



# Renal Safety of Repeated Intravascular Administrations of Iodinated or Gadolinium-Based Contrast Media within a Short Interval

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**Objective:** We aimed to investigate whether repeated intravascular administration of iodinated contrast media (ICM) or gadolinium-based contrast agents (GBCAs) within a short interval was associated with an increased risk of post-contrast acute kidney injury (PC-AKI).

**Materials and Methods:** This retrospective study included 300 patients (mean age  $\pm$  standard deviation, 68.5  $\pm$  8.1 years; 131 male and 169 female) who had undergone at least one ICM-enhanced perfusion brain CT scan, had their baseline and follow-up serum creatinine levels available, and had not undergone additional contrast-enhanced examinations 72 hours before and after a time window of interest were included. The study population was divided into three groups: single-dose group and groups of patients who had received multiple contrast administrations in the time window of interest with the minimum contrast repeat interval either within 4 hours (0–4-hour group) or between 4 to 48 hours (4–48-hour group). Multivariable logistic regression analysis was conducted to evaluate the association between AKI and repeated ICM administrations. A similar supplementary analysis was performed including both ICM and GBCA.

**Results:** When ICM was only considered ignoring GBCA, among 300 patients, 207 patients received a single dose of ICM, 58 had repeated doses within 4 hours (0–4-hour group), and 35 patients had repeated doses between 4 to 48 hours (4–48-hour group). Most patients (> 95%) had a baseline estimated glomerular filtration rate (eGFR) of  $\geq$  30 mL/min/1.73 m<sup>2</sup>. AKI occurred in 7.2%, 13.8%, and 8.6% of patients in the single-dose, 0–4-hour, and 4–48-hour groups, respectively. In the 0–4-hour and 4–48-hour groups, additional exposure to ICM was not associated with AKI after adjusting for comorbidities and nephrotoxic drugs (all *p* values > 0.05).

**Conclusion:** Repeated intravascular administrations of ICM within a short interval did not increase the risk of AKI in our study patients suspected of acute stroke with a baseline eGFR of  $\geq$  30 mL/min/1.73 m<sup>2</sup>.

**Keywords:** Contrast media; Acute kidney injury; Retrospective studies; Tomography, X-ray computed; Magnetic resonance imaging

## INTRODUCTION

Contrast media are indispensable in modern radiology, as they provide essential diagnostic information during CT and MR examinations. The use of iodinated contrast media (ICM)

and gadolinium-based contrast agents (GBCAs) is generally considered safe, although adverse drug reactions, including hypersensitivity reactions and ICM-induced nephrotoxicity, are possible. Traditionally, post-contrast acute kidney injury (PC-AKI) has been recognized as one of the major causes of

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AKI in hospitalized patients, with an incidence of 0.6–30% [1-3]. However, recent well-designed studies and meta-analyses that adjusted for other risk factors have suggested that the nephrotoxicity of ICM is overestimated [4-7].

Well-known risk factors for PC-AKI include impaired renal function, diabetes mellitus, cardiovascular disease, periprocedural hemodynamic instability, and nephrotoxic drugs [7,8]. PC-AKI is also associated with the type and route of administration of ICM. In contrast with high-osmolar ICMs, low- to iso-osmolar ICMs are less nephrotoxic [9-12]. Intra-arterial injections have been associated with a higher incidence of PC-AKI than intravenous administration [13]. Multiple doses of ICM within a short time interval have been proposed as another risk factor for PC-AKI [14].

Repeated ICM- or GBCA-enhanced examinations within a short interval are sometimes inevitable, particularly in emergent situations. For example, a patient with suspected acute or hyperacute stroke usually undergoes perfusion CT with CT angiography to determine intra-arterial thrombolysis, and intra-arterial thrombolysis also requires ICM administration, along with follow-up MR or CT examinations. A minimum dosing interval of 24 hours for repeated administrations of ICM has been suggested depending on the half-life of ICM [15]. With normal renal function, the half-life of ICMs is 1–2 hours; GBCAs have a similar half-life (1.3–1.6 hours). Therefore, most contrast media are eliminated before 24 hours [15-20]. Currently, the American College of Radiology (ACR) guidelines do not specify a threshold. On the other hand, the European Society of Urogenital Radiology (ESUR) guidelines recommend ensuring at least a 4-hour interval between repeated exposures to ICM [15,21]. Nevertheless, the renal safety of repeated exposure to ICM or GBCA within a short interval has rarely been investigated. Therefore, we aimed to investigate whether repeated intravascular administration of ICM or GBCA within a short interval was associated with an increased risk of AKI in patients recently exposed to ICM.

## MATERIALS AND METHODS

This retrospective cohort study received Institutional Review Board approval, and the requirement for informed consent was waived (IRB No. 1802-015-919).

### Study Population

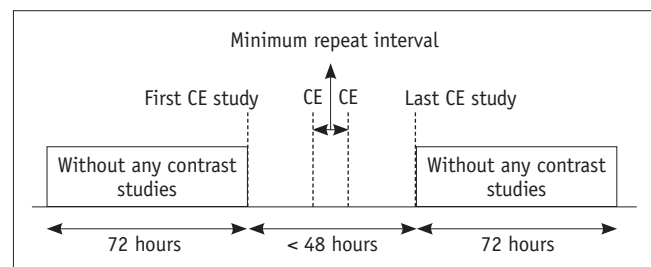
We retrospectively searched the medical records of

692 consecutive patients suspected of acute stroke who underwent standardized ICM-enhanced perfusion brain CT from June 2015 to December 2017. As it was possible for patients to undergo multiple contrast-enhanced examinations before and after perfusion brain CT, we applied the following criteria to determine patient eligibility: 1) availability of baseline serum creatinine level before the first contrast-enhanced examination in the time window of interest (Fig. 1), 2) follow-up renal function tests within 72 hours after the last contrast-enhanced examination in the time window of interest (Fig. 1), and 3) satisfying the time-window criteria as shown in Figure 1.

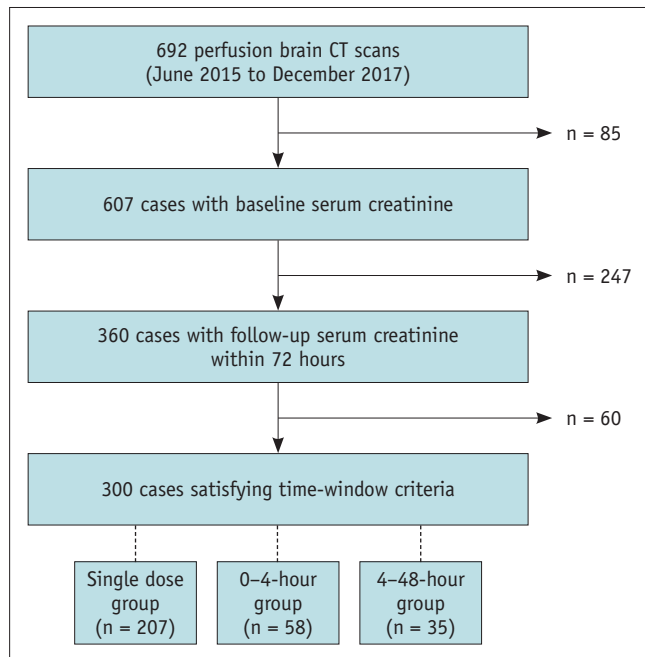
Eighty-five patients without baseline serum creatinine information were excluded, as well as 247 patients without follow-up renal function tests. A total of 300 patients (mean age  $\pm$  standard deviation, 68.5  $\pm$  8.1 years; 131 male and 169 female) were finally included in this study (Fig. 2). The patients were divided into three groups according to the 'minimum repeat interval' as shown in Figure 1: single-dose group (i.e., no repeat exam), 0–4-hour group (i.e., minimum repeat interval less than 4 hours), and 4–48-hour group (minimum repeat interval of 4 to 48 hours) (Fig. 2). As renal safety issues mostly arise with the use of ICMs, our study primarily focused on the analysis of repeat administrations of ICM. However, we have also performed additional analysis considering both ICM and GBCA.

### CT and MR Examinations

At our institution, iomeprol is routinely used for perfusion brain CT scans, making it the most common intravenous



**Fig. 1. Time-window criteria.** The time window criteria in our study were defined as follows: 1) the time interval between the first and last contrast medium administrations was within 48 hours; 2) no other contrast medium study was performed within 72 hours before the first contrast medium administration; and 3) no other contrast medium study was performed 72 hours after the last contrast medium injection. The first and the last contrast medium administrations represent the same examination if the patient did not undergo repeat contrast injections (i.e., single dose). Minimum repeat interval applies only when the patient underwent multiple contrast injections in the time window of interest. It is defined as the shortest interval of any adjacent contrast medium injections. CE = contrast-enhanced



**Fig. 2 Flow diagram for the study design.** The patient numbers for single-dose group, 0–4-hour group, and 4–48-hour group are according to the administrations of iodinated contrast media alone, ignoring gadolinium-based contrast agent.

ICM used in this study group. Other ICMs, including iohexol, ioversol, iopamidol, and iobitridol, were also administered for scans of other body parts or in patients with a history of hypersensitivity to iomeprol. For intra-arterial ICM, however, iopamidol was primarily administered, and ioversol and iobitridol were administered in exceptional cases similar to those that necessitated the use of other intravenous ICMs. We reviewed the type and volume of ICM administered for each CT examination.

Most of the MR examinations were for the brain, except the few cases for the abdominal, pelvic, and musculoskeletal areas. Either gadoterate meglumine or gadobutrol were used for contrast-enhanced MR studies. Contrast-enhanced T1-weighted MR imaging was performed after the intravenous administration of GBCA at a dose of 0.1 mmol/kg of body weight.

### Investigated Variables

Demographic information (age, sex, and body mass index), type and route of contrast medium administration (intravenous ICM, intra-arterial ICM, and GBCA), and serum creatinine levels were extracted from the electronic medical records. In addition, patient comorbidities (myocardial infarction, chronic heart failure, peripheral vessel disease, chronic pulmonary disease, dementia,

peptic ulcer, rheumatoid disease, cerebrovascular disease, paralysis, diabetes mellitus, chronic kidney disease, cancer, liver disease, and AIDS), recent history of potentially nephrotoxic medication (antibiotics, vancomycin, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, chemotherapeutic drugs, COX-2 inhibitors, loop diuretics, hydrochlorothiazide, immunosuppressant agents, sirolimus, nonsteroidal anti-inflammatory drugs [NSAIDs], and statins), and the use of N-acetylcysteine as a preventive measure were assessed. We calculated the Charlson comorbidity index [22,23].

### Definition of AKI

The definition of PC-AKI is quite different from that of AKI, although there is no solid basis for this discrepancy, as pointed out in the Acute Kidney Injury Network guideline [24]. For consistency with previous studies on PC-AKI, we defined AKI as an increase in serum creatinine by 0.3 mg/dL or 25% above the baseline value within 72 hours without an alternative etiology; this is a widely accepted definition of PC-AKI [7,20,25]. In patients who underwent multiple contrast-enhanced examinations, the occurrence of AKI was observed within the time window from the first exposure to contrast medium to 72 hours after the last exposure to contrast medium.

### Statistical Analysis

The Mann-Whitney U test (continuous variables) or the Fisher's exact test (categorical variables) was used for univariable analyses, and variables with *p* values less than 0.1 were selected as potential confounding factors in the subsequent multivariable logistic regression analysis conducted to examine the association between repeated contrast medium administration (independent variable) and PC-AKI (dependent variable). The odds ratio (OR) for the 0–4 and 4–48 groups was calculated considering the single-dose group as the reference. Statistical analysis was performed using SPSS version 25 (IBM Corp.).

## RESULTS

### Baseline Characteristics

In our study population, 47.3% of the patients had at least one additional contrast medium administration within 48 hours (Table 1). Ninety-three patients (31.0%) had additional administration of intravenous or intra-arterial ICM, while 79 patients (26.3%) underwent GBCA-

**Table 1. Distribution of the Number of Repeated Contrast Medium Administrations within 48 Hours**

	Total Times of ICM (IV + IA) within 48 Hours			
	1	2	3	4
Total times of GBCA (IV) within 48 hours				
0	158 (52.7)	53 (17.7)	7 (2.3)	3 (1.0)
1	48 (16.0)	25 (8.3)	3 (1.0)	0 (0)
2	1 (0.3)	2 (0.7)	0 (0)	0 (0)

Data are number of patients (%). GBCA = gadolinium-based contrast agent, IA = intraarterial, ICM = iodinated contrast media, IV = intravenous

enhanced MRI examination. When only ICM administrations were counted, 207 (69.0%), 58 (19.3%), and 35 (11.7%) patients were classified into the single-dose group, 0–4-hour group, and 4–48-hour group, respectively (Table 2). The mean amount  $\pm$  standard deviation of ICM used was 147.2  $\pm$  139.9 mL, and the mean volume  $\pm$  standard deviation of intravenous administrations of GBCA was 6.1  $\pm$  1.2 mL.

#### AKI and Baseline Renal Functions

When ICM administration was only considered, AKI occurred in 15 of 207 patients (7.2%; 95% confidence interval [CI], 3.7% to 10.8%) in the single-dose group, 8 of 58 patients (13.8%; 95% CI, 4.9% to 22.7% in the 0–4-hour group, and 3 of 35 patients (8.6%; 95% CI, 0% to 17.8%) in the 4–48-hour group (Table 2). The mean baseline estimated glomerular filtration rates (eGFRs)  $\pm$  standard deviation were 80.1  $\pm$  29.2, 75.7  $\pm$  18.5, and 70.5  $\pm$  51.6 mL/min/1.73 m<sup>2</sup> in the single-dose, 0–4-hour, and 4–48-hour groups, respectively (Table 2).

#### Association between AKI and Repeated Exposure to Contrast Medium

Univariable analyses found no significant difference in the incidence of AKI following the single and multiple ICM administrations ( $p = 0.783$  and  $p = 0.454$  for 0–4-hour and 4–48-hour groups, respectively). In the univariable analyses, baseline eGFR ( $p = 0.017$ ), myocardial infarction ( $p = 0.013$ ), congestive heart failure ( $p = 0.024$ ), diabetes mellitus ( $p = 0.046$ ), cancer ( $p = 0.084$ ), and the use of antibiotics ( $p = 0.003$ ), loop diuretics ( $p = 0.001$ ), NSAIDs ( $p = 0.021$ ), and statins ( $p = 0.062$ ) were selected as potential confounding factors in the subsequent multivariable logistic regression analysis (Table 2). Finally, the multivariable analysis showed the absence of a significant association between repeated contrast medium injections and the occurrence of PC-AKI ( $p = 0.147$ , OR =

2.217, 95% CI for OR: 0.756, 6.504 for 0–4-hour group; and  $p = 0.570$ , OR = 0.644, 95% CI for OR: 0.141–2.943 for the 4–48-hour group) (Table 3). In addition, when the analysis was extended with considerations of both ICM and GBCA, repeated contrast medium administration within a short interval did not increase the risk of PC-AKI (Table 4).

## DISCUSSION

PC-AKI has long been a concern in radiology, although some recent reviews have questioned the causal association between ICM and AKI [5]. The renal safety of shortly repeated ICM injections has not been investigated much, and previous reports on this issue have demonstrated controversial results [26–33]. Furthermore, conflicting evidence exists on the renal safety of GBCAs [34], and the mixed use of ICMs and GBCAs within a short interval remains unclear.

The primary pathophysiological pathway of PC-AKI involves impaired renal perfusion. Complex mediators triggered by ICM cause hypoxic damage to the renal medulla, which leads to acute tubular necrosis [35]. GBCAs, despite having entirely different chemical structures, share similar characteristics with ICM, including hypertonicity and renal clearance properties. It can be inferred that the pathophysiology of the nephrotoxicity of GBCAs may be similar to that of the nephrotoxicity of ICMs [34], as renal glomerular filtration is almost the exclusive mechanism underlying GBCA elimination [19,34]. Additionally, the release of free gadolinium ions in patients with decreased renal function may be another cause of nephrotoxicity [34,36].

It has been conventionally suggested that patients who have recently been exposed to ICM wait for 24 hours for the next dose. As ICMs and GBCAs have a half-life shorter than 2 hours, only 25% are left after 4 hours, and these agents are almost eliminated after 24 hours. The ACR guideline points out this ambiguity; therefore, it does not endorse a specific time interval or threshold volume for an additional contrast medium [15]. In the ESUR guidelines, different dosing intervals for different contrast media are suggested, as follows: 1) between two ICM injections: 4 hours in patients with a GFR  $> 30$  mL/min/1.73 m<sup>2</sup> and 48 hours in patients with a GFR of  $< 30$  mL/min/1.73 m<sup>2</sup>; 2) between two GBCA injections: 4 hours in patients with a GFR of  $> 30$  mL/min/1.73 m<sup>2</sup> and 7 days in patients with a GFR of  $< 30$  mL/min/1.73 m<sup>2</sup>; 3) between ICM and GBCA injections: 4

hours in patients with a GFR of > 30 mL/min/1.73 m<sup>2</sup> and 7 days for patients with a GFR of < 30 mL/min/1.73 m<sup>2</sup> [21].

Our study sheds light on this ambiguity. In the general population, analyzing this issue is challenging because repeated contrast medium administration within a short

time interval is uncommon, except for emergent situations. In patients suspected of an acute or hyperacute stroke, however, GBCA, intravenous ICM, and intra-arterial ICM are frequently administered shortly after each other within a limited time window. When neurological symptoms are at

**Table 2. Comparison between Single and Multiple Iodinated Contrast Medium Administrations**

Parameter	Single-Dose Group	0–4-Hour Group	4–48-Hour Group	<i>P</i>
Number of patients	207	58	35	
Age, years	67.6 (59.0, 76.8)	69.1 (61.2, 76.7)	70.6 (60.6, 74.9)	0.214*
Sex				
Male	83 (40.1)	28 (48.3)	20 (57.1)	0.410
Female	124 (59.9)	30 (51.7)	15 (42.9)	
Baseline renal function				
Baseline eGFR, mL/min/1.73 m <sup>2</sup>	80.1 (62.8, 93.3)	75.7 (62.3, 89.4)	70.5 (50.0, 102.6)	0.017*
CKD stage				
1–2	161 (77.8)	45 (77.6)	22 (62.9)	
3	39 (18.8)	12 (20.7)	7 (20.0)	
4–5	7 (3.4)	1 (1.7)	6 (17.1)	
Acute kidney injury comorbidity	15 (7.2)	8 (13.8)	3 (8.6)	
Myocardial infarction	19 (9.2)	4 (6.9)	2 (5.7)	0.013
Congestive heart failure	14 (6.8)	11 (19.0)	3 (8.6)	0.024
Peripheral vascular disease	24 (11.6)	10 (17.2)	7 (20.0)	1.000
Chronic pulmonary disease	15 (7.2)	10 (17.2)	4 (11.4)	0.489
Dementia	30 (14.5)	5 (8.6)	5 (14.3)	0.223
Peptic ulcer	10 (4.8)	3 (5.2)	2 (5.7)	1.000
Cerebrovascular disease	163 (78.7)	55 (94.8)	26 (74.3)	1.000
Paralysis	6 (2.9)	0 (0)	2 (5.7)	0.146
Diabetes mellitus	64 (30.9)	14 (24.1)	17 (48.6)	0.046
CKD	21 (10.1)	6 (10.3)	8 (22.9)	0.205
Cancer	68 (32.9)	18 (31.0)	16 (45.7)	0.084
Metastatic cancer	27 (13.0)	7 (12.1)	8 (22.9)	0.384
Liver disease	25 (12.1)	6 (10.3)	4 (11.4)	0.751
Drug				
Antibiotics	87 (42.0)	34 (58.6)	23 (65.7)	0.003
Vancomycin	8 (3.9)	4 (6.9)	5 (14.3)	0.649
ARBs	23 (11.1)	7 (12.1)	5 (14.3)	0.523
Chemotherapy	12 (5.8)	0 (0)	2 (5.7)	0.111
Loop diuretics	57 (27.5)	26 (44.8)	12 (34.3)	0.001
Hydrochlorothiazide	7 (3.4)	1 (1.7)	0 (0)	0.146
Immunosuppressant	9 (4.3)	0 (0)	2 (5.7)	0.245
NSAIDs	118 (57.0)	36 (62.1)	18 (51.4)	0.021
Statins	82 (39.6)	27 (46.6)	13 (37.1)	0.062
N-acetylcysteine	24 (11.6)	19 (32.8)	12 (34.3)	0.109
ICM volume within 48 hours				
Volume, mL	73.7 (19.1)	379.6 (144.3)	205.6 (93.7)	0.080

Unless otherwise specified, data are numbers of patients with percentages in parentheses. Data for age and baseline eGFR are presented as median values with interquartile ranges in parentheses and data for ICM volume within 48 hours as means with standard deviations in parentheses. *p* values are the result for the univariable analysis, which were analyzed either by the Mann-Whitney test (\*) for continuous variables or the Fisher exact test for categorical variables. 0–4 hours and 4–48 hours represent minimum dosing interval of the multiple contrast media administrations. ARBs = angiotensin II receptor blockers, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ICM = iodinated contrast media, NSAIDs = nonsteroidal anti-inflammatory drugs



**Table 3. Multivariable Analyses for the Association between Acute Kidney Injury and Repeated Exposures to Iodinated Contrast Medium**

	Odds Ratio	95% Confidence Interval	<i>P</i>
Single-dose group	Reference		
0–4-hour group	2.217	0.756–6.504	0.147
4–48-hour group	0.644	0.141–2.943	0.570

Variables with  $p < 0.1$  in the univariable analyses were included in the multivariable logistic regression analyses.

**Table 4. Multivariable Analyses for the Association between Acute Kidney Injury and Repeated Exposures to Iodinated Contrast Medium or Gadolinium-Based Contrast Agent**

	Odds Ratio	95% Confidence Interval	<i>P</i>
Single-dose group	Reference		
0–4-hour group	1.246	0.434–3.573	0.683
4–48-hour group	0.275	0.064–1.190	0.084

Variables with  $p < 0.1$  in the univariable analyses were included in the multivariable logistic regression analyses.

stake, a short dosing interval is recommended due to the temporal urgency of the situation, as is well-emphasized by “time is brain” [37]. With that in mind, we limited the study population to patients who underwent perfusion brain CT.

Additional exposure to ICM or GBCA within a short interval was not associated with AKI in this population, which mostly had a GFR of  $> 30$  mL/min/1.73 m<sup>2</sup>. In line with this, concerns about the total volume of ICMs within a short interval can be addressed. Repeated administration of contrast medium at short intervals can increase the volume of the contrast medium in the body. The risk of PC-AKI increased with larger volumes of intra-arterial ICM with a single injection, whereas the volume of intravenously injected ICM has not been reported to be an independent risk factor for PC-AKI [38]. The volume of ICM to be administered via intra-arterial injection was recommended to be below 100 mL in patients with an eGFR  $< 60$  mL/min/1.73 m<sup>2</sup> [39]. In our population, the total volume of contrast medium was generally 150 mL or less, while the volume of intra-arterial ICM was generally 60 mL or less. In addition, when analyzed as an independent variable, the volume of ICM demonstrated no statistical correlation with the risk of PC-AKI ( $p = 0.080$ ), which was omitted from our multivariable logistic regression model to avoid collinearity. The lack of an association between repeated exposure to contrast medium and AKI may be attributed to the relatively small volume of ICM (both total and intra-arterial)

administered in this population.

Interestingly, even an additional exposure to ICM or GBCA within 4 hours did not increase the risk of AKI beyond the recommendations of the ESUR guidelines, although the baseline eGFR should be considered. In this study, approximately three-quarters of the study population had a baseline eGFR of 60 mL/min/1.73 m<sup>2</sup> or higher. The number of patients with a baseline eGFR between 30 and 60 mL/min/1.73 m<sup>2</sup> was relatively small. Considering the distribution of the baseline eGFR values, our results may not be interpreted as fully confirming the safety of repeated ICM administration, particularly for patients with a baseline eGFR between 30 and 60 mL/min/1.73 m<sup>2</sup> who are potentially vulnerable to PC-AKI. Further studies with a well-organized cohort or randomized studies are warranted.

AKI occurred in 8.7% of patients in our study, which is a higher proportion than those reported in recent studies that used a single dose of contrast medium [4,7]. The higher proportion is attributable to the older age and more comorbidities in our study group than in the general population. Furthermore, the study population mostly comprised hospitalized patients since the inclusion criteria required follow-up renal function testing. The use of complex medications for managing stroke and underlying comorbidities may also have contributed to the high frequency of AKI.

Our study had several other limitations. First, this study analyzed a single-center retrospective cohort with a relatively small sample size. Second, a considerable proportion of the cohort population was excluded because of a lack of baseline or follow-up serum creatinine levels. Third, since it was not feasible to measure the exact concentrations of contrast medium used for the interventional radiological procedures, rough estimations were made based on the billing records, and the dose of contrast medium used was accounted in units of bottles (50 cc). Fourth, we could not quantitatively analyze intravenous hydration, which may be protective against AKI. Fifth, our results cannot exclude the possibility of subclinical nephrotoxicity from the repeated administration of contrast media due to a lack of diagnostic tools for detecting subclinical nephrotoxicity [40].

In conclusion, repeated exposure to iodinated or GBCA within a short interval did not increase the risk of AKI in our study patients suspected of acute stroke with a baseline eGFR of 30 mL/min/1.73 m<sup>2</sup> or higher.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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### Author Contributions

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