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Investigation on Risk Factors of Acute Kidney Injury after Iodine Contrast Agent CT Examination

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ABSTRACT

The objective of this study was to explore the risk factors of contrast-induced acute kidney injury (PC-AKI) in patients examined by computed tomography (CT) with iodine contrast agent. A retrospective analysis was made on 1591 patients (809 cases in contrast-enhanced CT group and 782 cases in plain CT group) who underwent CT examination in Yanbian University hospital from May 2012 to May 2022. Binary logistics regression analysis was used to determine the risk factors of PC-AKI in different examination methods. There was no significant difference compared with that in contrast-enhanced CT group (4.90%, P>0.05). The serum creatinine, uric acid and urea nitrogen in the contrast-enhanced CT group decreased, while cystatin C and eGFR increased after the examination, with statistical significance (P<0.05). But there was no significant difference in creatinine, urea, urea nitrogen, cystatin C and eGFR between the two groups at the same time point (P>0.05). The incidence of eGFR 5 patients in the two groups was higher than that in other stages, and the difference was statistically significant (P<0.05). Excessive serum creatinine before CT, diabetes, and female gender are independent risk factors for secondary AKI (OR>1, P<0.05). The incidence of PC-AKI after enhanced CT examination is low, and it has nothing to do with intravenous contrast agent. It is obviously unreasonable to blame iodine contrast agent for PC-AKI, and the risk of PC-AKI will increase only in patients with eGFR5. Attention should be paid to patients with high serum creatinine, diabetes before examination or female patients to avoid acute kidney injury after examination.

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SP conducted the experiments in this study. CY contributed to the design and interpretation of the current study and wrote the article.

Key words
Iodine contrast agent, CT, Acute kidney injury, Risk factors, Incidence

INTRODUCTION

The application of iodine contrast agent in the process of computed tomography (CT) is more helpful to distinguish and identify the density difference between different vascular tissues, and can help the classification of tumor tissues (Castaldo *et al*., 2019). Affected by the deepening of aging development in China, the number of elderly and chronic kidney disease (CKD) patients using iodine contrast agent for enhanced CT examination is increasing year by year. The application of iodine contrast agent will increase the risk of kidney injury. Under the objective environment of increasing enhanced CT examination, it is necessary to accurately assess the risk of contrast-induced nephropathy (CIN) in patients and the direct relationship between acute kidney injury (AKI) and clinical application of iodine contrast agent. A German study (Frank *et al*., 2021) even directly questioned the causal relationship between contrast media (CM) and AKI. In this study, 4% of patients suffered from AKI, and 77.5% of them had non-contrast-related renal damage. At present, there is no consensus on the influence of baseline renal function on the incidence of post-contrast acute kidney injury (PC-AKI) (Hinson *et al*., 2019; Kene *et al*., 2021). The purpose of this study is to evaluate the incidence of PC-AKI in hospitalized patients and its relationship with intravenous contrast agent, and to understand the risk factors of AKI, thus providing theoretical basis for clinical doctors to rationally apply enhanced CT and improve the quality of clinical decision-making.

MATERIALS AND METHODS

A total of 1591 inpatients who underwent CT examination in our hospital from May 2012 to May 2022 were eligible to join the study if they met the following

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inclusion criteria: Age ≥ 18 years old, receiving a routine CT examination or intravenous enhanced CT examination in Yanbian University hospital, and CT scans of abdomen, pelvis and chest. Patients were excluded from the groups if: with iodine contrast agent allergy, the level of serum creatinine (SCR) before and 7 days after CT examination cannot be obtained, patients who received contrast agent through intra-artery, only through coronary artery or through both intravenous and intra-arterial routes. A total of 1591 cases were selected, including 809 cases in the enhanced CT group (male/female 551/298), with an average age of 63.66±12.46 years old, and 782 cases (male/female 483/299) in plain CT group, with an average age of 63.73±13.31 years old; there was no significant difference in baseline data such as gender and age between the two groups before matching (P>0.05) (Table I).

The basic data of patients' gender, age and nationality were extracted from electronic medical records, combined with the past medical history of diabetes, hypertension and renal insufficiency. Serum creatinine, urea nitrogen, uric acid, cystatin C and estimated glomerular filtration rate (eGFR) levels before CT examination and 7 days after CT examination were extracted from clinical serological examination result. According to the serum creatinine level before CT scan, eGFR was calculated by CKD-EPI equation (Li *et al*., 2011). Based on the preoperative eGFR level, patients were divided into 6 stages: eGFR 1 (90-120ml/min/1.73^2), eGFR 2 (60-89ml/min/1.73^2), eGFR 3a (45-59ml/min/1.73^2), eGFR 3b (30-44ml/min/1.73^2), eGFR 4 (15-29ml/min/1.73^2) and eGFR 5 (<15ml/min/1.73^2); the patients having acute kidney injury 7 days after the examination were checked from the electronic medical record.

AKI is subject to the definition updated in KDIGO guideline (Stevens and Levin, 2013): When other possible causes of AKI are excluded, creatinine rises by no less than 0.3 mg/dL (26.5 ≥/L) within 48 hours, or rises more than 50% of the baseline within 7 days, or the urine volume is less than 0.5mL/kg/h for more than 6 h.

According to the difference of CT examination methods, patients were divided into plain scan samples and contrast-enhanced CT samples. To eliminate the influence of confounding factors on the results of this study, the caliper matching method of propensity score matching method was used, and statistical model was applied to calculate propensity score. According to the grouping variables, patients receiving the plain and enhanced CT were separated, and the corresponding matching tolerance was set to 0.02. 1 sample was selected from the enhanced samples, and compared with all the individuals in the plain CT group. N samples with the difference of propensity score within the caliper value were kept for matching.

Table I. Baseline data of patients before and after propensity score matching (PSM).

Item		Before PSM				After PSM			
		Plain group (n=809)	Enhanced group (n=782)	X^2/t	P	Plain group (n=735)	Enhanced group (n=735)	X^2/t	P
Age (M±S)		63.73±13.31	63.66±12.46	0.118	0.906	63.15±13.26	63.75±12.60	-0.881	0.378
Gender (n, S)	Male	483(61.8)	511(63.2)	0.332	0.564	453	459	0.104	0.747
	Female	299(38.2)	298(36.8)			282	276		
Nationality (n, S)	Han	357(45.7)	415(51.3)	5.083	0.079	344	361	1.229	0.541
	Korean	405(51.8)	376(46.5)			376	356		
	Other	20(2.5)	18(2.2)			15	18		
Diabetic (n, S)		173(22.1)	161(19.9)	1.183	0.277	151	152	0.004	0.949
Non-diabetic (n, S)		609(77.9)	648(80.1)			584	583		
Hypertensive (n, S)		234(29.9)	222(27.4)	1.198	0.274	214	213	0.003	0.954
Non-hypertensive (n, S)		548(70.1)	578(72.6)			521	522		
Renal dysfunction (n, S)		64(8.2)	718(91.8)	1.103	0.294	49	54	0.261	0.609
Non renal dysfunction (n, S)		55(6.8)	754(93.2)			686	681		
Preoperative renal function staging (n)	1	342	361	7.486	0.187	342	329	5.242	0.387
	2	151	151			151	139		
	3a	84	106			84	82		
	3b	87	81			82	81		
	4	70	50			31	45		
	5	48	60			45	59		

The samples were matched one by one, and the unmatched samples were eliminated. After that, the process of propensity score matching was completed. The groups that completed the matching process were named as plain CT group and enhanced CT group.

All the data in this study were statistically analyzed by SPSS 24.0 software. The counting data were expressed by frequency or percentage, and the measuring data were expressed by mean standard ± deviation. The measuring data between the two groups were compared by independent sample t test, and the counting data were compared by chi-square (X2) test. P<0.05 indicates that the difference is statistically significant. Propensity score matching was used to reduce potential selection bias and other confounding factors.

RESULTS

Before and after PSM, there was no significant difference in the distribution of gender, age, nationality and complications (diabetes, hypertension and renal insufficiency) between the plain CT group and the enhanced CT group (P > 0.05). But after PSM, the difference between the plain CT group and the enhanced CT group was more balanced, and the difference of propensity score was lower (Table I).

There were 38 patients with secondary AKI in plain CT group (Fig. 1A), and the incidence of AKI was 5.17%, which was not statistically significant compared with that of 36 patients in enhanced CT group (4.90%) (P>0.05). The serum creatinine, uric acid and urea nitrogen in the contrast-enhanced CT group (Fig. 1B) decreased, while cystatin C and eGFR increased after the examination, with statistical significance (P<0.05). However, there was no significant difference in creatinine, urea, urea nitrogen, cystatin C and eGFR levels between the two groups at the same time point (P>0.05) (Table II).

Patients with secondary AKI in the two groups mainly suffered from eGFR5, the incidence of which was 47.37% in plain CT group and 50.00% in enhanced CT group respectively. There was no significant difference between the two groups (P>0.05). The incidence of eGFR5 patients in the two groups was higher than that in other stages, and the difference was statistically significant (P<0.05) (Table III).

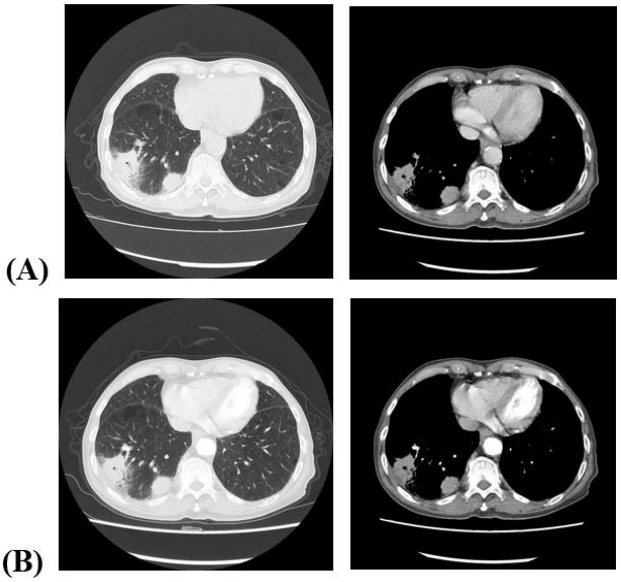

Fig. 1. CT scan results in study groups. (A) plain CT scan (Irregular soft tissue density mass in the lung, with uneven and rough edges and observable short burrs), (B) Enhanced CT scan (enhanced CT agentstinal window. The shape of blood vessels in the lesion can be seen in arterial phase, and the occupying effect of the lesion is obvious).

Table II. Renal function indexes in two groups before and after examination.

		Plain CT group (n=735)	Enhanced CT group (n=735)	X^2/t value	P value
Creatinine (mmol/L)	T1	117.60±127.95	129.34±145.97	-1.641	0.101
	T2	111.14±129.17*	120.82±139.61*	-1.381	0.168
Uric acid (mmol/L)	T1	337.05±181.20	343.08±188.29	-0.626	0.532
	T2	284.41±165.37*	286.16±165.23*	-0.204	0.839
Urea nitrogen (mmol/L)	T1	8.52±6.56	8.90±7.05	-1.053	0.293
	T2	7.97±6.21*	8.39±6.97*	-1.213	0.225
Cystatin C (mg/L)	T1	1.46±1.04	1.55±1.11	-1.605	0.109
	T2	1.46±1.02	1.57±1.10*	-1.935	0.053
eGFR (ml/min/1.73^2)	T1	77.45±34.31	74.50±35.50	1.621	0.105
	T2	80.92±34.56*	77.88±35.84*	1.658	0.098
Incidence of acute kidney injury [n(%)]		38(5.17)	36(4.90)	0.057	0.811

* P< 0.05, T1, before examination; T2, after examination.
eGFR, estimated glomerular filtration rate

Table III. Incidence of acute kidney injury between two groups of patients in different preoperative renal function stages [n (%)].

Group	eGFR1	eGFR2	eGFR3a	eGFR3b	eGFR4	eGFR5
Plain group (n=38)	3(7.89)	5(13.16)	4(10.53)	6(15.79)	2(5.26)	18(47.37)
Enhanced group (n=36)	3(8.33)	3(8.33)	4(11.11)	3(8.33)	5(13.89)	18(50.00)
X^2 value	0.127	0.086	0.086	0.391	0.757	0.051
P value	0.721	0.769	0.769	0.532	0.384	0.821

Table IV. Influencing factors of AKI after CT examination (n=1591).

Index	B	Standard error	Wald	Significance	Exp(B)	95% confidence interval	
						Lower limit	Upper limit
Urea nitrogen before CT	-0.184	0.040	20.752	< 0.001	0.832	0.769	0.901
Serum creatinine before CT	0.893	0.104	73.001	< 0.001	2.441	1.989	2.996
Diabetes	1.568	0.275	32.446	< 0.001	4.795	2.796	8.224
Gender	0.823	0.299	7.557	< 0.006	2.276	1.266	4.092
Constant	-6.237	0.716	75.785	< 0.001	0.002		

Taking the incidence of AKI as the dependent variable Y (yes=1, no=0), gender (male=1, female=2), age (specific age assignment), nationality (Han=1, Korean=2, others=3), complications (yes=1, no=0), renal function related indexes (specific data assignment), CT examination methods (plain CT=0, enhanced CT= 1) were substituted into binary logistics regression analysis as independent variables. The results showed that high serum creatinine and diabetes before CT and female gender were independent risk factors for secondary AKI (OR>1, P<0.05); the increase of pre-CT urea nitrogen was an independent protective factor for the incidence of AKI (OR<1, P<0.05) (Table IV).

DISCUSSION

In this large-scale, single-center, retrospective study with propensity score adjustment, the patients who received intravenous contrast agent were compared with those who didn't. It was found that there were 38 patients with secondary AKI in plain CT group, with an AKI incidence of 5.17%, and there were 36 patients in enhanced CT group, with an incidence of 4.90% (P > 0.05). There was no significant difference between the two groups. The incidence of AKI is consistent with many research conclusions in recent years (Moro *et al*., 2021; Werner *et al*., 2020). A survey by Barrios *et al*. (2021) showed that only one of 314 outpatients have acute kidney injury after receiving contrast agent examination, and the renal function has recovered after severe infection control. It is considered that AKI is caused by non-contrast agent-dependent causes. The reported incidence of PC-AKI in patients with acute stroke in recent years is 2.6%-7.3% (Qureshi *et al*., 2020). A giant retrospective study including 5,931,523 patients in the United States showed (Wilhelm-Leen *et al*., 2017) that the incidence of AKI was respectively 5.5% and 5.6% in patients who received CM and those who did not. Patients who receive IV-CM have a low risk of CIN, and previous literature and clinicians may overestimate the incidence of PC-AKI.

In this study, the serum creatinine, uric acid and urea nitrogen in the enhanced CT group decreased, while the cystatin C and eGFR increased, with statistical significance (P<0.05). However, there was no significant difference in creatinine, urea, urea nitrogen, cystatin C and eGFR between the two groups at the same time point (P > 0.05). In a well-controlled study (Hinson *et al*., 2017), 16,801 patients were stratified by baseline eGFR and serum creatinine for modeling analysis, which also showed that the incidence of AKI in all subgroups with eGFR before examination was similar, and receiving contrast agent did not increase the AKI risk in hospitalized patients. It is consistent with the study of Gorelik *et al*. (2019) and Chomicka *et al*. (2021) and many recent studies, challenges the long-standing hypothesis that intravenous contrast agent is related to the incidence of AKI, and questions the causal relationship between contrast agent use and kidney injury.

In the present study, it was found that the two groups of patients with secondary AKI mainly suffered from eGFR 5, the incidence of which was 47.37% in plain CT group and 50.00% in enhanced CT group respectively.

There was no significant difference between the two groups ($P > 0.05$). The incidence of eGFR 5 patients in the two groups was higher than that in other stages, and the difference was statistically significant ($P < 0.05$). It can be seen that patients with AKI are mainly patients with eGFR 5, and the incidence is significantly higher than those with other stages. With the decline of baseline renal function, the incidence of PC-AKI increased, especially in eGFR 5 group. However, there was no significant difference in the AKI risk among all baseline renal function subgroups with or without intravenous CM. Even patients with renal insufficiency did not have higher AKI risk, indicating that AKI had nothing to do with the use of contrast agent. Similar results have been obtained in emergency (Hinson *et al*., 2017; Su *et al*., 2021) or critically ill patients (Kene *et al*., 2021).

Studies have shown that nearly 4/5 CIN is non-contrast-agent-dependent. Various acute and chronic risk factors of hospitalized patients and physiological fluctuations of creatinine confuse the cause of PC-AKI, and the occurrence of AKI cannot be directly attributed to the use of contrast agents. Although animal experiments show that contrast agents may cause nephrotoxicity through direct toxicity, oxidative stress, renal vasoconstriction and other mechanisms (Kusirisin *et al*., 2020), its applicability to humans is highly controversial. From the independent risk factors observed in this study, it was not found that intravenous contrast agent would increase the AKI risk in patients undergoing CT examination, while factors such as serum creatinine and diabetes before examination and female gender would increase the risk of secondary AKI. Martinez *et al*. (2020) found that the AKI prediction model with serum creatinine as the main data can effectively predict the AKI risk. According to Rudnick *et al*. (2020), when the patient is accompanied by diabetes, the risk of secondary AKI in eGFR 5 patients will increase. As an independent risk factor for women, it is related to the special experience of pregnancy and childbirth that women need to undertake. During pregnancy, there will be kidney enlargement and urinary tract dilatation, which will have a certain impact on renal function. However, because there were no other relevant results to prove the factor female, the result error caused by data bias cannot be completely ruled out. In future, the age factor will be further matched to determine the influence of age on AKI.

CONCLUSION

The incidence of PC-AKI after enhanced CT examination is low, and it has nothing to do with intravenous contrast agent. It is obviously unreasonable to blame iodine contrast agent for PC-AKI, and the risk of PC-AKI will increase only in patients with eGFR5. Attention should be paid to patients with high serum creatinine, diabetes before examination or female patients to avoid acute kidney injury after examination.

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IRB approval

This research was carried out with the approval of University Students' Research Guidance Workshop Committee (Yanbian University and Yanbian University Hospital).

Ethical statement

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Statement of conflict of interest

The authors have declared no conflict of interest.

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