

Risk of Contrast-Induced Acute Kidney Injury in Computed Tomography

A 16 Institutional Retrospective Cohort Study

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Objectives: Concern about contrast-induced acute kidney injury (CI-AKI) may delay the timely administration of contrast media for computed tomography (CT). The precise causative effect of iodinated contrast media on CI-AKI and its relevant risk factors remains an area of ongoing investigation. Therefore, this study aimed to determine the risk of CI-AKI following contrast-enhanced CT and its predisposing risk factors.

Materials and Methods: This study employed a 1:1 propensity score matching analysis using electronic medical records gathered between January 2006 and December 2022 from 16 institutions in South Korea. Contrast-enhanced and nonenhanced CT scans in patients aged 18 years and above were matched for baseline estimated glomerular filtration rate (eGFR), demographic characteristics, and clinical variables to assess the risk of CI-AKI. Subgroup analyses were conducted to evaluate any significant risk factors for CI-AKI.

Results: A total of 182,170 CT scans with contrast were matched to 182,170 CT scans without contrast. The risk of CI-AKI in the entire study cohort was not statistically significant (odds ratio [OR], 1.036; 95% confidence interval [CI], 0.968–1.109; $P = 0.34$). Subgroup analyses revealed a significantly higher risk of CI-AKI in patients with eGFR <30 mL/min/1.73m² (OR, 1.176; 95% CI, 1.080–1.281; $P = 0.011$) or eGFR 30–45 mL/min/1.73m² (OR, 1.139; 95% CI, 1.043–1.244; $P = 0.019$), patients diagnosed with chronic kidney disease (OR, 1.215; 95% CI, 1.084–1.361; $P = 0.011$), and those administered with iso-osmolar contrast media (OR, 1.392; 95% CI, 1.196–1.622; $P = 0.011$).

Conclusions: The risk of CI-AKI following CT was minimal in the general population. However, caution is warranted for patients with chronic kidney disease and eGFR lower than 45 mL/min/1.73m², or those administered with iso-osmolar contrast media.

Key Words: computed tomography, contrast, acute kidney injury

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Iodinated contrast media used in computed tomography (CT) substantially enhance organ contrast, facilitating precise and timely diagnoses of various medical conditions. However, concerns surrounding contrast-induced acute kidney injury (CI-AKI) have traditionally overshadowed their usage in clinical practice. This hesitation impedes clinical decision-making and influences patient outcomes. Recent large-scale studies, employing propensity score matching (PSM) analysis, challenged longstanding perceptions by suggesting a notably lower and even negligible causative effect of CT contrast on AKI than previously anticipated,^{1–7} urging reconsideration of prevailing practices.

However, conflicts persist, particularly regarding patients with impaired kidney function. Some studies have reported a significant risk of CI-AKI in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m²,^{3,6,8} with odds ratios (ORs) ranging between 1.36 and 2.96, whereas other studies have shown no significant risks.^{1,4} One study showed an increased risk of CI-AKI in patients with an eGFR between 30 and 45 mL/min/1.73m², with a reported OR of 1.34.⁷ In contrast, another study showed inconsistent results according to different AKI definitions,⁶ and other studies did not show an increased risk.^{3,4,9} The conflicts might be attributed to the constraints in previous studies, including limitations in sample sizes and reliance on single-center settings. Additionally, while some potential clinical risk factors for CI-AKI are suggested in major guidelines,^{10–13} such as age, patient

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comorbidities, and potential nephrotoxic medications, they have not been rigorously confirmed, leading to significant gaps in our understanding. Furthermore, there are limited data regarding the differing risks associated with the types of contrast media.

Given the complexity and low prevalence of CI-AKI, conducting randomized controlled trials on this issue is impractical. Therefore, a multicenter study, leveraging a substantial patient cohort and utilizing meticulous covariate matching, is the practical option for obtaining a comprehensive understanding of CI-AKI risk and the associated risk factors. This study therefore aimed to assess the risk of CI-AKI following contrast-enhanced CT using a large-scale multicenter dataset, while employing PSM analysis with relevant covariates. Beyond quantifying the risk in the entire study cohort, our objective was to conduct a thorough examination of predisposing risk factors, in order to provide empirical evidence for clinical decision-making.

MATERIALS AND METHODS

Data Sources

We conducted a multicenter retrospective cohort study involving 16 institutions using a distributed research network. This study included 15,903,919 patients from Korea's electronic medical records database. Patient-level electronic medical record data were standardized and deidentified using the standard vocabulary of the Observational Medical Outcomes Partnership-Common Data Model (OMOP-CDM)¹⁴ and were stored in each hospital. Patient-level data were not shared between hospitals.

This study was approved by the institutional review board of Ajou University Medical Center (AJOURB-DB-2023-014), and the requirement for written informed consent was waived. The other hospitals are affiliated with the Research Border Free Zone of Korea, which requires approval from the research organizing center to use deidentified CDM data in studies. This study adhered to the principles of the Declaration of Helsinki and was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Detailed information about OMOP-CDM, participating hospitals, and the Research Border Free Zone is presented in the Supplementary Materials (<http://links.lww.com/RLI/A977>).

Study Patients

We extracted the records of adult patients over 18 years of age who underwent a CT scan and had medical records for more than 180 days prior to the scan. To ensure homogeneity during the patient selection period, we recruited adult patients who underwent CT scans at each hospital from January 2006 to December 2022. To be included in the study, patients were required to have at least 1 serum creatinine test within 48 hours before the CT scan and at least 1 more within 7 days after the CT scan. We excluded patients who underwent additional contrast-enhanced CT scans within 14 days before or 7 days after the initial CT to prevent a multidose effect. Furthermore, individuals who had a preexisting arteriovenous fistula, were diagnosed with kidney failure (end-stage renal disease), had a history of kidney transplantation, or underwent dialysis within 3 days of CT were excluded from the study. We divided the CT scans into 2 groups in each hospital based on the use of contrast media. If a patient underwent multiple CT scans, all were included. However, if a patient had both contrast and noncontrast CT scans at different times, only the data from the earlier group were included in the study. Finally, we created a 1:1 ratio (contrast:noncontrast) of matched cases, using nearest-neighbor PSM, achieving the same sample size in both groups. Figure 1 shows a flowchart of the study design.

Study Outcome

To define AKI, we used the Kidney Disease Improving Global Outcomes (KDIGO) criteria, which provide standardized guidelines

for classifying and diagnosing AKI.¹² The KDIGO criteria consist of 3 criteria: (1) an absolute increase of serum creatinine level of 0.3 mg/dL (26.5 μ mol/L) within 48 hours, (2) a relative increase of serum creatinine by 1.5 times from baseline within 7 days, and (3) urine output less than 0.5 mL/kg/h for 6 hours. Due to concerns regarding the reliability of urine output data, we did not use urine output as a criterion for our analysis. We considered the nearest creatinine measurement taken within 48 hours before the CT scan as the baseline creatinine value. Our primary outcome was AKI according to either the KDIGO criteria 1 or 2. The risk of AKI according to each KDIGO criteria 1 and 2 was also assessed as secondary outcomes. Furthermore, we assessed the risk of KDIGO stage 2 and 3 AKI within 1 week, as well as the need for dialysis within 1 month following CT, as additional secondary outcomes. The KDIGO criteria define stage 2 AKI as a relative increase in serum creatinine level by 2 to 3 times from the baseline, and stage 3 AKI as either an increase in serum creatinine more than 3 times from the baseline, serum creatinine >4.0 mg/dL, or initiation of dialysis within 1 week.

Propensity Score Matching

For PSM, we matched contrast and noncontrast CT scans in a 1:1 ratio and used a caliper width of 0.1 standardized logits. The covariates included baseline characteristics such as age, sex, baseline eGFR, comorbidities, disease severity indices, medication, current alcohol and cigarette intake, and the route of patient visits. Specific covariate characteristics are presented in the Supplementary Materials (<http://links.lww.com/RLI/A977>).

Before and after PSM, we calculated the percentages and used the χ^2 test to compare differences between the groups. We considered an absolute standardized difference (ASD) of 0.1 as balanced.¹⁵

Main Analysis

We deployed conditional logistic regression to calculate the ORs and 95% confidence intervals (CIs) from propensity-matched cohorts. We then used data from 16 institutions to calculate combined point estimates, 95% CIs, and *P* values using meta-analysis methodology. The meta-analysis was conducted based on a 2-stage individual patient data approach. By applying the same inclusion and exclusion criteria across individual hospitals and utilizing individual patient data to obtain aggregated statistics, we subsequently derived a single OR. We conducted statistical tests of heterogeneity by using χ^2 and *I*² statistics.¹⁶ This study included hospitals with distinct characteristics, ranging from secondary hospitals specializing in cardiology to tertiary teaching hospitals. We hypothesized that there are differences in risk levels among these institutions. Furthermore, since the *I*² statistic of the main analysis was greater than 50%, we employed a random-effects model for all meta-analyses.¹⁶

Subgroup Analysis

We conducted subgroup analysis based on baseline eGFR, sex, age, comorbidity, medication, patient care settings, and type of iodinated contrast media. Propensity scores were calculated for each subgroup and then rematched for all variables other than the variable of interest. Participants were categorized into 5 subgroups according to their baseline eGFR: <30, 30–45, 45–60, and >60 mL/min/1.73m². For comorbidities, we included patients with diabetes, hypertension, chronic kidney disease (CKD), or congestive heart failure (CHF) as distinct subgroups. For medication, we included patients using metformin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), or diuretics as different subgroups. Patient care settings were divided into hospitalized, emergency room, or outpatient settings. For the contrast type, we divided the participants into 2 groups based on the type of iodinated contrast media (ie, iso-osmolar contrast media [IOCM] including iohexanol, or low-osmolar contrast media [LOCM] including iobitridol, iohexol, iopamidol, iopromide, iomeprol, and ioversol).

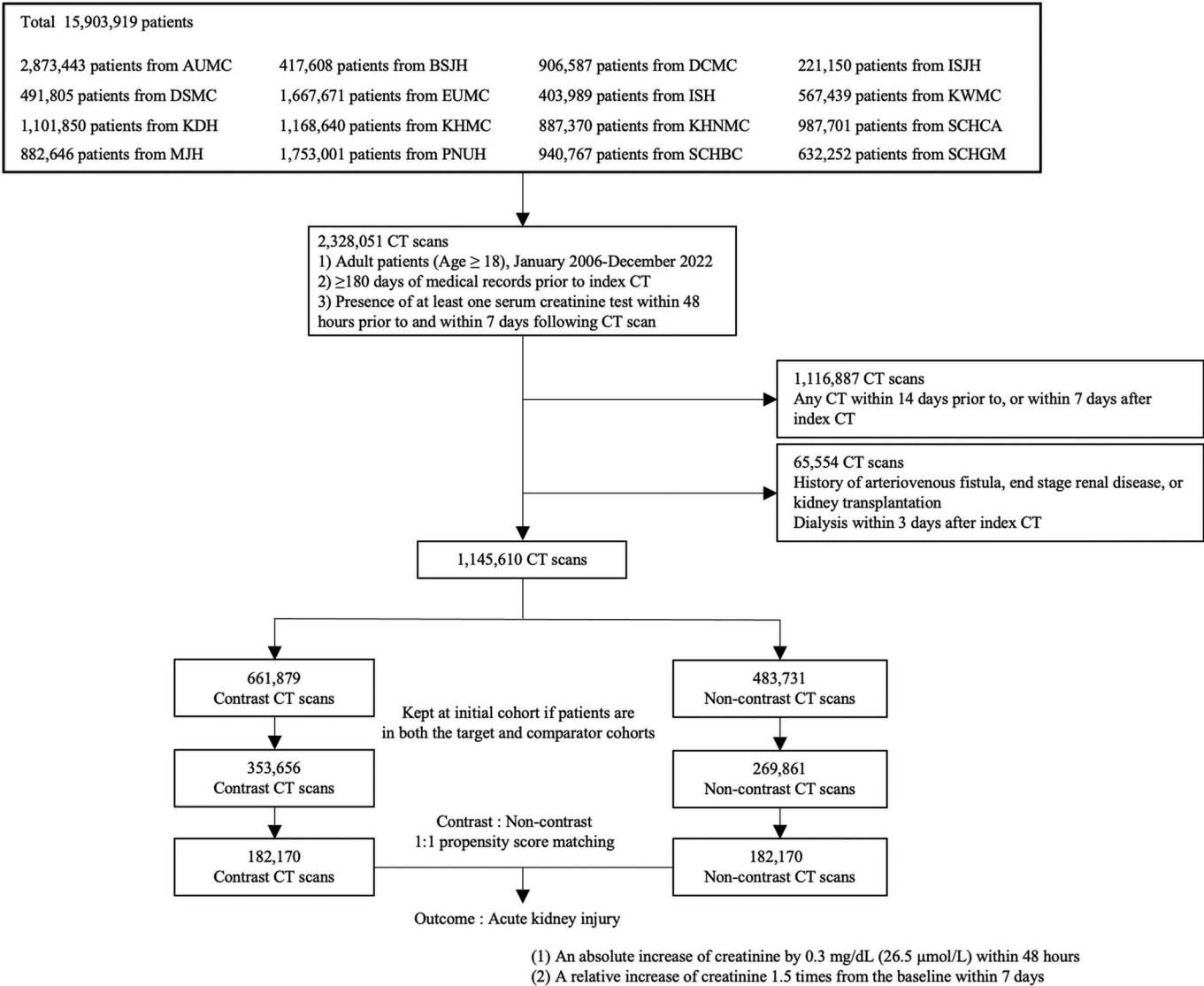


FIGURE 1. Study flowchart. We used deidentified, standardized electronic medical records databases of 15,903,919 patients from 16 hospitals in South Korea. A total of 2,328,051 CT scans met the inclusion criteria. After 1:1 propensity score matching, 182,170 CT scans with contrast were matched with 182,170 CT scans without contrast. AUMC, Ajou University Medical Center; BSJH, Bucheon Sejong Hospital; DCMC, Daegu Catholic University Medical Center; DSMC, Dongsan Medical Center; EUMC, Ewha Womans University Medical Center; ISH, International Saint Mary's Hospital; ISJH, Incheon Sejong Hospital; KHMC, Kyung Hee University Hospital; KDH, Kangdong Sacred Heart Hospital; KHNMC, Kyung Hee University Hospital at Gangdong; KWMC, Kangwon National University Hospital; MJH, Myong Ji Hospital; PNUH, Pusan National University Hospital; SCHGM, Soonchunhyang University Gumi Hospital; SCHBC, Sunchonhyang University Bucheon Hospital; SCHCA, Sunchonhyang University Cheonan Hospital.

Several post hoc analyses were performed. First, analysis was performed on subgroups categorized by baseline eGFR into 5 ranges: <15, 15–30, 30–45, 45–60, and >60 mL/min/1.73m². Second, the risk of CI-AKI in patients using IOCM was compared with that in patients using LOCM. Third, the risk of CI-AKI was further assessed across 6 different types of LOCM: iobitridol, iohexol, iopamidol, iopromide, iomeprol, and ioversol. Fourth, the risk of CI-AKI was evaluated after excluding patients who had undergone interventional angiography within 7 days of the CT scan, to mitigate the confounding effect of arterial angiography. Finally, a subgroup analysis of hospitalized patients was conducted, with stratified eGFR ranges and additional matching for key covariates related to acute conditions, such as infection, organ failure, and hemodynamic instability detected within 2 days prior to the CT scan. Details of the added covariates are provided in the Supplementary Materials.

We utilized single-variable meta-regression to calculate the *P* value for interaction (*P*_{int}) in each subgroup. Each subgroup variable was considered as the confounding moderator, and its significance was calculated as *P*_{int}.^{17,18} In some subgroups, calculating OR between contrast users and nonusers was not feasible in certain hospitals due to a limited number of AKI outcomes. To maintain consistency in our analysis, we only included hospitals that provided analyzable data in these specific subgroups, defined as having at least 1 outcome of AKI in both the contrast and noncontrast groups. To address multiple comparison issues in the subgroup analysis, we adjusted the *P* value using the Benjamini-Hochberg method. Subgroups with both a significant *P*_{int} and significant *P* value after adjusting for multiple comparisons were considered significant risk groups for CI-AKI. We used significance levels of adjusted *P* value <0.05.¹⁹

Sensitivity Analysis

In addition to the 1:1 PSM, 2 propensity score adjustment methods were used as sensitivity analyses: (1) propensity score stratification using deciles of the propensity score distribution and (2) variable-ratio PSM with a maximum ratio of 10. Additionally, another sensitivity analysis was conducted by narrowing the inclusion criteria for post-CT creatinine changes from a 7-day window to a 2-day window.

All statistical analyses were performed using R software (version 4.1.0; R Foundation for Statistical Computing) and Python (version 3.7; Python Software Foundation).

RESULTS

Study Patients

After 1:1 PSM, 182,170 contrast CT scans and 182,170 non-contrast CT scans were matched. The baseline characteristics of the

matched cohorts are shown in Table 1. The table demonstrates that before PSM, the group using contrast media had a lower prevalence of patients with eGFR <30 mL/min/1.73m² (2.3% vs 7.6%) and eGFR 30–45 mL/min/1.73m² (5.5% vs 7.5%) compared with the group not using contrast media. On the other hand, patients in the contrast group had a higher prevalence of eGFR higher than 60 mL/min/1.73m² (80.4% vs 74.9%) compared with the noncontrast group. After PSM, the ASDs of all covariates were 0.1 or less. The distribution of propensity scores according to the use of contrast for each hospital is presented in Figure 2.

Upon individual hospital-level analysis, it was observed that the ASDs for all covariates were 0.1 or less except for the ASDs of eGFR in one hospital (ASD 0.240 for ISH) and emergency room visits in another hospital (ASD 0.107 for EUMC). The improvements in the balance between covariates in other cohorts are depicted as changes in ASD in Supplementary Figure 1 (<http://links.lww.com/RLI/A977>).

TABLE 1. Baseline Characteristics of the Study Cohort Before and After Propensity Score Matching

	Before PS Adjustment			After PS Adjustment		
	Contrast	Noncontrast		Contrast	Noncontrast	
Characteristics	n (%)	n (%)	ASD	n (%)	n (%)	ASD
Total	353,656	269,861		182,170	182,170	
Age group (year)			0.011			0.012
<60	152,017 (43)	114,318 (42.4)		85,451 (46.9)	84,772 (46.5)	
60–79	153,822 (43.5)	112,886 (41.8)		72,368 (39.7)	72,583 (39.8)	
>80	47,817 (13.5)	42,657 (15.8)		24,351 (13.4)	24,815 (13.6)	
Male	191,362 (54.1)	145,069 (53.8)	0.007	98,118 (53.9)	97,592 (53.6)	0.006
eGFR (mL/min/1.73m ²)			0.148			0.003
0–30	8285 (2.3)	20,407 (7.6)		5827 (3.2)	6749 (3.7)	
30–45	19,606 (5.5)	20,159 (7.5)		11,838 (6.5)	12,227 (6.7)	
45–60	41,457 (11.7)	27,142 (10.1)		18,436 (10.1)	18,840 (10.3)	
≥60	284,308 (80.4)	202,153 (74.9)		146,069 (80.2)	144,354 (79.2)	
Comorbidities						
Hypertension	86,210 (24.4)	58,104 (21.5)	0.068	35,728 (19.6)	37,067 (20.3)	0.018
Diabetes	47,846 (13.5)	29,601 (11)	0.078	16,976 (9.3)	18,753 (10.3)	0.033
Congestive heart failure	17,472 (4.9)	12,884 (4.8)	0.008	6716 (3.7)	6797 (3.7)	0.002
Chronic kidney disease	6703 (1.9)	9144 (3.4)	0.093	3312 (1.8)	3616 (2)	0.012
Diabetic complication	25,988 (7.3)	19,867 (7.4)	0.001	9299 (5.1)	9662 (5.3)	0.009
Medication						
Metformin	17,175 (4.9)	13,419 (5.0)	0.005	8164	8534	0.01
ACE inhibitor	9223 (2.6)	6905 (2.6)	0.003	3360 (1.8)	3536 (1.9)	0.007
ARB	37,213 (10.5)	29,421 (10.9)	0.012	14,900 (8.2)	15,935 (8.7)	0.02
NSAID	43,123 (12.2)	35,304 (13.1)	0.027	18,637 (10.2)	19,724 (10.8)	0.019
Antifungal agents	11,982 (3.4)	5490 (2)	0.083	2488 (1.4)	2227 (1.2)	0.013
Diuretics	91,452 (25.9)	59,736 (22.1)	0.087	31,637 (17.4)	34,145 (18.7)	0.036
Social history						
Smoking	30,287 (8.6)	23,620 (8.8)	0.007	12,775 (7)	11,586 (6.4)	0.026
Alcohol drinker	43,383 (12.3)	31,444 (11.7)	0.019	22,194 (12.2)	19,965 (11)	0.038
Patient care setting						
Outpatient	61,261 (17.3)	47,108 (17.5)	0.001	33,113 (18.2)	32,877 (18)	0.007
Scheduled admission	119,004 (33.6)	91,860 (34)	0.005	62,151 (34.1)	62,609 (34.4)	0.004
Emergency room	78,545 (22.2)	64,092 (23.7)	0.049	39,151 (21.5)	38,636 (21.2)	0.012
Admission via emergency room	94,846 (26.8)	66,801 (24.8)	0.078	47,755 (26.2)	48,048 (26.4)	0.002

The numbers of patients in each group before and after propensity score matching are presented, with percentages in parentheses.

PS, propensity score; ASD, absolute standardized difference of each covariate; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drug.

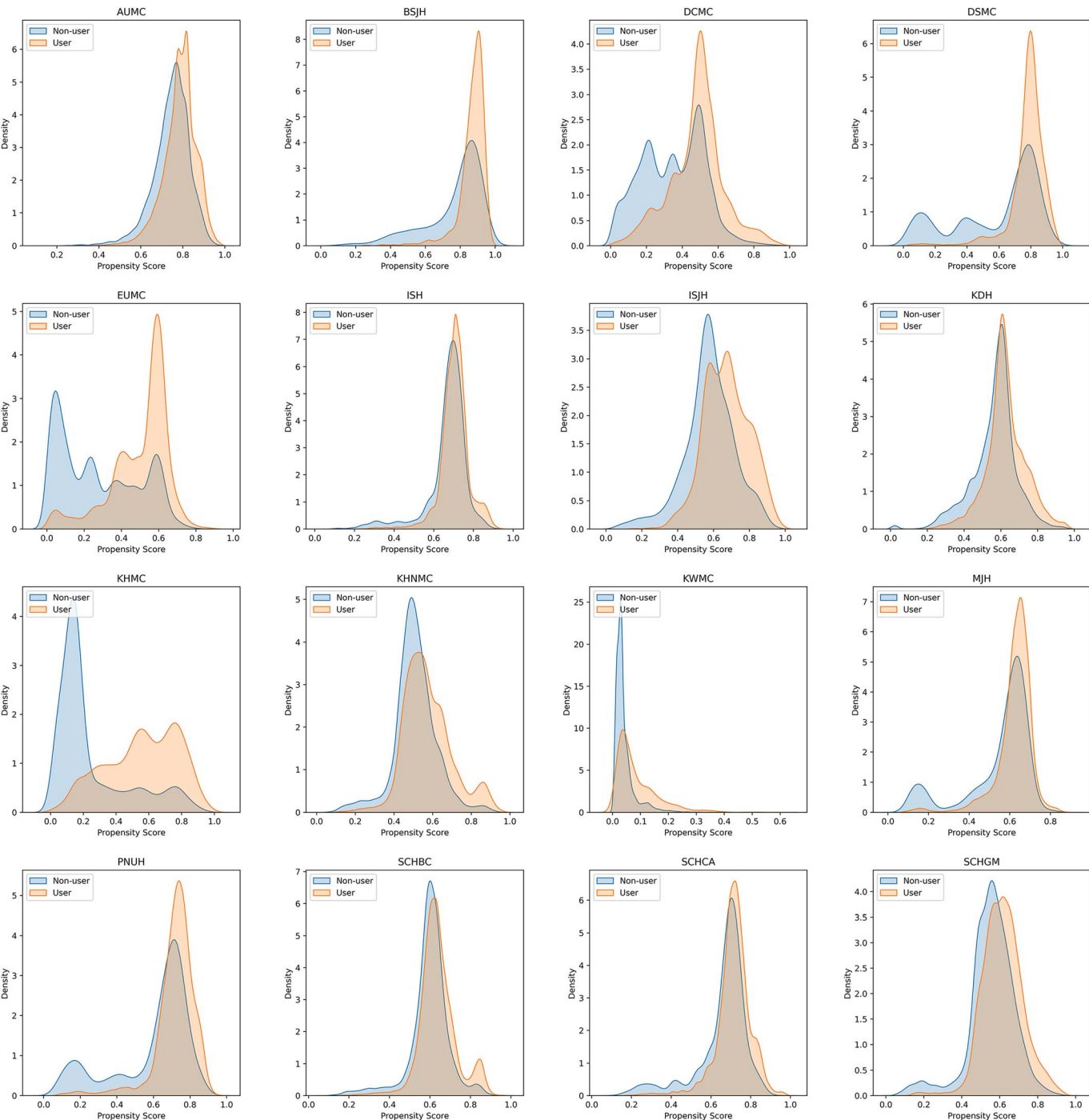


FIGURE 2. Propensity score plots of each hospital. Visual representations of propensity score matching is shown. The x axis of the plot represents the preference scores, which estimate the likelihood of receiving the treatment based on observed characteristics. The y axis represents the density, indicating the concentration or distribution of data points. When the data points of the treated and control groups overlap, it suggests that individuals with similar propensity scores have been successfully matched. AUMC, Ajou University Medical Center; BSJH, Bucheon Sejong Hospital; DCMC, Daegu Catholic University Medical Center; DSMC, Dongsan Medical Center; EUMC, Ewha Womans University Medical Center; ISH, International Saint Mary's Hospital; ISJH, Incheon Sejong Hospital; KHMC, Kyung Hee University Hospital; KDH, Kangdong Sacred Heart Hospital; KHNMC, Kyung Hee University Hospital at Gangdong; KWMC, Kangwon National University Hospital; MJH, Myong Ji Hospital; PNUH, Pusan National University Hospital; SCHGM, Soonchunhyang University Gumi Hospital; SCHBC, Suncheonhyang University Bucheon Hospital; SCHCA, Suncheonhyang University Cheonan Hospital.

AKI Incidence

In the matched population, the number of patients who developed AKI according to KDIGO criteria 1 or 2 after CT was 7486

(4.1%) in the contrast group and 7123 (3.9%) in the noncontrast group. When considering only KDIGO criteria 1, 6592 (3.6%) patients who received contrast developed AKI after CT compared with 5930 (3.3%)

who did not. When considering only KDIGO criteria 2, 4917 (2.7%) patients in the contrast group and 4690 (2.6%) in the noncontrast group developed AKI following CT. Among these, 3201 (1.8%) patients in the contrast group and 3115 (1.7%) patients in the noncontrast group developed stage 2 or 3 AKI, whereas 782 (0.4%) patients in the contrast group and 796 (0.4%) in the noncontrast group required dialysis within 1 month after CT.

Risk of CI-AKI in the Main Cohort

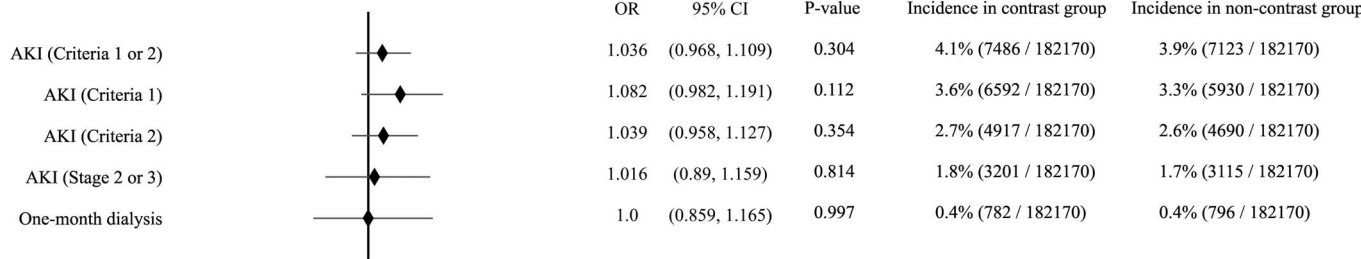
Meta-analysis showed that AKI defined using KDIGO criteria 1 or 2 was not significantly associated with contrast use (OR, 1.036; 95% CI, 0.968–1.109; $P = 0.304$). AKI assessed separately by either KDIGO criteria 1 or 2 was also not associated with contrast use (OR, 1.082; 95% CI, 0.982–1.191; $P = 0.112$ and OR, 1.039; 95% CI, 0.958–1.127;

$P = 0.354$, respectively). KDIGO stages 2 and 3, as well as the risk of dialysis, were not significantly associated with contrast use (OR, 1.016; 95% CI, 0.89–1.159; $P = 0.814$ for KDIGO stage 2 or 3; OR, 1; 95% CI, 0.859–1.165; $P = 0.997$ for 1-month dialysis risk). The sensitivity analysis also revealed similar trends, showing no increased risk of CI-AKI in the overall patient cohort. The main and sensitivity results are presented in Figure 3 and Supplementary Figure 2 (<http://links.lww.com/RLI/A977>).

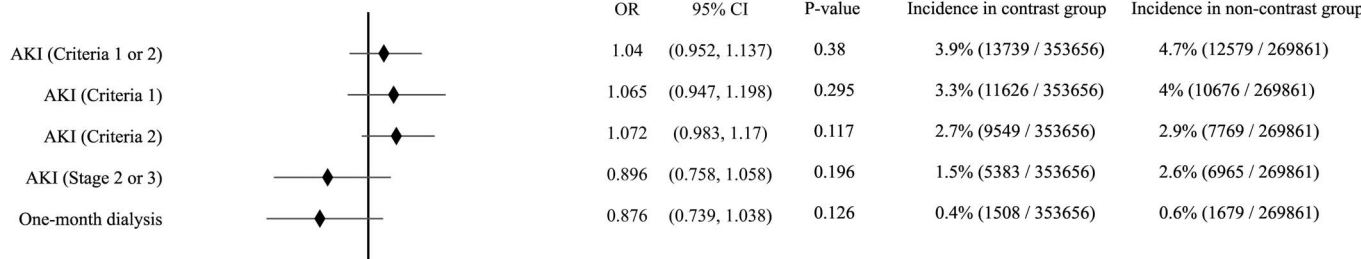
Subgroup Analysis

Detailed results of the subgroup analysis are presented in Table 2, with sensitivity analyses results in Supplementary Tables 1–3 (<http://links.lww.com/RLI/A977>). The subgroup analysis revealed a significant risk of CI-AKI in patients with eGFR <30 mL/min/1.73m²

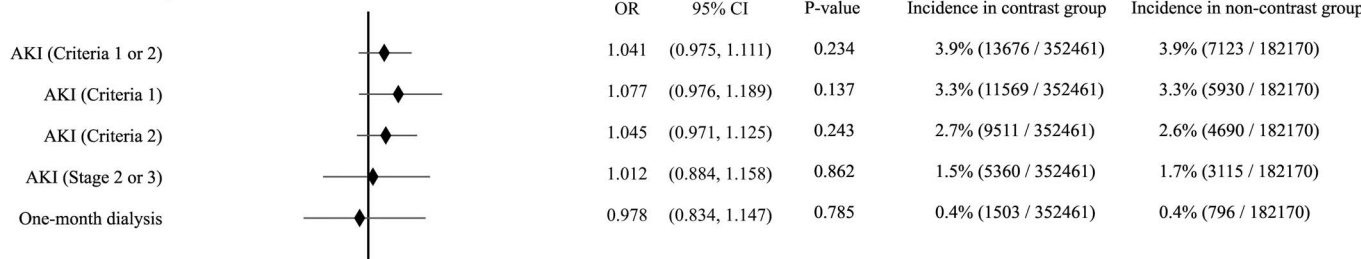
1:1 matching



Stratification



Variable matching



Altered inclusion

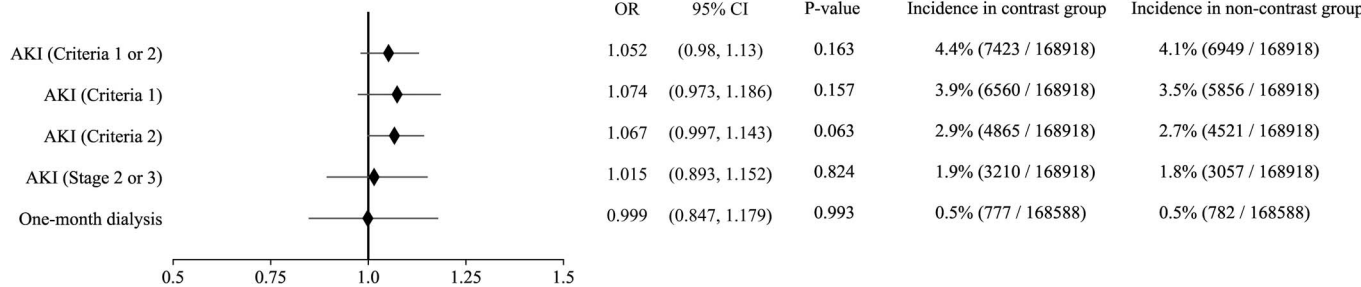


FIGURE 3. Risk of contrast-induced acute kidney injury in the total population under various analytical settings. Forest plots comparing the odds ratios (ORs) of AKI outcomes across 4 distinct matching methodologies (1:1 matching, variable matching, stratification, and altered inclusion criteria) are shown. Each row within a plot corresponds to a specific AKI criterion, whereas the plots are arranged horizontally to facilitate comparison between methods. AKI, acute kidney injury; CI, confidence interval.

TABLE 2. Subgroup Analysis

Subgroups	Odds Ratio	95% Confidence Interval	AKI Incidence in Contrast Group	AKI Incidence in Noncontrast Group	No. Hospitals	P	Adjusted P	P _{int}
Total patients Baseline eGFR	1.036	0.968–1.109	4.11% (7486/182,170)	3.91% (7123/182,170)	16	0.304	0.358	
	1.176	1.080–1.281	19.38% (1315/6786)	16.52% (1121/6786)	13	<0.001	0.011	0.029
	1.139	1.043–1.244	11.46% (1399/12,208)	10.04% (1226/12,208)	13	0.004	0.019	
	1.048	0.911–1.208	6.64% (1233/18,557)	6.14% (1139/18,557)	13	0.511	0.581	
	1.035	0.971–1.103	2.8% (3679/131,358)	2.7% (3549/131,358)	13	0.286	0.350	
Sex	1.071	1.018–1.127	3.79% (3083/81,304)	3.54% (2878/81,304)	15	0.008	0.033	0.668
	1.086	0.995–1.185	4.57% (4233/92,691)	4.2% (3894/92,691)	15	0.065	0.125	
Age	1.02	0.956–1.089	2.92% (2329/79,830)	2.85% (2272/79,830)	15	0.542	0.596	0.065
	1.083	1.011–1.160	4.65% (3296/70,891)	4.31% (3055/70,891)	15	0.023	0.069	
	1.136	1.048–1.231	7.08% (1843/26,013)	6.21% (1616/26,013)	15	0.002	0.016	
Comorbidity	1.113	1.024–1.210	6.32% (1169/18,488)	5.68% (1050/18,488)	15	0.012	0.044	0.293
	1.062	0.990–1.140	4.01% (6373/159,031)	3.78% (6010/159,031)	15	0.094	0.155	
	1.107	1.036–1.182	5.51% (2072/37,580)	4.99% (1874/37,580)	15	0.003	0.016	0.195
	1.042	0.984–1.104	3.91% (5515/141,067)	3.71% (5238/141,067)	15	0.158	0.217	
	1.215	1.084–1.361	16.95% (671/3959)	13.97% (553/3959)	14	0.001	0.011	0.023
Medication	1.059	0.997–1.125	3.94% (6772/172,044)	3.72% (6397/172,044)	14	0.063	0.125	
	1.069	0.970–1.179	11.84% (847/7155)	11.06% (791/7155)	15	0.178	0.235	0.794
	1.079	1.010–1.153	3.92% (6660/169,849)	3.62% (6141/169,849)	15	0.025	0.069	
	1.072	0.946–1.216	5.47% (516/9436)	5.09% (480/9436)	15	0.276	0.350	0.992
	1.069	1.011–1.131	4.16% (7017/168,638)	3.88% (6547/168,638)	15	0.019	0.063	
	1.168	0.947–1.441	10.36% (395/3813)	8.5% (324/3813)	13	0.147	0.211	0.083
	1.067	1.005–1.133	4.05% (6746/166,378)	3.81% (6331/166,378)	13	0.035	0.082	
	1.118	1.009–1.240	7.28% (915/12,561)	6.54% (821/12,561)	15	0.034	0.082	0.343
	1.05	0.987–1.116	4.03% (6693/166,238)	3.8% (6319/166,238)	15	0.121	0.190	
	1.133	1.002–1.281	6.73% (1349/20,050)	5.86% (1175/20,050)	15	0.047	0.103	0.036
Contrast type vs noncontrast	1.044	0.987–1.104	3.91% (6192/158,281)	3.74% (5924/158,281)	15	0.132	0.198	
	1.065	0.994–1.142	9.81% (3621/36,896)	9.12% (3365/36,896)	15	0.072	0.125	0.996
	1.075	1.025–1.127	3.07% (4494/146,226)	2.86% (4177/146,226)	15	0.003	0.016	
	1.392	1.196–1.622	8.7% (408/4711)	6.22% (293/4711)	12	<0.001	0.011	0.01
	1.014	0.954–1.078	4.1% (5285/128,120)	4.04% (5176/128,120)	12	0.659	0.702	
	1.000	0.955–1.047	3.33% (3955/118,880)	3.32% (3952/118,880)	13	0.996	0.996	0.045
	1.102	0.992–1.224	6.13% (2327/37,957)	5.50% (2088/37,957)	13	0.069	0.125	
	1.009	0.917–1.109	2.39% (810/33,854)	2.39% (808/33,854)	13	0.858	0.885	

*Denotes P value <0.05. To conduct subgroup analysis, propensity score matching was performed within each subgroup, comparing contrast users and nonusers, to calculate odds ratios. In some subgroups, calculating the odds ratio was not possible for some hospitals due to an insufficient number of patients for propensity score matching or a limited number of outcomes. We excluded these hospitals from the meta-analysis. The number of hospitals denotes participating hospitals in each subgroup meta-analysis.

P value refers to the P value of the odds ratio obtained from each individual subgroup analysis. A P value below 0.05 indicates that the contrast had a significant impact on the AKI incidence in that subgroup. Adjusted P value refers to the P value after adjustment with the Benjamini-Hochberg method. P_{int} refers to the P value of interaction between subgroup variables and contrast use.

ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin II receptor blockers; CHF, congestive hepatic failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug.

(OR, 1.176; 95% CI, 1.080–1.281; adjusted $P = 0.011$) and eGFR 30–45 mL/min/1.73m² (OR, 1.139; 95% CI, 1.043–1.244; adjusted $P = 0.019$), with P_{int} of 0.029. Significant risk of CI-AKI was also observed in patients diagnosed with CKD (OR, 1.215; 95% CI, 1.084–1.361; adjusted $P = 0.011$; P_{int} 0.032) and in those using IOCM (OR, 1.392; 95% CI, 1.196–1.622; adjusted $P = 0.011$; P_{int} 0.01). NSAID use showed a significant P_{int} ($P = 0.036$), but the adjusted P value was 0.103. Subgroups with female sex, age over 80, diabetes, and hypertension had significant adjusted P values, but the P_{int} was not significant. The risk of CI-AKI was not significant in the patient subgroups based on different care settings.

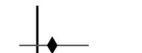
CI-AKI risks stratified by eGFR in the 1:1 PSM and other sensitivity analyses are shown in Figure 4. The incidence of AKI following CT

increased as baseline eGFR decreased in both the contrast and noncontrast groups. The eGFR <30 mL/min/1.73m² subgroup showed a significantly increased risk of CI-AKI in 1:1 PSM, PS stratification, and variable matching methods (OR, 1.16–1.176; $P \leq 0.007$). As for the eGFR 30–45 mL/min/1.73m² subgroup, 1:1 PSM and PS stratification showed an increased risk (OR, 1.139–1.144; $P \leq 0.046$), whereas the variable matching method did not (OR, 1.11; 95% CI, 1.015–1.213; $P = 0.084$). Sensitivity analysis with altered inclusion showed significant P values for the eGFR <30 mL/min/1.73m² and 30–45 mL/min/1.73m² subgroups, but not a significant P_{int} value ($P_{\text{int}} = 0.114$). Results of subgroup analysis with patients divided into 5 eGFR categories (<15, 15–30, 30–45, 45–60, and >60 mL/min/1.73m²) are presented in Supplementary Table 4 (<http://links.lww.com/RLI/A977>).

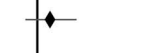
1:1 matching

		OR	95% CI	P-value	Incidence in contrast group	Incidence in non-contrast group	P_{int}
Total		1.036	(0.968, 1.109)	0.358	4.1% (7486 / 182170)	3.91% (7123 / 182170)	
eGFR <30		1.176	(1.08, 1.281)	0.011	19.4% (1315 / 6786)	16.52% (1121 / 6786)	0.029
eGFR 30-45		1.139	(1.043, 1.244)	0.019	11.5% (1399 / 12208)	10.04% (1226 / 12208)	
eGFR 45-60		1.048	(0.911, 1.208)	0.581	6.6% (1233 / 18557)	6.14% (1139 / 18557)	
eGFR >60		1.035	(0.971, 1.103)	0.35	2.8% (3679 / 131358)	2.7% (3549 / 131358)	

Stratification

		OR	95% CI	P-value	Incidence in contrast group	Incidence in non-contrast group	P_{int}
Total		1.04	(0.952, 1.137)	0.448	3.88% (13739 / 353656)	4.66% (12579 / 269861)	
eGFR <30		1.17	(1.091, 1.254)	0.007	18.15% (1659 / 9139)	16.87% (3344 / 19824)	0.047
eGFR 30-45		1.144	(1.031, 1.269)	0.046	10.52% (2308 / 21947)	10.4% (2031 / 19531)	
eGFR 45-60		1.049	(0.908, 1.212)	0.589	6.27% (2905 / 46338)	6.38% (1678 / 26309)	
eGFR >60		1.06	(0.976, 1.15)	0.248	2.92% (8004 / 274031)	3.01% (5770 / 191673)	

Variable matching

		OR	95% CI	P-value	Incidence in contrast group	Incidence in non-contrast group	P_{int}
Total		1.041	(0.975, 1.111)	0.322	3.88% (13676 / 352461)	3.91% (7123 / 182170)	
eGFR <30		1.162	(1.066, 1.265)	0.007	18.13% (1640 / 9044)	16.52% (1121 / 6786)	0.041
eGFR 30-45		1.11	(1.015, 1.213)	0.084	10.49% (2263 / 21581)	10.04% (1226 / 12208)	
eGFR 45-60		1.044	(0.91, 1.196)	0.614	6.26% (2848 / 45473)	6.14% (1139 / 18557)	
eGFR >60		1.034	(0.968, 1.105)	0.391	2.92% (7962 / 273045)	2.7% (3549 / 131358)	

Altered inclusion

		OR	95% CI	P-value	Incidence in contrast group	Incidence in non-contrast group	P_{int}
Total		1.052	(0.98, 1.13)	0.224	4.39% (7423 / 168918)	4.11% (6949 / 168918)	
eGFR <30		1.16	(1.062, 1.267)	0.003	19.6% (1353 / 6902)	16.92% (1168 / 6902)	0.114
eGFR 30-45		1.142	(1.029, 1.267)	0.026	11.58% (1405 / 12129)	10.17% (1233 / 12129)	
eGFR 45-60		1.042	(0.921, 1.18)	0.57	6.86% (1261 / 18393)	6.35% (1168 / 18393)	
eGFR >60		1.05	(0.975, 1.131)	0.256	2.91% (3751 / 128738)	2.75% (3546 / 128738)	

0.5 0.75 1.0 1.25 1.5

FIGURE 4. Risk of CI-AKI stratified by eGFR. The figure presents the results of 1:1 propensity score matching analysis along with sensitivity analyses examining the risk of contrast-induced acute kidney injury, stratified by pre-CT estimated glomerular filtration rate (eGFR). The term “1:1 matching” refers to propensity score matching conducted in a 1:1 ratio, which is the main result of this study. “Stratification” refers to propensity score stratification based on deciles. “Variable matching” refers to propensity score matching in which 1 noncontrast user could be matched to up to 10 contrast users. “Altered inclusion criteria” refers to a modification of the inclusion criteria, where post-CT creatinine measurement within 2 days was used for evaluating CI-AKI instead of 7 days. Data from 13 hospitals were included in the eGFR subgroup analysis. The P value represents the adjusted P value using the Benjamini-Hochberg method to correct for multiple comparisons. $P_{\text{int}} = P$ for interaction.

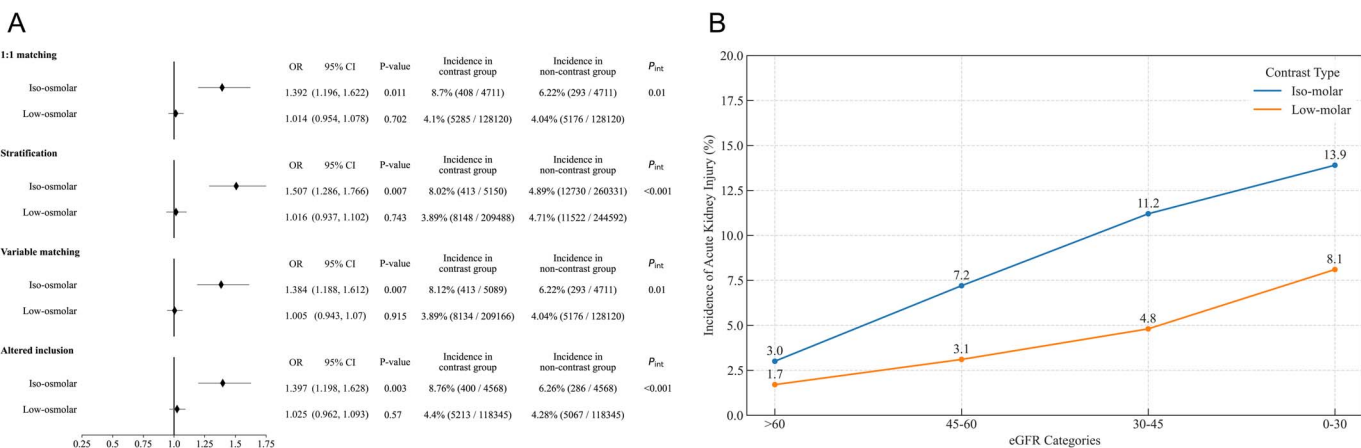


FIGURE 5. Risk of CI-AKI stratified by contrast type. A, Forest plots illustrating the risk of CI-AKI when comparing iso-osmolar and low-osmolar contrast media using various matching methods. The term “1:1 matching” refers to propensity score matching conducted in a 1:1 ratio, which serves as the main result of this study. “Stratification” refers to propensity score stratification based on deciles. “Variable matching” refers to propensity score matching in which 1 noncontrast user could be matched to up to 10 contrast users. “Altered inclusion criteria” refers to a modification of the inclusion criteria, where post-CT creatinine measurement within 2 days was used for evaluating CI-AKI instead of 7 days. Data from 13 hospitals were included in the eGFR subgroup analysis. The P value represents the adjusted P value using the Benjamini-Hochberg method to correct for multiple comparisons. P_{int} = P for interaction. B, The graph shows the incidence of AKI following the administration of iso-osmolar and low-osmolar contrast media across different estimated glomerular filtration rate (eGFR) categories. The iso-osmolar medium consists exclusively of iobitridol, iohexol, iopamidol, iopromide, iomeprol, and ioversol.

CI-AKI risks stratified by the contrast type in the 1:1 PSM and other sensitivity analyses are shown in Figure 5. We observed a significant risk of CI-AKI for patients using IOCM in the 1:1 PSM and across all sensitivity analyses (OR, 1.384–1.507; $P \leq 0.011$; $P_{int} \leq 0.01$). Patients using LOCM also demonstrated a significantly higher risk of CI-AKI compared with those using IOCM (OR, 1.244; 95% CI, 1.014–1.526; $P = 0.037$). When the 6 different types of LOCM were analyzed separately as subgroups, no significant risk of CI-AKI was observed for any of the types compared with the matched noncontrast groups ($P = 0.207$ – 0.986) (Table 3).

The risk of CI-AKI was also not significant in the patient group after excluding those who had undergone interventional angiography within 7 days of the CT scan (Supplementary Table 5, <http://links.lww.com/RLI/A977>). In the subgroup of hospitalized patients, the risk of CI-AKI was initially not significant in any eGFR range. After matching for key covariates reflecting acute conditions, the risk of CI-AKI became significant in the baseline eGFR <30 mL/min/1.73m² group (OR, 1.202; 95% CI, 1.080–1.339; $P = 0.008$) and showed a

trend toward significance in the eGFR 30–45 mL/min/1.73m² group (OR, 1.142; 95% CI, 1.000–1.304; $P = 0.102$) (Supplementary Table 6, <http://links.lww.com/RLI/A977>).

DISCUSSION

In this 1:1 PSM analysis including 16 institutions and 182,170 matched pairs of study samples, we found no significant risk of CI-AKI in the entire cohort. On the other hand, a significant risk was observed in patients with an eGFR of less than 30 mL/min/1.73m², between 30 and 45 mL/min/1.73m², and in patients previously diagnosed with CKD. Moreover, our study identified that the use of IOCM was significantly associated with the risk of CI-AKI. Other precipitating risk factors, such as patient comorbidities and nephrotoxic medications, did not significantly increase the risk of CI-AKI. These findings provide valuable evidence for the risk-benefit assessment and clinical decision-making concerning contrast-enhanced CT.

TABLE 3. Subgroup Analysis With Specific Contrast Media Type

Contrast type		Odds Ratio	95% Confidence Interval	AKI Incidence in Contrast Group	AKI Incidence in Noncontrast Group	No. Hospitals	P	P_{int}
Iso-osmolar	Iodixanol	1.392	1.196–1.622	8.66% (408/4711)	6.22% (293/4711)	12	<0.001	<0.001
Low-osmolar	Iobitridol	1.001	0.914–1.096	3.98% (932/23,391)	3.98% (930/23,391)	8	0.986	
	Iohexol	0.956	0.886–1.032	3.57% (3118/87,287)	3.74% (3262/87,287)	16	0.250	
	Iopamidol	0.987	0.806–1.211	3.97% (1109/27,918)	4.44% (1240/27,918)	14	0.903	
	Iopromide	0.94	0.811–1.09	4.82% (2060/42,712)	4.85% (2070/42,712)	11	0.412	
	Iomeprol	0.94	0.855–1.035	3.23% (822/25,444)	3.44% (875/25,444)	7	0.207	
	Ioversol	0.94	0.834–1.061	3.37% (984/29,188)	3.62% (1056/29,188)	10	0.317	

Due to the divergence in the primarily utilized contrast agents among different hospitals, it was not possible to conduct an analysis by exclusively grouping hospitals that commonly use low-osmolar contrast media. Consequently, our approach involved utilizing the analysis results from all hospitals.

P value refers to the P value of the odds ratio obtained from each individual subgroup analysis. A P value below 0.05 indicates that the contrast had a significant impact on the AKI incidence in that subgroup. P_{int} refers to the P value of interaction between subgroup variables and contrast use.

AKI, acute kidney injury.

Our study aligns with several previous studies,^{1–7,20} affirming the overall absence of evident CI-AKI risk among unselected patients. Notably, our study is the first multicenter study focusing on the patients regardless of the patient care settings (ie, emergency room, outpatient, or hospitalized), distinguishing it from previous single-center studies^{1–5,20} or studies limited to specific patient subgroups such as those attending the emergency department^{6,7} or hospitalized patients.^{7,8} Additionally, our study boasts the largest sample size to date, encompassing various AKI definitions, conducting multiple sensitivity analyses, and adjusting for multiple comparisons. Consequently, it provides more definitive evidence that the overall risk of CI-AKI may be negligibly low.

In contrast, a significantly increased risk of CI-AKI was observed in patients with a baseline eGFR of less than 30 mL/min/1.73m². Previous studies yielded conflicting results in this subgroup,^{3,4,6–8} with a recent meta-analysis suggesting an existing risk.²¹ This meta-analysis included a pooled population of 1757 patients with an eGFR of <30 mL/min/1.73m² and undergoing contrast-enhanced CT, potentially limiting its statistical power. In our study, the incidence of AKI in contrast and noncontrast groups with an eGFR <30 mL/min/1.73m² was 19.4% and 16.5% respectively, closely resembling the incidence reported by the meta-analysis (19% vs 15%).²¹ Given these incidences, a sample size exceeding 5500 would be required to confirm the difference with 80% power at a 2-sided level of 0.05, a threshold not achieved by previous studies or meta-analyses. Consequently, our study, which included over 13,000 patients from 13 institutions with a baseline eGFR of <30 mL/min/1.73m², has sufficient power to safely conclude the current risk of CI-AKI in this subgroup, emphasizing caution when using contrast media.

Further uncertainty existed in patients with an eGFR between 30 and 45 mL/min/1.73m², with only 1 previous study reporting a significantly increased risk⁷ in patients presenting to the emergency department or hospitalized. Our study also revealed a significant risk of CI-AKI in this subgroup regardless of the patient care settings. However, it is worth noting that although the risk was significant, the difference in the incidence of AKI between the contrast and noncontrast groups (11.5% and 10.0%, respectively) was not substantial. A large number of patients (n = 24,416) were included in this subgroup analysis, potentially enabling the detection of small risks. Therefore, caution must be taken when interpreting this result for clinical application; as in many clinical scenarios, the benefits of contrast-enhanced CT may outweigh the potential harm of a small increased risk of CI-AKI.

Another important finding of our study is that the risk of CI-AKI increased with the use of IOCM, whereas LOCMs did not show a significant risk. IOCMs have dimeric structures that increase their viscosity to about twice that of LOCMs, which have monomeric structures, and up to 11 times the viscosity of plasma.^{22–24} The difference in urine viscosity between IOCM and LOCM becomes even more pronounced during the tubular concentration process in the nephron.^{25,26} The high viscosity of tubular fluid caused by IOCM can initiate a cascade of intrarenal disturbances,²⁷ starting with increased resistance, which raises tubular pressure and hinders glomerular filtration. Moreover, increased resistance slows tubular flow, prolonging the intrarenal retention time of contrast media and thereby increasing the risk of direct tubular damage from the cytotoxicity of iodine.²⁴ Additionally, the increased tubular pressure distends the tubules, promoting higher renal interstitial pressure and constriction of the descending vasa recta,²⁸ ultimately leading to medullary hypoxia—a key underlying pathophysiology of CI-AKI.^{27,29} Previous studies have reported mixed results on this issue,^{9,30–33} with some limitations due to varying study settings and smaller sample sizes. Our study, with the largest matched sample size to date (9422 patients) for the use of IOCM, may provide stronger real-world clinical evidence for its potential risk. Furthermore, our analysis showed that the IOCM group also demonstrated a significantly increased risk when directly matched with patients using LOCMs, further supporting the existing risk. As there are no specific guidelines for the use of

IOCM in daily practice, LOCM could be recommended over IOCM for CT scans, especially in patients with other risk factors such as kidney impairment.

In a subgroup analysis of hospitalized patients, the results showed that the risk of CI-AKI was not significant across the different eGFR ranges. However, after adjusting for acute conditions during hospitalization, such as infection, organ failure, and hemodynamic instability, the risk became significant in the eGFR <30 mL/min/1.73m² group and showed a trend toward significance in the 30–45 mL/min/1.73m² group. This finding may be explained by the potential confounding effect of acute kidney functional recovery, which refers to the improvement of kidney function following interventions targeting acute illness in hospitalized patients unrelated to the contrast-enhanced CT.^{34,35} This recovery may partially mask AKI caused by CT contrast media, leading to an underestimation of its true impact—a bias that adjusting for acute conditions may have helped to mitigate.

There are several limitations to our study. First, the retrospective setting may have introduced some selection bias, although we attempted to minimize it through propensity-score matching of clinically relevant covariates and by utilizing a large number of patients from multiple centers. One major source of bias inherent to the retrospective design is the inclusion of only patients with eGFR measurements within 7 days from the CT scan. This limitation was unavoidable, as the eGFR measurement is crucial for defining the study outcome (ie, AKI as per the KDIGO criteria) and aligns with the methodology used in previous retrospective studies on this topic.^{1–7} Future prospective studies may help eliminate this bias. Another potential selection bias may stem from the differing baseline characteristics between the contrast and noncontrast groups prior to matching. For instance, before matching, the proportion of patients with different eGFR levels varied significantly between the 2 groups (eg, 2.3% of patients with eGFR 0–30 mL/min/1.73m² in the contrast group compared with 7.6% in the noncontrast group). This reflects the clinical practice of more conservative contrast media use in patients with lower eGFR. However, this bias was largely mitigated by matching for baseline eGFR.

Second, despite our attempt to adjust for as many clinically relevant covariates as possible, residual confounders may still remain. For instance, we were unable to adjust for the specific indications of the CT scans due to missing records of exact indications across the hospitals in the CDM database, which may have introduced some confounding effects. However, adjusting for factors such as patient age, comorbidities, and patient care settings likely mitigated some of this effect. Another potential confounder not included as a covariate is the use of AKI prophylaxis (ie, fluid hydration and *N*-acetylcysteine), which may have led to an underestimation of CI-AKI risk in the contrast group. However, current evidence for the protective effect of these measures is weak. Recent randomized controlled trials found no significant benefit of hydration in preventing CI-AKI during contrast-enhanced CT,^{36–38} and a recent meta-analysis showed no reduction in AKI risk with *N*-acetylcysteine.³⁹ Additionally, these prophylactic measures are typically used in patients with low eGFR, and our study demonstrated a significant risk of CI-AKI in patients with eGFR ≤45 mL/min/1.73m². Thus, even if a protective effect exists, it would not alter the direction of our findings, though it might affect the magnitude of the observed risk. Lastly, the use of diagnostic codes instead of validated clinical criteria to assess the baseline comorbidities of patients may have introduced bias.

In conclusion, the risk of CI-AKI may be negligible in the general population. However, precautions should be taken in subgroups of patients with risk factors, including eGFR <45 mL/min/1.73m², CKD, and the use of IOCM.

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