


A risk prediction model for contrast-induced nephropathy associated with gadolinium-based contrast agents

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ABSTRACT

Objective: This is the first study to explore the risk factors for nephropathy caused by gadolinium-based contrast agents and establish a prediction model to identify high-risk patients.

Methods: A total of 1404 patients who received gadolinium-based contrast agents in our hospital were included. The participants were randomly assigned in a 7:3 ratio to the modeling and validation groups. The modeling group was divided into a contrast-induced nephropathy group and a non-contrast-induced nephropathy group. The clinical characteristics before the use of contrast agents were compared between the two groups. The risk factors for contrast-induced nephropathy were analyzed by logistic regression. A nomogram that could predict the incidence of contrast-induced nephropathy was plotted. The validation group was used to verify the predictive model.

Results: The incidence of contrast-induced nephropathy caused by gadolinium-based contrast agents was 3.92% (55/1404). The logistic stepwise regression analysis showed that sex, systolic pressure (SBP), absolute neutrophil count, albumin, fasting blood glucose level, and furosemide use were significant predictors of contrast-induced nephropathy caused by gadolinium-based contrast agents. The above predictors were then included in the nomogram construction. The area under the receiver operating characteristic (ROC) curve was 0.82 ($p < 0.001$). The specificity and sensitivity corresponding to the optimal cutoff point (0.039) based on the area under the ROC curve were 71.9% and 80.5%, respectively.

Conclusion: Sex, SBP, absolute neutrophil count, albumin, fasting blood glucose levels, and furosemide use are significant predictors of contrast-induced nephropathy caused by gadolinium-based contrast agents. Therefore, the incidence of contrast-induced nephropathy may be estimated by the prediction model established in this study before the use of contrast agents.

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Introduction

With the increasing incidence of coronary heart disease, coronary angiography and percutaneous coronary interventions have gradually improved. One study indicated that approximately 8,000,000 L of contrast agents are used worldwide every year [1]. However, with the application of contrast agents, contrast-induced nephropathy (CIN) is a growing concern. CIN is an acute renal injury after the administration of contrast agents, and it is the third most frequent cause of acute renal failure in hospitalized patients, which leads to increased medical expenses, irreversible renal injuries, prolonged hospital stays, and increased mortality [2]. The incidence of CIN varies widely in different reports. In a meta-analysis that included 29 randomized controlled trials, the incidence

of CIN varied from 2% to 25% [3]. The incidence rate depends on the diagnostic criteria of CIN, the risk factors, the amount and type of contrast agent used, the type of radiographic operation, etc. For patients with preexisting renal damage or with high-risk factors such as diabetes, the incidence can even reach 50%. At present, there is no clear treatment for CIN, so preventive measures should be actively taken to avoid its occurrence, especially in high-risk patients. Therefore, CIN has become a great concern for nephrologists, cardiologists, radiologists, angiologists, and interventionalists.

At present, some researchers have proposed different models to predict the incidence of CIN. Mehran et al. [4] proposed the CIN Mehran scoring model in 2004, and Gurm et al. [5] proposed a new CIN scoring model with 15 variables in 2013. However, most of the

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CIN data were collected from iodine-based contrast agents, while there are few studies on gadolinium-based contrast agents, and to our knowledge, there is no predictive model thus far. The KDIGO guidelines make it clear that gadolinium-based contrast agents can also cause acute kidney injuries [6]. The ESUR guidelines indicate that gadolinium-based contrast agents are more nephrotoxic at the same X-ray attenuation dose than iodine-based contrast agents. Therefore, exploring the risk factors for nephropathy caused by gadolinium-based contrast agents is an urgent clinical problem to be solved.

This study aimed to explore the risk factors for CIN caused by gadolinium-based contrast agents in contrast-enhanced magnetic resonance imaging (MRI), establish a predictive model, identify high-risk patients, implement early interventions and fill the gaps in the field regarding renal damage caused by gadolinium-based contrast agents.

Methods

From 1 January 2016 to 28 February 2019, 20,059 patients who used gadolinium-based contrast agents during hospitalization in Dongyang Hospital of Wenzhou Medical University were screened. These data were obtained using the Le Jiu scientific research

platform. The exclusion criteria were as follows: patients with missing creatinine values at baseline (defined as within 7 days before contrast agents' administration) or within 3 days after using contrast agents; patients aged < 18 years; patients with a dosage of meglumine gadopentetate \neq 15 mL; patients with missing values of more than 20%; and patients on maintenance dialysis. According to the inclusion and exclusion criteria, a total of 1404 patients using gadolinium-based contrast agents were included in this study, including 55 patients with CIN and 1349 patients with non-CIN. The other 18,655 patients were excluded, including 18,058 patients who were missing creatinine values at baseline or within 3 days after using contrast agents, 27 patients who were under 18 years old, and 29 patients whose gadolinium meglumine dosage was \neq 15 mL (Figure 1).

According to the guidelines of the European Association of Genitourinary Radiology, CIN was defined as a 25% increase in the serum creatinine value from baseline or as an increase of 0.5 mg/dL (44.2 μ mol/L) in the absolute serum creatinine value within 3 days of contrast agent administration. Ethical approval was obtained from the hospital ethics committee (2019-YX-053).

The variables included demographic and clinical data before the use of contrast agents: age, sex, height, weight, smoking history, drinking history, length of

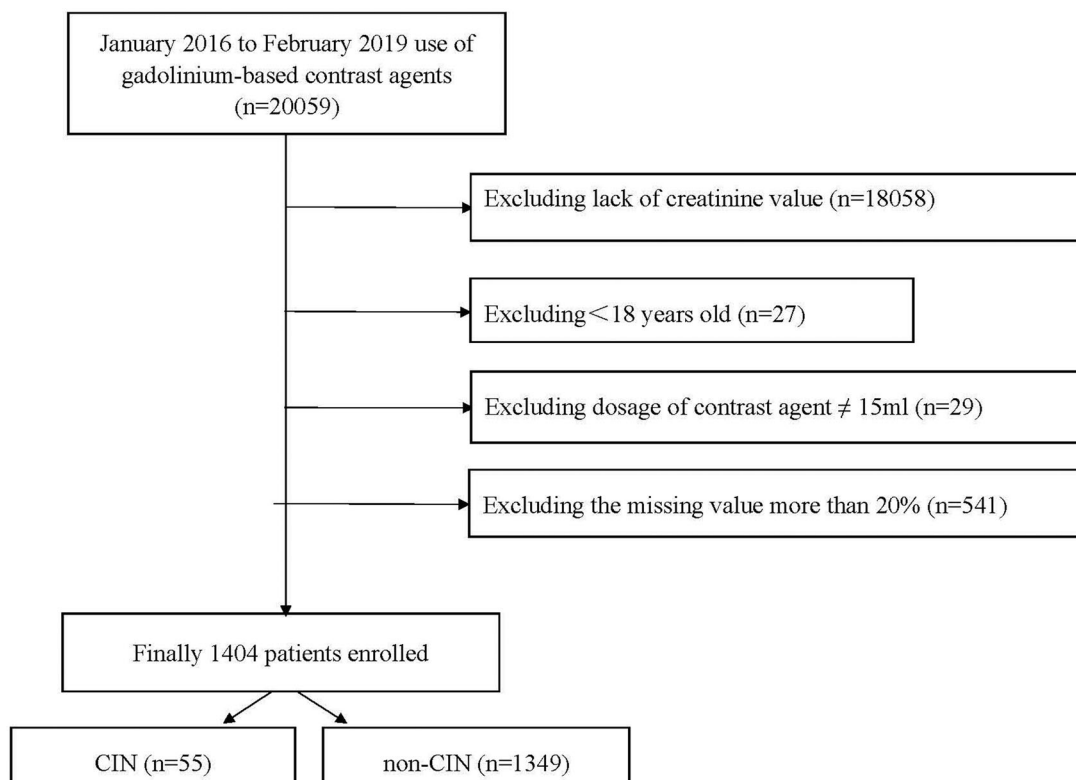


Figure 1. Flowchart of subjects included in study.

hospital stay, systolic blood pressure, diastolic blood pressure, hemoglobin level, hematocrit level, red cell distribution width, the absolute neutrophil count, the absolute lymphocyte count, creatinine level, glomerular filtration rate, uric acid levels, albumin levels, high-density lipoprotein level, low-density lipoprotein level, triglyceride level, cholesterol level, fasting blood glucose level, lactate dehydrogenase level, creatine kinase isoenzyme level, total bilirubin level, alanine aminotransferase level, aspartate aminotransferase level, sodium level, potassium level, calcium level, the international standardized ratio, Pro-B-natriuretic peptide level, ejection fraction, diabetes, heart failure, myocardial infarction, liver cirrhosis, tumor, and the use of furosemide, spironolactone, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, aspirin, celecoxib, metformin, platinum chemotherapeutic drugs, kanamycin, amikacin, and statins. The variables with missing values of more than 20% were excluded. We dealt with the missing data by using R multivariate imputation by chained equation package. The estimated glomerular filtration rate was calculated according to Chronic Kidney Disease Epidemiology Collaboration formula [7].

Statistical analyses were performed using the R language version 3.5.1 and SPSS version 26. Continuous variables were expressed as mean \pm SD, and categorical variables were expressed as actual numbers. The continuous variables with normal distribution were compared by the *t*-test. The chi-square test was used to compare the categorical variables. By using the random sampling function of R language, 1404 patients using gadolinium-based contrast agents were randomly divided into the modeling and validation groups, and the modeling group was statistically analyzed. According to the backward stepwise regression analysis, the risk factors of CIN were explored, the minimum criterion of the AIC was adopted, the prediction model was established, and the prediction map of CIN was presented in a nomogram. The clinical data of the validation group was applied for validation. The receiver operating characteristic curve (ROC) was used to evaluate the prognostic accuracy of the model.

Results

In this study, 55 patients experienced CIN (3.92%), 31 patients were male (56%), aged 64.75 ± 13.60 years, with baseline creatinine levels of 71.33 ± 78.77 μ mol/L, and glomerular filtration rates of 95.74 ± 27.26 mL/min 1.73 m². Twenty patients had a history of smoking (36%), 19 patients had a history of drinking (35%), and the length of hospital stay was 13.56 ± 7.31 days. The

systolic blood pressure was 120.20 ± 18.89 mmHg, the diastolic blood pressure was 74.44 ± 13.29 mmHg, the hemoglobin level was 115 ± 23.75 g/L, and the hematocrit level was $35.31 \pm 6.70\%$. There were 10 patients with diabetes (18%), 20 patients using furosemide (36%), and 14 patients using spironolactone (25%) (Table 1). There were significant differences in the levels of systolic blood pressure, hemoglobin, hematocrit, red cell distribution width, absolute neutrophil count, absolute lymphocyte count, the neutrophil/lymphocyte ratio (NLR), albumin, high-density lipoprotein, fasting blood glucose, furosemide use, and spironolactone use between the two groups (all $p < 0.05$).

By using the random sampling function of R language, 1404 patients using gadolinium-based contrast agents were randomly divided into a modeling group and a validation group at a ratio of 7:3. In the modeling group, there were 650 males (66%), aged 63.60 ± 14.83 years, with a baseline creatinine level of 70.37 ± 32.23 μ mol/L, and glomerular filtration rate of 92.12 ± 20.58 mL/min 1.73 m². The systolic and diastolic blood pressure were 130.08 ± 20.83 mmHg and 76.53 ± 12.27 mmHg, respectively. A total of 109 patients had diabetes (11%), 137 patients used furosemide (14%), and 108 patients used spironolactone (11%). There were no significant differences in inclusion factors between the two groups ($p > 0.05$).

In the modeling group, 44 variables, including demographic characteristics and clinical data, were compared between the CIN group and the non-CIN group (Table 2). Logistic regression was used to analyze the risk factors for CIN. Univariate logistic regression analysis showed that sex, systolic blood pressure, diastolic blood pressure, hemoglobin level, hematocrit level, red cell distribution width, absolute neutrophil count, the neutrophil/lymphocyte ratio, albumin level, high-density lipoprotein, fasting blood glucose level, furosemide, and spironolactone use had *p* values that were less than 0.1.

Using the minimum AIC criterion, the above variables were used to explore the best predictors for CIN by backward stepwise regression analysis. The results showed that sex, systolic blood pressure, the absolute neutrophil count, albumin level, fasting blood glucose level, and furosemide use were the best predictors of CIN caused by gadolinium-based contrast agents, with OR values of 0.435, 0.970, 1.086, 0.919, 1.207, and 2.310, respectively. All *p* values were < 0.05 (Table 3). A nomogram was used to intuitively and effectively present risk model results. The independent variable score was assigned according to the coefficient (Figure 2). Finally, a total score was calculated, and the higher the total

Table 1. General characteristics of the study population.

Variable	Non-CIN (n = 1349)	CIN (n = 55)	p Value
Sex			0.098
Female	444 (33%)	24 (44%)	
Male	905 (67%)	31 (56%)	
Age (year)	63.39 ± 14.67	64.75 ± 13.60	0.499
Creatinine (μmol/L)	70.80 ± 27.25	71.33 ± 78.77	0.902
eGFR (mL/min-1.73 m ²)	91.68 ± 20.55	95.74 ± 27.26	0.157
CKD			0.661
Stage 1	799 (59%)	38 (69%)	
Stage 2	444 (33%)	12 (22%)	
Stage 3	95 (7%)	3 (5%)	
Stage 4	10 (1%)	1 (2%)	
Stage 5	1 (0%)	1 (2%)	
Smoking history	570 (42%)	20 (36%)	0.386
Drinking history	489 (36%)	19 (35%)	0.797
Length of hospital stay (days)	14.29 ± 11.13	13.56 ± 7.31	0.633
SBP (mmHg)	130.79 ± 20.54	120.20 ± 18.89	<0.001
DBP (mmHg)	77.02 ± 12.61	74.44 ± 13.29	0.138
HGB (g/L)	123.63 ± 22.13	115 ± 23.75	0.012
HCT (%)	37.08 ± 6.23	35.31 ± 6.70	0.040
RDW	0.13 ± 0.02	0.14 ± 0.03	0.011
NEUT (×10 ⁹ /L)	4.93 ± 3.15	6.62 ± 4.12	<0.001
LYMPH (×10 ⁹ /L)	1.32 ± 0.74	1.07 ± 0.54	0.011
NLR	5.11 ± 5.27	7.60 ± 5.06	0.001
Albumin (g/L)	37.17 ± 5.29	34.44 ± 5.38	<0.001
HDL (mmol/L)	1.00 ± 0.37	0.85 ± 0.29	0.003
LDL (mmol/L)	2.39 ± 0.94	2.38 ± 0.79	0.936
Triglyceride (mmol/L)	1.52 ± 1.16	1.55 ± 0.99	0.875
Triglyceride/HDL	2.14 ± 4.23	2.34 ± 2.21	0.729
Cholesterol (mmol/L)	4.18 ± 1.16	4.05 ± 1.13	0.414
FBG (mmol/L)	5.75 ± 1.82	7.23 ± 4.33	<0.001
UA (μmol/L)	286.32 ± 103.64	264.49 ± 121.82	0.129
LDH (U/L)	239.55 ± 152.33	254.98 ± 256.90	0.477
TBIL (μmol/L)	24.18 ± 42.35	26.29 ± 50.01	0.719
ALT (U/L)	74.04 ± 167.95	53.56 ± 115.88	0.371
AST (U/L)	71.63 ± 153.84	63.13 ± 106.67	0.685
Sodium (mmol/L)	140.64 ± 3.92	140.26 ± 3.97	0.480
Potassium (mmol/L)	3.94 ± 0.42	3.89 ± 0.41	0.452
Calcium (mmol/L)	2.23 ± 0.17	2.24 ± 0.27	0.547
Diabetes	148 (11%)	10 (18%)	0.097
Myocardial infarction	9 (1%)	0 (0%)	0.544
Liver cirrhosis	164 (12%)	5 (9%)	0.494
Tumor	521 (39%)	24 (44%)	0.455
Furosemide	180 (13%)	20 (36%)	<0.001
Spirolactone	140 (10%)	14 (25%)	<0.001
ARB	141 (10%)	4 (7%)	0.448
ACEI	30 (2%)	1 (2%)	0.841
Aspirin	80 (6%)	2 (4%)	0.477
Celecoxib	82 (6%)	1 (2%)	0.189
Metformin	27 (2%)	1 (2%)	0.924
Platinum chemotherapeutic drugs	32 (2%)	2 (4%)	0.550
Statins	250 (19%)	8 (15%)	0.455

CIN: contrast-induced nephropathy; GFR: glomerular filtration rate; CKD: chronic kidney disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HGB: hemoglobin; HCT: hematocrit; RDW: red cell distribution width; NEUT: the absolute neutrophil count; LYMPH: the absolute lymphocyte count; NLR: neutrophil/lymphocyte ratio; HDL: high-density lipoprotein; LDL: low-density lipoprotein; FBG: fasting blood glucose; UA: uric acid; LDH: lactate dehydrogenase; TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ARB: angiotensin II receptor blockers; ACEI: angiotensin converting enzyme inhibitors.

score was, the higher the risk of CIN. The area under the ROC curve of the model (AUC) was 0.820 (95%CI 0.766–0.874, $p < 0.001$) (Figure 3). The ROC curve showed that the best cutoff value was 0.039, with a specificity of 71.9% and a sensitivity of 80.5%. The data

Table 2. Univariate logistic regression analyses of CIN.

Variable	p Value	OR	95% CI
Sex (male = 1, female = 0)	0.087	0.577	0.308–1.082
Age (year)	0.509	1.007	0.986–1.029
Creatinine (μmol/L)	0.146	1.004	0.998–1.010
eGFR (mL/min-1.73 m ²)	0.882	0.999	0.984–1.014
CKD stage	0.672	1.101	0.705–1.718
Smoking history	0.841	0.937	0.493–1.778
Drinking history	0.796	0.917	0.474–1.772
Length of hospital stay (days)	0.858	0.997	0.969–1.027
SBP (mmHg)	<0.001	0.966	0.949–0.984
DBP (mmHg)	0.059	0.975	0.949–1.001
HGB (g/L)	0.003	0.980	0.967–0.993
HCT (%)	0.010	0.939	0.895–0.985
RDW	0.010	1.147	1.033–1.273
NEUT (×10 ⁹ /L)	0.002	1.118	1.041–1.202
LYMPH (×10 ⁹ /L)	0.107	0.644	0.377–1.100
NLR	0.035	1.047	1.003–1.092
Albumin (g/L)	<0.001	0.888	0.838–0.941
HDL (mmol/L)	0.005	0.256	0.098–0.666
LDL (mmol/L)	0.998	1.000	0.721–1.389
Triglyceride (mmol/L)	0.614	1.058	0.849–1.320
Triglyceride/HDL	0.719	1.009	0.963–1.056
Cholesterol (mmol/L)	0.532	0.915	0.692–1.209
FBG (mmol/L)	<0.001	1.203	1.093–1.324
UA (μmol/L)	0.426	0.999	0.996–1.002
LDH (U/L)	0.152	0.997	0.993–1.001
TBIL (μmol/L)	0.473	0.996	0.985–1.007
ALT (U/L)	0.152	0.996	0.990–1.002
AST (U/L)	0.291	0.998	0.993–1.002
Sodium (mmol/L)	0.356	0.965	0.894–1.041
Potassium (mmol/L)	0.670	0.850	0.403–1.794
Calcium (mmol/L)	0.754	1.333	0.220–8.073
Diabetes	0.218	1.693	0.732–3.919
Myocardial infarction	0.999	<0.001	
Liver cirrhosis	0.561	0.733	0.257–2.092
Tumor	0.752	1.108	0.587–2.090
Furosemide	<0.001	3.448	1.760–6.757
Spirolactone	0.002	3.190	1.550–6.568
ARB	0.773	0.838	0.253–2.775
ACEI	0.901	0.880	0.116–6.647
Aspirin	0.837	0.859	0.202–3.655
Celecoxib	0.318	0.361	0.049–2.668
Metformin	0.930	1.095	0.144–8.347
Platinum chemotherapeutic drugs	0.998	<0.001	
Statins	0.380	0.653	0.253–1.690

CIN: contrast-induced nephropathy; GFR: glomerular filtration rate; CKD: chronic kidney disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HGB: hemoglobin; HCT: hematocrit; RDW: red cell distribution width; NEUT: the absolute neutrophil count; LYMPH: the absolute lymphocyte count; NLR: neutrophil/lymphocyte ratio; HDL: high-density lipoprotein; LDL: low-density lipoprotein; FBG: fasting blood glucose; UA: uric acid; LDH: lactate dehydrogenase; TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ARB: angiotensin II receptor blockers; ACEI: angiotensin converting enzyme inhibitors.

of the validation group were substituted into the prediction model for validation, and the AUC of the validation group was 0.723 (95%CI 0.584–0.861, $p < 0.001$) (Figure 3).

Discussion

In this study, we used an integrated scientific research platform to obtain data and set exclusion and inclusion criteria, and finally included 1404 patients using gadolinium-based contrast agents. The results showed that sex, systolic blood pressure, the absolute neutrophil

count, albumin level, fasting blood glucose level, and furosemide use were the best predictors of CIN induced by gadolinium-based contrast agents. Then, a prediction model was established, and a nomogram was used to present the risk model results. Therefore, the incidence of CIN could be estimated by the predictive model before the use of contrast agents. This study is the first to explore the risk factors for CIN caused by gadolinium-based contrast agents and construct a predictive model. The model has good sensitivity, specificity, is simple and convenient to use, and has important practical value for identifying high-risk patients.

This study showed that the incidence of CIN caused by gadolinium-based contrast agents was 3.92%. We found that specific target populations, including women and patients with hypotension and hypoalbuminemia, should avoid enhanced MRI as the preferred examination. If MRI examination for a high-risk patient is inevitable, the ESUR guidelines recommend that dialysis be performed as soon as possible after the injection of a gadolinium-based contrast agent for removal.

Table 3. Multivariate logistic stepwise regression analyses of CIN.

Variable	p Value	OR	95% CI
Sex (male = 1, female = 0)	0.016	0.435	0.221–0.859
SBP (mmHg)	0.001	0.970	0.953–0.988
NEUT ($\times 10^9/L$)	0.036	1.086	1.006–1.173
Albumin (g/L)	0.010	0.919	0.862–0.980
FBG (mmol/L)	0.001	1.207	1.085–1.342
Furosemide	0.032	2.310	1.076–4.958

CIN: contrast-induced nephropathy; SBP: systolic blood pressure; NEUT: the absolute neutrophil count; FBG: fasting blood glucose.

Gilbert et al. [8] conducted an open-label, multi-center prospective RESCUE study on patients with stage 3–4 chronic kidney disease to compare the renal safety of contrast-enhanced MRI with plain MRI in high-risk patients with meglumine gadolinium. The results showed that there was no significant difference in CIN incidence. This conclusion is consistent with our study that baseline renal function is not a predictor of CIN caused by gadolinium-based contrast agents. Chien et al. [9] conducted a retrospective

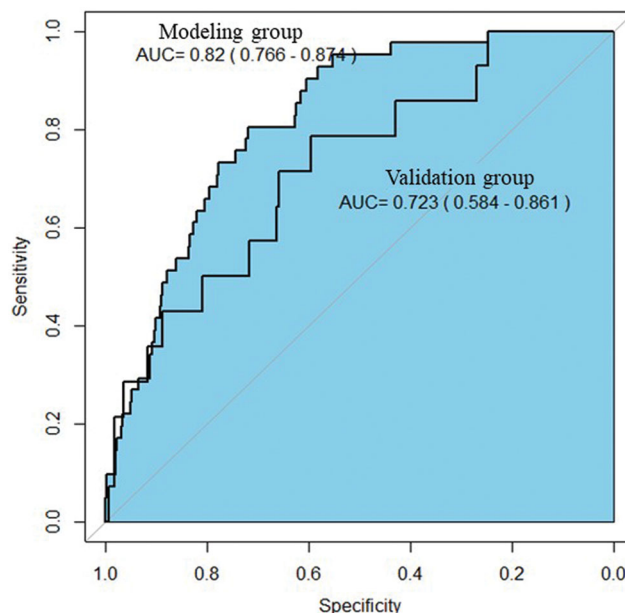


Figure 3. ROC curve for the prediction model in the modeling and validation groups.

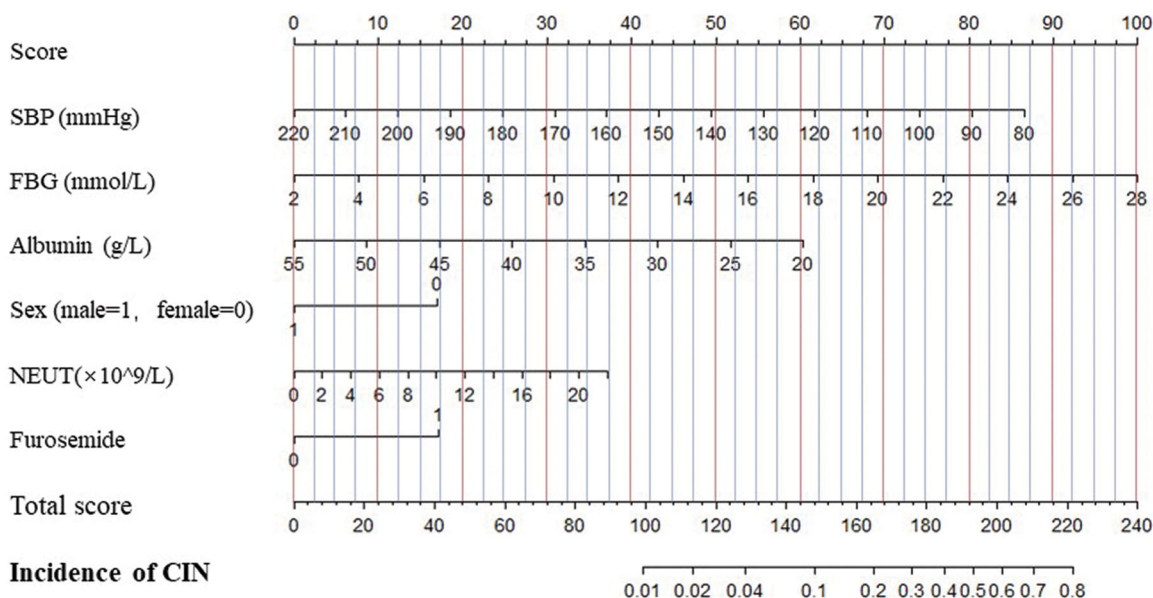


Figure 2. Nomogram for predicting CIN.

study and found that age, gender, baseline GFR, diabetes mellitus, hypertension, coronary artery disease, and liver cirrhosis were not associated with acute kidney injury (AKI) after administration of gadolinium-based contrast agents. However, it is potential AKI after administration of gadolinium-based contrast agents under sepsis condition. The American Society of Radiology no longer recommends that outpatients be screened for renal function before using macrocyclic gadolinium contrast agents.

After intravenous injection, meglumine gadopentetate was rapidly distributed to the extracellular fluid and maintained a balance between plasma and interstitial fluid, and the concentration in blood and tissue reached its peak at 1 min. It has a serum half-life of 20–100 min. Within 24 h, approximately 90% is eliminated *via* the kidney through glomerular filtration without being affected by tubular secretion. Hemodialysis can remove meglumine gadopentetate from the body. Although the toxicity of lanthanide ions is well known [10–12], the mechanism of nephrotoxicity caused by gadolinium-based contrast agents is not fully understood. Elmstahl et al. [13], in a study on pigs, injected different concentrations of iodine-based contrast agents or gadolinium-based contrast agents (meglumine gadopentetate, gadolinium diamine) through the right renal artery. Compared with iodine-based contrast agents, gadolinium-based contrast agents have a higher risk of nephrotoxicity. The main mechanisms are that hyperosmotic stress leads to erythrocyte shrinkage [14,15], endothelial cell injury, platelet accumulation, microthrombosis [16], and microcirculation disturbance. The above mechanisms of nephrotoxicity support the osmolarity-related predictors derived from this study: systolic blood pressure, albumin level, fasting blood glucose level, and furosemide use.

The present study has shortcomings. First, there was an insufficient number of cases. In particular, we formulated stringent exclusion criteria. Thus, our study may suffer from a patient selection bias. In addition, this retrospective study included single-center data from China and lacks an external validation process. Multicenter, multinational, prospective studies are still needed to justify causality and validate the accuracy of the prediction model. Subsequently, a web link or application could be created to predict the incidence of CIN due to gadolinium-based contrast agents to facilitate clinical application. Finally, the data of our study were obtained from platform, and the major limitation was the lack of specific clinical situations.

Conclusion

Sex, systolic pressure, the absolute neutrophil count, albumin level, fasting blood glucose level and furosemide use are significant predictors of CIN caused by gadolinium-based contrast agents. Therefore, the incidence of CIN may be estimated by the prediction model established in this study before the use of contrast agents.

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Disclosure statement

The authors have no conflicts of interest to disclose.

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