CHEST

Association of Contrast and Acute Kidney Injury in the Critically Ill

A Propensity-Matched Study

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BACKGROUND: Despite evidence that low osmolar radiocontrast media is not associated with acute kidney injury, it is important to evaluate this association in critically ill patients with normal kidney function.

METHODS: This retrospective observational study included 7,333 adults with an ICU stay at a six-hospital health system in south Florida. Patients who received contrast were compared with unexposed control subjects prior to and following propensity score (PS) matching derived from baseline characteristics, admission diagnoses, comorbidities, and severity of illness. Acute kidney injury (AKI), defined as initial onset (stage I) or increased severity, was determined from serum creatinine levels according to Kidney Disease: Improving Global Outcomes guidelines.

RESULTS: Based on 2,306 PS-matched pairs obtained from 2,557 patients who received IV contrast and 4,776 unexposed control subjects, the increase in AKI attributable to contrast was 1.3% (19.3% vs 18.0%; $P = .273$), and no association was found between contrast and the pattern of onset and recovery. Hospital mortality increased by 14.3% subsequent to AKI (18.0 vs 3.6; $P < .001$), but the risk ratio in relation to patients with stable AKI did not vary when stratified according to contrast. Multivariable regression identified sepsis, metabolic disorders, diabetes, history of renal disease, and severity of illness as factors that were more strongly associated with AKI.

CONCLUSIONS: In critically ill adults with normal kidney function, low osmolar radiocontrast media did not substantively increase AKI. Rather than limiting the use of contrast in ICU patients, efforts to prevent AKI should focus on the susceptibility of patients with sepsis, diabetes complications, high Acute Physiology and Chronic Health Evaluation scores, and history of renal disease.

CHEST 2020; 157(4):866-876

KEY WORDS: acute kidney injury; community hospital; contrast; critical care; ICU; propensity score matching

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ABBREVIATIONS: AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range; LOS = length of stay; PS = propensity score

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FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

Preliminary results of this study were presented at the Society of Critical Care Medicine Congress, January 26, 2017, Honolulu, HI.

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DOI: https://doi.org/10.1016/j.chest.2019.10.005

Research addressing the question of whether radiocontrast media increases the likelihood of kidney injury has evolved from reports of adverse effects in the context of coronary angiography to a growing body of evidence that the use of contrast in hospitalized patients does not need to be restricted out of concern for nephropathy. Few studies, however, have focused on critically ill patients whose high disease burden raises particular concern. A report by McDonald et al[1] concluded that contrast was not associated with increased acute kidney injury (AKI) and called for additional studies in critically ill patients, noting the importance of large cohorts and analytic methods that account for a variety of clinical covariates. The current study provides confirmatory evidence based on several thousand ICU admissions at a six-hospital health system serving a diverse south Florida community.

Patients and Methods

Setting and Data Sources

We identified adult patients at a six-hospital health system in south Florida between January 1, 2010, and June 30, 2014, who had a single stay of at least 24 h in an ICU commencing within 24 h of admission. For patients requiring contrast, a low osmolar agent was administered in accordance with an institution-wide protocol that included prophylactic fluid management. The Baptist Health South Florida Institutional Review Board approved this retrospective study (IRBNet ID: 1150443-2).

Study Variables and Definitions

The primary outcome was worsening AKI defined as initial onset (stage I) or increased severity according to Kidney Disease:

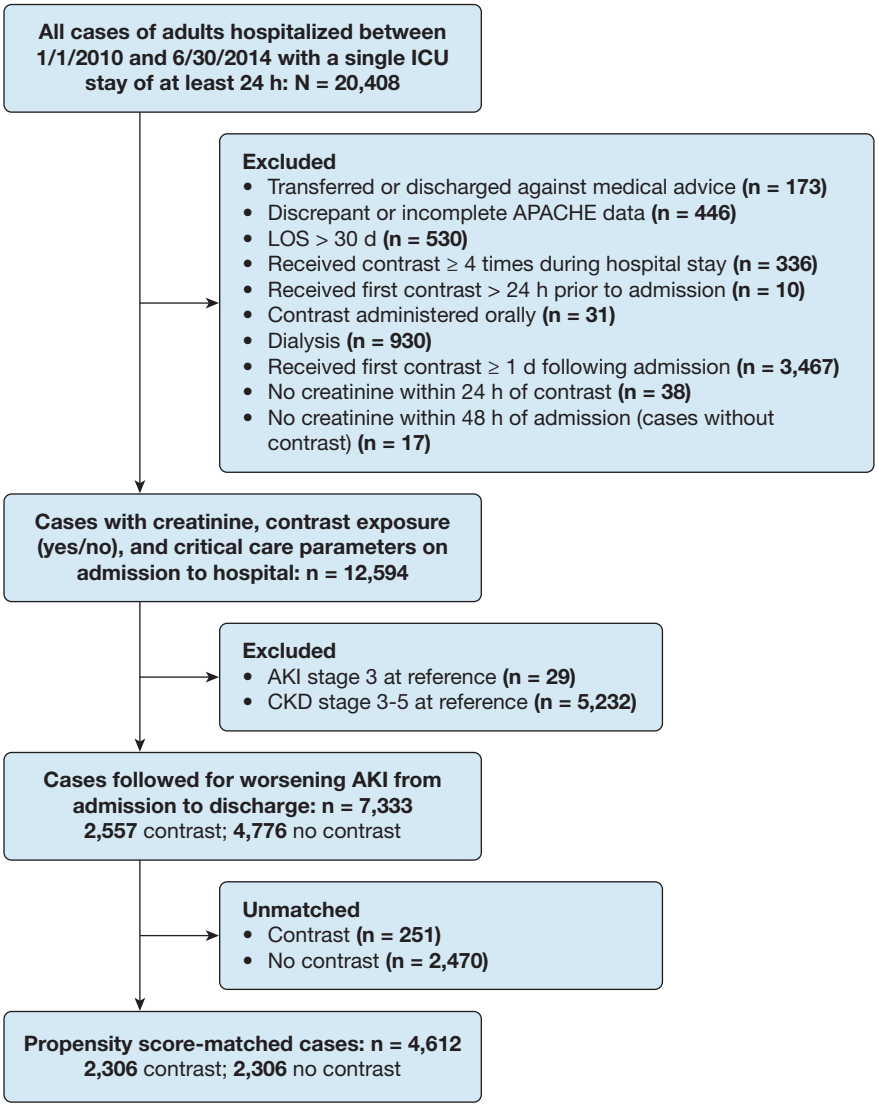

Figure 1 – *Flow diagram of case selection and matching. AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; CKD = chronic kidney disease; LOS = length of stay.*

TABLE 1] Case Characteristics According to Contrast Exposure Prior to and Following PS Matching

Characteristic	Cases With Contrast (n = 2,557)	Cases Without Contrast (n = 4,776)	SDif	VR	PS-Matched Cases With Contrast (n = 2,306)	PS-Matched Cases Without Contrast (n = 2,306)	SDif	VR
Age, median (p25, p75), y	63.0 (51.0, 74.0)	64.0 (50.0, 77.0)	−0.01	0.82	64.0 (51.0, 75.0)	65.0 (52.0, 76.0)	−0.05	1.02
Sex								
Female	1,136 (44.4)	2,350 (49.2)	−0.10	0.99	1,030 (44.7)	1,057 (45.8)	−0.02	1.00
Male	1,421 (55.6)	2,426 (50.8)	0.10	0.99	1,276 (55.3)	1,249 (54.2)	0.02	1.00
Race								
White Hispanic	1,416 (55.4)	2,498 (52.3)	0.06	0.99	1,257 (54.5)	1,264 (54.8)	−0.01	1.00
White	700 (27.4)	1,416 (29.6)	−0.05	0.95	658 (28.5)	664 (28.8)	−0.01	0.99
Black	267 (10.4)	655 (13.7)	−0.10	0.79	257 (11.1)	252 (10.9)	0.01	1.02
Other/Unknown	174 (6.8)	207 (4.3)	0.11	1.53	134 (5.8)	126 (5.5)	0.01	1.06
BMI								
Underweight, < 19 kg/m^2	114 (4.5)	295 (6.2)	−0.08	0.75	109 (4.7)	94 (4.1)	0.03	1.15
Normal, 19 to < 25 kg/m^2	897 (35.1)	1,674 (35.1)	0.00	1.00	817 (35.4)	788 (34.2)	0.03	1.02
Overweight, 25 to < 30 kg/m^2	799 (31.2)	1,417 (29.7)	0.03	1.03	702 (30.6)	728 (31.6)	−0.02	0.98
Obese, 30 to < 40 kg/m^2	618 (24.2)	1,073 (22.5)	0.04	1.05	553 (24.0)	577 (25.0)	−0.02	0.97
Morbidly obese, > 40 kg/m^2	129 (5.0)	317 (6.6)	−0.07	0.77	125 (5.4)	119 (5.2)	0.01	1.05
Admission								
ED	2,160 (84.5)	3,701 (77.5)	0.17	0.75	1,923 (83.4)	1,902 (82.5)	0.02	0.96
Other	397 (15.5)	1,075 (22.5)	−0.17	0.75	383 (16.6)	404 (17.5)	−0.02	0.96
Reference AKI								
0	2,452 (95.9)	4,463 (93.4)	0.11	0.64	2213 (96.0)	2,213 (96.0)	0.00	1.00
1	79 (3.1)	221 (4.6)	−0.08	0.68	73 (3.2)	73 (3.2)	0.00	1.00
2	26 (1.0)	92 (1.9)	−0.08	0.53	20 (0.9)	20 (0.9)	0.00	1.00
Critical care parameters								
APACHE score, median (p25, p75)	45.0 (34.0, 59.0)	47.0 (36.0, 60.0)	−0.07	1.03	46.0 (35.0, 59.0)	46.0 (36.0, 59.0)	−0.02	1.09
APS, median (p25, p75)	33.0 (25.0, 45.0)	35.0 (27.0, 46.0)	−0.07	1.05	34.0 (26.0, 45.0)	34.0 (26.0, 46.0)	−0.02	1.09
Predicted ICU LOS, median (p25, p75), d	2.8 (1.9, 4.6)	2.6 (1.7, 4.3)	0.14	1.08	2.8 (1.9, 4.5)	2.7 (1.8, 4.4)	0.04	0.93
Predicted LOS, median (p25, p75), d	8.6 (6.4, 11.3)	8.3 (6.3, 10.8)	0.08	1.22	8.5 (6.4, 11.2)	8.4 (6.2, 11.0)	0.01	0.99

(Continued)

TABLE 1] *(Continued)*

Characteristic	Cases With Contrast (n = 2,557)	Cases Without Contrast (n = 4,776)	SDif	VR	PS-Matched Cases With Contrast (n = 2,306)	PS-Matched Cases Without Contrast (n = 2,306)	SDif	VR
Predicted ICU death > 0.05	653 (25.5)	1,053 (22.0)	0.08	1.11	559 (24.2)	554 (24.0)	0.01	1.01
Predicted hospital death > 0.10	719 (28.1)	1,207 (25.3)	0.06	1.07	623 (27.0)	633 (27.5)	−0.01	0.99
Primary diagnosis								
Cardiovascular	842 (32.5)	999 (20.9)	0.27	1.33	756 (32.4)	747 (32.0)	0.01	1.01
Respiratory: parenchymal	236 (9.1)	594 (12.4)	−0.10	0.77	235 (10.1)	236 (10.1)	0.00	1.00
Other	144 (5.6)	593 (12.4)	−0.24	0.48	144 (6.2)	154 (6.6)	−0.01	0.96
Digestive	259 (10.0)	423 (8.9)	0.02	1.08	247 (10.6)	245 (10.5)	−0.01	0.97
Cerebrovascular	392 (15.1)	286 (6.0)	0.31	2.31	288 (12.3)	260 (11.1)	0.04	1.10
Injury/poisoning	154 (6.0)	459 (9.6)	−0.14	0.64	154 (6.6)	188 (8.0)	−0.06	0.83
Neoplasms	124 (4.8)	369 (7.7)	−0.12	0.65	119 (5.1)	123 (5.3)	−0.01	0.98
Septicemia/other infections	148 (5.7)	297 (6.2)	−0.03	0.91	146 (6.3)	138 (5.9)	0.01	1.03
Metabolic/immune[a]	35 (1.4)	388 (8.1)	−0.32	0.18	35 (1.5)	34 (1.5)	0.01	1.09
Peripheral vascular	168 (6.5)	129 (2.7)	0.18	2.32	126 (5.4)	121 (5.2)	0.01	1.04
Respiratory: airway	62 (2.4)	172 (3.6)	−0.07	0.67	62 (2.7)	63 (2.7)	−0.01	0.97
Genitourinary	24 (0.9)	67 (1.4)	−0.05	0.64	24 (1.0)	27 (1.2)	−0.02	0.85
ICU admit diagnosis								
Cardiovascular	1,070 (41.3)	1,492 (31.2)	0.22	1.13	977 (41.8)	982 (42.0)	0.00	1.00
Neurology	596 (23.0)	904 (18.9)	0.11	1.16	487 (20.8)	476 (20.4)	0.02	1.03
Respiratory	449 (17.3)	909 (19.0)	−0.04	0.94	421 (18.0)	411 (17.6)	0.02	1.03
GI	317 (12.2)	586 (12.3)	−0.02	0.95	296 (12.7)	305 (13.1)	−0.03	0.93
Metabolic/endocrine	38 (1.5)	351 (7.3)	−0.29	0.22	38 (1.6)	36 (1.5)	0.01	1.08
Other	89 (3.4)	243 (5.1)	−0.25	0.43	88 (3.8)	95 (4.1)	−0.02	0.93
Genitourinary	29 (1.1)	291 (6.1)	−0.28	0.18	29 (1.2)	31 (1.3)	−0.02	0.84
Comorbidities								
Hypertension	1,570 (60.7)	2,641 (55.3)	0.11	0.96	1,384 (59.2)	1,412 (60.4)	−0.02	1.01
Diabetes	685 (26.5)	1331 (27.9)	−0.03	0.97	642 (27.5)	646 (27.7)	−0.01	0.99
Chronic pulmonary disease	637 (24.6)	1254 (26.3)	−0.04	0.96	603 (25.8)	616 (26.4)	−0.01	0.99
Congestive heart failure	488 (18.9)	962 (20.1)	−0.03	0.95	469 (20.1)	484 (20.7)	−0.02	0.98
Vascular	372 (14.4)	457 (9.6)	0.15	1.43	305 (13.1)	295 (12.6)	0.01	1.03

(Continued)

TABLE 1] *(Continued)*

Characteristic	Cases With Contrast (n = 2,557)	Cases Without Contrast (n = 4,776)	SDif	VR	PS-Matched Cases With Contrast (n = 2,306)	PS-Matched Cases Without Contrast (n = 2,306)	SDif	VR
Cancer	256 (9.9)	351 (7.3)	0.09	1.32	217 (9.3)	234 (10.0)	−0.02	0.95
Liver	182 (7.0)	372 (7.8)	−0.03	0.90	166 (7.1)	164 (7.0)	0.00	1.00
Coagulopathy/bleeding	119 (4.6)	353 (7.4)	−0.13	0.62	118 (5.1)	125 (5.4)	−0.01	0.95
Paralysis	196 (7.6)	221 (4.6)	0.13	1.60	157 (6.7)	144 (6.2)	−0.02	0.93
Dehydration/hypovolemia	103 (4.0)	256 (5.4)	−0.07	0.75	100 (4.3)	84 (3.6)	0.03	1.17
Dementia	64 (2.5)	192 (4.0)	−0.09	0.62	63 (2.7)	77 (3.3)	−0.04	0.81
Renal[b]	57 (2.2)	154 (3.2)	−0.06	0.70	55 (2.4)	61 (2.6)	−0.02	0.90
Connective tissue, rheumatic	68 (2.6)	144 (3.0)	−0.02	0.87	62 (2.7)	66 (2.8)	−0.01	0.95

Data are presented as No. (%) unless otherwise indicated. A characteristic can be said to have a similar distribution in cases with and without contrast when −0.10 ≤ standardized difference, cases with vs without contrast (SDif) ≤ 0.10 and 0.80 ≤ variance ratio, cases with vs without contrast (VR) ≤ 1.25. AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; APS = Acute Physiology Score; LOS = length of stay; p25 = 25th percentile; p75 = 75th percentile; PS = propensity score.

[a]Mainly diabetes with complications (65.5%) and electrolyte or fluid disorder (19.6%).

[b]History of renal disease documented as secondary diagnosis in patients with normal kidney function on admission; many of these patients also had diabetes, specifically 51 (44.0%) in the PS-matched sample.

Improving Global Outcomes creatinine criteria.[2] The exposure of interest was administration of low osmolar radiocontrast media within 24 h of admission. The reference for determining onset/worsening vs stable AKI was the earliest creatinine measurement within 24 h of contrast or 48 h of admission. Secondary outcomes include dialysis, hospital mortality, and length of stay (LOS).

Statistical Analysis

Case characteristics are reported as median and interquartile range (IQR) for continuous variables, and as count and percentage for categorical variables. Categorization of the primary diagnosis was based on the clinical classification system developed by the Health Care Cost and Utilization Project,[3,4] and comorbidities consisted of those in the Charlson Comorbidity *Index*[5] plus additional kidney-related conditions. We report the primary outcome as the absolute and relative difference in AKI according to contrast exposure with corresponding 95% CIs.

To adjust for confounding, a propensity score (PS) was derived by regressing contrast administration on patient characteristics, emergency admission, reference AKI, primary and ICU admission diagnoses, Acute Physiology and Chronic Health Evaluation (APACHE) IV scores and predictions, and 13 comorbidities.[6-8] Standardized differences and variance ratios were used to assess comparability of cases with and without contrast exposure prior to and following PS matching.[6,9] Analyses were conducted by using the MatchIt package in R (version 3.2.2; R Foundation for Statistical Computing)[10,11] and SAS/STAT software (version 9.3; SAS Institute, Inc.). Additional details are provided in e-Appendix 1.

Results

From 20,408 eligible cases, we identified 12,625 for which contrast exposure, onset of intensive care, and AKI status could be determined on hospital admission taken as the reference. After exclusions were applied, the resulting analysis set of 7,333 cases comprised 2,557 patients (34.9%) who received contrast and 4,776 control subjects, from which 2,306 PS-matched pairs were obtained (Fig 1).

Table 1 summarizes case characteristics according to contrast exposure prior to and following PS matching. Matching criteria were satisfied for 2,306 (90.2%) contrast cases and improved comparability in relation to control subjects as indicated by standardized differences (columns 3 and 7) and variance ratios (columns 4 and 8). Worsening AKI occurred in a total of 1,382 cases (18.8%) and in 858 (18.6%) cases following PS matching. The rate of AKI was higher in patients receiving contrast compared with control subjects; that is, a difference of 0.9% (95% CI, −1.0 to 2.8) based on all cases and 1.3% (95% CI, −0.9 to 3.6) in the PS-matched subset. Risk ratios were 1.05 (95% CI, 0.95–1.16) prior to adjustment and 1.07 (95% CI, 0.95–1.21) following matching (Table 2).

Hospital mortality was fourfold higher in patients with worsening AKI, and there was no evidence of

nonhomogeneity according to contrast exposure ($P = .462$ all cases; $P = .352$ matched cases) (Table 2). In the PS-matched sample, stratified estimates of the risk ratio for hospital death according to AKI status were 4.52 (95% CI, 3.28-6.23) in the contrast group (15.8% vs 3.5% mortality) and 5.41 (95% CI, 4.02-7.28) for unexposed control subjects (20.3% vs 3.8% mortality). Thus, the slightly higher rate of AKI among patients exposed to contrast (1.3%) did not amplify mortality despite the association between AKI and hospital mortality.

AKI was associated with longer hospital LOS. In the PS-matched sample, patients with worsening AKI were discharged alive following a median LOS of 7 days (IQR, 5-12 days) compared with 4.0 days (IQR, 3-7 days) for stable AKI ($P < .001$). Among hospital deaths, median LOS was 5.5 days (IQR, 3-10 days) with AKI and 4.0 days (IQR, 3-7 days) without AKI ($P = .003$).

In the PS-matched subset, most of the 858 cases of worsening AKI developed within 72 h. The majority recovered to their AKI stage of reference, or lower, within 72 h of onset/worsening regardless of contrast (Fig 2).

An exploratory analysis of AKI in relation to patient demographic characteristics, medical conditions, and severity of illness is presented in Table 3. With respect to patient characteristics and medical conditions (model A), an age difference of 20 years, male sex, black race, and obesity each independently increased the odds of worsening AKI by 13% to 35%, estimates only somewhat greater than the 11% attributable to contrast. Importantly, renal comorbidity (ie, a history of renal disease despite normal kidney function on admission) increased the odds of AKI fourfold. (We note that diabetes was present in 51 [44.0%] of the 116 patients with renal comorbidity). The effects of septicemia and renal comorbidity are illustrated in Figures 3A and 3B according to the predicted probability of AKI at various ages, with and without contrast. Estimates shown are for the largest patient group defined by remaining model A covariates; that is, male sex, non-black race, and BMI < 30.

In the critical care model (model B), male sex, black race, and obesity increased the odds of AKI by 44% to 71%, whereas a twofold increase was estimated per 20-point increase in APACHE score. The corresponding predicted probability of AKI in relation to APACHE score is shown in Figure 3C for a low-risk group of nonobese white female subjects and a high-risk group of obese black male subjects.

Discussion

In an analysis of 2,306 PS-matched pairs of critically ill adult patients, we found only a slight increase in the rate of AKI for those exposed to low osmolar contrast media (19.3% vs 18.0%), yielding an absolute difference of 1.3% and a relative increase of 7%. Contrast was not associated with the time of AKI onset or worsening, rate of recovery, time to recover, or need for dialysis. Moreover, the fourfold increase in mortality for patients with AKI compared with others did not vary according to contrast exposure.

Our main finding aligns closely with that reported for the low-risk strata in a study by McDonald et al.[1] Using Kidney Disease Improving Global Outcomes creatinine criteria and PS methods, they found 14% AKI regardless of contrast in an analysis of 1,223 matched pairs of ICU patients with an estimated glomerular filtration rate $>$ 45 mL/min/1.73 m^2. Our postmatch cohort was roughly twice as large and similar in age, sex, and severity of illness to that of McDonald et al. We used many of the same PS covariates with the addition of BMI and a distinction between Hispanic and non-Hispanic white subjects as befits our institution's demographic region.

Several smaller studies have also reported an absence of association between contrast and AKI in the critically ill. Ehrman et al[12] found similar rates of AKI (using Acute Kidney Injury Network criteria) regardless of contrast in an analysis of 146 patient pairs matched on a PS that accounted for a limited set of clinical covariates such as ventilation, infection, and fluid balance. Two other studies of patients undergoing CT scanning in an ICU, which matched case subjects on a limited set of covariates rather than a PS, reported no significant difference in postscan serum creatinine levels. One was based on 81 pairs of oncology patients,[13] and the other was a prospective study that analyzed 53 patient pairs.[14] These findings were contrary to an earlier report by Polena et al[15] of an estimated 14-fold increased risk of creatinine rising $\geq$ 25% above baseline following a contrast-enhanced scan. Specifically, contrast-induced AKI occurred in 18.6% of 75 contrast case subjects vs 2% of 75 control subjects of comparable age, sex, and conditions such as history of diabetes.

TABLE 2] Worsening AKI, Dialysis, and Hospital Mortality, Prior to and Following PS Matching

Outcome	Exposure	All Cases			PS-Matched Cases		
		Events/No. (%)	RR (95% CI)	*P* Value	Events/No. (%)	RR (95% CI)	*P* Value
Worsening AKI							
	Contrast	497/2,557 (19.4)	1.05 (0.95-1.16)	.35	444/2,306 (19.3)	1.07 (0.95-1.21)	.27
	No contrast	885/4,776 (18.5)	Reference		414/2,306 (18.0)	Reference	
Dialysis							
	Contrast	12/2,557 (0.47)	2.49 (1.05-5.90)	.04	10/2,306 (0.43)	1.69 (0.61-4.64)	.33
	No contrast	9/4,776 (0.19)	Reference		6/2,306 (0.25)	Reference	
Died in hospital							
	Worsening AKI	217/1,382 (15.7)	4.17 (3.49-4.98)	< .001[a]	154/858 (17.9)	4.95 (3.98-6.16)	< .001[a]
	Stable AKI	224/5,951 (3.8)	reference		136/3,754 (3.6)	Reference	

RR = relative risk. See Table 1 legend for expansion of other abbreviations.
[a]No difference when stratified according to contrast: *P* = .462 all case subjects, *P* = .352 PS-matched case subjects.

Another point of comparison comes from research focused on high-risk patients defined by using criteria other than an ICU stay. Based on 7 million cases from the Nationwide Inpatient Sample (NIS), Wilhelm-Leen et al[16] reported AKI rates in the top comorbidity stratum of 22.5% with contrast exposure vs 19.9% without, which is only slightly higher than the rates we observed. We overcame one limitation noted in that study by using dated information on contrast exposure and subsequent creatinine to identify AKI rather than relying on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes.

In this current exploratory multivariable analysis, contrast was neither associated with AKI (OR, 1.11; 95% CI, 0.95-1.29; *P* = .19) nor an effect modifier of factors that achieved significance. We estimated a two-fold increase in the odds of AKI for a primary diagnosis of septicemia/other infection or metabolic/immune disorder (primarily complicated diabetes) and a fourfold increase for patients with a documented history of renal disease despite normal kidney function on admission. Older age (13% increased odds per 20 years), male sex (24%), black race (35%), and obesity (21%) also increased the likelihood of worsening AKI, as did certain

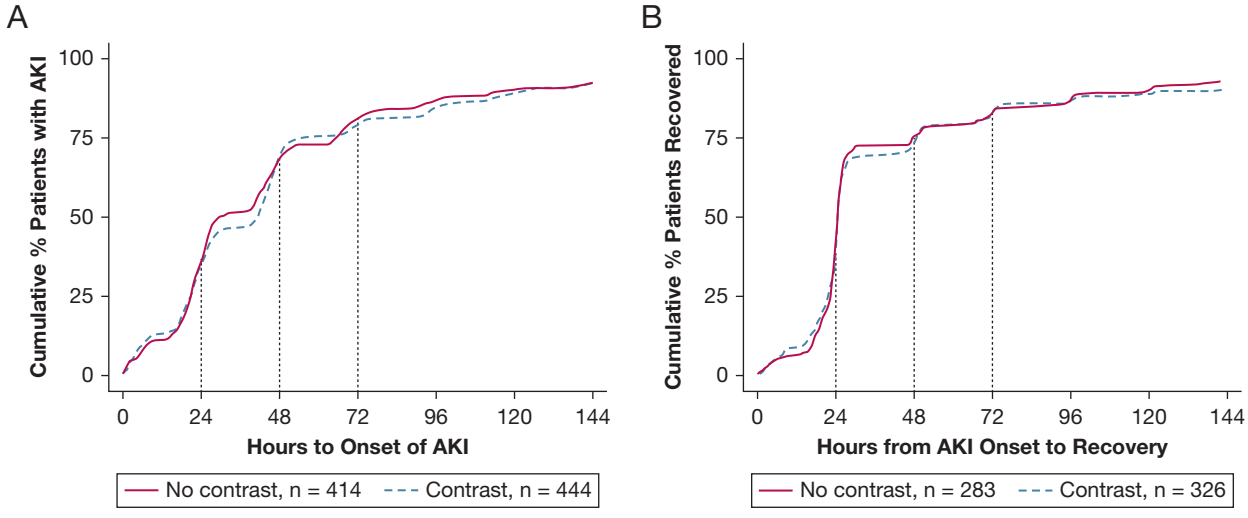

Figure 2 – *A-B, Time to onset of AKI and recovery. A, Time from admission to onset in propensity score-matched cases with worsening AKI. B, Time to recovery in propensity score-matched cases whose worsening AKI resolved to reference stage (or better). See Figure 1 legend for expansion of abbreviation.*

TABLE 3] Multivariable Analysis of Factors Associated With Worsening AKI in PS-Matched Cases

	Worsening AKI	Model A (medical conditions)		Model B (critical care)	
Factor	No. (%)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Contrast					
Contrast	444 (19.3)	1.11 (0.95-1.29)	.189	1.10 (0.94-1.28)	.246
No contrast	414 (18.0)	Reference	…	Reference	…
Age, per 20 y[a]	…	1.13 (1.02-1.26)	.018	Not included	
Sex					
Male	510 (20.2)	1.24 (1.06-1.46)	.007	1.44 (1.23-1.69)	< .001
Female	348 (16.7)	Reference	…	Reference	…
Race					
Black	123 (24.2)	1.35 (1.06-1.70)	.013	1.71 (1.35-2.15)	< .001
White, white Hispanic, or other	435 (17.9)	Reference	…	Reference	…
Obesity					
BMI ≥ 30 kg/m^2	328 (20.7)	1.21 (1.02-1.43)	.026	1.55 (1.31-1.83)	< .001
BMI < 30 kg/m^2	530 (17.5)	Reference	…	Reference	…
Primary diagnosis					
Respiratory: parenchymal	129 (27.7)	1.64 (1.29-2.08)	< .001		
Septicemia/other infection	90 (32.4)	2.48 (1.88-3.27)	< .001	Not included	
Metabolic/immune	18 (26.9)	2.32 (1.31-4.09)	.004		
All other[b]	621 (16.3)	Reference	…		
Comorbidity					
Diabetes	315 (24.7)	1.38 (1.16-1.63)	< .001		
Chronic pulmonary disease	296 (24.7)	1.22 (1.02-1.46)	.029		
Congestive heart failure	274 (29.1)	1.75 (1.45-2.10)	< .001	Not included	
Liver	98 (30.2)	1.93 (1.47-2.51)	< .001		
Renal	65 (56.0)	4.68 (3.17-6.91)	< .001		
APACHE score, per 20 points[c]		Not included		1.97 (1.82-2.12)	< .001

C-statistics: 0.67 (95% CI, 0.65-0.69) for Model A and 0.69 (95% CI, 0.67-0.71) for Model B. See Table 1 legend for expansion of abbreviations.
[a]Age increment of 20 years represents one SD to the nearest multiple of 10.
[b]In the reference group of all other primary diagnoses, the rate of worsening AKI ranged from 13.2% for cerebrovascular disease to 20.0% for genitourinary diseases.
[c]APACHE score increment of 20 points represents approximately one SD. Patient age, APS, predicted LOS, and predicted mortality were not significant additions to Model B.

comorbidities: diabetes (38%), chronic pulmonary disease (22%), congestive heart failure (75%), and liver disease (93%). The effect of contrast was similar (OR, 1.10; 95% CI, 0.94-1.28; $P = .25$) in a separate model that found a doubling in the odds of AKI per 20-point increment in APACHE score and retained sex, race, and obesity as factors that increased odds of AKI by 44% to 71%. Hinson et al[17] also identified age, black race, hypertension, and diabetes as AKI risks but, contrary to our findings, reported higher AKI in women. Davenport et al[18] reported increased AKI risk for men, black race, diabetes, coronary artery disease, and sepsis, and Danziger et al[19] reported increased AKI among critically ill patients with obesity. Lastly, the association of APACHE IV with AKI in our analysis is consistent with studies of critically ill patients that incorporated Simplified Acute Physiology Score,[20] Sequential Organ Failure Assessment,[1] APACHE II scores,[1,21] or other composite scores.[16]

The current study comprises a large sample of critically ill adults with a comprehensive range of diagnoses and comorbidities restricted only by the requirement of normal kidney function on admission. Based on > 2,000 cases exposed to contrast and an equal number of matched control subjects, we estimated the difference in the rate of AKI to within 2.2% with 95% confidence and the risk ratio to within 14%. In addition to high

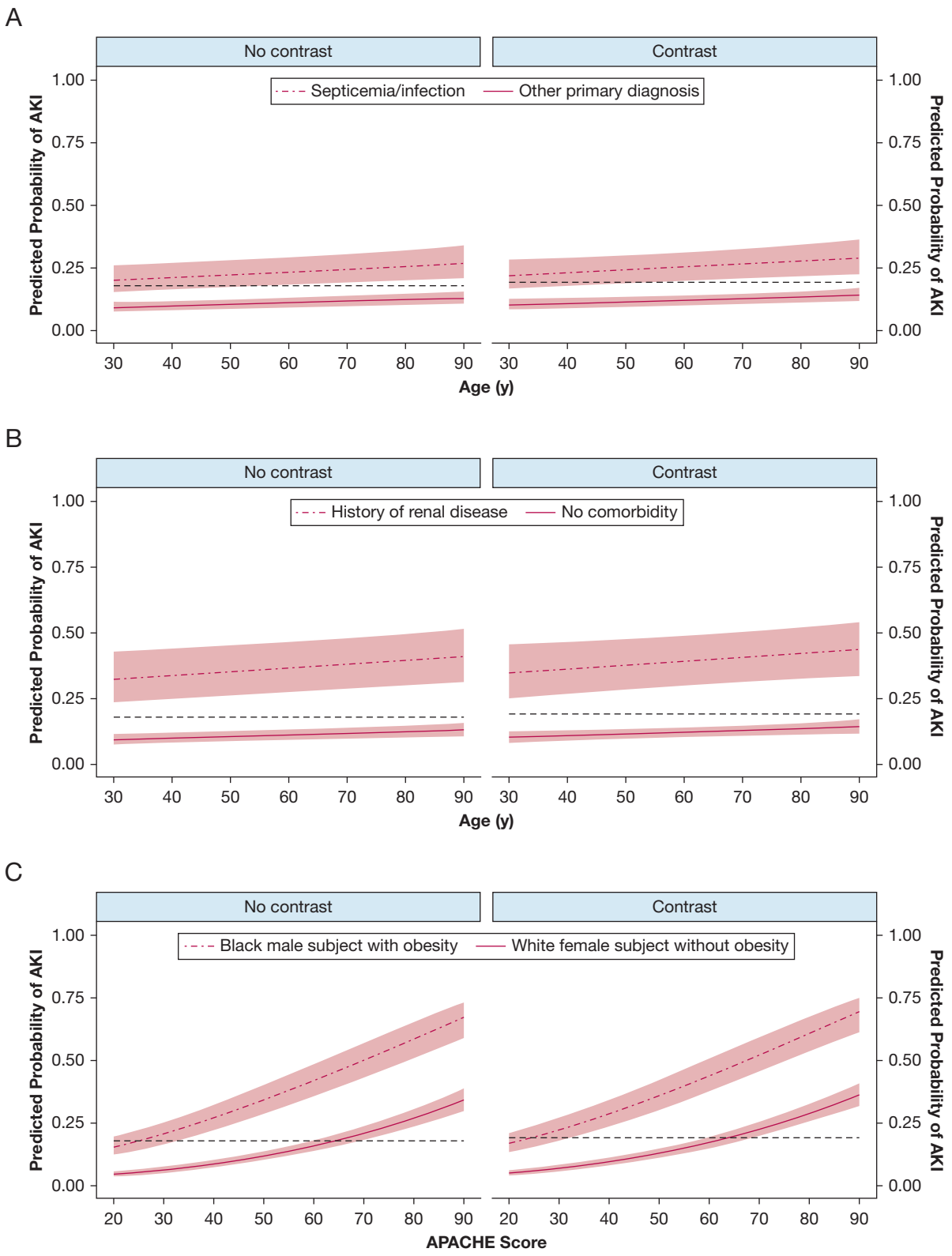

Figure 3 – *A-C, Predicted probability of AKI. A, Risk of AKI in relation to age and contrast exposure for a primary diagnosis of septicemia/infection (dashed line), or any condition in the reference group (solid line), estimated for white men without obesity or comorbidity (Model A, Table 3). B, Risk of AKI in relation to age and contrast exposure for a history of renal disease (dashed line), or no comorbidity (solid line), estimated for nonobese white men with primary diagnosis other than septicemia/infection, metabolic/immune disorders, or parenchymal lung disease (Model A, Table 2). C, Risk of AKI in relation to APACHE score and contrast exposure for black male subjects with obesity (dashed line) and nonobese white female subjects (solid line) (Model B, Table 3). Red bands depict 95% confidence bounds. Horizontal single-dash lines indicate the rate of AKI in all propensity score-matched cases. Horizontal axis (age or APACHE score) spans approximately the fifth to 95th percentile of study data. See Figure 1 legend for expansion of abbreviations.*

precision, the study size allowed us to consider a broad range of potential confounders, including some uncommon comorbidities. Most notably, renal comorbidity occurred in only 2.5% of the 4,612 matched cases, but more than one-half of these 116 patients developed AKI and the estimated effect was a fourfold increase. These patients presented with normal kidney function and a history of renal disease identified from a secondary *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic code.

An important methodological strength of our study is its rigorous application of PS matching to select from the large population of critically ill patients with no contrast exposure, a subset with characteristics closely resembling those who received contrast in accordance with institutional guidelines limiting its use. This method of establishing a valid comparison in the absence of randomization is increasingly found in the medical literature[22-25] and has been recommended for studying the association between contrast and AKI.[1,25] PS matching, which allows direct estimation of the risk difference and ratio, was performed in our study according to current recommendations for evaluating comparability of the matched groups by using standardized differences and variance ratios. This method allows comparison of covariate balance across different measurement scales and, importantly, avoids the issue of reduced power when applying significance tests to the smaller postmatch sample.[21,26] Furthermore, we retained 90.2% of the target population (ICU patients exposed to contrast) following matching, compared with 30.6% in the study by McDonald et al.[1] The difference is explained by the fact that McDonald et al studied only patients who had a CT scan in the ICU, and a majority of those procedures entailed contrast enhancement. Consequently, postmatch analysis in McDonald et al was conducted in a substantially reduced subset of contrast-exposed case subjects who closely mirrored unexposed control subjects, while being less representative of the target population in which contrast is used. Similar concern pertains to other propensity-adjusted studies[10] in which a majority of eligible case subjects have the exposure of interest.

An inherent limitation of the current study is that PS adjustment, even when based on a large number of covariates, cannot rule out possible effects of unmeasured confounders not included in study data. Although this was a single-institution study, the diversity of the patient population allowed us to identify higher rates of AKI among black patients, who comprised $>$ 10% of study cases, while ruling out a difference between Hispanic and non-Hispanic Caucasian subjects, with the former accounting for slightly more than one-half of cases. Lastly, we note the lack of data on fluid intake, making it likely that the small increase in AKI following contrast exposure (1.3%) is underestimated to the extent that our protocol for administering contrast resulted in better fluid management of these patients.

Thus, this study of critically ill patients admitted with normal or mildly reduced kidney function adds to a growing body of evidence that the risk of AKI in relation to administration of contrast media has been overstated, leading to unnecessary guidelines limiting its use and diverting the focus of preventive measures away from more significant susceptibilities.

Conclusions

In critically ill adults with normal kidney function, low osmolar contrast media does not increase AKI to an extent that justifies its avoidance when otherwise indicated. Furthermore, the substantial increase in mortality following AKI, estimated at fourfold in the current study, was not heightened by contrast exposure. Exploratory multivariable analysis suggests that regardless of contrast exposure, factors such as a primary diagnosis of septicemia or complications of diabetes, a history of renal disease, or elevated APACHE score, can help identify ICU patients with a heightened susceptibility to AKI and should be the focus of preventive measures to reduce AKI in the critical care setting.

Acknowledgments

Author contributions: L. S. W. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. All authors contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Financial/nonfinancial disclosures: None declared.

Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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