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ORIGINAL

Association between intravenous contrast media exposure and non-recovery from dialysis-requiring septic acute kidney injury: a nationwide observational study

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Abstract

Purpose: This study aimed to examine the association between the use of intravenous contrast and non-recovery from dialysis-requiring acute kidney injury (AKI-D) and in-hospital mortality among patients with sepsis.

Methods: This was a retrospective observational study using the Japanese Diagnosis Procedure Combination inpatient database between January 2011 and December 2016. We identified patients with septic AKI who began continuous renal replacement therapy (RRT) within 2-days of admission and underwent computed tomography. We compared patients with AKI-D with and without the use of intravenous contrast for computed tomography and performed propensity score matching to adjust for confounders for the association between exposure to intravenous contrast and outcomes, including a composite outcome of in-hospital mortality and RRT dependence at discharge and RRT duration.

Results: From 3782 and 6619 patients with septic AKI-D with and without intravenous contrast exposure, respectively, 3485 propensity score-matched pairs were generated. No significant differences were found in the outcomes between the propensity score-matched groups: a composite outcome of in-hospital mortality and RRT dependence, 49.6% vs. 50.2% (odds ratio (OR) 0.98; 95% CI (confidence interval) 0.88, 1.07); in-hospital mortality, 45.3% vs. 46.1% (OR 0.97; 95% CI 0.87, 1.06); RRT dependence, 4.4% vs 4.1% (OR 1.08; 95% CI 0.85, 1.31); and median (interquartile range) of RRT duration, 4 [2–11] days vs. 4 [2–11] days ($P = 0.58$).

Conclusions: This large observational study did not support an association between intravenous contrast media and adverse in-hospital outcomes in patients with septic AKI-D. Further studies are warranted to assess the generalizability.

Keywords: Acute kidney injury, Sepsis, Continuous renal replacement therapy, Contrast-induced nephropathy

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Introduction

Acute kidney injury (AKI) frequently complicates critical illness. Mortality has been reported to exceed 50% especially in patients with AKI who require dialysis (AKI-D) [1, 2]. Moreover, 10–30% of survivors of AKI-D remain dependent on renal replacement therapy (RRT) at hospital discharge [3]. Previous studies have shown that early recovery from AKI, or no need for acute RRT at discharge, were associated with improved long-term outcomes [4, 5]. Some experts have suggested that targeting optimal fluid balance and avoiding nephrotoxins may be effective in achieving renal recovery [6].

Sepsis is a leading cause of mortality in critical care [7] and septic AKI has been associated with the highest mortality among the various etiologies of AKI [8, 9]. Important aspects in the care of septic patients include the prompt initiation of broad-spectrum antibiotics, removal of the infectious source and providing respiratory and hemodynamic support as needed. Assessment for a hidden infectious source (e.g., abscess) using appropriate diagnostic imaging is critical in the initial management of sepsis [7].

The use of contrast media to improve the diagnostic accuracy of computed tomography (CT) is common [10]. However, contrast media have potential toxicity on the kidneys via two main mechanisms suggested in animal and in vitro experiments: (i) direct toxic effect on tubular epithelial cells, leading to acute tubular necrosis and apoptosis, and (ii) indirect effect related to ischemia caused by changes of vasoactive mediators, leading to intrarenal vasoconstriction and reduction in glomerular blood flow [11]. Reduction in glomerular blood flow contributes to the release of reactive oxygen species and ischemia of the outer regions of the medulla, further worsening tubular cell injury [11, 12].

Many studies have examined the association between the use of contrast media and development or progression of AKI [13–18]. Notably, the use of contrast media for CT scan was not associated with increased risk of AKI, requirement for RRT, or death based on the recent meta-analyses [19, 20]. Based on these results, there have been a great deal of discussion over the risk of contrast media use in intensive care units (ICUs) [21, 22], and some experts have suggested that the risk of contrast-associated AKI may be lower than previously estimated [23].

However, all the aforementioned studies and discussions focused on pre-dialysis patients without AKI or those at an early stage of AKI. To the best of our knowledge, the examination of the association of IV contrast and increased risk of adverse outcomes, including mortality and delayed short-term renal recovery (e.g., liberation from RRT) in patients already on acute RRT, have not been reported in the literature. Sepsis is the leading cause of AKI requiring RRT [8, 9], and its management often requires exploration of infectious origin. Contrast media could assist in the identification of the infectious origin (which could lead to more appropriate treatment and better outcomes); however, it can potentially lead to an additional damage to the kidneys (which could lead to worse in-hospital outcomes). Continuous RRT (CRRT) is preferentially used for patients in the critical care setting for hemodynamic management [24]. Therefore, we examined the association between the use of contrast media and in-hospital outcomes by focusing on patients with septic AKI already on CRRT. This paper was originally presented at the International Society of Nephrology 2019 in Melbourne [25].

Take-home message

Our research showed that exposure to contrast media when performing CT was not associated with in-hospital mortality and renal recovery from RRT in patients with septic AKI-D treated with CRRT. Our findings suggest that it may not be necessary to avoid IV contrast in such patients with septic AKI-D if deemed beneficial.

Methods

Data source

We performed a retrospective observational cohort study using a Japanese inpatient database (the Diagnosis Procedure Combination database), the details of which are described elsewhere. Briefly, the database includes administrative claims and abstracted discharge data. Currently the database includes patients from approximately 1000 acute care hospitals, which account for about half of all acute admissions in Japan. The database includes the following information: patient's age and sex, admission and discharge dates, discharge status, primary admission diagnosis, comorbidities at admission, post-admission complications coded by the International Classification of Diseases, 10th revision (ICD-10), types of surgical procedures coded with the original Japanese operation codes, daily records of procedures (including CRRT, acute intermittent RRT and maintenance dialysis), diagnostic examinations (including CT scan with or without IV contrast media) and drugs used during hospitalization. Data at the time of hospital discharge were recorded by the attending physicians, and the quality of which is constantly monitored. A validation study of the database suggested high sensitivity and specificity for the procedure records, while most diagnoses had high specificity, but moderate sensitivity [26].

Study approval was obtained from the institutional review board of the University of Tokyo. Since the data

were anonymous, informed consent from patients was waived.

Study participants and exposure variable

We included patients 18 years of age and older who met the following criteria: (a) the admission diagnosis was an infectious disease indicated by ICD-10 codes listed previously [27], (b) there was evidence of other organ dysfunction (mechanical ventilation, vasopressor use or platelet transfusion) at the initiation of CRRT [28], (c) CRRT was started within 2 days following admission, (d) a CT scan was performed at admission and (e) discharge occurred between January 1st 2011 and December 31th 2016. We excluded patients who underwent coronary angiography or percutaneous coronary intervention and who had end-stage renal disease, based on the ICD-10 code of N18.0 at admission. Patients who received a CT scan with IV contrast were defined as the IV contrast media user group and those who received a CT scan without IV contrast were defined as the IV contrast media non-user group based on the procedure code.

Definition of outcomes

The primary outcome was a composite outcome of in-hospital death or RRT dependence at discharge. In-hospital mortality and RRT dependence were also assessed separately. The secondary outcome was duration of RRT, including both CRRT and intermittent RRT during hospitalization, and length of hospital stay. We defined RRT dependence at discharge as the patient being discharged alive and receiving RRT within 2 days prior to discharge. The definition of RRT dependence as a requirement for RRT within 2 days before discharge was based on usual clinical practice in Japan. Patients dependent on RRT at discharge and requiring outpatient RRT after discharge are scheduled to undergo RRT thrice weekly in Japan as conventional intermittent HD [29]. Therefore, we considered that the definition of RRT dependence as the requirement for RRT "within 2 days prior to discharge" is plausible.

Covariates

Covariates included age, sex, Charlson comorbidity index (CCI) [30], level of consciousness at admission according to the Japan Coma Scale (JCS) [31], discharge year, source of infection and an emergency operation for the source of infection. We treated the JCS as a categorical variable and classified the grades as grade 0 (alert), grades 1–3 (awake without any stimuli), grades 10–30 (arousable with stimulation) or grades 100–300 (unarousable) for analysis. The JCS is widely used in Japan and is well correlated with the Glasgow Coma Scale [31]. We also identified a recorded diagnosis of congestive heart failure (ICD-10 code; I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0), diabetic nephropathy (ICD-10 code; E10.2X and E11.2X), chronic kidney disease (CKD) (ICD-10 code; N18.X except for N18.0) as a complication at admission.

We identified sites of infection for each patient using a specified list of ICD-10 codes [27] and operation codes: abdominal, hepatobiliary, respiratory, skin/soft tissue/musculoskeletal, urinary tract and others. In categorizing patients suspected of having infections at multiple sites, we prioritized the main diagnosis, followed by comorbidity at admission. Each patient was allocated to one of the subgroups. We identified the following treatments performed on the day of admission: mechanical ventilation; transfusion including red blood cell concentrates, fresh frozen plasma or platelet concentrates; vasoactive agents including dopamine, dobutamine, norepinephrine, epinephrine or vasopressin; nephrotoxins such as non-steroidal anti-inflammatory drugs, calcineurin inhibitors, angiotensin converting enzyme inhibitors and angiotensin receptor blockers and prescription of diuretics or antibiotics. Hospital volume was defined as the mean annual number of patients who fulfilled the inclusion and exclusion criteria, and was categorized into three groups based on tertiles.

Statistical analysis

One-to-one propensity score matching was performed between the IV contrast media users and non-users [32]. To estimate the propensity score, we fitted a logistic regression model for IV contrast use as a function of the patient and hospital factors (age, sex, CCI, congestive heart failure, diabetic nephropathy, CKD, level of consciousness using JCS, discharge year, source of infection, emergency operation for an infectious source, hospital volume and treatments performed within 2 days following admission). We selected these covariates for the calculation of propensity score based on the clinical importance [33], as well as previous ICU studies in our administrative database [34]. We also adjusted for discharge year because of potential changes in practice pattern by year. We evaluated C-statistics as a measure of discrimination. One-to-one matched analysis using nearest-neighbor matching was performed based on the estimated propensity score of each patient. A match occurred when a patient in the IV contrast user group had an estimated score within 0.2 standard deviations of a patient in the non-user group. For balance assessment after matching, we calculated standardized mean difference (SMD) and considered values less than 0.1 as acceptable [35]. We also reported C-statistic after matching as a metrics of balance [36]. Two-sided $P < 0.05$ was considered statistically significant. Categorical outcomes were compared

using the Chi square test in an unmatched cohort and using the McNemar test in a matched cohort [37]. RRT duration was compared using the *t* test in an unmatched cohort and using the paired *t* test for a matched cohort. Data were analyzed using R software version 3.5.0. In our study population, we grouped patients based on presence or absence of each diagnosis code or procedure code, by assuming that people without it did not have the condition, therefore no information was missing in any key covariates.

Sensitivity analysis

Due to potential uncertainty of the data, we conducted several sensitive analyses to test the robustness of our findings. First, we defined RRT dependence as a requirement for RRT within 7 days (instead of 2 days in the main analysis) before discharge. Second, we estimated the propensity score using generalized estimating equations with hospitals as clusters to consider hospitals for the correlation structure of individual patients within hospitals. Third, we restricted the study population to patients who started CRRT on the day of admission (instead of within 2 days of admission in the main analysis).

Results

We identified 11,756 patients who fulfilled the inclusion criteria and subsequently excluded 1355 patients who either who had end-stage renal disease or required coronary angiography/percutaneous coronary intervention (Fig. 1). The remaining 10,401 eligible patients were divided into IV contrast users ($n=3782$) and non-users ($n=6619$), from which 3485 propensity score-matched pairs were generated. C-statistics was 0.69 in the propensity score-matched model.

The baseline characteristics of the unmatched and propensity score-matched groups are noted in Tables 1 and 2. In the unmatched group, the IV contrast users tended to have smaller CCI scores, and were more likely to have abdominal infection, and an emergency operation for infection source control than the non-user group. The IV user group received more intensive treatment, including catecholamines (except for dobutamine), transfusion, nephrotoxic drugs, glycopeptide, and antifungal agents

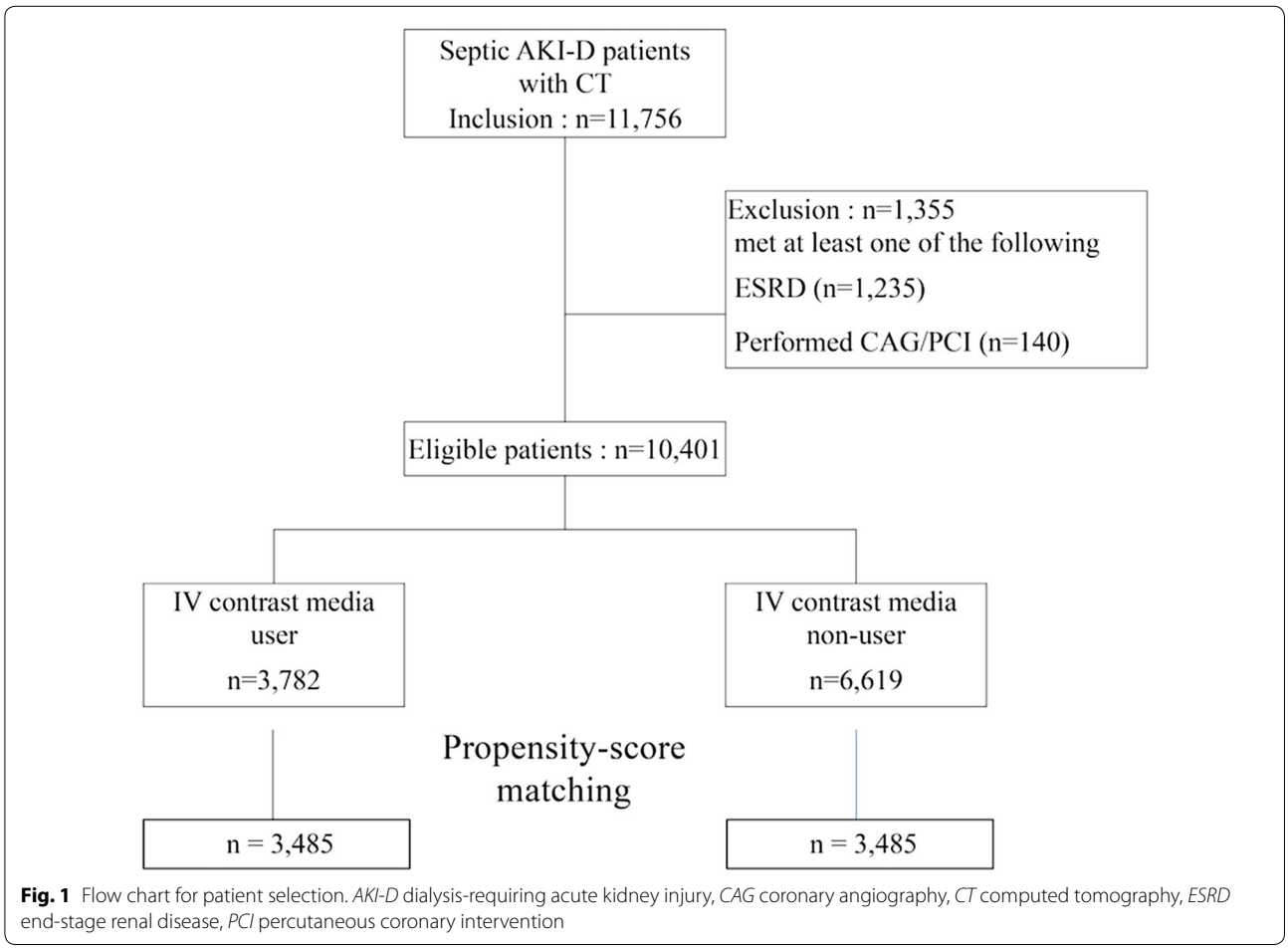

Fig. 1 Flow chart for patient selection. *AKI-D* dialysis-requiring acute kidney injury, *CAG* coronary angiography, *CT* computed tomography, *ESRD* end-stage renal disease, *PCI* percutaneous coronary intervention

Table 1 Baseline characteristics of patients in unmatched and propensity score matched groups

	Unmatched groups			Matched groups[1)]			Matched groups[2)]		
	Contrast	Control	SMD	Contrast	Control	SMD	Contrast	Control	SMD
Subjects, *N*	3782	6619		3485	3485		3490	3490	
Age, mean (SD)	69.9 (13.8)	70.2 (13.6)	0.03	69.8 (13.7)	69.9 (14.1)	0.01	69.7 (13.7)	70.1 (14.0)	0.02
Male (%)	60.5	61.3	0.02	60.9	60.1	0.02	61.0	61.1	0.00
Hospital volume for septic AKI-D per 1 year (%)			0.37			0.01			0.02
Low	24.8	38.6		26.9	26.6		26.8	26	
Medium	32.9	34.7		34.4	34.7		34.3	35.2	
High	42.3	26.7		38.8	38.7		38.8	38.7	
Charlson comorbidity index (%)			0.18			0.03			0.03
0	61.3	54.7		60	60.3		60.3	59.3	
1	9.7	12.7		10.1	10.5		10.1	10.9	
2	20.7	20.8		21.1	20.3		20.9	20.9	
3	3.2	5.9		3.4	3.2		3.4	3.5	
≥ 4	5.2	5.8		5.3	5.5		5.3	5.3	
Congestive heart failure (%)	8.9	12.7	0.12	9.4	9	0.01	9.3	9.4	0
Chronic kidney disease (%)	8.6	11.9	0.11	8.9	9.6	0.02	8.9	9.2	0.01
Diabetic nephropathy (%)	1.3	2	0.06	1.3	1.3	0.01	1.4	1.3	0.01
Japan Coma Scale (%)			0.05			0.02			0.04
0	39.6	41.5		39.8	39.9		39.4	41.4	
1–3	25.1	23.7		24.7	24.3		25	24.2	
10–30	12.1	12.6		11.9	12.6		11.9	11.3	
100–300	23.2	22.2		23.6	23.2		23.7	23.2	
Year (%)			0.04			0.01			0.02
2011	11.2	12		11.4	11.3		11.3	12	
2012	15.2	14.9		15.2	15		15.3	14.9	
2013	15.9	15.3		15.8	16		15.8	15.8	
2014	16	17		16.1	16.5		16.1	16.2	
2015	20.9	20.6		20.7	20.5		20.7	20.6	
2016	20.9	20.2		20.8	20.7		20.8	20.5	
Source of infection (%)			0.42			0.02			0.03
Abdominal	39.5	23.9		35.9	35.6		35.6	36.2	
Hepatobiliary	5	5.2		5.3	5.3		5.4	5.4	
Respiratory	8.9	18.5		9.7	9.4		9.7	10	
Skin/Soft/Musculoskeletal	4.7	3.8		4.7	4.9		4.7	4.3	
Urinary tract	6.3	10.5		6.9	7.4		6.9	6.3	
Others	35.6	38.2		37.6	37.4		37.7	37.8	
Emergency operation for source control (%)	40.8	29	0.25	38.2	38.7	0.01	38.1	38.7	0.01

"Contrast" denotes use of intravenous contrast media, while "control" denotes non-use of intravenous contrast media when receiving computed tomography

than the non-user group. After propensity score matching, the baseline characteristics were similar between the two groups. After matching, C-statistics was 0.50.

A composite outcome of in-hospital mortality and RRT-dependence at discharge was not significantly different between the two groups (unmatched 49.3% vs 50.9%, $P=0.10$, odds ratio (OR) 0.93; 95% confidence interval (CI) 0.86–1.01; propensity score-matched 49.6% vs 50.2%, $P=0.68$, OR 0.98; 95%CI 0.88–1.07) (Fig. 2; Table 3). In-hospital mortality and RRT-dependence at discharge, respectively, was not significantly different between the two groups both in the unmatched and matched populations (Fig. 2; Table 3). There was no significant difference between the two groups in the duration of RRT (median [interquartile range] RRT duration, 4 [2–11] vs 4 [2–11] days, $P=0.58$), length of hospital stay in survivors (44 [25–73] vs 43 [26–71] days, $P=0.47$).

Table 2 Treatment within 2 days of admission in unmatched and propensity score matched groups

	Unmatched groups			Matched groups[1]			Matched groups[2]		
	Contrast	Control	SMD	Contrast	Control	SMD	Contrast	Control	SMD
Dopamine	39.3	42.5	0.06	38.8	39.8	0.02	38.5	40.9	0.05
Dobutamine	13.8	13.6	0.00	14.1	13.7	0.01	14.0	13.8	0.01
Noradrenaline	79.0	72.6	0.15	78.2	78.0	0.00	78.5	77.9	0.01
Adrenaline	16.3	12.3	0.12	15.6	15.1	0.02	15.9	15.1	0.02
Vasopressin	17.8	13.8	0.11	16.8	16.8	0.00	17.0	16.0	0.03
Blood transfusion (%)									
Red blood cells	36.1	26.9	0.20	33.9	34.4	0.01	34.2	34.3	0.00
Platelets	13.1	11.3	0.05	13.0	12.7	0.01	13.0	13.3	0.01
Fresh frozen plasma	37.2	25.7	0.25	34.7	35.1	0.01	34.7	35.1	0.01
Mechanical ventilation (%)	51.7	53.2	0.03	52.5	52.1	0.01	52.6	51.6	0.02
Use of nephrotoxins (%)	6.3	4.8	0.07	6.0	6.1	0.00	5.8	6.0	0.01
Use of diuretics (%)	9.1	14.4	0.16	9.4	9.3	0.00	9.4	9.3	0.00
Initial antibiotics (%)									
Penicillin	0.8	1.1	0.02	0.9	1.0	0.01	0.9	1.1	0.01
Penicillin with beta-lactamase inhibitor	17.1	18.4	0.03	17.7	16.7	0.03	17.9	16.4	0.04
Broad-spectrum penicillin	1.4	0.7	0.07	1.2	1.2	0.00	1.2	1.1	0.01
First-generation cephalosporin	4.0	2.5	0.08	3.6	3.8	0.01	3.8	3.7	0.01
Second-generation cephalosporin	10.9	6.9	0.14	10.5	9.9	0.02	10.5	10.3	0.00
Third-generation cephalosporin, good activity against Pseudomonas	2.1	3.1	0.06	2.3	2.4	0.01	2.3	3.0	0.04
Third-generation cephalosporin, poor activity against Pseudomonas	5.6	9.7	0.15	6.0	6.1	0.00	6.0	5.4	0.02
Fourth-generation cephalosporin	1.3	2.0	0.05	1.4	1.6	0.01	1.4	1.7	0.02
Carbapenem	64.6	60.0	0.10	63.4	64.7	0.03	63.0	63.9	0.02
Aminoglycoside	2.9	2.3	0.04	2.8	2.8	0.00	2.9	3.1	0.01
Fluoroquinolone	3.7	6.9	0.14	3.8	3.5	0.02	3.8	3.8	0.00
Tetracycline	0.6	1.4	0.08	0.6	0.6	0.00	0.6	0.5	0.01
Macrolide	2.1	4.2	0.12	2.3	2.2	0.01	2.3	2.8	0.04
Glycopeptide	13.5	11.6	0.06	13.2	13.3	0.00	13.3	12.7	0.02
Antifungal	4.1	3.1	0.05	3.6	3.6	0.00	3.8	3.5	0.02

"Contrast" denotes use of intravenous contrast media, while "control" denotes non-use of intravenous contrast media when receiving computed tomography

Hospital volumes are defined as the average annual number of patients who met inclusion and exclusion criteria in each hospital, and were categorized as "low" for ≤ 4, "medium" for 4–8, and "high" for ≥ 8

Nephrotoxin includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcineurin inhibitors and non-steroidal anti-inflammatory drugs

IV intravenous, *SMD* standardized mean difference

(1) Estimating propensity score using logistic regression model. C-statistics was 0.69 and post-matching C-statistics was 0.50

(2) Estimating propensity score using generalized estimating equations with hospitals as clusters to taking hospitals into account for the correlation structure of the individual patients within hospitals. C-statistics was 0.69 and post-matching C-statistics was 0.50

The results were similar (supplemental table) in the sensitivity analysis defining RRT dependence at discharge differently (as the requirement for RRT within 7 days before discharge). In the sensitivity analysis, considering hospitals as an additional unit of clustering, we estimated the propensity score using generalized estimating equations with hospitals as clusters, and propensity score matching was performed. We observed similar results (Tables 1, 2, 3). In the sensitivity analysis restricting the study population to patients who started CRRT on the day of admission, no association was found between IV contrast use and outcomes in each subgroup (supplemental table).

Discussion

Using a national database, we compared the mortality and recovery from RRT between the IV contrast users and the non-users in septic AKI-D. Propensity score-matching analyses found no significant difference between the two groups in the composite outcome of

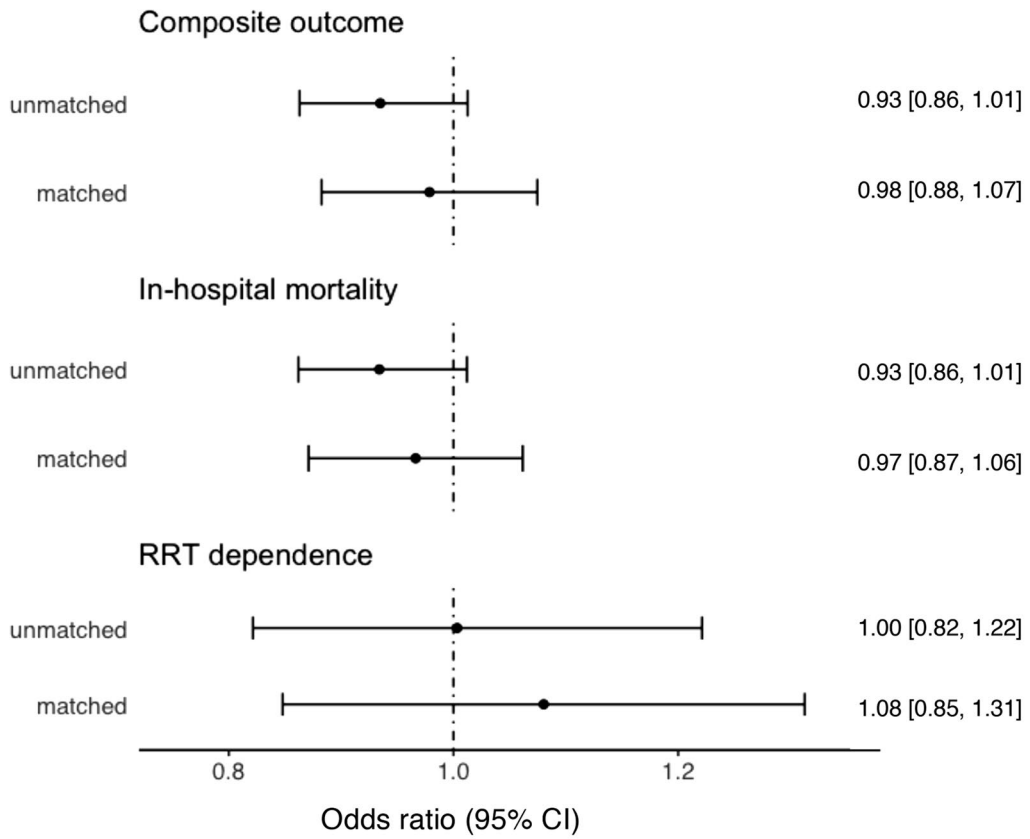

Fig. 2 Association of intravenous contrast media and the primary outcomes. Composite outcome includes in-hospital death or RRT-dependence at discharge. *CI* confidence interval, *OR* odds ratio

Table 3 Study outcomes before and after propensity score matching

Outcomes	Unmatched groups			Matched groups[1]			Matched groups[2]		
	Contrast (*N* = 3782)	Control (*N* = 6619)	*P* value	Contrast (*N* = 3485)	Control (*N* = 3485)	*P* value	Contrast (*N* = 3490)	Control (*N* = 3490)	*P* value
Composite outcome at discharge, *n* (%)	1863 (49.3)	3372 (50.9)	0.10	1730 (49.6)	1748 (50.2)	0.68	1738 (49.8)	1744 (50.0)	0.90
In-hospital mortality, *n* (%)	1702 (45.0)	3091 (46.7)	0.10	1577 (45.3)	1606 (46.1)	0.50	1586 (45.4)	1598 (45.8)	0.79
RRT–dependence at discharge, *n* (%)	161 (4.3)	281 (4.2)	1.00	153 (4.4)	142 (4.1)	0.55	152 (4.4)	146 (4.2)	0.77
Length of hospital stay among survivors, *n* (%)	44 [26, 73]	42 [25, 70]	0.13	44 [25, 73]	43 [26, 81]	0.47	44 [25, 73]	43 [26, 71]	0.90
RRT duration (median [IQR])	4 [2, 11]	4 [2, 11]	0.39	4 [2, 11]	4 [2, 11]	0.58	4 [2, 11]	4 [2, 11]	0.63

"Contrast" denotes use of intravenous contrast media, while "control" denotes non-use of intravenous contrast media when receiving computed tomography

Composite outcome is a composite of in-hospital death and dialysis-dependency

RRT-dependence at discharge as the patient being discharged alive and receiving RRT within 2 days prior to discharge

CRRT continuous renal replacement therapy, *IQR* interquartile range, *RRT* renal replacement therapy

[1] Estimating propensity score using logistic regression model

[2] Estimating propensity score using generalized estimating equations with hospitals as clusters to taking hospitals into account for the correlation structure of the individual patients within hospitals

in-hospital mortality and RRT-dependence at discharge at discharge, length of hospital stay, and RRT duration.

Our findings support previous reports suggesting that contrast-induced nephropathy might be clinically less relevant than suggested [19, 20]. Several reports have noted that the risk of contrast-induced nephropathy may be overestimated [13, 18]. In addition, recent meta-analyses showed exposure to IV contrast did not contribute to a significant increase in AKI in critically ill patients [19, 20]. However, the studies in these meta-analyses did not focus on septic AKI, and the prognosis of septic AKI is worse than that of AKI due to other etiologies [9]. Our study found minimal effects of IV contrast on recovery from AKI-D, and those effects might be explained by the multifactorial pathological mechanism of septic AKI [6, 8]. It has been suggested that several factors other than exposure to IV contrast, particularly inflammatory reactions or renal ischemia due to hemodynamic compromise, might be the major contributors to the pathogenesis of AKI [8].

The primary goal of this study was to determine mortality and short-term renal non-recovery in patients with AKI-D. Non-recovery from AKI-D is a known risk factor for death [5]. Therefore, avoiding non-recovery is one of the important components of management. Measures to promote recovery overlap with those to prevent renal harm, and avoiding nephrotoxins such as IV contrast in patients with AKI is currently recommended in guidelines [24, 38]. However, in our study, the use of IV contrast was not associated with short-term non-recovery from RRT in patients with AKI-D, the most severe form of AKI. Some studies have suggested that the use of IV contrast is helpful in diagnosing the source of infection in critically ill patients with an acute abdomen [10], although there are still paucity of evidence strongly supporting the apparent clinical benefit of contrast administration. Our findings suggest that it may not be necessary to avoid IV contrast in such patients with AKI-D, if deemed otherwise beneficial.

Our study has several limitations. First, the database does not include vital signs or laboratory data. Second, this was a retrospective observational study. Potential unmeasured confounders between those with and without IV contrast use may be present, although the comparability between the two groups was increased by restricting the study population to patients with community-acquired sepsis and adjusting for differences in baseline characteristics using propensity score matching. Although we adjusted for congestive heart failure, CKD, and diabetic nephropathy to minimize confounding factors, sensitivity of these diagnostic codes may be somewhat low, and it could lead to unmeasured confounder [39]. Although our sensitivity analysis considering centers as a unit of clustering did not significantly change the main results, hospital-related residual confounding may be present in the association between contrast media and in-hospital outcomes. Furthermore, we were unable to obtain data regarding medications before admission, including statin, which may have a protective effect against AKI. Third, we were unable to assess long-term renal outcomes following hospital discharge. Fourth, in this study, we defined sepsis using the diagnostic code of infectious disease and the evidence of organ support therapy based on procedure codes, such as mechanical ventilation and vasopressor use. We believe that our definition in this research is more sensitive than using diagnostic codes of sepsis because sepsis coding generally demonstrates low sensitivity [40]. However, the studied population based on our definition may still be different from the "true" septic population. Finally, our results are not generalized to patients other than those who fulfilled our inclusion criteria on admission, although our study design was oriented to the increased comparability between the groups with and without contrast media. Although our research has strengths in patients with septic AKI-D on admission due to comparability, further studies are warranted to assess the adverse effects of contrast media, especially in other populations, wherein researches have not been well conducted.

Conclusions

This study, using a nationwide inpatient database, suggested that the diagnostic use of IV contrast media neither increases the composite outcome of in-hospital mortality and RRT dependence at discharge nor increases RRT duration in patients with septic AKI-D. Excessive avoidance of the diagnostic use of IV contrast media for patients with septic AKI-D may not be warranted if deemed beneficial. Further studies are warranted to assess the generalizability of the results to patient population other than our study population.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05755-2) contains supplementary material, which is available to authorized users.

Abbreviations

AKI: Acute kidney injury; AKI-D: Acute kidney injury requiring dialysis; CCI: Charlson comorbidity index; CKD: Chronic kidney disease; CRRT: Continuous renal replacement therapy; CT: Computed tomography; ICD: The international classification of diseases; IV: Intravenous; RRT: Renal replacement therapy.

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Author contributions
YM, MI, HY and KD designed the study. YM, SA, HM and HY were involved in acquiring data. YM, MI and SA were responsible for the statistical analysis. YM and MI interpreted the data and wrote the first draft of the report. SA, HY, YM, MN, and KD revised the report critically for important intellectual content. All authors approved the final version of the manuscript. The corresponding author confirms to have had full access to the data in the study and final responsibility for the decision to submit for publication.

Compliance with ethical standards

Conflicts of interest
The authors declare that they have no competing interests.

Research involving human participants and/or animals
Ethics approval and consent for each institution to participate in the study was approved by the institutional research ethics committee in accordance with local ethical regulations.

Informed consent
Informed consent was not required due to the observational and anonymous nature of data collection.

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