Intravenous Contrast Material Exposure Is Not an Independent Risk Factor for Dialysis or Mortality[1]

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Purpose: To determine the risk of emergent dialysis and short-term mortality following intravenous iodinated contrast material exposure.

Materials and Methods: This single-center retrospective study was HIPAA compliant and institutional review board approved. All contrast material–enhanced (contrast group) and unenhanced (noncontrast group) abdominal, pelvic, and thoracic computed tomography scans from 2000–2010 were identified. Patients in the contrast and noncontrast groups were compared following propensity score–based 1:1 matching to reduce intergroup selection bias. Patients with preexisting diabetes mellitus, congestive heart failure, or chronic or acute renal failure were identified as high-risk patient subgroups for nephrotoxicity. The effects of contrast material exposure on the rate of acute kidney injury (AKI) (serum creatinine level ≥ 0.5 mg/dL [44.2 μmol/L] above baseline within 24–72 hours of exposure) and dialysis or death within 30 days of exposure were determined by using odds ratios (ORs) and covariate-adjusted Cox proportional hazards models. Results were validated with a bootstrapped sensitivity analysis.

Results: The 1:1 matching on the basis of the propensity score yielded a cohort of 21 346 patients (10 673 in the contrast group, 10 673 in the noncontrast group). Within this cohort, the risks of AKI (OR, 0.94; 95% confidence interval [CI]: 0.83, 1.07; $P = .38$), emergent dialysis (OR, 0.96; 95% CI: 0.54, 1.60; $P = .89$), and 30-day mortality (hazard ratio [HR], 0.97; 95% CI: 0.87, 1.06; $P = .45$) were not significantly different between the contrast group and the noncontrast group. Although patients who developed AKI had higher rates of dialysis and mortality, contrast material exposure was not an independent risk factor for either outcome for dialysis (OR, 0.89; 95% CI: 0.40, 2.01; $P = .78$) or for mortality (HR, 1.03; 95% CI: 0.82, 1.32; $P = .63$), even among patients with compromised renal function or predisposing comorbidities.

Conclusion: Intravenous contrast material administration was not associated with excess risk of AKI, dialysis, or death, even among patients with comorbidities reported to predispose them to nephrotoxicity.

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Although contrast material–induced nephropathy (CIN) is generally reported to be a self-limited phenomenon, concern remains that intravenous iodinated contrast material exposure can lead to irreversible nephrotoxicity (1,2). The results of prior uncontrolled studies of contrast material administration suggest that patients who develop CIN have an increased risk of dialysis and death compared with patients who do not develop CIN (3–5).These concerns are greatest among individuals with preexisting renal dysfunction, particularly those with acute renal failure (ARF) or chronic renal failure (CRF) and diabetes mellitus (DM) (6,7). Patients with congestive heart failure (CHF) are also reportedly at higher risk of CIN because of poor renal perfusion from atherosclerosis, chronic hypertension, or diminished cardiac output (6,7). In light of these concerns, the guidelines of the European Society of Urogenital Radiology (7) and the American College of Radiology (8) recommend more restricted use of intravenous contrast material among these "high-risk" patient populations.

The nephrotoxic risk of intravenous contrast material exposure has come under scrutiny for several reasons (9,10). First, much of the risk attributed to intravenous contrast material exposure has been extrapolated from studies of intraarterial contrast material administration (3–5). Because these intraarterial studies inherently lacked a control population of patients who did not receive contrast material, the incidence of adverse outcomes attributable to contrast material cannot be extricated from contrast material–independent causes. Second, a recent systematic review of controlled studies of intravenous contrast material exposure demonstrated that adverse outcomes directly attributable to intravenous contrast material administration are extremely rare (11–16). Specifically, clinically important outcomes, particularly dialysis and death, have not been clearly linked to intravenous contrast material exposure. Third, whereas researchers in prior uncontrolled retrospective studies have reported CIN incidence rates as high as 30% (17), investigators in more recent controlled retrospective studies of intravenous contrast material exposure have shown that contrast material–independent causes of acute kidney injury (AKI) occur at an equivalent rate as contrast material–dependent AKI so as to preclude detection of true CIN (18,19).

In our study, we therefore sought to determine the true incidence of emergent dialysis and short-term mortality following intravenous iodinated contrast material exposure among individuals with closely matched demographic and clinical characteristics by using propensity score analysis.

Advances in Knowledge

- Following propensity score adjustment for differences in presumed risk factors of contrast material–induced nephropathy, the rate of emergent dialysis (odds ratio [OR], 0.96; 95% confidence interval [CI]: 0.54, 1.60; $P = .89$) and short-term mortality (hazard ratio [HR], 0.97; 95% CI: 0.87, 1.06; P = .45) among patients who underwent contrast-enhanced CT scans were not significantly different when compared with those who underwent unenhanced CT scans.
- Patients who developed acute kidney injury (AKI) had a higher risk of dialysis (OR, 15.75; 95% CI: 9.10, 27.2; $P < .0001$) and short-term mortality (HR, 4.51; 95% CI: 3.91, 5.21; $P < .0001$) than patients who did not develop AKI, independent of contrast material administration.
- Patients with an increased baseline serum creatinine level, diabetes mellitus, congestive heart failure, preexisting renal dysfunction, or a history of acute renal failure had higher rates of AKI, dialysis, and short-term mortality compared with patients without these comorbidities, independent of contrast material administration.

Implications for Patient Care

- The frequency of new cases of dialysis following administration of intravenous iodinated contrast material is low (<1%).
- AKI is associated with worse overall short-term outcomes (dialysis, 30-day mortality), but these outcomes are independent of contrast material exposure.
- The nephrotoxic risk associated with administration of intravenous iodinated contrast material appears to have been overstated.

Materials and Methods

Investigator-initiated grant support for our 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 herein. Study design and implementation for this retrospective study was overseen

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Abbreviations:
AKI = acute kidney injury
ARF = acute renal failure
CHF = congestive heart failure
CI = confidence interval
CIN = contrast material–induced nephropathy
CRF = chronic renal failure
DM = diabetes mellitus
EMR = electronic medical record
HR = hazard ratio
ICD-9 = *International Classification of Diseases, Ninth Revision*
OR = odds ratio
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; approval of final version of submitted manuscript, all authors; literature research, R.J.M., J.S.M., R.P.H., R.W.K.; clinical studies, E.E.W.; experimental studies, R.J.M.; statistical analysis, R.J.M., J.S.M.; and manuscript editing, all authors

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

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.

Study Population

Patients and criteria for our study have been included in a previous publication that did not specifically examine death and dialysis outcomes following contrast material administration (19). The inclusion criteria and exclusion criteria for this study are shown in Figure 1. Briefly, patients were included if they underwent either a contrast material–enhanced (hereafter, contrast group) or an unenhanced (hereafter, noncontrast group) abdominal, pelvic, or thoracic CT scan at our institution between January 1, 2000, and December 31, 2010; they had sufficient SCr level laboratory data to allow diagnosis of AKI; and they had sufficient clinical variables to allow development of a propensity score to stratify their AKI risk. Exclusion criteria included *(a)* patients with preexisting dialysis needs; *(b)* patients who underwent more than one contrast-enhanced CT scan or received any other intravenous or intraarterial iodinated contrast material dose within 30 days of the scan to avoid confounding bias of the effects of the prior scan on the measured renal function and outcomes associated with the most recent scan; *(c)* patients who were lost to follow-up; or *(d)* patients who died as a result of an anaphylactic contrast material reaction (Appendix E1 [online]). To eliminate sampling bias and maximize the probability of identification of disease, we examined only the most recent scan record for those patients who met all inclusion and exclusion criteria who underwent more than one scan during the study time frame on the basis of the recommendations of Horwitz and Feinstein (20).

Data Sources

All clinical data were extracted from our institutional electronic medical record (EMR) with relational database software (Data Discovery and Query Building; IBM, Armonk, NY), as previously described (19). All procedures and clinical diagnoses were identified from the EMR by using *International Classification of Diseases, Ninth Revision* (ICD-9), diagnostic codes and *Current Procedural Terminology* procedure

Figure 1

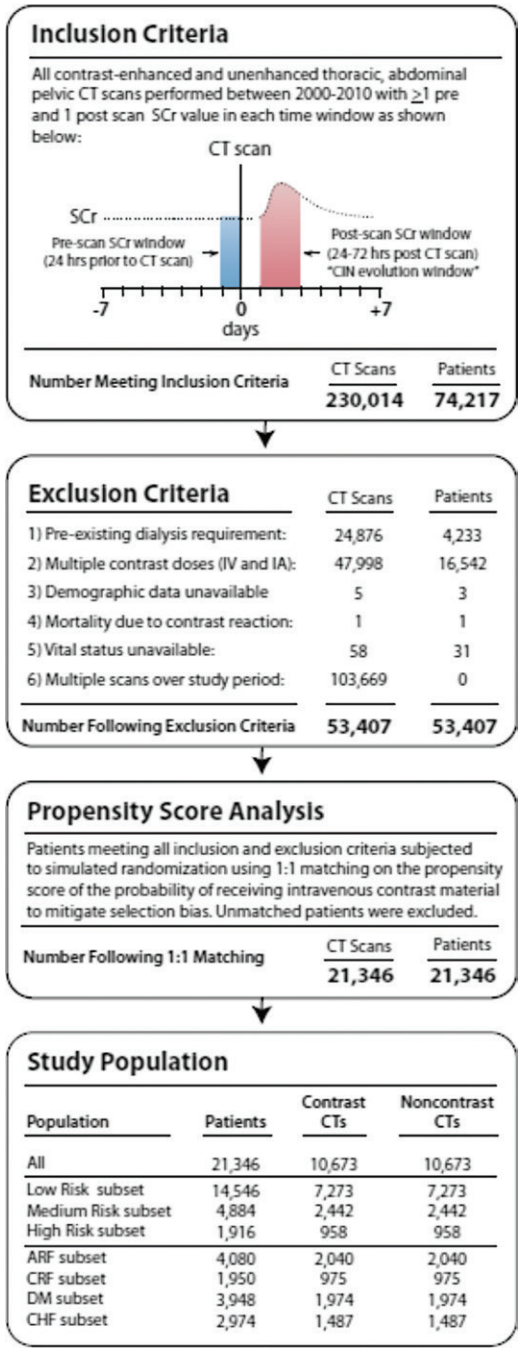

Figure 1: Study flowchart. *Contrast CTs* = contrast-enhanced CT scans, CT = computed tomography, *IA* = intraarterial, *IV* = intravenous, *noncontrast CTs* = unenhanced CT scans, SCr = serum creatinine.

codes (Appendix E1 [online]). The SCr data were extracted from our institutional laboratory information system and were associated with the date and time of the CT examination by using a Beowolf-style supercomputing cluster. The fidelity of electronic data extraction and manipulation from the EMR was verified against a hand-searched subset of the patient population, representing approximately 10% of the total study size; no systematic errors were identified.

Clinical Variables

Data extracted from the EMR included demographic variables (age, sex, ethnicity), metrics of clinical status (Charlson score, inpatient status), and pre- and postscan SCr results. Patients were categorized into contrast and noncontrast groups according to intravenous iodinated contrast material administration at the time of CT examination and subsequently were stratified with respect to their presumptive risk for AKI according to the baseline SCr level into the following subgroups: low risk (SCr level, <1.5 mg/dL [<132.6 μmol/L]), medium risk (SCr level, 1.5–1.9 mg/dL [132.6–168.0 μmol/L]), and high risk (SCr level, ≥2.0 mg/dL [≥176.8 μmol/L]). Patients were independently subclassified into four comorbidity subgroups reportedly associated with development of AKI following contrast material administration, which included DM, CRF, ARF, and CHF, for subsequent outcomes analysis (19). Specific diagnoses of DM, CRF, and CHF were associated with each patient if they were diagnosed and reported in the EMR up to 30 days following the date of the CT scan, whereas diagnoses of prior ARF were associated with each patient if the diagnosis was present 30 days prior to CT scanning to avoid confounding this diagnosis with AKI following CT scanning. Patients were classified as having CRF if they had ICD-9 diagnostic codes for either chronic renal disease or chronic renal pathophysiologic findings, as previously described (19). Similarly, patients were classified as having DM if they were assigned ICD-9 codes for either DM or diabetic nephropathy (19).

Outcome Variables

Outcomes in our study were AKI, emergent dialysis, and short-term mortality. AKI was defined as an increase in the SCr level of 0.5 mg/dL (44.2 μmol/L) or more over the baseline level in the 24–72 hours following CT scanning. This terminology was applied to both contrast material–dependent renal injury following contrast-enhanced CT (CIN) and contrast material–independent renal injury following unenhanced CT to provide a uniform definition of AKI (21). Cases of emergent dialysis were defined as cases in patients with no prior history of dialysis therapy who required dialysis within 30 days following CT scanning and were identified by using a combination of CPT codes and a natural language processing–based search of all institutional clinical notes (Appendix E1 [online]). Vital status and date of death were determined up to January 1, 2012, via iterative search of our institutional EMR, State of Minnesota electronic death certificates, death tapes, and the Centers for Disease Control and Prevention National Death Index records to exhaustively identify patients who died within 30 days following CT scanning (22).

Contrast Material Administration

Contrast material administration at our institution is protocol-specific but based on a standardized dose 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. On the basis of institutional guidelines, patients with a baseline SCr level less than 2.0 mg/dL (176.8 μmol/L) receive the low-osmolar agent iohexol (Omnipaque 300; GE Healthcare), whereas patients with a baseline SCr level of 2.0 (176.8 μmol/L) or more receive the isoosmolar agent iodixanol (Visipaque; GE Healthcare).

Statistical Analysis

All statistical analyses were performed by two authors (R.J.M. and J.S.M., with 18 and 14 years of experience, respectively) by using R software (version 2.15.3; R Foundation for Statistical Computing, Vienna, Austria) (23). Continuous data were displayed as median scores with interquartile ranges because of nonnormal distributions and were compared by using the Wilcoxon signed-rank test of significance. Categorical data were displayed as relative frequencies (percentages) and were compared by using χ^2 tests of significance. Odds ratios (ORs) and hazard ratios (HRs) were reported with their associated 95% confidence interval (CIs). Significance was assigned to differences with a P value of .05 or less. Nonsignificant differences were assessed in the context of CI width. Using this method, the distance between the point estimate and the upper confidence limit represents a conservative estimate of the smallest significant difference detectable by the study (24–26).

Propensity Score Analysis

Propensity score analysis was performed to compare patients of similar demographic and clinical characteristics at similar risk for AKI (27). Propensity scores, representing the probability of intravenous contrast material administration for each patient in both contrast and noncontrast groups, were estimated as previously described by using a nonparsimonious multivariable logistic regression model derived from 160 individual ICD-9 codes and seven additional clinical covariates grouped as shown in Figure 2 (19). The propensity score model was developed by using only contrast material exposure and the baseline covariates so that the propensity score estimation was not influenced by the outcome variables. Baseline covariates included comorbidities, clinical variables, and demographic variables reportedly associated with development of CIN on the basis of American College of Radiology (8) and European Society of Urogenital Radiology (7) consensus statements and variables associated with clinical status and predictors of mortality. In some cases, multiple variables associated with the same disease process were used in an attempt to better stratify disease severity and renal involvement.

Figure 2

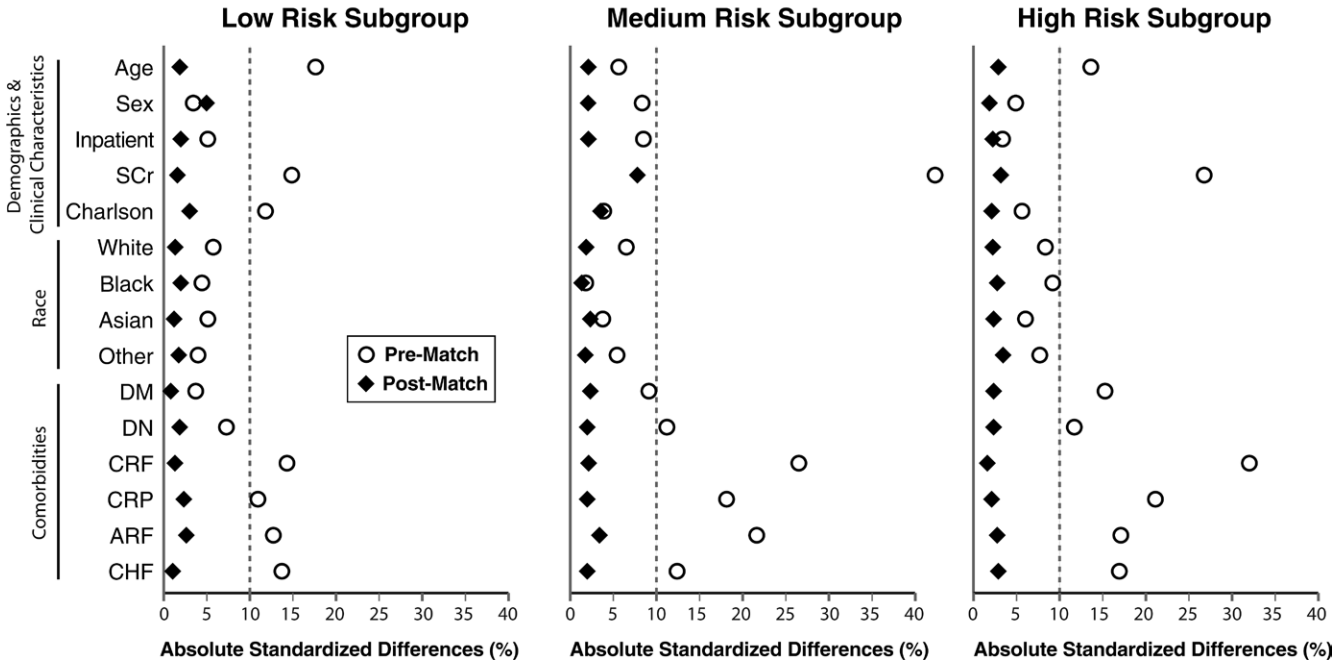

Figure 2: Propensity score covariate balance. Love plot for absolute standardized differences for propensity score model–grouped covariates before and after one-to-one greedy-type matching between patients who underwent a contrast-enhanced CT examination (contrast group) and patients who underwent an unenhanced examination (noncontrast group). Absolute standardized differences of 0% indicate no bias, and values of less than 10% suggest inconsequential bias. *Charlson* = Charlson score, *CRP* = chronic renal pathophysiologic findings, *DN* = diabetic nephropathy.

Matching between contrast and noncontrast groups was performed by using 1:1 nearest neighbor (greedy-type) matching with a caliper width of 0.15 standard deviations of the logit distance measure by using the R package MatchIt, as previously described (19,27,28). Separate propensity score–matched subsets were generated for each AKI risk subgroup (low, medium, high) and comorbidity subgroup (DM, ARF, CRF, CHF) variable as a means of covariate blocking to minimize the risk of confounding bias via suboptimal 1:1 matching (eg, patients with similar propensity scores but dissimilar clinical characteristics) and to address the expectation of intersubgroup heterogeneity in propensity score weighting of each covariate. Improvement in covariate balance following matching was measured by using both conditional logistic regression and absolute standardized differences (29). Matched results were then used to estimate the association between contrast material exposure and outcomes, including AKI, dialysis, and mortality, by using univariate logistic regression.

Survival Analysis

Survival analyses were performed on the 1:1 matched data sets by using the R package Survival (30,31). Unadjusted survival curves were estimated by using the Kaplan-Meier method (32). To estimate the effect of intravenous contrast material exposure on survival, adjusted Cox proportional hazards models were constructed by using the propensity score model covariates for the entire matched population, the AKI risk subgroups (high, medium, and low risk), and comorbidity subgroups.

Sensitivity Analysis

The effect of intravenous contrast material exposure on each outcome (AKI, dialysis, death) was assessed by using a bootstrap-based sensitivity analysis with the R package PSAboot (33). The propensity score was reestimated over 100 bootstrap cycle draws by using five differing propensity score estimation methods to provide a more robust estimate of the sampling distribution and to externally validate the nonparametric MatchIt method. Aggregate exposure effects for each method were assessed with pooled outcome estimates.

Results

Patient Population and Demographics

A total of 157076 scan records from 53407 individual patients met inclusion and exclusion criteria summarized in Figure 1. Study inclusion failure was primarily a result of outpatients who typically do not return for postscan SCr assessment or the small subset of inpatients who underwent CT immediately before discharge. Additional exclusion of all but the most recent scan among patients who underwent multiple scans over the study period (n = 103669) reduced the number of scans to 53407 scans among 53407

Table 1

Patient Demographics and Clinical Characteristics of Study Population before and after Propensity Score Adjustment

Variable	Entire 1:1 Matched Data Set			
	Contrast Group	Noncontrast Group	Unmatched *P* Value*	Matched *P* Value†
No. of patients	10673	10673	…	…
Age (y)‡	65.2 (51.8–75.5)	65.6 (51.6–76.3)	<.001	.83
Female sex§	4977 (46.6)	4953 (46.4)	<.001	.95
Race§				
White	8714 (81.6)	8888 (83.3)	.89	.60
Black	157 (1.5)	128 (1.2)	.07	.95
Asian	77 (0.7)	78 (0.7)	.93	.89
Other or not specified	1725 (16.2)	1579 (14.8)	.71	.59
Inpatient vs outpatient§	9723 (91.1)	9605 (90.0)	<.001	.80
Baseline SCr level (mg/dL)‖	1.1 (0.9–1.5)	1.2 (0.9–1.6)	<.001	.25
Charlson score‡	2 (1–3)	2 (1–3)	<.001	.24
Comorbidities§				
DM	2232 (20.9)	2028 (19.0)	<.001	.42
Diabetic nephropathy	63 (0.6)	67 (0.6)	<.001	.94
Chronic renal disease	818 (7.7)	890 (8.3)	<.001	.78
Chronic renal pathophysiologic findings	238 (2.2)	249 (2.3)	<.001	.96
Acute renal disease	2149 (20.1)	2255 (21.1)	<.001	.93
CHF	1503 (14.1)	1621 (15.2)	<.001	.75

* Unmatched *P* values were derived from the unadjusted differences between the contrast group ($n = 40709$) and the noncontrast group ($n = 12698$).

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

‡ Data are medians, and numbers in parentheses are interquartile ranges, except as otherwise indicated.

§ Numbers in parentheses are percentages. Percentages were rounded.

‖ Data are medians, and numbers in parentheses are interquartile ranges, except as otherwise indicated. To convert SCr values to Système International units in micromoles per liter, multiply by 88.4.

patients (40709 in the contrast group and 12698 in the noncontrast group) (19). Following 1:1 matching on the propensity score for each AKI risk group, a total of 21346 patient records (high-risk group, 1916; medium-risk group, 4884; low-risk group, 14546) were included in this study, with 10673 in the contrast group and 10673 in the noncontrast group of scans in each study arm of the entire matched cohort. Improvement in covariate balance between contrast and noncontrast groups are displayed for the entire cohort in Table 1 and for each matched AKI risk subgroup in Figure 2. After matching, absolute standardized differences for all propensity score model covariates were less than 10%, suggesting matching achieved favorable intertreatment group covariate balance. Demographic and clinical characteristics of the entire matched cohort are shown in Table 1, and the propensity score distribution is shown in Figure E1 (online). Within this cohort, a total of 10016 (47.0%) patients were associated with at least one or more of the four selected "at-risk" comorbidity subgroups (Tables E1–E4 [online]).

Effect of Contrast Material Exposure on the Incidence of AKI

Within the entire matched cohort, the incidence of AKI was 5.0% (1059 of 21346) (Table 2). There was no significant difference in the rate of AKI between patients in the contrast group (4.8% [515 of 10673]) and the noncontrast group (5.1% [544 of 10673]; OR = 0.94 [95% CI: 0.83, 1.07]; $P = .38$). Among selected "at-risk" comorbidity subgroups, patients with DM had a similar incidence of AKI as the entire cohort (6.9%, 271 of 3948), while patients with a history of ARF, CRF, and CHF had a higher incidence of AKI (12.1% [494 of 4080], 9.6% [187 of 1950], and 9.2% [273 of 2974], respectively). Patients previously diagnosed with ARF and CHF demonstrated a slightly higher frequency of AKI in the contrast group compared with the noncontrast group, although these differences did not reach significance for ARF (OR, 1.10; 95% CI: 0.91, 1.32; $P = .36$) or CHF (OR, 1.18; 95% CI: 0.92, 1.52; $P = .18$).

Effect of Contrast Material Exposure on 30-Day Emergent Dialysis

Within the entire matched cohort, a total of 52 cases of emergent dialysis were identified that occurred within 30 days of the CT scan (Table 2). The incidence of emergent dialysis was similar between the contrast group (0.2%, 25 of 10673) and the noncontrast group (0.3%, 27 of 10673). Emergent dialysis increased with worsening renal function occurring in up to 1.3% (12 of 958) of cases among patients in the high-risk noncontrast subgroup. Regardless of baseline renal function, contrast material exposure was not associated with an increased risk of dialysis for the entire matched cohort (OR, 0.96; 95% CI: 0.54, 1.60;

Table 2

Propensity Score–adjusted Outcomes

Data Set and Outcome	Contrast Group	Noncontrast Group	Statistics	
			ORs and HRs*	*P* Value
Entire matched data set	10673	10673	. . .	. . .
AKI	515 (4.8)	544 (5.1)	0.94 (0.83, 1.07)†	.38
30-d dialysis	25 (0.2)	27 (0.3)	0.96 (0.54, 1.60)†	.89
30-d mortality	850 (8.0)	875 (8.2)	0.97 (0.87, 1.06)‡	.45
AKI risk groups§				
Low-risk group	7273	7273	. . .	. . .
30-d dialysis	7 (0.1)	8 (0.1)	0.88 (0.32, 2.41)†	.79
30-d mortality	417 (5.7)	426 (5.9)	0.95 (0.83, 1.09)‡	.44
Medium-risk group	2442	2442	. . .	. . .
30-d dialysis	7 (0.3)	7 (0.3)	1.00 (0.35, 2.86)†	.79
30-d mortality	303 (12.4)	314 (12.9)	0.97 (0.83, 1.14)‡	.64
High-risk group	958	958	. . .	. . .
30-d dialysis	11 (1.1)	12 (1.3)	0.92 (0.40, 2.09)†	.84
30-d mortality	130 (13.6)	135 (14.1)	0.93 (0.73, 1.18)‡	.56
Comorbidity subgroups				
DM subset	1974	1974	. . .	. . .
AKI	133 (6.7)	138 (7.0)	0.96 (0.75, 1.23)†	.75
30-d dialysis	10 (0.5)	11 (0.6)	0.91 (0.39, 2.14)†	.83
30-d mortality	173 (8.8)	162 (8.2)	1.07 (0.84, 1.33)‡	.54
ARF subset	2040	2040	. . .	. . .
AKI	257 (12.6)	237 (11.6)	1.10 (0.91, 1.32)†	.36
30-d dialysis	19 (0.9)	13 (0.6)	1.47 (0.72, 2.98)†	.38
30-day mortality	273 (13.4)	263 (12.9)	1.02 (0.86, 1.21)‡	.82
CRF subset	975	975	. . .	
AKI	93 (9.5)	94 (9.6)	0.99 (0.73, 1.34)†	.94
30-d dialysis	8 (0.8)	6 (0.6)	1.34 (0.46, 3.87)†	.79
30-day mortality	117 (12.0)	107 (11.0)	1.06 (0.82, 1.36)‡	.65
CHF subset	1487	1487	. . .	. . .
AKI	147 (9.9)	126 (8.5)	1.18 (0.92, 1.52)†	.18
30-d dialysis	9 (0.6)	4 (0.3)	2.26 (0.69, 7.35)†	.27
30-d mortality	208 (14.0)	214 (14.4)	0.96 (0.79, 1.16)‡	.67

Note.—Data are numbers of patients, and numbers in parentheses are percentages, except where otherwise specified. Percentages were rounded.

* Data are ORs and HRs and are for the contrast group versus the noncontrast group. Numbers in parentheses are 95% CIs.

† Data are ORs.

‡ Data are HRs. HRs were estimated using Cox proportional hazards models adjusted for propensity score variables and the presence of dialysis, as discussed in Materials and Methods.

§ The incidence of AKI within each risk subgroup of this data set has been previously demonstrated to increase with worsening renal function, without significant differences ($P > .05$ between contrast and noncontrast groups [19]).

$P = .89$). Among individuals within predisposing comorbidities, the frequency of dialysis ranged between 2.5- and 4.5-fold higher (0.5%–0.9%) than for the entire matched cohort but again was not significantly different between the contrast and the noncontrast groups (Table 2). Despite the lack of a significant difference, the number of cases of emergent dialysis was slightly higher in the contrast group compared with the noncontrast group for those patients diagnosed with ARF, CRF, and CHF, but not for those diagnosed with DM.

Effect of Contrast Material Exposure on 30-Day Mortality

Within the entire matched cohort, a total of 1725 individuals died within 30 days of the CT scan (Table 2). Unadjusted mortality estimates for each group are shown as solid lines in Figure 3, while adjusted estimates are shown in Table 2. The 30-day mortality rates were not significantly different between the contrast group (850 of 10673, 8.0%) and the noncontrast group (875 of 10673, 8.2%) (Fig 3), as shown by the solid lines ($P = .5$). The adjusted risk of 30-day mortality was not significantly different between the contrast group and the noncontrast group (HR, 0.97; 95% CI: 0.87, 1.06; $P = .45$). Mortality rates increased with worsening renal function (Fig 3) (AKI risk subgroups) and were higher among patients with ARF, CRF, and CHF when compared with the entire matched subgroup overall (Fig 3) (comorbidity subgroups). Notwithstanding increased overall mortality within these high-risk comorbidity subgroups, unadjusted and adjusted mortality rates were not significantly different between the contrast group and the noncontrast group. Similar outcomes were seen after adjustment according to the estimated glomerular filtration rate–defined Kidney Disease Quality Initiative stages of chronic kidney disease (Table E5 [online]).

Effect of AKI on Adverse Outcomes

Clinical outcomes, including adjusted mortality estimates, among patients who developed AKI are shown in Table 3; unadjusted mortality estimates for the AKI cohorts are shown as dotted lines in Figure 3. Within the entire matched cohort, 1059 patients developed AKI in the 24–72-hour window following CT scanning; in the contrast group, 515 of 10673 (4.8%) developed it, and in the noncontrast group, 544 of 10673 (5.1%) developed it. Within this AKI cohort, the incidence and risk of emergent dialysis was significantly higher than in patients who did not meet laboratory criteria for AKI (OR, 15.75; 95% CI: 9.10, 27.26; $P < .0001$) but was not significantly different between the contrast group and the noncontrast group (OR, 0.89; 95% CI: 0.40, 2.01; $P = .78$). Compared with the entire matched data set of patients who developed AKI, the incidence of dialysis was higher among individuals with compromised renal function or within

Figure 3

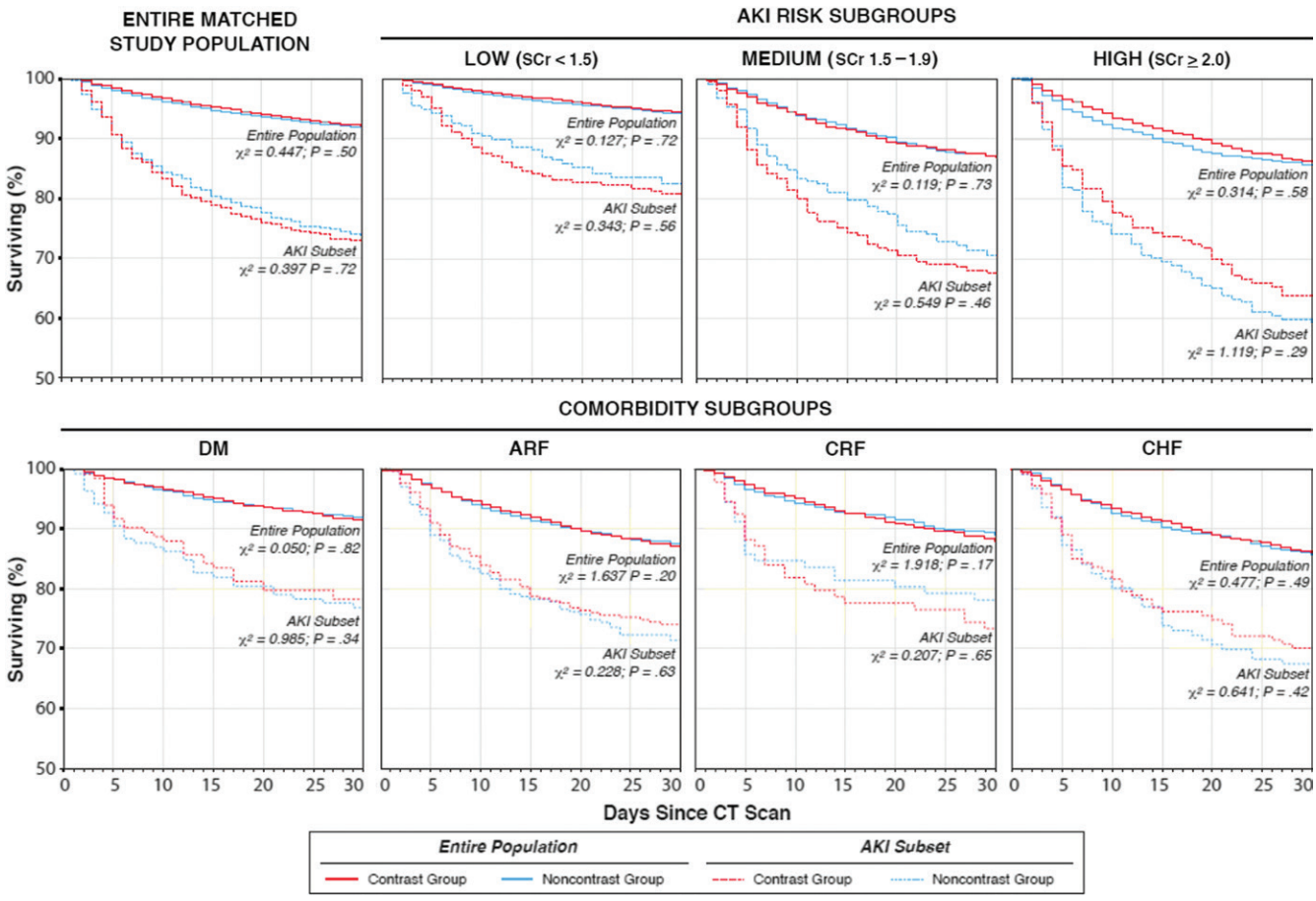

Figure 3: Survival analysis. The survival of the entire matched study cohort, AKI risk subgroups, and comorbidity subgroups, sorted according to contrast material exposure history, is shown with Kaplan-Meier survival curves for the entire cohort (solid lines) and the subset that experienced AKI 24–72 hours following CT scanning (dashed lines). SCr values are in milligrams per deciliter; to convert to Système International units in micromoles per lliter, multiply by 88.4.

high-risk comorbidity subgroups, yet similar nonsignificant differences were observed between the contrast and the noncontrast groups (Table 3).

Within the entire AKI cohort, the risk of mortality was much higher when compared with patients who did not develop AKI (HR, 4.51; 95% CI: 3.91, 5.21; $P < .0001$), yet no significant differences in mortality between the contrast group (143 of 515, 27.8%) and the noncontrast group (145 of 544, 26.7%) were identified (HR, 1.03; 95% CI: 0.82, 1.32; $P = .63$) (Table 3). Although mortality was highest among individuals with compromised renal function and predisposing comorbidities, the adjusted risk of mortality was not significantly different between the contrast and the noncontrast groups (Table 3).

Sensitivity Analysis

Bootstrapped reestimates of study outcomes determined by using the MatchIt nearest-neighbor nonparametric matching method are shown in Table 4; comprehensive results from all matching methods are shown in Figure E2 (online). For all AKI risk groups, pooled estimates of each outcome were clustered about unity by using the MatchIt method, in agreement with our propensity score–derived point estimates (Fig E2 [online]). Examination of the sampling distribution revealed that the reestimated findings failed to identify a significant contrast material exposure effect in most of the cases; 90% or more of the reestimated CIs spanned unity (Table 4, Fig E2 [online]). In the case of emergent dialysis, the extremely low incidence of this outcome and granularity of computed outcomes manifested as much wider sampling distributions. Despite subtle differences in reestimated outcomes, the MatchIt method provided very similar results to four unrelated methods (Fig E2 [online]).

Discussion

The results of our large, single-center, propensity score–adjusted retrospective study failed to demonstrate an excess risk of short-term mortality or excess incidence of emergent dialysis among

Table 3

Propensity Score–adjusted Outcomes among Individuals Who Developed AKI

Data Set and Outcome	Contrast Group	Noncontrast Group	Statistics	
			ORs and HRs*	*P* Value
Entire matched data set	515	544	. . .	. . .
30-d dialysis	11 (2.1)	13 (2.4)	0.89 (0.40, 2.01)†	.78
30-d mortality	143 (27.8)	145 (26.7)	1.03 (0.82, 1.32)‡	.63
AKI risk groups				
Low-risk group	210	226	. . .	. . .
30-d dialysis	2 (1.0)	2 (0.9)	1.08 (0.15, 7.70)†	.99
30-d mortality	40 (19.0)	38 (16.8)	1.01 (0.64, 1.59)‡	.98
Medium-risk group	209	215	. . .	. . .
30-d dialysis	5 (2.4)	4 (1.9)	1.29 (0.34, 4.88)†	.75
30-d mortality	68 (32.5)	64 (29.8)	1.11 (0.79, 1.53)‡	.50
High-risk group	96	103	. . .	. . .
30-d dialysis	4 (4.2)	7 (6.8)	0.60 (0.17, 2.10)†	.54
30-d mortality	35 (36.5)	43 (41.7)	0.84 (0.51, 1.40)‡	.35
Comorbidity subgroups				
DM subset	133	138	. . .	. . .
30-d dialysis	6 (4.5)	7 (5.1)	0.88 (0.29, 2.68)†	.82
30-d mortality	29 (21.8)	31 (22.5)	0.97 (0.56, 1.58)‡	.81
ARF subset	257	237	. . .	. . .
30-d dialysis	8 (3.1)	8 (3.4)	0.92 (0.34, 2.49)†	.87
30-d mortality	64 (24.9)	67 (28.3)	0.94 (0.66, 1.33)‡	.65
CRF subset	93	94	. . .	. . .
30-d dialysis	3 (3.2)	2 (2.1)	1.53 (0.25, 9.39)†	.44
30-d mortality	25 (26.9)	20 (21.3)	1.21 (0.57, 2.53)‡	.57
CHF subset	147	126	. . .	. . .
30-d dialysis	5 (3.4)	2 (1.6)	2.18 (0.41, 11.45)†	.33
30-d mortality	43 (29.3)	40 (31.7)	0.92 (0.59, 1.43‡	.70

Note.—Data are numbers of patients, and numbers in parentheses are percentages, except where otherwise specified. Percentages were rounded.

* Data are ORs and HRs and are for the contrast group versus the noncontrast group. Numbers in parentheses are 95% CIs.

† Data are ORs.

‡ Data are HRs. HRs of the subset of patients who developed AKI were estimated by using Cox proportional hazards models adjusted for propensity score variables and the presence of dialysis, as discussed in Materials and Methods.

patients who were exposed to intravenous contrast material compared with a similar matched group of patients who were not exposed to intravenous contrast material. These results were observed even among patients with compromised renal function and comorbidities associated with greater purported risk for contrast material–mediated nephrotoxicity. Further, these findings were validated against other propensity score methods by using a sensitivity analysis. These results challenge the long-held assumption that intravenous contrast material exposure is associated with excess morbidity and mortality and the purported causal association between contrast material exposure and nephrotoxicity. Although higher rates of dialysis and death were observed among individuals who experienced AKI following CT scanning, our findings suggest that these outcomes are unrelated to intravenous iodinated contrast material exposure.

Although researchers in prior studies have assessed the effect of contrast material exposure on outcomes such as death and dialysis, most did not include control groups of patients in whom contrast material was not administered (1,2,10). The few remaining controlled studies demonstrated similar risks of dialysis and death between contrast material and control groups; however, these studies were small and did not control for selection bias (11–16). Our current study corroborates the findings of these studies and offers several advances. First, the large sample size of our clinical database permits the detection of uncommon outcomes, such as dialysis, that may have been missed by the researchers in smaller studies. Such differences in sample size probably explain why the investigators in some prior studies failed to detect any cases of subsequent short-term dialysis (10,34–36). In addition, the size of our study permitted independent examination of patients considered to be at high risk for nephrotoxicity and subsequent adverse outcomes. Second, the use of propensity score methods mimics some characteristics of a randomized study insofar as it balances the observed covariates used to generate this score (27). This approach permits comparisons of demographically and clinically similar patients in the contrast and noncontrast groups. Such methodological tools minimize selection bias, allowing us to discern the true incidence of adverse outcomes attributable to intravenous iodinated contrast material. Third, our study utilized additional statistical tests to examine the effect of AKI on the incidence of dialysis and death, independent of intravenous contrast material exposure. Such findings add clarity to the widely misunderstood relationship among contrast material exposure, development of AKI, and the incidence of adverse outcomes.

Expanding on our previous efforts, we found no significant increase in the incidence of AKI following intravenous contrast material exposure among patients with selected comorbidities reportedly associated with greater nephrotoxic risk (19). Individuals with ARF and CHF demonstrated a nonsignificantly higher incidence of contrast material–dependent AKI than contrast material–independent AKI. Although this finding could be interpreted as evidence of true contrast material–dependent AKI, given the relatively high

Table 4

Sensitivity Analysis Using MatchIt Method

Risk Group and Outcome	Distribution of Reestimated 95% CIs		
	Below Unity	Crosses Unity	Above Unity
Low-risk group			
AKI	2	98	0
30-d dialysis	0	100	0
30-d mortality	3	97	0
Medium-risk group			
AKI	2	96	2
30-d dialysis	0	100	0
30-d mortality	0	100	0
High-risk group			
AKI	2	97	1
30-d dialysis	10	90	0
30-d mortality	4	94	2

Note.— Data are bootstrap-based reestimations of each study outcome, sorted according to AKI risk subgroup by using the MatchIt propensity score matching method, and are expressed as percentages. For each outcome-subgroup combination, the outcome was reestimated 100 times. CIs of these reestimated outcomes were clustered into the following groups: the total number that cross unity (nonsignificant results), the total number below unity (significantly greater incidence in the noncontrast group compared with contrast group), and the total number above unity (significantly greater incidence in the contrast group compared with noncontrast group). In any given cluster, summed results of 90% or greater are indicative of minimal matching variability and values of 100% suggest no matching variability. Figure E2 (online) details complete sensitivity analysis results.

frequency of contrast material–independent AKI in the matched noncontrast groups and the small absolute differences in frequency between contrast and noncontrast groups, such a conclusion cannot be drawn from these data.

While the frequency of emergent dialysis was extremely low and not significantly different between contrast and noncontrast groups overall, slightly higher incidences of dialysis were present in the contrast group compared with the noncontrast group among patients with a baseline CHF, prior ARF, or CRF. These findings may be a result of several factors. First, as this outcome was extremely uncommon in our large study population, significant differences should be interpreted with caution, as they reflect small absolute differences in the incidence between contrast and noncontrast groups. Second, insofar as treatment bias affects the decision to administer contrast material, similar bias probably affects the decision to initiate dialysis. Because generations of clinicians have been trained with the a priori assumption of nephrotoxicity from contrast material exposure, they may be more likely to initiate dialysis if AKI develops in the setting of intravenous contrast material exposure as compared with AKI without prior contrast material exposure. Third, it is possible that patients in the contrast group were more likely to receive contrast material because of acute changes in clinical status reflected in clinical indicators not included in our propensity score model.

Following propensity score matching, in our study, we detected no excess risk of short-term mortality from intravenous contrast material exposure. This finding corroborates our previous observation that AKI appears to be independent of intravenous iodinated contrast material exposure. However, as we did not investigate the causes of death in our study, it remains possible that contrast material recipients were more likely to die of renal complications. Such a scenario would require an equal excess of contrast material–independent causes of death in the noncontrast patient group. In addition, because of difficulties in loss to follow-up, we did not address long-term mortality in our study. However, given the low frequency of dialysis following contrast material exposure, long-term mortality would also not be expected to be substantially different between groups.

The absence of significant differences in our results warrants further consideration. As traditional post hoc tests of sample size adequacy are flawed, we used equivalence tests as a framework to retrospectively assess the effects of study sample size on the precision of the CI to detect clinically relevant differences among nonsignificant results (37). Using the upper limit of the CI for the OR and the event rate in the noncontrast group, the smallest detectable differences in dialysis ranged from 0.2% in the low-risk subgroup, 1.3% in the high-risk group, and was less than 1.7% in the comorbidity subgroups. The smallest detectable differences in 30-day mortality ranged from 0.5% in the low-risk subgroup to 2.1% in the high-risk subgroup, was less than 3.4% in the comorbidity subgroups. As the magnitude of these differences is smaller than the reported rates of dialysis and mortality in the literature, the sample size and precision of the OR estimates for our study appear to be sufficient to make meaningful interpretations of the results (10,16). However, such tests are not definitive proof of sample size adequacy, in the case of rare outcomes.

Pooled sensitivity analysis results corroborate our point estimates for the risk of AKI, dialysis, and mortality and strengthen our conclusions by providing a more robust assessment of the estimated treatment effect magnitude and precision. In addition, we externally validated our matching method against four unrelated well-established propensity score matching methods. However, as these analyses are not a comprehensive assessment of the propensity score model, potential limitations persist. First, despite efforts to generate a robust propensity score to approximate the probability of receiving intravenous contrast material, some variables that factor into the decision to administer contrast material are neither quantifiable nor retrievable from a retrospective

database. Further, although propensity score models mimic some characteristics of a randomized study, they do not directly balance covariates that are not included in the propensity score model. Accordingly, our model may have a small amount of residual bias from the effects of an unmeasured confounder. Second, despite efforts to stratify disease severity using several related covariates, propensity score models built from binary variables cannot discriminate between mild and severe cases of the same disease, potentially introducing uncertainty into the logistic model. Third, certain covariates thought to influence treatment propensity were not included because of concerns over possible invalidation of the propensity score model caused by insufficient temporal granularity of the data (eg, hydration status) or inconsistent charting in the EMR (eg, nephrotoxic drug use).

Our study had several additional limitations. First, our study relied on an SCr level–based definition of AKI in lieu of potentially more accurate and sensitive markers of renal function. However, as CIN has traditionally been a diagnosis based on SCr measurements, use of other nonstandard biomarkers risks confounding interpretation of the findings. Second, errors in ICD-9 coding as a means to identify comorbidities are well documented. Such errors are expected to occur at random and thus not to manifest in a manner to cause systematic error or bias. Third, administration of isoosmolar contrast agents to our high-risk patient subgroup could potentially attenuate adverse outcomes in this patient group. However, investigators in a meta-analysis (38) in which isoosmolar agents were compared with low-osmolar agents have not demonstrated differences in the incidence of AKI following administration of these agents. Fourth, estimates of dialysis risk in our study are somewhat limited by the extremely low incidence of this outcome. As prospective studies would be unable to achieve sufficient sample size to address this clinical question, large multicenter or nationwide retrospective studies are needed to better define the true incidence and risk of dialysis following contrast material administration.

In conclusion, our findings suggest that intravenous contrast material administration is not associated with an excess risk of AKI, dialysis, or death, even among patients with compromised renal function or comorbidities reported to predispose them to nephrotoxicity. Conversely, AKI, irrespective of contrast material administration, is strongly predictive of adverse outcomes and confounds the potential causal relationship among contrast material exposure, AKI, and these adverse outcomes. Although additional large-scale controlled studies are needed, our results suggest that modern low- and isoosmolar intravenous contrast agents are substantially safer than what has been extrapolated from prior uncontrolled studies.

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