failure§			
≥90	41 (5)	34 (4)	.96
60–89	135 (7)	159 (8)	.57
30–59	826 (30)	866 (31)	.45
<30	368 (50)	364 (49)	.86
Congestive heart failure§			
≥90	47 (6)	52 (6)	.4
60–89	112 (6)	138 (7)	.77
30–59	445 (16)	473 (17)	.23
<30	135 (18)	132 (18)	.89

* Subgroup values for eGFR were measured in milliliters per minute per 1.73 m^2.

† *P* values were determined by using conditional logistic regression, controlling for matched-pair identification.

‡ Numbers are medians, with interquartile ranges (IQRs) in parentheses.

§ Data are numbers of patients. Numbers in parentheses are percentages, and percentages were rounded.

‖ Numbers are medians, with IQRs in parentheses. Values for eGFR were measured as milliliters per minute per 1.73 m^2.

Numbers are medians, with IQRs in parentheses. To convert to Système International units in micromoles per liter, multiply by 88.4.

heart failure were observed as baseline eGFR decreased.

Propensity Score–adjusted Incidence of AKI

Following propensity score matching, the incidence of AKI in both the contrast material and the non–contrast material groups significantly increased with diminishing eGFR (Table 2). The rate of AKI ranged from 1% (21 of 1642) in the subgroup with eGFR of 90 mL/min/1.73 m^2 or higher to 14% (207 of 1486) in the subgroup with eGFR of lower than 30 mL/min/1.73 m^2 ($P < .0001$). The risk of AKI was similar among the contrast material and non–contrast material groups for all eGFR subgroups. For the subgroup with eGFR of 90 mL/min/1.73 m^2 or higher, OR was 0.91 (95% CI: 0.38, 2.15) and $P = .82$; for the subgroup with eGFR of 60–89 mL/min/1.73 m^2, OR was 1.03 (95% CI: 0.66, 1.60) and $P = .99$; for the subgroup with eGFR of 30–59 mL/min/1.73 m^2, OR was 0.94 (95% CI: 0.76, 1.18) and $P = .65$; for the subgroup with eGFR of lower than 30 mL/min/1.73 m^2, OR was 0.97 (95% CI: 0.72, 1.30) and $P = .89$.

Discussion

This retrospective, single-center study demonstrates that intravenous contrast material administration in doses used for CT scanning is not associated with an increased risk of AKI in a predominantly inpatient cohort. The current study builds on our prior publication in which we applied similar methods to patient populations and in which we defined renal dysfunction and risk thresholds for AKI according to baseline SCr rather than eGFR (5). In both the prior and the current studies, we observed that the incidence of AKI increased in patients with worsening baseline renal function. However, rates of SCr-defined AKI were similar between propensity score–matched groups of patients who received intravenous contrast material and those who did not receive it. The current findings provide additional evidence that the incidence of intravenous contrast material–mediated AKI is obscured by comparable rates of contrast material–independent AKI and suggest that eGFR-based definitions of AKI risk are incapable of aiding identification of true contrast material–mediated AKI from contrast material–independent AKI.

Our finding of similar likelihoods of AKI between contrast material and non–contrast material groups in any eGFR subgroup was not affected by sample size limitations. The smallest subgroups in our analysis were patients at lowest risk (the subgroup with a baseline eGFR ≥ 90 mL/

Figure 1

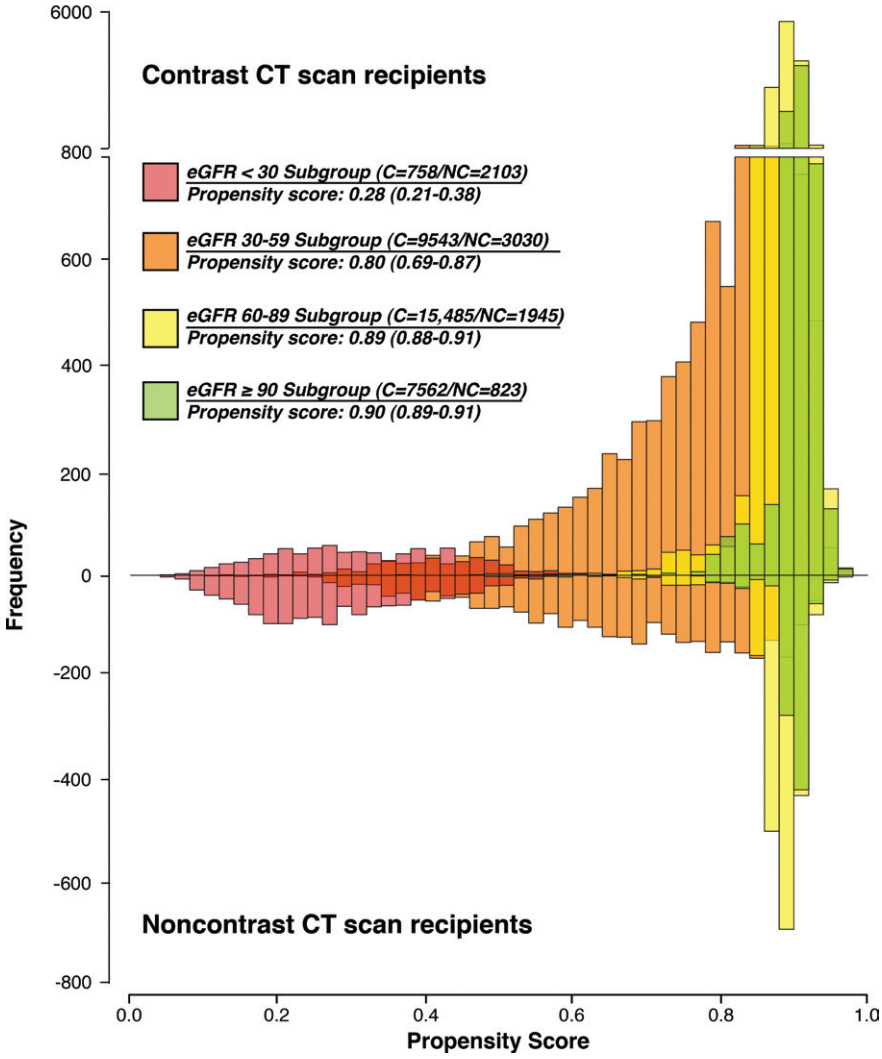

Figure 1: Distribution of propensity scores in study population. Patients who underwent contrast-enhanced CT (contrast material group *[Contrast CT scan recipients]*) are shown above the x-axis, and patients who underwent unenhanced CT (non–contrast material group *[Noncontrast CT scan recipients]*) are shown below the x-axis. Distributions are broken down according to eGFR subgroups (green = ≥90 mL/min/1.73 m^2, yellow = 60–89 mL/min/1.73 m^2, orange = 30–59 mL/min/1.73 m^2, red = <30 mL/min/1.73 m^2). Propensity scores are medians, and IQRs are in parentheses for each eGFR subgroup. *C* = number of patients in the contrast material group, *NC* = number of patients in the non–contrast material group.

min/1.73 m^2, n = 1642) and patients at highest risk (the subgroup with a baseline eGFR < 30 mL/min/1.73 m^2, n = 1486) of developing AKI. The CIs for the ORs of developing AKI can be used to determine the smallest significant difference between contrast material and non–contrast material groups that can be detected with our study. Among lowest-risk patients, significant differences in the incidence of AKI as small as 1.1% can be detected (assuming an AKI rate of 1% and an upper CI limit of 2.15). Among highest-risk patients, significant differences in the incidence of AKI as small as 3.5% can be detected (assuming an AKI rate of 14% and an upper CI limit of 1.30). Because the magnitude of these differences is smaller than previously reported rates of CIN, our study sample size did not negatively affect the precision of our OR estimates.

In two recent studies, a meta-analysis of controlled studies (4) and a retrospective study (5), we also demonstrated a similar risk of AKI between patients who received intravenous contrast material and control groups of patients who did not (4,5). In our prior propensity score–based study in which we stratified patients according to baseline SCr level into low-risk (SCr level of < 1.5 mg/dL [<132.6 μmol/L]), medium-risk (SCr level of 1.5–2.0 mg/dL [132.6–176.8 μmol/L]), and high-risk (SCr level of ≥ 2.0 mg/dL [≥176.8 μmol/L]) subgroups, we also found no significant differences in the incidence of AKI between patients who underwent contrast-enhanced and unenhanced CT in any risk subgroup (5). Our current study results expand on the findings in these prior studies by using measurement and stratification of patient baseline renal function according to eGFR, which more accurately reflects actual GFR compared with SCr level (9,10). Investigators in few prior studies of contrast material–mediated AKI utilized baseline eGFR as a means of risk stratification (17–22), and none of these studies were appropriately controlled with a matched patient cohort not exposed to intravenous contrast material. In our studies, we utilized propensity score matching to balance contrast material and non–contrast material groups with a wide range of clinical characteristics, including age, sex, Charlson comorbidity score, and the presence of comorbidities that can predispose patients to AKI.

However, two large propensity score–adjusted studies by Davenport et al (23,24) showed apparent escalating incidence of AKI in patients with a baseline SCr level of greater than 1.5 mg/dL (>132.6 μmol/L) and in patients in the group with a baseline eGFR lower than 30 mL/min/1.73 m^2 in whom a contrast-enhanced CT scan was obtained compared with patients in whom an unenhanced scan was obtained. Despite the seemingly similar

Figure 2

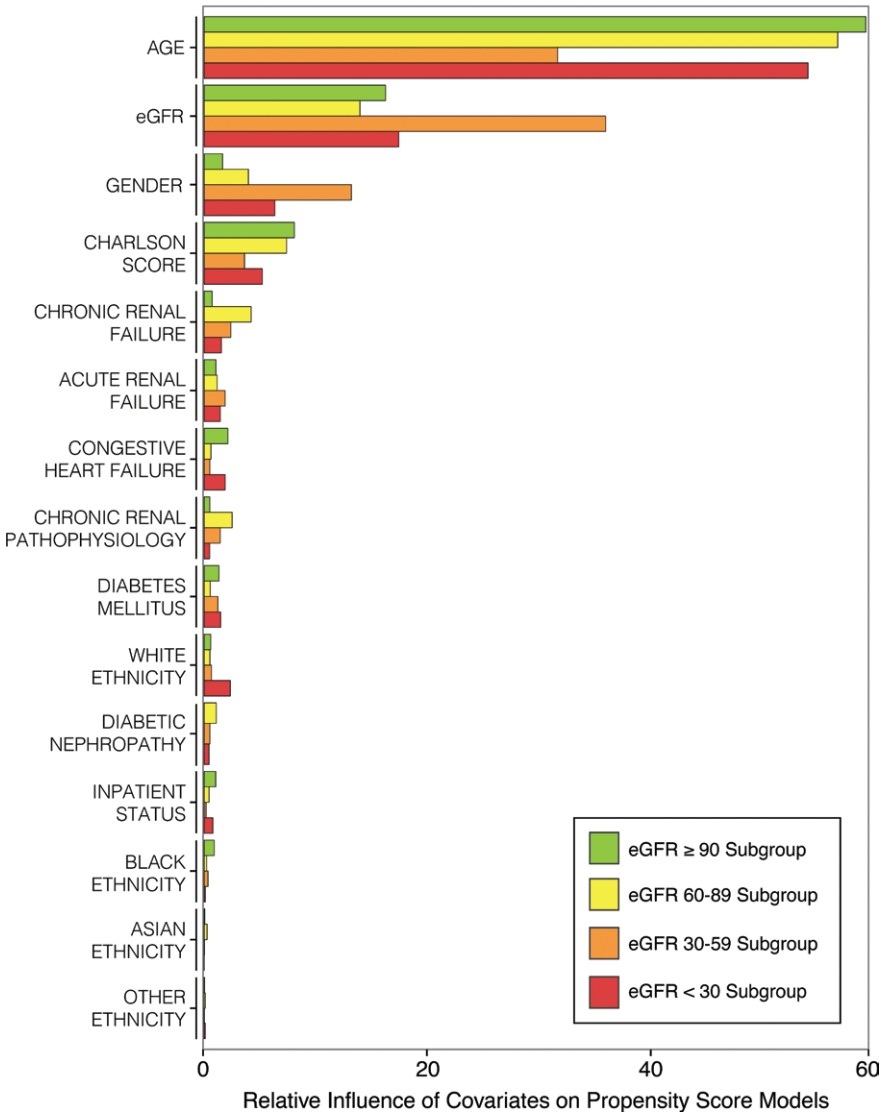

Figure 2: Relative influence of clinical covariates on estimated propensity scores. Distributions are broken down according to eGFR subgroup (green = ≥90 mL/min/1.73 m^2, yellow = 60–89 mL/min/1.73 m^2, orange = 30–59 mL/min/1.73 m^2, red = <30 mL/min/1.73 m^2).

statistical methods utilized by Davenport et al (23,24) and those utilized in our current and prior study (5), several key methodological differences may account for the disparate results. First, our findings were derived from propensity scores generated for each distinct renal function subgroup (defined by eGFR in the current study and SCr level in the prior study) instead of the approach of Davenport et al where a single propensity score model was applied to the entire cohort. Because both study cohorts consisted predominantly of patients with normal renal function and only a small fraction of patients with significant renal insufficiency, a single propensity score model of the entire cohort would be heavily influenced by most of the patients with normal renal function. As such, this approach may not account for the different clinical characteristics of the renal insufficiency patient groups and could lead to suboptimal matching on the basis of incorrect clinical covariates. These concerns are highlighted by our findings, where clinical differences between normal and abnormal renal function groups manifested as both vastly different propensity score distributions and different relative influences of each covariate on the propensity score models in each eGFR subgroup. Second, we performed 1:1 matching on each eGFR subgroup, while Davenport et al performed 1:1 matching on the entire cohort before performing logistic regression analysis to examine specific renal function subgroups, which may have affected the results. Finally, we examined a large number of patients, particularly those with compromised renal function (eGFR of < 30 mL/min/1.73 m^2), which increased the precision of the resulting ORs.

The incidence rates of AKI in our current study are similar to those in other published studies in which the researchers examined AKI following contrast-enhanced CT. In our previous SCr level–stratified propensity score–adjusted study (5), we also included unadjusted eGFR–stratified results, as shown in table E1 of that article. In that prior study, unadjusted AKI rates ranged from 2% (613 of 34 149) in the group with an eGFR of higher than 90 mL/min/1.73 m^2 to 12% (1322 of 11 484) in the group with an eGFR of lower than 30 mL/min/1.73 m^2 (5). In the current study, adjusted AKI rates ranged from 1% (21 of 1642) in the group with an eGFR of higher than 90 mL/min/1.73 m^2 to 14% (207 of 1486) in the group with an eGFR of lower than 30 mL/min/1.73 m^2. These rates of AKI are consistent with results in prior published studies by Thomsen and Morcos (20) and Kim et al (17) who reported an incidence rate of 8% (four of 51) and 12% (seven of 58), respectively, in patients with a baseline eGFR of lower than 30 mL/min/1.73 m^2. Weisbord et al (22) reported an AKI incidence rate of 10% (five of 51) in patients with a baseline eGFR of 45 mL/min/1.73 m^2 or lower. Our study improves on these prior eGFR studies

Table 2

Propensity Score–adjusted Risk of AKI Following Contrast-enhanced or Unenhanced CT

eGFR Subgroup (mL/min/1.73 m^2)	AKI Following Contrast-enhanced Scanning*	AKI Following Unenhanced Scanning*	OR†	*P* Value‡
≥ 90	10/821 (1.2)	11/821 (1.3)	0.91 (0.38, 2.15)	.82
60–89	40/1935 (2.1)	39/1935 (2.0)	1.03 (0.66, 1.60)	.99
30–59	161/2755 (5.8)	170/2755 (6.2)	0.94 (0.76, 1.18)	.65
< 30	102/743 (14)	105/743 (14)	0.97 (0.72, 1.30)	.89

* Numbers in parentheses are percentages, and percentages were rounded.

† The odds ratio (OR) refers to the OR of AKI in the contrast material group compared with that in the non–contrast material group. Numbers in parentheses are 95% confidence intervals (CIs).

‡ *P* values were determined by using the Yates corrected χ^2 test.

by examining a much larger patient population and by matching contrast material recipients with a control group of patients by using propensity score adjustment.

Selection bias remains a concern of all nonrandomized retrospective studies. In an effort to address this limitation, we performed in silico randomization and matching on the basis of a propensity score of the probability of receiving iodinated contrast material. This propensity score incorporated many clinical variables associated with the development of AKI that can affect the decision to administer iodinated contrast material, including baseline SCr level, age, sex, race, relevant comorbidities, and Charlson comorbidity score. This approach minimized selection bias by balancing the relevant common covariates among contrast material and non–contrast material patient groups. Despite these efforts, unmeasured confounders may exist that could have affected our results. In particular, patients who received contrast material may have been more likely to receive intravenous hydration or other prophylactic measures compared with patients who underwent unenhanced CT. Likewise, patients who were administered potentially nephrotoxic medications at the time of scanning may have been less like to receive contrast material. This information, which could not be easily retrieved from the medical record, could have affected our study results. However, our prior counterfactual analysis on this patient cohort represents a fairly robust sensitivity analysis and suggests that these confounders probably had a minimal effect on our findings (5).

Our study had several additional limitations. First, our study population consisted predominantly of inpatients; our results are therefore not generalizable to outpatient populations. Second, we specifically excluded patients who received multiple doses of contrast material within a 14-day interval. Our study findings may not extend to these patients. Third, our cohort consisted of a mix of patients who received low-osmolar or iso-osmolar contrast material. Because our institutional use of iso-osmolar contrast material is largely limited to patients with a baseline SCr level of greater than 2.0 mg/dL (>176.8 μmol/L) (approximately an eGFR of < 40 mL/min/1.73 m^2), we were unable to directly compare a similar patient population to assess contrast material specificity. Fourth, our use of *ICD-9-CM* codes to identify comorbidities may have been affected by coding errors; however, these errors were probably present in a similar distribution between the contrast material and non–contrast material groups. Fifth, the MDRD equation is known to lead to an underestimation of GFR in patients with normal renal function (eGFR > 60 mL/min/1.73 m^2) (25), and such underestimation may lead to improper classification of baseline renal function and potentially aberrant estimates of AKI in these groups. However, the MDRD equation is accurate in patients with compromised renal function who are most at risk for developing AKI, and in our study, we did not observe evidence of contrast material–mediated AKI in those groups. Sixth, while we used KDOQI chronic kidney disease stage cutoffs to stratify patients according to the eGFR, it is possible that some patients in the more severe risk strata were assigned to the stratum only because of transiently diminished renal function. While the KDOQI stages are relevant to long-term assessment of renal function, this practice is not commonly performed to assess risk prior to contrast material administration. Finally, it is possible that the incidence of contrast material–independent AKI in our cohort was high enough to obscure true contrast material–mediated AKI. Additional studies are necessary to further assess a causal association between contrast material and AKI.

In conclusion, our findings provide additional evidence that the administration of intravenous contrast material does not increase the risk of AKI, even in patients with substantially compromised renal function.

Disclosures of Conflicts of Interest: J.S.M. Financial activities related to the present article: received an investigator-initiated research grant for contrast material–induced nephropathy research from GE Healthcare. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **R.J.M.** No relevant conflicts of interest to disclose. **R.E.C.** No relevant conflicts of interest to disclose. **R.W.K.** No relevant conflicts of interest to disclose. **D.F.K.** Financial activities related to the present article: received a grant in support for research associate from

GE Healthcare. Financial activities not related to the present article: served on advisory board and institution received funding from GE Healthcare. Other relationships: none to disclose. **E.E.W.** Financial activities related to the present article: received investigator-initiated research grant not specific to this research but GE Healthcare does make contrast from GE Healthcare. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose.

References

1. 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.
2. Benko A, Fraser-Hill M, Magner P, et al. Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. Can Assoc Radiol J 2007;58(2):79–87.
3. American College of Radiology. ACR Manual on Contrast Media. Version 8. ACR Committee on Drugs and Contrast Media. http://www.nxtbook.com/nxtbooks/acr/contrastmediamanual2012/. Published 2012. Accessed March 15, 2013.
4. McDonald JS, McDonald RJ, Comin J, et al. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. Radiology 2013;267(1):119–128.
5. McDonald RJ, McDonald JS, Bida JP, et al. Intravenous contrast material–induced nephropathy: causal or coincident phenomenon? Radiology 2013;267(1):106–118.
6. Katzberg RW, Lamba R. Contrast-induced nephropathy after intravenous administration: fact or fiction? Radiol Clin North Am 2009;47(5):789–800.
7. 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.
8. Newhouse JH, RoyChoudhury A. Quantitating contrast medium-induced nephropathy: controlling the controls [editorial]. Radiology 2013;267(1):4–8.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461–470.
10. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–612.
11. 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.
12. Goldfarb S, McCullough PA, McDermott J, Gay SB. Contrast-induced acute kidney injury: specialty-specific protocols for interventional radiology, diagnostic computed tomography radiology, and interventional cardiology. Mayo Clin Proc 2009;84(2):170–179.
13. 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.
14. Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. J Stat Softw 2011;42(8):1–28.
15. 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, 2012.
16. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2012.
17. Kim SM, Cha RH, Lee JP, et al. Incidence and outcomes of contrast-induced nephropathy after computed tomography in patients with CKD: a quality improvement report. Am J Kidney Dis 2010;55(6):1018–1025.
18. 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.
19. 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.
20. Thomsen HS, Morcos SK. Risk of contrast-medium-induced nephropathy in high-risk patients undergoing MDCT: a pooled analysis of two randomized trials. Eur Radiol 2009;19(4):891–897.
21. Utsunomiya D, Yanaga Y, Awai K, et al. Baseline incidence and severity of renal insufficiency evaluated by estimated glomerular filtration rates in patients scheduled for contrast-enhanced CT. Acta Radiol 2011;52(5):581–586.
22. Weisbord SD, Mor MK, Resnick AL, Hartwig KC, Palevsky PM, Fine MJ. Incidence and outcomes of contrast-induced AKI following computed tomography. Clin J Am Soc Nephrol 2008;3(5):1274–1281.
23. Davenport MS, Khalatbari S, Dillman JR, Cohan RH, Caoili EM, Ellis JH. Contrast material–induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. Radiology 2013;267(1):94–105.
24. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material–induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. Radiology 2013;268(3):719–728.
25. Lin J, Knight EL, Hogan ML, Singh AK. A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. J Am Soc Nephrol 2003;14(10):2573–2580.