



Screening of Influencing Factors for AKI Based on Lasso Regression

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ABSTRACT

Background: Acute kidney injury (AKI) is one of the common critical diseases in hospitalized patients. There are many factors affecting acute kidney injury, difficult to obtain disease data, and short treatment time window. Early detection of AKI is critical to reducing mortality. **Methods:** MIMIC-IV data were used to establish the prediction model of AKI in critical patients after operation. 1585 intensive care unit (ICU) patients were randomly divided into a training set (n=1109) and a prediction set (n=476) on a 7:3 basis. LASSO regression analysis was performed on the data, area under the operating characteristic curve (AUROC) was used to evaluate the model, and Hosmer-Lemeshow (HL) was used to test the degree of fit. **Results:** Spinal injury, implantation of temporary cardiac pacemaker, esophageal disease, contrast media, diuretic, epinephrine, aminoglycoside antibiotics, tumor chemotherapy drugs, age, gender and red blood cells were determined to be independent risk factors for acute kidney injury. The AUROC of the model in the train set was 0.901 (95% confidence interval: 0.856~0.946). In the validation set, AUROC was 0.851 (95% confidence interval: 0.808~0.894). AUROC of the above two groups indicated that the model had a good degree of differentiation, which was

greater than 70% in both groups. Hosmer-Lemeshow (HL) test showed $P > 0.05$, indicating a good fit of the model. Conclusion: This prediction model can be used for the identification of post-operative AKI patients and provide a basis for clinicians or inpatients to more quickly self-measure the risk.

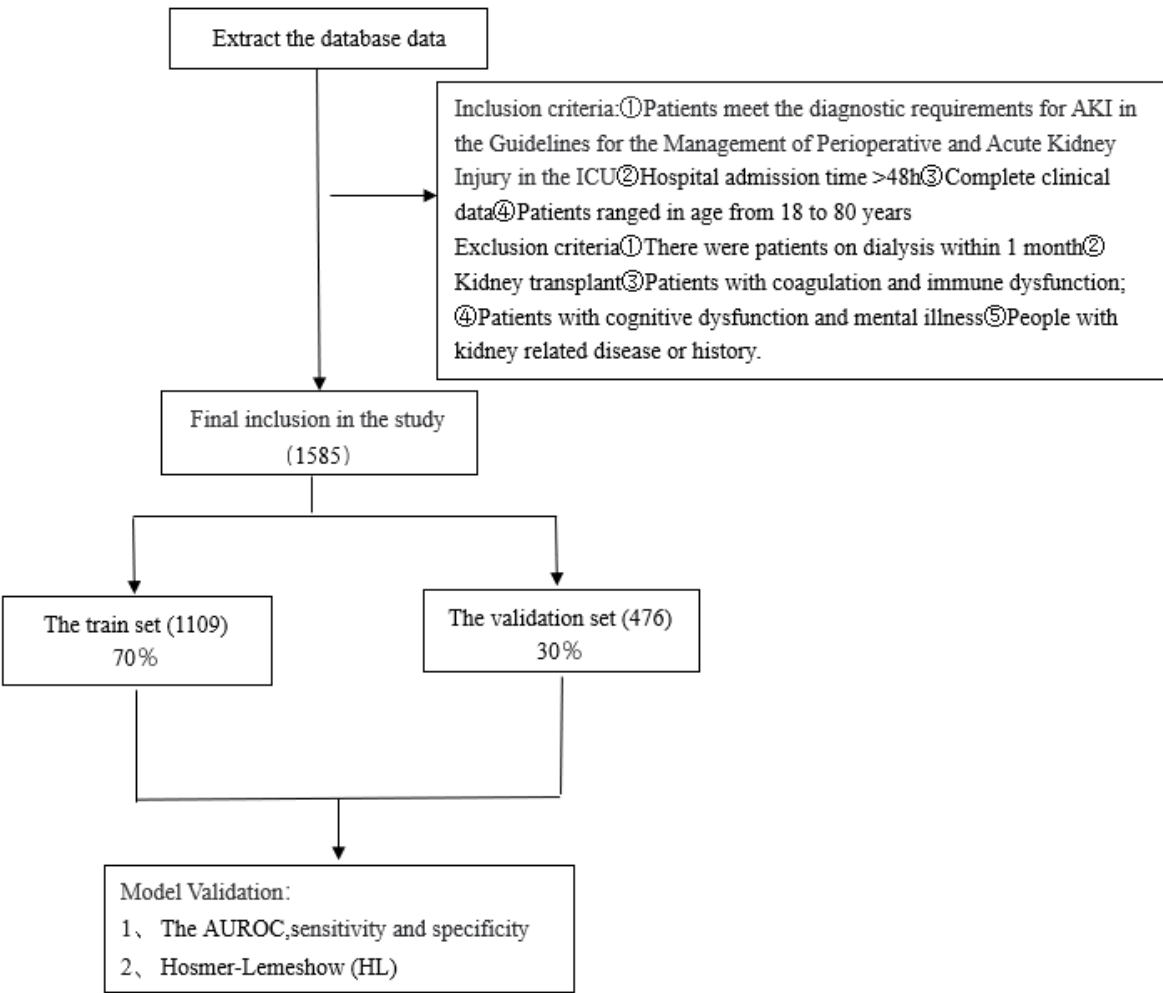
Keywords: acute kidney injury, LASSO regression, prediction model, independent risk factors, data extraction.

INTRODUCTION

Acute kidney injury occurs mostly in inpatients, and is a clinical critical disease with high morbidity and mortality. Due to chronic diseases and related renal toxic drug therapy, the morbidity and mortality of acute kidney injury still show an increasing trend. In recent years, studies on the influencing factors of acute kidney injury in inpatients at home and abroad only considered drug prescription, laboratory value, vital signs, blood creatinine and other influencing factors. Moreover, current studies on the prediction of acute kidney injury include the use of biomarkers that can reflect the glomerular filtration rate, tubular stress and other biomarkers and miRNA to diagnose acute kidney injury, etc. However, most of the existing biomarkers of acute kidney injury are still insufficient in specificity and sensitivity, and further research is needed. In addition, the linear relationship between the stage of acute kidney injury and mortality can be used to detect acute kidney injury and implement appropriate intervention measures, as well as the semi-quantitative assessment of acute kidney injury by urine analysis with a microscope. Although such methods can predict, the process is complex and cannot predict made fast. There are still some problems in all kinds of prediction studies, such as small amount of data, incomplete and non-standard clinical information, cross-validation method for most data processing, no independent test set, and lack of comprehensive and in-depth analysis of important factors affecting the occurrence of acute kidney injury. In addition to its harmful effects on the human body, acute kidney injury can lead to other acute diseases such as immune deficiency, electrolyte abnormalities, fluid overload, and chronic kidney disease, which can lead to increased mortality in hospitalized patients, longer hospital stays and higher treatment costs.

In this situation, it is very important to identify the main influencing factors of acute kidney injury and to make early risk prediction and prevention. The project aims to capture data and clinical information from a large number of inpatients and establish predictive models in conjunction with criteria for identifying acute kidney injury.

LASSO regression method can make the final model more concise and efficient by adding penalty terms, thus reducing the complexity of the model[1]. At the same time, LASSO regression method has more advantages in processing multicollinearity sample data[2]. Therefore, LASSO regression method was adopted in this study to construct a model suitable for the risk of AKI patients, which can provide a reference for the prognosis of clinical patients.



MATERIALS AND METHODS

Data Sources

This study obtained the required patient information from MIMIC-IV database, which provided great help for us to quickly find the target patient information. A total of 15 different types of AKI exists in MIMIC-IV database, and these 15 types of kidney failure are all attributed to AKI, and their models were constructed and tested.

Screening was conducted according to 15 types of AKI and the following criteria. Inclusion criteria: ①Patients meet the diagnostic requirements for AKI in the Guidelines for the Management of Perioperative and Acute Kidney Injury in the ICU②Hospital admission time >48h ③Complete clinical data. Exclusion criteria①There were patients on dialysis within 1month ②Kidney transplant③Patients with coagulation and immune dysfunction; ④Patients with cognitive dysfunction and mental illness⑤People with kidney related disease or history. A total of 33,568 patients with acute kidney injury were identified. In MIMIC-IV's database, patients' dates of birth have been altered to conceal their ages and keep their information secret. Since the age of patients older than 89 years old will be changed to 300 years old, and considering the influence of excessive age on information, the age range of patients in this paper is 18-80 years old.

Medical data sets are often accompanied by the problem of missing data, which will affect the prediction effect and performance of the model. For the processing of missing values, statistical knowledge or machine learning algorithms can be used to fill in. Using the mean of variance is the most widely used imputation method in statistics. It is suitable for missing variables that are normally distributed or have small variance. In this paper, due to the high missing rate of some variables, 1585 patients were finally screened as samples, and the missing rate of all variables was less than 10%.

Relevant Diagnostic Criteria and Definitions

Acute kidney injury is defined according to the criteria for the detection of acute kidney Injury in the 2019 National Institute for Health and Clinical Excellence (NICE) Guidelines for the Prevention, Detection and Management of acute Kidney Injury.

Spinal injuries: The spine is mainly divided into cervical vertebrae, thoracic vertebrae, lumbar vertebrae, and sacrococcygeal vertebrae. Injuries at different spinal positions can cause spinal cord or nerve injuries at corresponding positions. Spinal injury is mainly associated with spinal and peripheral joint involvement, and may be accompanied by kidney, lung, heart and other organ system lesions.

Cardiac pacemaker: It is an implanted electronic therapy device in the body, which could stimulate the electrode contact of the myocardium and make the heart excited and contracted through the pulse generator to send out the electric pulse powered by the battery and the conduction of the lead electrode, so as to achieve the purpose of treating the heart dysfunction caused by some arrhythmia.

Contrast agent: Contrast agent is one of the most commonly used drugs in interventional radiology procedures, mainly for the visualization of blood vessels and body cavities. There are various types of contrast agents, and most of the contrast agents currently used in interventional radiology are iodized preparations. Contrast agents can be divided into two main classes: high-density contrast agents with high atomic weight and high specific gravity, and low-density contrast agents with low atomic weight and low specific gravity.

Aminoglycoside antibiotics: Glycoside antibiotics consisting of an amino sugar linked to an amino cyclic alcohol by an oxygen bridge. They mainly include natural aminoglycosides such as streptomycin from *Streptomyces*, gentamicin from *micromonospora*, and semisynthetic aminoglycosides such as amikacin.

Statistical Processing

1585 intensive care unit (ICU) patients were randomly divided into the training set and the prediction set by 7:3. The training set included 1109 samples and the prediction set included 476 samples.

LASSO algorithm was used for regression analysis. It was used to analyze the data obtained from MIMIC-IV database, and the independent risk factors for AKI in patients with acute kidney injury were obtained by analysis and verification. The model fit was evaluated by Hosmer-Lemeshow (HL), and the predictive value was evaluated by Receiver Operating Characteristic (ROC) curve and Accuracy Score. The importance of the predictors is shown by various

regression coefficients. LASSO regression method is suitable for processing high-dimensional data [3], [4].

It can compress those minimal regression coefficients by adding penalty items in model training. When the regression coefficient is compressed to a certain threshold, it will be directly assigned as 0[5]. Lasso regression is a model in which the cost function of the linear regression model is followed by the constraint term of the L1 norm. It is widely used in the medical field for variable screening and complexity adjustment through the control parameter lambda.[6], [7]

RESULTS

Prediction Model Construction

In this study, the relationship between λ and the regression coefficient is first plotted, and then the optimal superparameter λ is selected by the generalized cross validation method with the minimum mean square error. The model is constructed based on the optimal hyperparameter λ of the output. After solving the model, variables corresponding to zero estimation parameters can be directly excluded from the index pool in the final index. After the coefficients of LASSO regression were obtained, Hosmer-Lemeshow test was conducted on the model established after regression analysis to verify the good fit of the model. The results showed that the model was well fitted ($P=0.556$). After the fitting degree test, we drew the operating characteristic curve for the model, and obtained the area under the operating characteristic curve (AUROC) to evaluate the model. Then we output the accuracy score of the model to evaluate the accuracy of the prediction model, and the results show that the accuracy is good.

On this basis, a regression model was established with acute kidney injury as the dependent variable. The expression of regression is as follows:

$$y_i = \beta_0 + \sum_{n=1}^q \beta_n x_{in} + \varepsilon_i \quad i=1,2,\dots,n$$

In the above expression y_i indicates whether patient i has acute kidney injury. x_{in} is the indicator for the n patient. ε_i is the error term. β_n is the regression coefficient. q is the number of variables. n is the number of indices.

The LASSO regression formula is as follows:

$$\min_{\beta} \frac{1}{2} (Y - X\beta)^T (Y - X\beta) + \lambda \sum_{n=1}^p |\beta_n|$$

Where λ is a hyperparameter, the larger λ is, the fewer variables are filtered into the model. [8]

Because the parameter estimates obtained by LASSO method are biased, the coefficients of the acute kidney injury impact factors cannot be correctly analyzed. To ensure the robustness of the model, we performed another regression on the variables screened by the LASSO method. indicators were selected by LASSO and regression analysis was performed. We end up with the following expression:

$$y_i = \beta_0 + \sum_{n=1}^q \beta_n x_{in} + \varepsilon_i$$

After further screening by LASSO regression analysis, ten independent risk factors were finally obtained: spinal injuries, implantation of temporary cardiac pacemaker, esophageal disease, contrast media, diuretics, epinephrine, aminoglycoside antibiotics, tumor chemotherapy drugs, gender, and red blood cells can be considered as the influencing factors of acute kidney injury after screening. In view of the medical clinical data: ① Age is widely considered in clinical practice and should be included as a criterion for the diagnosis of AKI; ② Red blood cells include hemoglobin, and its influence is considered in this paper as the influence of red blood cells, so 11 independent risk factors were finally obtained. The other indicators did not reflect the important degree of influence in the figure, and there were almost no reference studies and articles about them, so this paper does not take it into consideration.

The final AKI risk probability prediction model is as follows:

$$\begin{aligned} \text{AKI_risk_probability} = & (-0.404 \times \text{Spinal_injuries} - 0.302 \times \text{Implantation_temporary_cardiac_pacemaker} \\ & - 0.069 \times \text{Esophageal_disease} - 0.145 \times \text{Contrast_media} - 0.029 \times \text{Diuretics} + 0.023 \times \text{Epinephrine} \\ & + 0.022 \times \text{Aminoglycoside_antibiotics} - 0.391 \times \text{Tumor_chemotherapy_drugs} + 0.001 \times \text{Age} \\ & + 0.120 \times \text{Red_blood_cells} - 0.025 \times \text{Gender}) + 0.000327 \end{aligned}$$

We conducted LASSO regression screening on 227 AKI related influencing factors, and finally obtained 27 results in Figure 1, respectively: gender, 225789: sheath (venous), 228125: left atrial pressure, 229580: line placement at bedside, 225474: Fall, 225465: chest pain, 225464: cardioversion/ defibrillation, 225463: spinal injuries, 225966: nasal swab, 226477: implantation of temporary cardiac pacemaker, 226476: esophageal disease, 225448: percutaneous tracheostomy, 225315: tunneled (Hickman) Line, 221219: contrast media, 225821: unplanned line/ catheter removal (patient initiated), 224274: 22 Gauge, 224264: PICC Line, 8173: diuretics, 66419: epinephrine, 16926: calcium ion antagonist, 9299: aminoglycoside antibiotics; 58624: tumor chemotherapy drugs, age, 225690: hemoglobin, 220228: total bilirubin, 51006: BUN, 51279: red blood cells

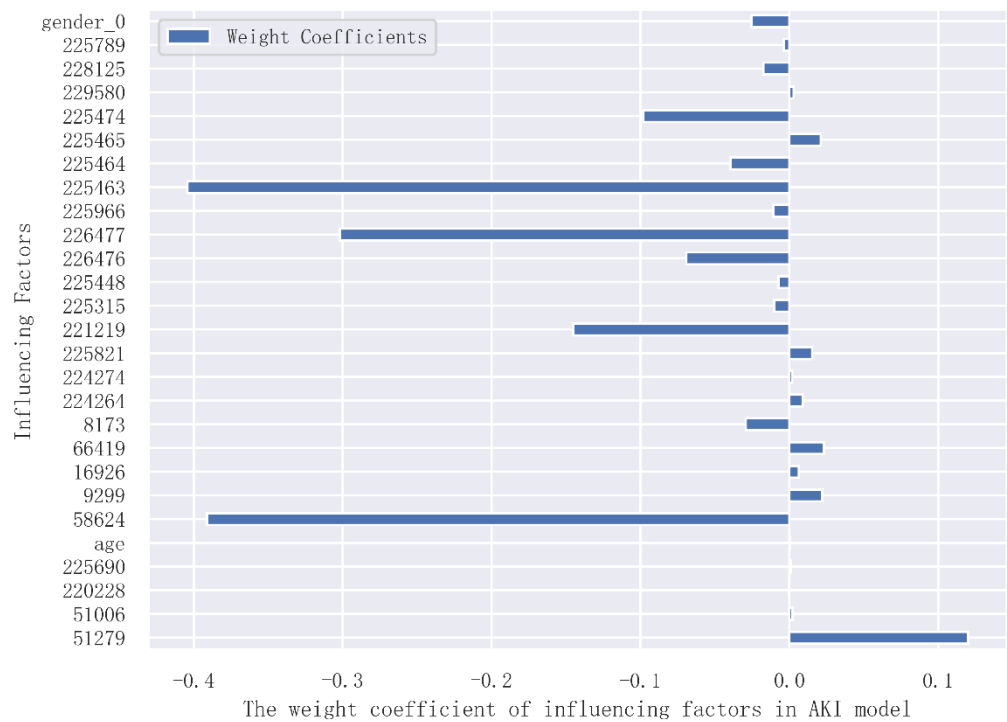


Figure 1. The weight coefficient of influencing factors in final AKI model

Different variables with λ punishment, its coefficient changes, we keep in the case of the target λ value, coefficient is not 0 variable. In Figure 2, we can see that some variables only become 0 when the value of λ is large, indicating that this variable is very important in this model.[9], [10]

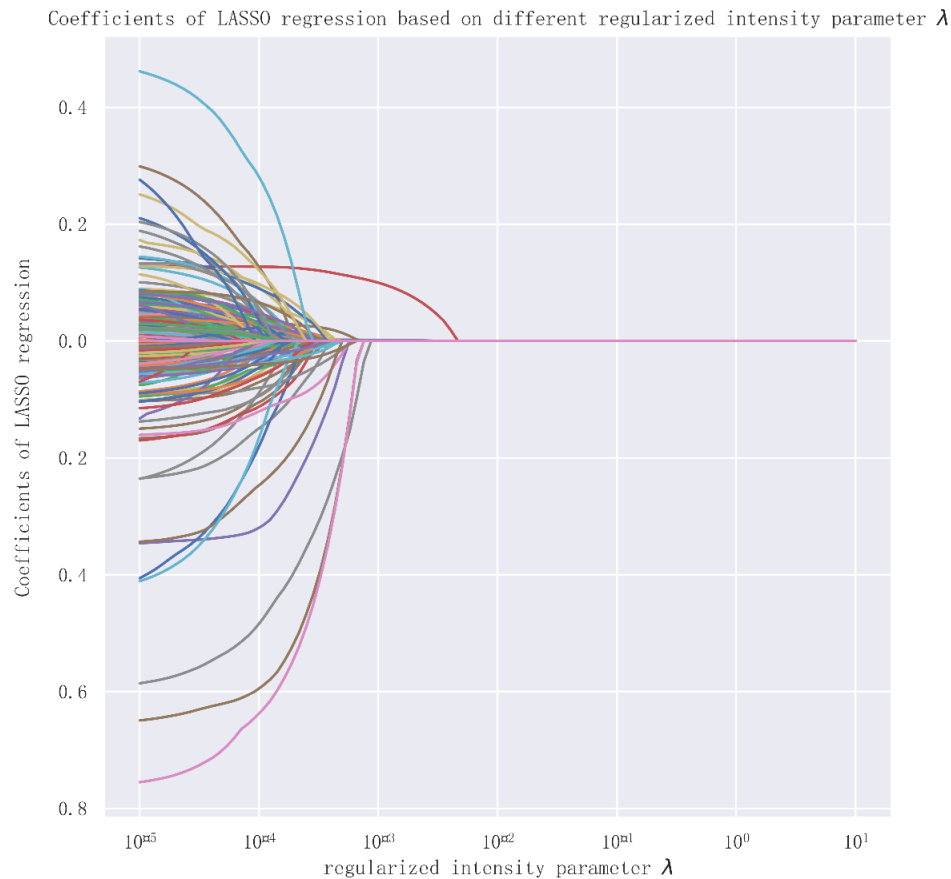


Figure 2. The optimization process of the regularized intensity parameter based on LASSO cross validation

Validation of the Model

Accuracy score of the model: Accuracy score of training set: 0.883, accuracy score of prediction set: 0.889. The results show as Figure 3, indicating that the model has good accuracy.

Discrimination of the model: The AUROC of the model in the train set was 0.901(95% confidence interval (CI): 0.856-0.946), In the validation set, the AUROC was 0.851 (95% CI: 0.808-0.894), indicating that the model has good differentiation.

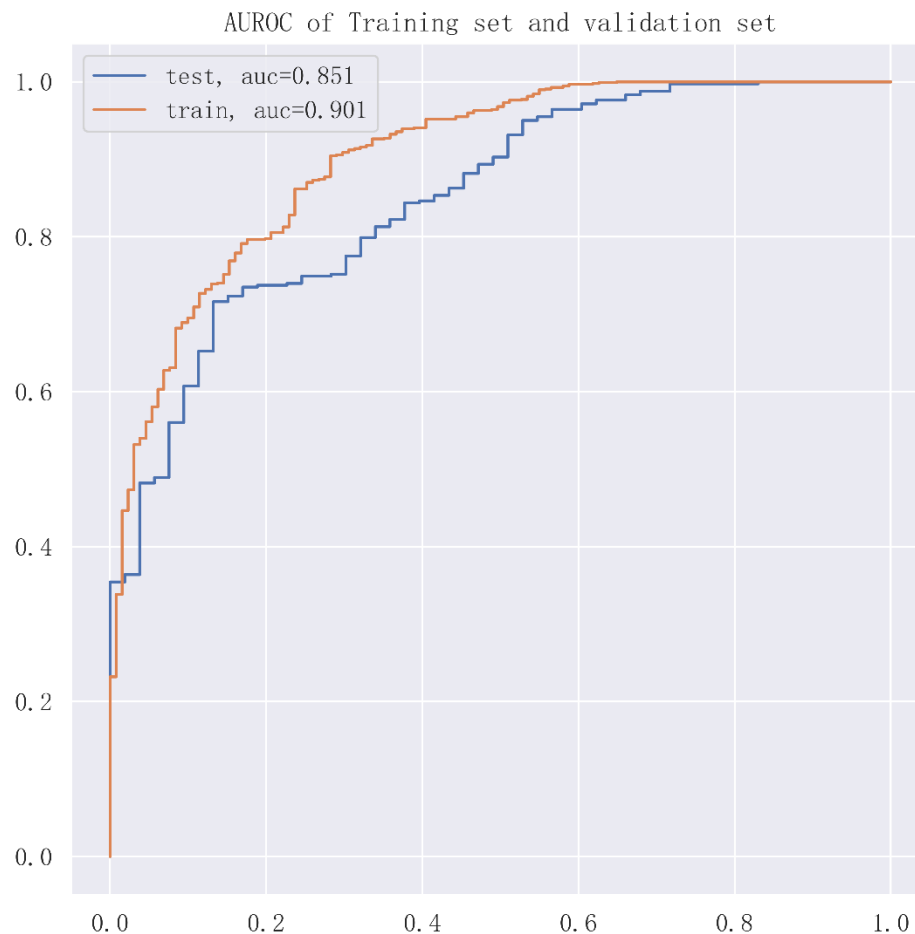


Figure 3. AUROC of Training set and validation set

Model fit evaluation: The results of Hosmer Lemeshow (HL) showed that the significance (P value) of both groups was greater than 0.05, indicating that the model had excellent goodness of fit.

DISCUSSION AND CONCLUSION

In recent years, the incidence of acute kidney injury in clinical practice has increased year by year, with high mortality and poor prognosis, which seriously threatens human health and has become a prominent social public health problem. China is also deeply troubled by the treatment and prognosis of acute kidney injury. Previous studies have shown that 50% of patients with acute kidney injury do not recover in the second or third stage, and the mortality rate of patients with acute kidney injury is as high as 44%[11]. Identification and quantification of risk factors related to acute kidney injury and the establishment of acute kidney injury prediction models are essential for the prediction of early acute kidney injury.

In this study, the patients were randomly assigned to a 7:3 group, and the factors associated with acute kidney injury were analyzed, aiming to identify the occurrence of acute kidney injury by changes in early clinical indicators. This study used LASSO regression analysis to screen out 11 key factors of acute kidney injury, which were spinal injury, implantation of temporary

cardiac pacemaker, esophageal site disease, contrast agent, diuretic agent, epinephrine, aminoglycoside antibiotics, tumor chemotherapy drugs, age, gender, and red blood cells.

Patients with spinal injuries have often experienced severe trauma and the main symptoms are pain, difficulty in mobility and movement, which can also cause nerve compression. Renal injury secondary to spinal injury is not uncommon, which includes non-steroidal anti-inflammatory drug-related nephrotoxicity (including acute kidney injury). Previous studies have shown that AKI is an important postoperative complication in patients with idiopathic scoliosis[12], so spinal injury can be regarded as an important influencing factor of AKI, which is consistent with the results of this study.

Relevant studies have shown that pacemaker implantation can successfully treat acute kidney injury based on chronic renal failure, and renal function remains well after half a year of follow-up[13]. The pacemaker sends tiny electrical pulses to the heart, which stimulates the heart to beat and increases cardiac output, thereby increasing kidney blood flow and improving kidney function[14]. Temporary cardiac pacemaker implantation can effectively control many bradyarrhythmia and change renal perfusion and other problems, which could improve renal function and efficaciously reduce the occurrence of acute kidney injury[15]. Pacemaker provides great help for the treatment of acute kidney injury, so whether to implant temporary pacemaker is of great significance for the prediction of acute kidney injury.

There are various sites that can induce acute kidney injury. Studies have shown that postoperative acute kidney injury in patients with esophageal cancer is much common and easily overlooked.[16] Attention should be paid to whether patients with esophageal disease will have secondary acute kidney injury after surgery, and their renal function should be strictly tested.

With the rapid development of imaging diagnosis and interventional therapy technology, contrast agent-mediated therapy is widely used, and the probability of acute kidney injury after radiological angiography is significantly increased[17], [18]. Contrast agents have direct toxic effects on vascular endothelial cells and renal tubular epithelial cells. The common cause of acute kidney injury is renal ischemia-reperfusion, and renal tubular injury is an important pathogenesis of renal ischemia-reperfusion. Contrast media significantly increased the risk for acute kidney injury.

Studies have shown that the use of aminoglycoside antibiotics (gentamicin, amikacin) will increase the probability of acute kidney injury in patients, and aminoglycoside antibiotics are nephrotoxic drugs. The use of diuretics is mainly aimed at the clearance of contrast agent, and diuretics are also nephrotoxic drugs, often acting on the kidney to promote the excretion of electrolytes and water, thereby accelerating the excretion of contrast agent. However, nephrotoxic drugs need to be taken for a long time or a large amount in a short period of time, which can cause cell apoptosis or other irritant reactions. It is well known that the use of nephrotoxic drugs is an important factor affecting acute kidney injury, and it has also been shown that the use of diuretics is an important factor causing acute kidney injury[19], which is also consistent with our study.

Epinephrine is an α - and β -receptor agonist, which can act on the α 1-receptor on vascular smooth muscle to cause vasoconstriction (mainly in skin, mucosa and renal vessels).It also activates β 2 receptors to relax blood vessels (mainly in skeletal muscle, liver and coronary vessels).Additionally, it acts on β -receptors in the myocardium, sinoatrial node and conduction system to enhance myocardial contraction, increase heart rate, accelerate conduction and enhance cardiac output. The renal blood flow can affect the occurrence of acute kidney injury to a large extent, that is, the change of epinephrine has many large effects on the cardiac blood flow, thus affecting the occurrence of acute kidney injury.

The number of cancer patients is increasing, and the population treated with cancer chemotherapy drugs is also increasing. Malignant tumors can directly or indirectly affect renal function, among which chemotherapy drugs will increase the risk of kidney injury. The use of common chemotherapy drugs such as cisplatin, ifosfamide, pemetrexed, methotrexate, pamidronate, zoledronic acid, etc., will lead to clinical manifestations of acute kidney injury. During tumor treatment, it is often accompanied by renal complications because the kidney is the main excretion route of these tumor chemotherapy drugs. For example, cisplatin and ifosfamide mainly cause tubular toxicity, which can lead to acute kidney injury.

The normal reference value for hemoglobin is 11-16 g/dL. Hemoglobin is commonly used in clinical practice for the differential diagnosis of various anemia diseases and the determination of the increase or decrease of red blood cells in the blood. The high-risk group of AKI includes patients with severe anemia. When the patient has severe anemia, the kidney will also be in a state of relative ischemia and hypoxia, and the sensitivity and susceptibility to nephrotoxic factors and damage will be relatively increased. And previous studies have shown that anemia is an important influencing factor for acute kidney injury[20].

In addition, acute kidney injury is more common in the elderly over 65 years old. With the increase of age, renal function will gradually decline. After the age of 40 renal function decline is 0.8%-1% per year rate of decline, so after a certain age renal function itself is weak, the patient's renal reserve function is also weak, often prone to acute kidney injury. And relevant studies have shown that the incidence of AKI in young women after surgery is low, and it gradually increases with age. Among them, women older than 50 years old, men younger than 50 years old and men older than 50 years old are more likely to develop AKI than women younger than 50 years old[21].

In this study, 11 key factors of acute kidney injury were selected by LASSO regression analysis, and a prediction model was established. The AUROC of the training set and the validation set of the prediction model are 0.901 (95% confidence interval: 0.856-0.946) and 0.851 (95% confidence interval:0.808-0.894), respectively, all greater than 0.8, indicating that the model has good discrimination and the possibility of overfitting is very small, which can be used to predict the risk probability of acute kidney injury in hospitalized patients. Hosmer-Lemeshow (HL) test showed that the prediction deviation between the predicted risk value of the prediction model and the clinical observation value was not statistically significant ($P=0.556$), indicating that the model had a good fit. The risk prediction model based on LASSO regression is more in line with the practical theory in the analysis of influencing factors, and has good clinical application value in the risk prediction of AKI. In conclusion, this prediction model can

be used to identify post-operative AKI patients, providing a more convenient way for clinicians or inpatients to measure their own risks.

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