

## Original Article

# Risk factors of postoperative acute kidney injury in patients with complex congenital heart disease and significance of early detection of serum transcription factor Nkx2.5

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**Abstract:** Objective: This study was designed to investigate the risk factors of postoperative acute kidney injury (AKI) in patients with complex congenital heart disease (CHD) and the significance of early detection of serum transcription factor Nkx2.5. Methods: A total of 121 CHD patients admitted to the Shengli Clinical Medical College of Fujian Medical University were selected as study participants, among whom 69 patients with AKI after cardiac surgery were set as the research group (RG), and the rest of the 52 patients without AKI were set as the control group (CG). Cardiopulmonary bypass (CPB) duration, aortic occlusion time, postoperative creatinine (Cr) level and mechanical ventilation (MV) time were compared between the two groups. The expression and clinical significance of Nkx2.5 in the two groups were detected. Intensive Care Unit (ICU) residence time and total hospital stay were compared, and the risk factors were analyzed. Results: The RG presented remarkably longer CPB duration and aortic occlusion time, evidently higher postoperative Cr level and longer MV time, and observably lower Nkx2.5 level in comparison to the CG (all  $P < 0.05$ ). According to the analysis of receiver operating characteristic (ROC) curves, Nkx2.5 displayed a favorable diagnostic value in predicting the occurrence of CHD complicated with AKI. ICU residence time and total hospital stay were longer in the RG than in the CG ( $P < 0.05$ ). CPB time and aortic occlusion time were independent risk factors for AKI in CHD patients, while surgical methods and Nkx2.5 detection were independent protective factors ( $P < 0.05$ ). Conclusions: CPB time, aortic occlusion time and surgical methods, as well as Nkx2.5 detection are independent factors affecting AKI in patients with CHD. Early detection of serum transcription factor Nkx2.5 is of particular importance for clinical diagnosis of CHD patients complicated with AKI.

**Keywords:** Congenital heart disease, acute kidney injury, Nkx2.5

## Introduction

Congenital heart disease (CHD) refers to a class of cardiovascular malformations existing at birth due to abnormal development of the heart and great vessels in the fetal period [1]. In the embryonic period, abnormalities of heart structure and function can occur, such as patent ductus arteriosus, stenosis of aortic or pulmonary valve lumen, and paroxysmal tachycardia, which is a common type of heart disease in children [2]. Studies have shown that the incidence of CHD in live newborns is 0.6%-1%, which seriously threatens the growth and development of these children [3]. If left

unattended without timely treatment, CHD will cause death of some children due to complications after birth [4]. Some scholars suggest that CHD is mostly caused by virus infection, genetic factors and environmental factors during pregnancy [5], but the exact cause remains unknown. Covering a wide spectrum of diseases, CHD can be comorbid with multiple deformities, posing a serious threat to the life and safety of patients [6]. Its clinical presentation ranges from palpitations, chest tightness, asthma and fatigue, to body swelling. As to its treatment, surgery is the common choice for patients, though the best suitable approach is depended on the patient's conditions [7]. How-

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ever, recent decades have failed to witness a significant decrease in the morbidity and mortality of patients following cardiac surgery. By exploring the causes, it is found that acute kidney injury (AKI) in patients after cardiac surgery is one of the important influencing factors and also one of the high-risk complications [8].

As to AKI, it is a clinical syndrome characterized by impaired renal function in a short period of time, which is not a single disease [9]. In patients with AKI, urine volume will be reduced and abnormalities in respiration, digestion, nerve, blood and circulatory systems will occur, which will easily lead to multi-organ failure, aggravating the patient's condition, destroying the therapeutic effect, and greatly increasing the mortality after cardiac surgery [10, 11]. At present, the factors igniting AKI after cardiac surgery are not completely clear, but some scholars have proposed that it is triggered by the unstable postoperative hemodynamics of patients [12]. Other evidence shows that the kidney is damaged due to its inability to tolerate hypoxia and low blood oxygen [13]. In light of this, this study adopts a prospective analysis of the related risk factors of AKI in patients with CHD in our hospital, so as to make timely intervention and treatment in the future diagnosis and treatment of CHD, to reduce the incidence of AKI, and thus avoid any resulting death following cardiac surgery.

### Materials and methods

#### *Clinical data of patients*

A total of 121 patients with complex CHD admitted to the Shengli Clinical Medical College of Fujian Medical University from May 2014 to May 2019 were enrolled, among whom 69 patients with AKI after cardiac surgery were set as the research group (RG), and the rest of the 52 patients without AKI were set as the control group (CG). This experiment was approved by the Ethics Committee of the Shengli Clinical Medical College of Fujian Medical University, and all the enrolled participants signed an informed consent.

#### *Inclusion and exclusion criteria*

**Inclusion criteria:** Aged no more than 18 or over, all the enrolled patients were diagnosed with complex CHD by laboratory and imaging diagnosis in our hospital and underwent surgi-

cal treatment, with complete case data. Besides, patients in the RG met the criteria for identification of AKI after surgery [14]. After diagnosis, all the patients were treated in our hospital, and agreed to cooperate with the arrangements of medical staff. The informed consent form was signed by the patient's legal guardian(s).

**Exclusion criteria:** Patients comorbid with chronic kidney failure, other malignancies or multiple chronic diseases, cardiovascular and cerebrovascular diseases, organ dysfunction, drug allergy, or referred patients were excluded, as well as those who had undergone dialysis.

#### *Surgical methods*

**Total correction of tetralogy of Fallot:** All patients underwent radical surgery under general anesthesia and hypothermia circulation, and their body temperature and blood flow were adjusted according to the intraoperative collateral circulation and returned blood volume. First, a small longitudinal incision was made in the right ventricular outflow tract to excise the abnormally hypertrophic muscular bundles and part of the hypertrophic septal and parietal muscle bundles. The stenosis of the pulmonary valve or annulus was incised according to the specific condition of the patient, and the stenosis of the main pulmonary artery was incised along the pulmonary artery to the bifurcation of the left and right pulmonary arteries. Then, bovine pericardium was used to repair the ventricular septal defect. Intermittent mattress suture with 3-5 needle belt gasket 5-0 Prolene was performed in the posterior inferior region of the ventricular septal defect, and continuous suture was performed in the remaining part. Next, bovine pericardial was used to widen the right ventricular outflow tract or/and the pulmonary artery. The standard of pulmonary artery widening was based on the patient's weight, and a corresponding probe was used for testing.

**Anomalous pulmonary venous drainage:** In supracardiac patients, vertical veins were separated first. The right atrium and the posterior wall of the left atrium were incised transversely, and the common pulmonary vein was incised longitudinally. Then, the common pulmonary vein was anastomosed to the posterior wall of the left atrium. The incision of the common pulmonary vein was 3.5-4.5 cm above the anasto-

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motoc site, and the middle point of the lower edge and the left top were sutured with one stitch. Next, continuous suture was performed with 5-0 Prolene suture, anastomosing from the left side up and down to the right side, and the vertical vein was ligated before stopping the machine. In intracardiac patients, the left and right pulmonary veins converged into the common pulmonary vein and returned to the right atrium through the coronary sinus. When the coronary sinus was significantly dilated, the residual room between the ASD and the coronary sinus orifice was cut open to enlarge the ASD. Autopericardium was used to repair the ASD and the pulmonary vein and the coronary sinus orifice were separated from the left atrium.

**Ebstein's anomaly of the tricuspid valve:** Routine extracorporeal circulation was established, and right atrium incision was made after cardiac arrest. First, all useful tricuspid valve leaves were cut off, generally including part of the septal valve, all the posterior valve and most of the anterior valve. Then, the chordae tendinae at the root of the corresponding valve were dissociated, and the atrialized ventricle was folded longitudinally at the junction of the posterior valve. Care was taken to avoid damaging the coronary artery when folding. Part of the amputated septal valve, posterior valve and anterior valve were sutured clockwise to the normal tricuspid valve annulus, and the autogenous pericardial strip was sutured continuously at the root of the valve to rebuild the annulus.

### Detection methods

#### *Western blot analysis of Nkx2.5*

The protein was extracted from the cultured cells of each group with RIPA buffer as instructed, and the lysate was centrifuged at 10,000×g for 20 min to collect the supernatant. The protein concentration was then determined by the bicinchoninic acid (BCA) kit (with bovine serum albumin as the standard). Then sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed to separate equal amounts of protein, which was then transferred to a membrane for 1 h of sealing with 5% skim milk powder at room temperature. Using a membrane transfer apparatus, the protein was transferred to a polyvinylidene fluoride (PVDF) membrane after electro-

phoresis, blocked with 5% skim milk for membrane sealing for 2 h, washed, added with the primary antibody (1:1000), and sealed overnight at 4°C. After that, the membrane was washed to remove the first antibody, added with Horseradish peroxidase labeled goat anti-rabbit secondary antibody (1:5000), and developed.

### *Outcome measures*

CPB duration: the total time of CPB. Aortic occlusion time: the short-term blocking time during CPB. Mechanical ventilation (MV) time: the total time from mechanical intubation ventilation to extubation after operation. Intensive Care Unit (ICU) residence time: the total time from the patient's admission to the ICU to the transfer to the general ward. Expression and clinical significance of Nkx2.5: western blot detection of Nkx2.5 for the diagnosis of CHD complicated with AKI. Total hospital stay: total time from admission to discharge. Risk factors: the risk factors of AKI were analyzed by Logistic regression analysis with patients' clinical baseline data and all the comparative indicators in the study as variables.

### *Statistical methods*

The data were statistically analyzed by SPSS 22.0, and the acquired images were plotted by Graphpad 7. The counting data were expressed in the form of percentage (%), and compared by the chi-square test between two groups. The measurement data were expressed as mean ± standard deviation, and the t-test was applied for inter-group comparisons. The diagnostic and predictive value was analyzed by receiver operating characteristic (ROC) curves. P<0.05 was considered to indicate statistical significance.

## Results

### *Comparison of general information*

Patient characteristics showed no significant differences between the two groups in age, body mass index (BMI), gender, living environment, smoking history, drinking history, family medical history and ethnicity (P>0.05), while a significant difference was present concerning surgical methods (P<0.05) (**Table 1**).

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**Table 1.** General information

	Research group (n=69)	Control group (n=52)	t or X <sup>2</sup>	P
Age (years old)	2.8±6.6	3.2±7.5	0.700	0.485
BMI (KG/cm <sup>2</sup> )	23.52±3.05	24.46±4.72	1.328	0.187
Gender			0.056	0.813
Male	33 (47.83)	26 (50.00)		
Female	36 (52.17)	26 (50.00)		
Living environment			0.017	0.898
Urban	39 (56.52)	30 (57.69)		
Rural	30 (43.48)	22 (42.31)		
Smoking history			0.034	0.853
Yes	32 (46.38)	25 (48.08)		
No	37 (53.62)	27 (51.92)		
Drinking history			0.439	0.508
Yes	29 (42.03)	25 (48.08)		
No	40 (57.97)	27 (51.92)		
Family medical history			0.062	0.804
Yes	9 (13.04)	6 (11.54)		
No	60 (86.96)	46 (88.46)		
Ethnicity			0.476	0.490
Han	58 (84.06)	46 (88.46)		
Ethnic minorities	11 (15.94)	6 (11.54)		
Surgical method			17.420	<0.001
Total correction of tetralogy of Fallot	19 (27.54)	30 (57.69)		
Anomalous pulmonary venous drainage	26 (37.68)	4 (7.69)		
Ebstein's anomaly of the tricuspid valve	24 (34.78)	18 (34.62)		

### *Comparison of CPB duration and aortic occlusion time between the two groups*

The comparison showed that the CPB duration and aortic occlusion time in the RG (88.23±24.36, 58.73±17.69) were longer than those in the CG (72.45±23.65, 43.58±15.91) (P<0.05) (**Figure 1**).

### *Postoperative Cr level and MV time in the two groups*

The Cr level was (107.34±35.78) in the RG postoperatively, which was evidently higher than (89.77±27.84) in the CG (P<0.05); moreover, postoperative MV time was found to be notably longer in the RG (56.12±8.75) than in the CG (26.64±7.69), and the difference was statistically significant (P<0.05) (**Figure 2**).

### *Expression and clinical significance of Nkx2.5 in the two groups*

Nkx2.5 expression was detected in the two groups, and the results showed that the Nkx2.5

level in the RG was remarkably lower than that in the CG (P<0.05). According to ROC curve analysis, when  $Nkx2.5 > 0.91$ , the diagnostic sensitivity to predict CHD complicated with AKI was 65.38%, and the specificity was 91.30% (**Figure 3; Table 2**).

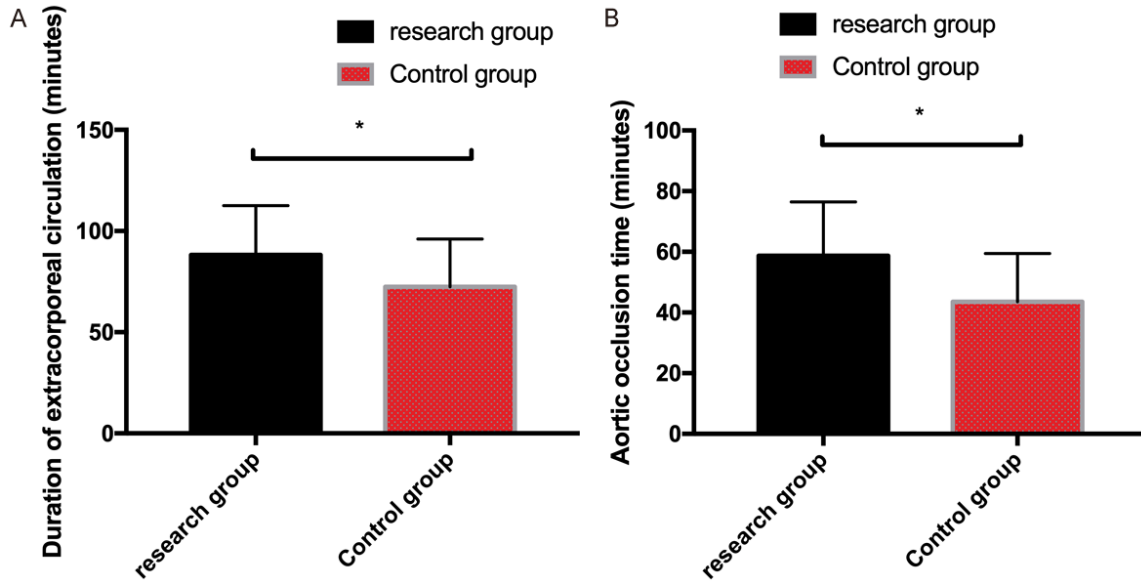
### *ICU residence time and total hospital stay in the two groups*

ICU residence time and total hospital stay were observed. The results identified statistically longer ICU residence time and total hospital stay in the RG (32.54±4.25, 15.67±3.24) than in the CG (21.16±3.22, 11.55±3.12), with statistically significant differences (P<0.05) (**Figure 4**).

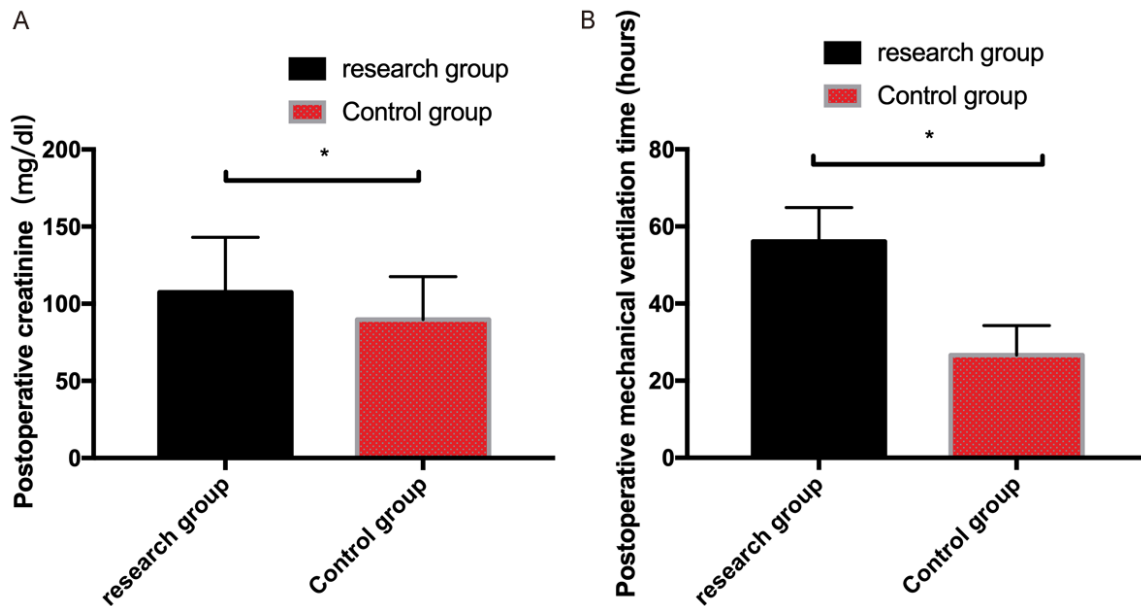
### *Risk factor analysis*

*Multivariate analysis of AKI:* With **Table 1** showing the result of univariate analysis, the variables with differences were included in the assignment (see **Table 4** for assignment), fol-

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**Figure 1.** Comparison of CPB duration and aortic occlusion time between the two groups. A: Duration of CPB in the two groups. B: Aortic occlusion time in the two groups.



**Figure 2.** Postoperative Cr level and MV time in the two groups. A: Postoperative Cr level in the two groups. B: Postoperative MV time in the two groups.

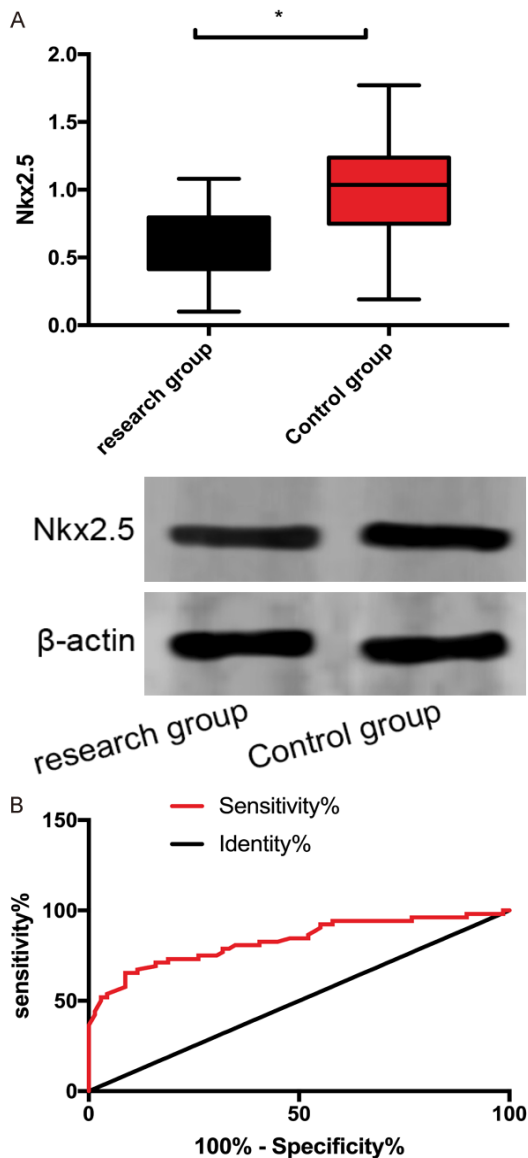
lowed by Logistic regression analysis. The results showed that CPB duration and aortic occlusion time were independent risk factors for AKI in CHD patients ( $P < 0.05$ ), while surgical methods and Nkx2.5 were independent protective factors ( $P < 0.05$ ) (Tables 3, 4).

### Discussion

Congenital heart disease, or CHD, is a vascular malformation caused by fetal cardiovascular abnormalities and is a primary cause of neonatal death and disability [15]. As its incidence



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**Figure 3.** Expression and clinical significance of Nkx2.5 in the two groups. A: Expression of Nkx2.5 in the two groups. B: ROC curve of Nkx2.5 in the diagnosis of CHD complicated with AKI.

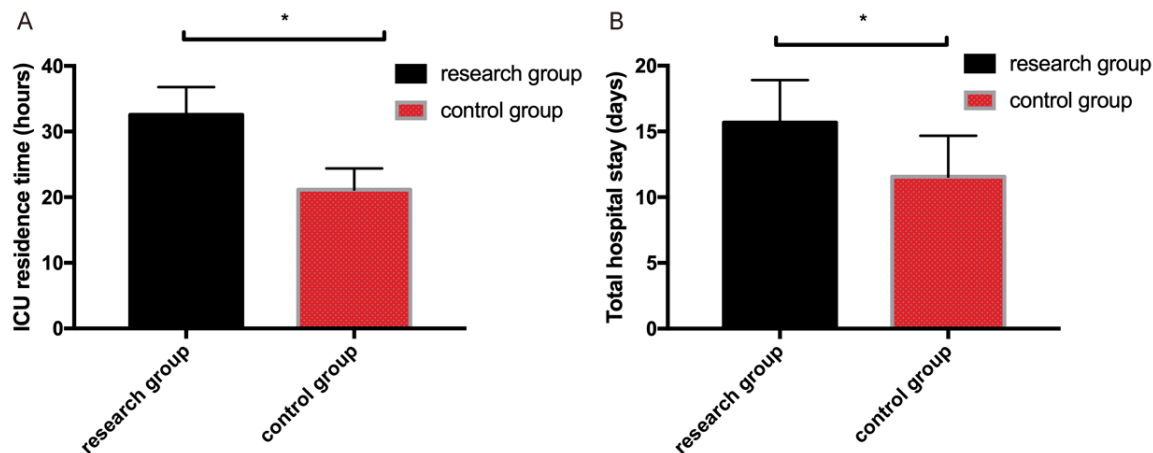
**Table 2.** Diagnostic effect of Nkx2.5 on CHD complicated with AKI

	Nkx2.5
AUC	0.832
Std. Error	0.039
95% CI	0.756-0.909
Cut-off	>0.91
Sensitivity (%)	65.38
Specificity (%)	91.30
Youden index	56.68
P	<0.001

increases annually, it imposes a certain economic burden on the society [16]. Although the cause remains elusive, it is believed that genetic factors and environmental factors play a combined role in causing cardiac vascular dysplasia [17]. Also, transcription factors have been confirmed to be closely associated with cardiac development [18]. Some scholars have pointed out that finding the therapeutic genes for CHD patients can improve the survival rate of patients to some extent [19]. Of these, transcription factor Nkx2.5 is vital in the early development of the heart [20]. In addition, reducing postoperative adverse complications in patients with CHD is also the primary task to ensure the postoperative efficacy [21]. AKI, one of the common complications following cardiac surgery, is also one of the most life-threatening complications for patients [22]. Therefore, this study focuses on the analysis of the risk factors of postoperative AKI in patients with CHD and the predictive value of early detection of serum transcription factor Nkx2.5 in CHD.

First of all, we analyzed the statistics on patient general clinical data, and found no marked difference in age, BMI, gender, living environment, smoking history, drinking history, family history and ethnicity between the two groups, while there was a statistical difference in surgical methods (total correction of tetralogy of Fallot, anomalous pulmonary venous drainage, Ebstein's anomaly of the tricuspid valve), suggesting that different surgical methods had a certain impact on the occurrence of AKI in patients. AKI associated with cardiac surgery is a recognized complication. Some studies have proposed that the type of cardiac surgery is an important factor affecting the occurrence of AKI [23], which supports the results of this experiment. AKI is a syndrome that covers minor changes in renal function, which not only seriously affects renal function, but also causes inflammation in distant organs of the body, further increasing the risk of disease and death [24]. A review of past data shows that AKI is now a global health burden, which warrants more attention to be paid to the prevention of AKI. A longer CPB duration and aortic occlusion time were observed in patients with AKI than in those without, indicating that these two parameters may also be the influencing factors of AKI. CPB, with the aim of maintaining the blood supply of tissues and organs throughout the body

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**Figure 4.** ICU residence time and total hospital stay in the two groups. A: ICU residence time in the two groups. B: Total hospital stay in the two groups.

**Table 3.** Assignment table

Factors	Assignment
CPB duration	Analyzed with raw data
Aortic occlusion time	Analyzed with raw data
Surgical methods	0= Total correction of tetralogy of Fallot, 1= Anomalous pulmonary venous drainage, 2= Ebstein's anomaly of the tricuspid valve
Nkx2.5	Analyzed with raw data

**Table 4.** Logistic regression analysis

	S.E.	B	Wald X <sup>2</sup>	P	OR	95% CI
CPB duration	3.876	4.761	11.763	0.002	2.234	0.693-4.783
Aortic occlusion time	4.163	5.012	10.972	0.003	3.031	2.162-5.653
Surgical methods	1.231	7.32	4.542	0.023	0.431	-0.034-12.433
Nkx2.5	0.313	-1.311	16.297	0.000	0.321	0.012-2.313

during open-heart surgery, is a life support technology that uses a series of special artificial devices to drain the venous return blood to the outside of body, artificially exchange the gas, regulate the temperature and filter it, and then inject it back into the arterial system, which is an important technique in clinical medicine [25]. In cardiac surgery, blood needs CPB, but due to the complexity of the surgery itself, it is easy to cause renal hypoxia, which further aggravates renal injury. It is shown that AKI is a common complication of CPB and exerts marked effects on patient prognosis [26]. At the same time, it is necessary to block circulation during cardiac surgery, and the resulting sudden cardiac arrest, cooling and heating will directly affect renal blood flow and renal ischemia [27], leading to renal injury. Some data suggest that off-pump surgery can give rise to

renal hypoperfusion, which can also trigger AKI [28]. Subsequently, we checked the postoperative Cr level of the two groups of patients and recorded the MV time. It was observed that the Cr level in the RG increased after surgery, and the MV time was longer than that in the CG, further confirming that the cardiac surgery can cause some damage to the patients. Further, the Nkx2.5 expression was found to be lower in the RG, indicating that Nkx2.5 may be involved in the development of CHD complicated with AKI. Referring to previous literature, it is found that Nkx2.5 has vital application value in CHD [29], which is consistent with our research results. Through ROC curves, we then found that Nkx2.5 showed good diagnostic value in predicting the occurrence of CHD complicated with AKI, with predictive sensitivity of 65.38% and specificity of 91.30%, confirming its great sig-

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nificance for the future clinical diagnosis of CHD complicated with AKI. We therefore suspect that it can be an important auxiliary examination factor in the future. Furthermore, longer ICU residence time and total hospital stay were observed in the RG as compared to the CG, indicating that AKI seriously affects the prognosis and recovery of patients and causes extra economic burden on patients. Summarizing the above experiments, we realized that we had not taken effective intervention measures before the occurrence of AKI, nor had we identified influencing factors to intervene. Therefore, based on the general information of the patients and the above experiments, we analyzed the influencing factors of AKI at the end of the study. The results demonstrated that CPB duration and aortic occlusion time were independent risk factors that affected the occurrence of AKI in CHD patients, while surgical methods and Nkx2.5 detection were independent protective factors. Hence, in the future clinical diagnosis and treatment of CHD, we can make early predictions and early prevention of risk factors to reduce the incidence of AKI and shorten the hospital stay of patients.

The purpose of this study is to explore the risk factors of AKI in CHD patients and the significance of early detection of serum transcription factor Nkx2.5, but there are still deficiencies due to the limited experimental conditions. First of all, only three surgical methods were presented in this study, so it is not ruled out that different experimental results will be obtained with other surgical methods. In addition, we had not yet analyzed the long term prognosis of the patients due to the short study time. In view of the above shortcomings, we will conduct a more in-depth experimental analysis as soon as possible to obtain better experimental results.

To sum up, CPB duration, aortic occlusion time, surgical methods and Nkx2.5 detection are independent factors affecting the occurrence of AKI in patients with CHD. Early detection of serum transcription factor Nkx2.5 is paramount for the future clinical diagnosis of CHD complicated with AKI.

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### Disclosure of conflict of interest

None.

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