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Original Article

Differences in the effects of contrast agents on kidney injury and inflammatory response between diabetic and non-diabetic patients and their clinical significance

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Abstract

With the increasing incidence of coronary heart disease (CHD), contrast-associated nephropathy (CAN) caused by contrast agents required in coronary angiography has gradually become a clinical concern that needs to be solved urgently. At present, CAN has become one of the most common causes of hospital-acquired acute kidney injury, which seriously affects the prognosis and health of patients. How to effectively identify high-risk CAN patients and prevent the occurrence of CAN has become a hotspot of clinical research. In this study, we attempted to evaluate the effect of contrast agents on renal injury in diabetes mellitus (DM) and non-DM patients by observing some indexes of early renal injury and inflammatory factors, so as to provide a more comprehensive reference for early identification of CAN in the future. The results showed that compared with non-DM patients, contrast agents caused more obvious renal damage in DM patients and more significantly activated inflammatory responses, increasing the risk of CAN. Cystatin C (CysC), neutrophil gelatinase-associated lipocalin (NGAL), C-reactive protein (CRP), and neutrophil-lymphocyte ratio (NLR) all showed excellent predictive effects for the occurrence of CAN after coronary angiography in both DM and non-DM patients.

Keywords: Coronary heart disease, Contrast-associated nephropathy, Renal function, Inflammatory response, Diabetes mellitus.

1. Introduction

Coronary heart disease (CHD) is currently one of the most common cardiovascular diseases worldwide and has an extremely high incidence in the elderly, with the World Health Organization statistics indicating a global incidence of about 6.8% in 2022 [1]. As global aging becomes increasingly intensified, CHD has shown a rising incidence and become a global public health issue affecting people's health and life safety [2]. Coronary angiography is the gold standard for the diagnosis of CHD. Along with the increasing prevalence of CHD, contrast-associated nephropathy (CAN) caused by contrast agents used in coronary angiography has also become a clinical concern to be solved urgently [3]. The contrast agent is generally hypertonic with an iodine content as high as 37%, which is filtered by the glomeruli in its original form in the body without being absorbed by the renal tubules. Elevated concentrations of the drug in the kidneys during dehydration can lead to renal impairment and acute renal failure, resulting in CAN [4]. According to statistics, CHD is found in approximately 11 percent of patients after coronary angiography, making it the third major cause of hospital-acquired acute kidney injury [5].

Currently, there are no effective drugs to treat CAN in clinical practice. How to effectively identify high-risk CAN patients and prevent the occurrence of CAN has become a hotspot of clinical research [6]. Diabetes mellitus (DM) is one of the major risk factors for CAN, with the patient's blood sugar level being positively correlated with the occurrence of CAN [7]. But for non-DM patients, the potential risk of CAN remains unclear. At present, clinical research mostly focuses on the diagnosis and treatment of CAN or diabetic nephropathy, but less on the early damage of renal function before nephropathy [8].

Therefore, this study attempts to determine the influence of contrast agents on renal injury in DM and non-DM patients and provide more comprehensive evidence for the early identification of CAN in the future by observing some early renal injury indexes and inflammatory factors, which is a great guarantee for the safety of CHD patients undergoing coronary angiography or interventional therapy in the future.

2. Materials and methods

2.1. Study subjects

This study selected 108 CHD patients admitted to our hospital from January 2021 to December 2021, including 44 DM cases and 124 non-DM cases. The Ethics Committee of our hospital approved this study, and the guidelines of the Declaration of Helsinki were strictly followed

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throughout the research. All subjects signed informed consent by themselves.

2.2. Eligibility and exclusion criteria

Inclusion criteria: (1) Age range: 18-80; (2) Confirmed diagnosis of CHD by coronary angiography; (3) Complete preoperative and postoperative clinical data and intact renal function records. Exclusion criteria: (1) Type 1 DM and special DM (e.g. gestational DM); (2) Acute complications such as ketoacidosis and hyperosmotic nonketonic coma; (3) Severe liver dysfunction; (4) Use of contrast agents 2 weeks ago or allergies to contrast media; (5) Nephritis, renal artery stenosis, or other kidney diseases; (6) Malignant tumor, acute/chronic lung disease, urinary tract infection, electrolyte disturbance, abnormal coagulation function, thyroid dysfunction, etc.

2.3. Sample collection and detection

All patients underwent coronary angiography after admission. Before angiography, the basic information of the patients, such as age, gender, and DM course, was collected and recorded. Fasting venous blood and urine were collected before and 24 hours after angiography for the quantification of cystatin C (CysC), neutrophil gelatinase-associated lipocalin (NGAL), C-reactive protein (CRP), and neutrophil-lymphocyte ratio (NLR) by an automatic biochemical analyzer.

2.4. CAN diagnostic criteria

The occurrence of CAN was assessed with reference to the diagnostic criteria proposed by the European Society of Urogenital Radiology in 2008 [9]: CAN is diagnosed based on an Scr level ≥44.2 μmol/L or an increase of ≥25% relative to the basal value within 72 hours of contrast agent application.

2.5. Outcome measures

Differences in CysC, NGAL, CRP, and NLR between DM and non-DM patients, as well as their predictive value for CAN in DM and non-DM patients, were analyzed.

2.6. Statistical methods

Statistical analysis was carried out using SPSS26.0 software. Patients' gender, smoking history, and other count data [n(%)] were compared using the Chi-square test; CysC, NGAL, and other measurement data ($\bar{\chi}\pm s$) were compared using the independent sample t-test. The diagnostic value was analyzed by receiver operating characteristic (ROC) curves, and the diagnostic efficiency was evaluated by the area under the curve (AUC). In combined diagnosis, the Log(P) value was obtained by binary Logistic regression analysis, and then ROC curve analysis was performed. A significance level of P<0.05 was used in all analyses.

3. Results

3.1. Comparison of clinical data between DM patients and non-DM patients

By comparison, it was found that there was no significant difference in age, sex, and high blood pressure between DM and non-DM patients (P>0.05). Among them, the contrast agent dosage was (103.82±41.32) mL in DM patients and (99.29±55.51) mL in non-DM patients (Table 1).

3.2. Comparison of renal function between DM patients and non-DM patients

The two groups were not evidently different in CysC and NGAL before angiography (P>0.05). After angiography, the levels of CysC and NGAL in both groups increased, with higher levels in DM patients than in non-DM patients (P<0.05). Fig. 1

3.3. Comparison of inflammatory reactions between DM patients and non-DM patients

Similarly, no significant inter-group difference was found in CRP and NLR before angiography (P>0.05). An elevation in CRP and NLR was observed in both groups after angiography, with even higher levels in DM patients (P<0.05). Fig. 2

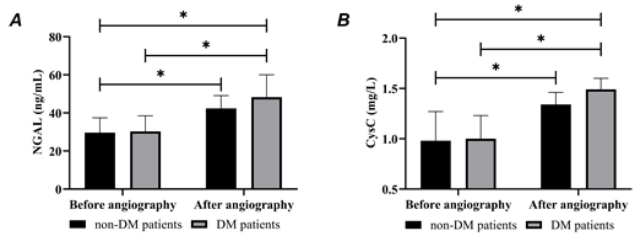

Fig. 1. Comparison of renal function. (A) Comparison of NGAL. (B) Comparison of Cys-C. *P<0.05.

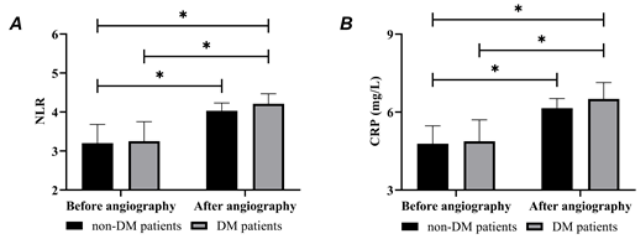

Fig. 2. Comparison of inflammatory reactions. (A) Comparison of NLR. (B) Comparison of CRP. *P<0.05.

Table 1. Comparison of clinical data.

Types of patients	Age	Sex		High blood pressure		Smoking		Contrast agent dosage (mL)
		male	female	yes	no	yes	no	
Non-DM patients (n=124)	62.22±13.27	82 (66.13)	42 (33.87)	68 (54.84)	56 (45.16)	47 (37.90)	77 (62.10)	99.29±55.51
DM patients (n=44)	65.89±12.52	32 (72.73)	12 (27.27)	36 (81.82)	8 (18.18)	13 (29.55)	31 (70.45)	103.82±41.32
t (χ^2)	1.598	0.648		2.626		2.287		1.255
P	0.112	0.421		0.120		0.150		0.211

Table 2. Comparison of the incidence of CAN.

Types of patients	CAN	non-CAN
Non-DM patients (n=124)	19 (15.32)	105 (84.68)
DM patients (n=44)	14 (31.82)	30 (68.18)
χ^2	5.599	
P	0.018	

3.4. Comparison of the incidence of CAN

According to statistics, CAN occurred in 14 patients with DM and 19 patients without DM, with a higher incidence in DM patients compared with non-CAN patients (P<0.05) (Table 2).

3.5. Predictive value of renal function indexes for the occurrence of CAN

Through binary Logistic regression analysis, the log (P) of the combined detection of CysC and NGAL for the occurrence of CAN in DM patients was obtained as 19.008+(-0.071×NGAL)+(-9.735×CysC). When the log (P) was less than 0.775, the sensitivity and specificity for predicting CAN in DM patients were 100.0% and 60.00%, respectively. In non-DM patients, the combined detection formula of CysC and NGAL was Log(P)=20.376+(-0.148×NGAL)+(-8.772×CysC), and its sensitivity and specificity in predicting the occurrence of CAN in non-DM patients were 89.47% and 64.76%, respectively (P<0.05) (Fig. 3 and Table 3).

3.6. Predictive value of inflammatory factors for the occurrence of CAN

In DM patients, the formula Log(P)=32.963+(-4.804×NLR)+(-1.786×CRP) of CRP and NLR combined detection had a sensitivity of 71.43% and a specificity of 96.67% (P<0.05) in predicting the occurrence of CAN in DM patients. In non-DM patients, the log (P) of the combined detection of CRP and NLR was 38.798+(-4.536×NLR)+(-2.953×CRP), and its sensitivity and specificity for predicting the occurrence of CAN in non-DM patients were 78.94% and 74.29%, respectively (P<0.05) (Fig. 4 and Table 4).

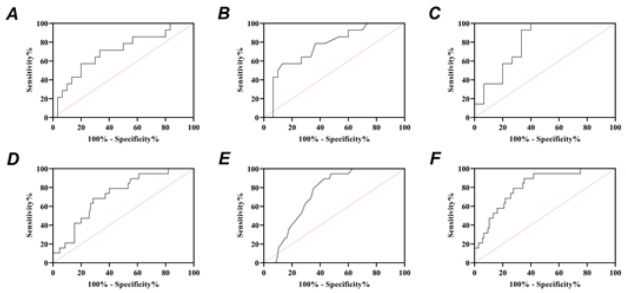

Fig. 3. ROC curves for renal function indices to diagnose the occurrence of CAN. (A) ROC curves for NGAL diagnosis of CAN occurrence (in DM patients). (B) ROC curves for CysC diagnosis of CAN occurrence (in DM patients). (C) ROC curves for the combined diagnosis of CAN occurrence by NGAL and CysC (in DM patients). (D) ROC curves for NGAL diagnosis of CAN occurrence (in non-DM patients). (E) ROC curves for CysC diagnosis of CAN occurrence (non-DM patients). (F) ROC curves for the combined diagnosis of CAN occurrence by NGAL and CysC (in non-DM patients).

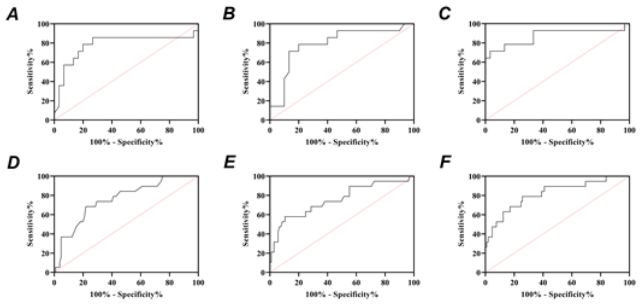

Fig. 4. ROC curves for inflammatory factor indices to diagnose the occurrence of CAN. (A) ROC curves for NLR diagnosis of CAN occurrence (in DM patients). (B) ROC curves for CRP diagnosis of CAN occurrence (in DM patients). (C) ROC curves for the combined diagnosis of CAN occurrence by NLR and CRP (in DM patients). (D) ROC curves for NLR diagnosis of CAN occurrence (in non-DM patients). (E) ROC curves for CRP diagnosis of CAN occurrence (non-DM patients). (F) ROC curves for the combined diagnosis of CAN occurrence by NLR and CRP (in non-DM patients).

4. Discussion

CAN has become one of the most common causes of hospital-acquired acute kidney injury and one of the most important complications after angiography or PCI [10]. Once CAN occurs, it can obviously prolong the hospital stay of patients, increase hospitalization expenses, and elevate the incidence of cardiovascular adverse events. In some patients, the disease can even progress to acute

Table 3. Predictive value of renal function indexes for the occurrence of CAN.

Types of patients	Parameters	NGAL	CysC	NGAL+CysC
Non-DM patients	AUC	0.705	0.758	0.800
	95%CI	0.536-0.873	0.608-0.908	0.672-0.928
	Cut-off	>48.77	>1.545	<0.775
	Sensitivity	71.43	57.14	100.0
	Specificity	66.67	86.67	60.00
	P	0.030	0.006	0.002
DM patients	AUC	0.721	0.737	0.812
	95%CI	0.609-0.833	0.647-0.828	0.717-0.906
	Cut-off	>45.070	>1.335	<0.879
	Sensitivity	68.42	94.74	89.47
	Specificity	71.43	52.38	64.76
	P	0.002	0.001	<0.001

Table. 4. Predictive value of inflammatory factors for the occurrence of CAN.

Types of patients	Parameters	NLR	CRP	NLR+CRP
Non-DM patients	AUC	0.782	0.793	0.871
	95%CI	0.602-0.962	0.641-0.944	0.730-1.000
	Cut-off	>4.165	>6.64	<0.492
	Sensitivity	85.71	78.57	71.43
	Specificity	73.33	80.00	96.67
	P	0.003	0.002	<0.001
DM patients	AUC	0.760	0.756	0.818
	95%CI	0.646-0.874	0.642-0.888	0.705-0.931
	Cut-off	>4.14	>6.51	<0.856
	Sensitivity	68.42	57.89	78.95
	Specificity	78.10	89.52	74.29
	P	<0.001	<0.001	<0.001

or chronic renal insufficiency that requires temporary or permanent dialysis, seriously threatening the survival and prognosis of patients [11]. In this study, we found a higher incidence of CAN in DM patients than in non-DM patients, confirming that DM is a risk factor affecting CAN. Its mechanism is related to changes in vascular endothelial cell activity, leukocyte adhesion, infiltration and activation, biochemical and metabolic disorders, oxidative stress, abnormal cytokine expression, etc. in DM patients [12]. Subsequently, we compared the potential effects of contrast agents on DM and non-DM patients and evaluated the incidence of CAN by early renal injury indicators and inflammatory factors, which may provide new references for future clinical prevention of CAN.

The pathogenesis of CAN is mainly summarized as follows [13]: (1) Oxygen free radicals, proinflammatory cytokines, and complement activation can cause cytoplasmic vacuolization and mitochondrial damage, leading to protein deposition and obstruction of renal tubules, thus damaging the renal tubules. (2) Contrast agents induce renal hemodynamics changes, resulting in renal medullary ischemia due to renal vasoconstriction. (3) Contrast agents cause direct toxicity to renal tubular epithelial cells. After the application of contrast agents, the production of angiotensin, vasopressin and endothelin increased, while nitric oxide decreased, resulting in damage to renal vasoconstriction and vasodilation, and leading to a decrease in renal medullary blood flow. Therefore, we mainly evaluated the difference in the CAN incidence between DM and non-DM patients from the perspective of renal injury and inflammatory responses.

The diagnostic guidelines for CAN were proposed by the European Society of Urogenital Radiology in 2008, among which Scr is an important observational index and the most classic evaluation index of renal injury [14]. However, Scr is influenced by many factors, such as age, sex, protein intake, and metabolic level, and it is mainly an indicator of glomerular damage, presenting a gradually rising level 48 hours after renal function injury [15]. Therefore, changes in Scr levels can not timely and accurately diagnose early acute renal injury. Moreover, the early renal injury caused by contrast agents mainly occurs in renal tubules [16], so the use of Scr to evaluate CAN is deficient and lagging. In this study, we mainly observed the differences in CysC and NGAL. The results showed that CysC and NGAL in both groups increased significantly after angiography, suggesting the presence of certain renal damage in both groups. While the higher CysC and NGAL levels in DM patients compared with non-DM patients suggest more obvious contrast agent-induced renal damage in DM patients, consistent with previous research results [17]. Of them, NGAL, closely related to matrix metalloproteinase 9 (MMP-9), is a special granular component discovered by Kjeldsen et al. when they studied neutrophils in 1993. Recently, it has been found that NGAL can be used as a stress protein, which can be secreted from cells under the stimulation of external harmful substances, preventing tissues and cells from apoptosis [18]. Therefore, in the event of acute organ function injury, the concentration of NGAL usually increases rapidly, which has an excellent damage assessment effect. CysC, on the other hand, has the characteristics of constant production rate and release rate into the bloodstream, free filtration through glomeruli, complete reabsorption and rapid metabolism and decomposition in proximal convoluted tubules, and no complex formation with other proteins [19]. Its serum concentration is not affected by inflammation, infection, tumor and liver function, and is independent of sex, diet, body surface area, and muscle mass, making it an ideal endogenous marker to reflect changes in GFR [20]. Therefore, CysC and NGAL are theoretically better than traditional renal injury markers in evaluating CAN. This study also showed that the combined diagnosis of CysC and NGAL had an excellent effect on predicting the occurrence of CAN in both DM and non-DM patients, with an AUC of up to 0.87 and 0.94, respectively, suggesting high reference value.

On the other hand, in the comparison of inflammatory factors, CRP and NLR of both groups increased after angiography, with more significant increases in DM patients than in non-DM patients, indicating a more pronounced inflammatory response in DM patients, which is also due to the hypercoagulability of DM patients caused by hyperglycemia [21]. Similarly, according to the ROC curve analysis, CRP and NLR showed excellent predictive value for CAN occurrence in both DM and non-DM patients, but their AUC was not as significant as the predictive performance of CysC combined with NGAL mentioned above. This may be due to the fact that the increase in CRP and NLR may not only be influenced by CAN, but also be related to factors such as puncture and underlying diseases. Nonetheless, the evaluation value demonstrated by CRP and NLR can also provide some reference for clinical eva-

luation of CAN, which can further improve the accuracy of early prediction.

However, in the follow-up study, we need to increase the number of research cases and extend the follow-up period to further evaluate the prognostic evaluation effect of CysC, NGAL, CRP, and NLR on CAN. Besides, more indicators should be included to provide a more reliable and comprehensive reference for the clinical evaluation of CAN.

5. Conclusion

Compared with non-DM patients, contrast agents cause more severe renal damage and more significantly activate inflammatory responses in DM patients, increasing the risk of CAN. CysC, NGAL, CRP, and NLR all show excellent predictive value for the occurrence of CAN after coronary angiography in DM and non-DM patients, which can provide important help for the prevention of CAN in the future.

Consent for publications

The author read and proved the final manuscript for publication.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Nanjing Tongren Hospital (No.TRLLKY2021016).

Interest conflict

The authors report no conflict of interest.

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Not applicable.

Availability of data and material

All data generated during this study are included in this published article.

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