

Development and Validation of a Model to Predict Acute Kidney Injury Following Wasp Stings: A Multicenter Cohort Study

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Research

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Abstract

Background

Acute kidney injury (AKI) following wasp stings is a serious and common health hazard, however the early prediction remains challenging. The study aimed to establish a model to predict AKI following wasp stings and validate it.

Methods

In the multicenter prospective cohort study, 508 patients with wasp stings from Jul 2015 to Dec 2019 were randomly divided into the training set ($n = 381$) and validation set ($n = 127$) for internal and external validation. A model that based on the multivariable logistic regression analysis was utilized to predict the probability of AKI following wasp stings by a predictive formula and a nomogram. The performances of the model were assessed by using the area under the curve (AUC) and accuracy (ACC) of the receiver operating characteristic curve. The calibration curves were utilized for estimating the consistency between the actual observed outcome and the nomogram predicted AKI probability. Decision curve analysis (DCA) demonstrated the net benefit associated with the use of the nomogram-derived probability for the prediction of AKI following wasp stings.

Results

Number of stings, hemoglobin (HB) < 110 g/dl, total bilirubin (TBI) > 34 mg/dl, alanine transaminase (ALT) > 40 U/L and activated partial thromboplastin time (APTT) > 47 s were demonstrated as the independent risk factors for AKI following wasp stings (all P value < 0.05) and were incorporated into the model. The performances of the model were validated (AUC = 0.912, ACC = 0.869 and AUC = 0.936, ACC = 0.898 in the training set and validation set respectively). The predictive formula and nomogram of the model could be utilized to predict the AKI following wasp stings, which having sufficient accuracies, good predictive capabilities and good net benefits.

Conclusion

In conclusion, we proved that number of stings, HB < 110 g/dl, TBI > 34 mg/dl, ALT > 40 U/L and APTT > 47 s were independence risk factors for AKI following wasp stings. The predictive formula and the individual nomogram of the model might serve as promising predictive tools to assess the probability of the AKI following wasp stings.

Introduction

Wasps and bees are the members of the order Hymenoptera, suborder Apocrita, and superfamily Vespoidea[1], and the wasp or bee stings are frequently reported [2–6]. Wasp or bee stings may cause acute kidney injury (AKI), intravascular hemolysis, rhabdomyolysis and even death[7–10]. The incidence rate of AKI following wasp stings ranges from 20–50%[11–13]. According to a study reported, of patients

who with AKI following wasp stings, 20% -58% patients are developed to chronic kidney disease (CKD)[12, 14] and 5.6– 50.5% patients die although some of them receiving renal replacement therapy (RRT)[13– 15].

At present, the mechanism of AKI following wasp stings is not completely clear. Wasp venoms is thought having direct toxic effect for kidney, in which main effective poisonous components include phospholipase A₂ (PLA₂) and melittin [11, 16, 17]. Besides, hemoglobin (HB) released by hemolysis and myoglobin released by rhabdomyolysis are considered that may cause secondary damage to kidney[18, 19].

At present, the AKI following wasp stings is a serious health hazard[17]. Besides, it's worth noting that our previous study indicated that patients with AKI following wasp stings usually died within 72 hours after admission, so that a better understanding of AKI following wasp stings is helpful to early diagnose and treat[12]. Therefore, we performed a multicenter center prospective cohort to identify risk factors associated with AKI following wasp stings and established an individual nomogram and formula of the model to predict the probability of AKI following multiple wasp stings.

Materials And Methods

Database and Patient Selection

This was a multicenter prospective observational cohort study that was conducted in 18 hospitals in China from Jul 2015 to Dec 2019 and 508 patients with AKI following wasp stings were included. Patients who suffering from stings by wasp or other bee species, whether AKI occurred or not, were included. Patients who met the following criteria were excluded: (1) lack of enough clinical data to analyze; or (2) disapprove of participating. The study was approved by Institutional Research Ethics Committees of our institution (Approval No. of the ethics committee: 2014-156). Written informed consents were obtained from all included patients or their legally authorized representatives.

The data were recorded and collected from the electronic medical records system. Demographic and clinical characteristics, such as age, sex, number of stings, time from sting to admission, Sequential Organ Failure Assessment (SOFA) score et al, and important laboratory measures, such as the lactated dehydrogenase (LDH), HB, total bilirubin (TBI), aspartate aminotransferase (AST), urine volume, alanine aminotransferase (ALT), and activated partial thromboplastin time (APTT), creatine kinase (CK) and serum creatinine (Scr) et al, were recorded and analyzed.

Definition

In the study, the patients with wasp stings were divided into AKI group or non-AKI group. AKI was defined by the 2012 Kidney Disease Improving Global Outcomes guidelines[20]: (1) Scr increased to $\geq 26.5 \mu\text{mol/L}$ (0.3 mg/dL) within 48 hours; (2) Scr increased to 1.5 times within 7 days ; or (3) urine volume $< 0.5 \text{ ml}/(\text{kg}\cdot \text{h})$ for 6 hours.

In the logistic regression analysis, continuous variables were transformed into categorical variables according to their reference range and common clinical transformation methods.

Statistical Analysis

We excluded some variables that missing more than 15% and interpolated some variables that missing less than 15% according to multiple interpolation method. And some patients were excluded for lack of enough data to analyze. All eligible patients were randomly assigned 3:1 into the training set and the validation set. The training set mainly constructed a nomogram and a predictive formula of the model for predicting the AKI following multiple wasp stings and the validation set was constructed for external validation.

Continuous variables are expressed as the mean (standard deviation [SD]) which were compared by t test or the median (interquartile range [IQR]) which were compared by Wilcoxon test according to whether the variable coincided with a normal distribution. Categorical variables were expressed as proportions, which were compared by the chi-squared test or Fisher's exact test as appropriate.

The univariable logistic regression analysis to detect the risk factors of AKI following wasp stings and the variables with P-value < 0.1 were introduced into the multivariable logistic regression analysis. In addition, the individual nomogram and the predictive formula of the model were constructed according to the result of multivariable logistic regression analysis. The predictive formula was constructed according to the previous study[21]. The internal validation and external validation were performed in the training set and validation set respectively to assess the accuracy of the model by a bootstrap validation method with 200 resamples. The receiver operating characteristic curve (ROC) analysis was performed to assess the model. Cut off of the model was obtained based on Youden Index. The calibration curves were utilized for estimating the consistency between the actual observed outcome and the nomogram predicted AKI probability. Decision curve analysis (DCA) demonstrated the net benefit associated with the use of the nomogram-derived probability for the prediction of AKI following wasp stings.

All statistical analyses were performed by SPSS (SPSS Inc., Chicago, IL) software for Windows version 23.0. and the packages (rms, hmisc, etc.) in R software version 3.6.1 (<http://www.r-project.org>), with a two-sided P value < 0.05 considered statistically significant.

Results

Characteristics of Eligible Patients

In the study, 547 patients with wasp stings were screened, and 39 patients were excluded due to missing necessary data (as shown in the Fig. 1). Finally, 508 eligible patients were randomly assigned into the training set (n = 381) and the validation set (n = 127). There was no significant difference between the training set and the validation set in the distributions of demographic and disease characteristics such as year, gender, number of AKI, condition of wasp stings (see Table A1 in Additional file 1). In the training set,

of the 381 patients, 118 (31.0%) patients with AKI and 263 (69.0%) without AKI. The demographic and clinical characteristics between the AKI group and non-AKI group in the training set were presented in the Table 1. The proportion of patients received renal replacement therapy (RRT) were higher and the time from stings to admission was longer in the AKI group than those in the non-AKI group (all P value < 0.05). Meanwhile, the proportion of wasp stings, sting at head and face, number of stings ≥ 30 , area of stings $\geq 25\%$ and the level of ALT, AST, LDH, TBI, CK in the AKI group were higher than those in the non-AKI group (all P value < 0.05).

Table 1
Demographic and disease characteristics of patient in training set

Variables	Overall (381)	No AKI (263)	AKI (118)	P-value
Year, y	55.2 (15.4)	54.2 (16.5)	57.3 (12.7)	0.07
Gender, No (%)				0.06
Male	191 (50.1)	123 (46.8)	68 (57.6)	
Female	190 (49.9)	140 (53.2)	50 (42.4)	
RRT, No. (%)				< 0.001
No	229 (60.1)	207 (78.7)	22 (18.6)	
Yes	152 (39.9)	56 (21.3)	96 (81.4)	
Time from stings to admission, h	14.0 (33.0)	9.8 (28.7)	23.5 (39.6)	< 0.001
Wasp, No (%)				0.04
No	141 (37.0)	107 (40.7)	34 (28.8)	
Yes	240 (63.0)	156 (59.3)	84 (71.2)	
Sting at head and face				0.001
No	71 (18.6)	61 (23.2)	10 (8.5)	
Yes	310 (81.4)	202 (76.8)	108 (91.5)	
Number of stings, No (%)				< 0.001
≤100	36 (9.4)	10 (3.8)	26 (22.0)	
≤50	38 (10.0)	11 (4.2)	27 (22.9)	
≤30	72 (18.9)	36 (13.7)	36 (30.5)	
≤15	235 (61.7)	206 (78.3)	29 (24.6)	
Area of stings, No (%)				< 0.001
≤100%	15 (3.9)	6 (2.3)	9 (7.6)	
≤50%	48 (12.6)	13 (4.9)	35 (29.7)	
≤25%	79 (20.7)	43 (16.3)	36 (30.5)	
≤10%	239 (62.7)	201 (76.4)	38 (32.2)	
SBP, mmHg	144.3 (56.1)	138.1 (24.2)	157.9 (92.9)	0.001
DBP, mmHg	86.1 (15.5)	84.1 (15.4)	90.6 (14.9)	< 0.001
Creatinine, mg/dl	70 (46.3)	65.8 (24.2)	180.5(214)	< 0.001

Variables	Overall (381)	No AKI (263)	AKI (118)	P-value
Urine volume, ml/24 h	1461.5 (826.9)	1757.2 (501.2)	802.2 (1011.5)	< 0.001
Hemoglobin, g/dl	132.8 (36.7)	135.8 (19.4)	126.2 (58.9)	0.02
Leukocyte, X10 ⁹ /L	16.8 (17.3)	13.0 (8.6)	25.3 (26.5)	< 0.001
Platelet, X10 ⁹ /L	175.0 (71.5)	170.6 (64.3)	184.8 (84.8)	0.07
TBI, mg/dl	22.8 (33.7)	18.9 (13.1)	66.6(55.7)	< 0.001
ALT, U/L	36.1 (65.1)	26 (34.2)	154.5(321.5)	< 0.001
AST, U/L	52.4 (213.0)	32.6 (50.8)	686.5(1121.4)	< 0.001
TP, g/L	68.2 (11.3)	67.7 (7.7)	69.3 (16.7)	0.18
Albumin, g/L	42.1 (5.0)	42.7 (4.3)	40.5 (5.9)	< 0.001
UA, μmol/L	337.8 (121.5)	312.2 (89.4)	394.8 (159.2)	< 0.001
CK, U/L	317 (1047.2)	195 (562.8)	2656.5(5274.5)	< 0.001
LDH, U/L	309 (1045.2)	235.1 (143.0)	2051.5(1781.3)	< 0.001
Potassium, mmol/L	4.1 (1.9)	3.9 (2.2)	4.5 (0.9)	0.008
Calcium, mmol/L	2.25 (0.17)	2.28 (0.14)	2.18 (0.19)	< 0.001
PT, s	14.3 (9.9)	14.3 (11.0)	14.4 (6.7)	0.9
APTT, s	51.1 (28.6)	44.1 (21.2)	66.8 (36.0)	< 0.001
Data represent the mean (SD) or median (interquartile ranges) as appropriate; categorical data represent percentage				
AKI: acute kidney injury				
RRT: renal replacement therapy				
SBP: systolic pressure				
DBP: diastolic blood pressure				
TBI: total bilirubin				
ALT: alanine transaminase				
AST: aspartate aminotransferase				
TP: total protein				
UA: uric acid				
CK: creatine kinase				

Variables	Overall (381)	No AKI (263)	AKI (118)	P-value
LDH: lactate dehydrogenase				
PT: prothrombin time				
APTT: activated partial thromboplastin time				

Risk Factors Related to AKI following wasp stings

To determine the risk factors for AKI following wasp stings, the univariable and multivariable logistic regression analysis were performed in the training set. Variables with $P < 0.1$ in the univariable logistic regression analysis introduced into multivariable logistic regression analysis (see Table A2 in Additional file 2). Subsequently, multivariable logistic regression analysis identified five variables as independence risk factors for AKI following wasp stings: number of stings, HB < 110 g/dl, TBI > 34 mg/dl, ALT > 40 U/L and APTT > 47 s (as shown in the Table 2).

Table 2
Multivariable logistic regression analysis results to predict AKI following wasp stings

Variables	B value	Adjusted OR	95% CI		P-value
Number of stings, n					< 0.001
15–50	1.79	6.00	2.99	12.05	< 0.001
> 50	2.07	7.89	2.87	21.67	< 0.001
HB < 110 g/dl	1.65	5.22	2.30	11.85	< 0.001
TBI > 34 mg/dl	1.41	4.09	2.12	7.87	< 0.001
ALT > 40 U/L	1.87	6.52	3.30	12.85	< 0.001
APTT > 47 s	1.18	3.27	1.65	6.47	0.001
Constant	-4.36	0.01			< 0.001
Data represent the mean (SD) or median (interquartile ranges) as appropriate; categorical data represent percentage					
CI: confidence interval					
HB: hemoglobin					
TBI: total bilirubin					
ALT: alanine transaminase					
APTT: activated partial thromboplastin time					

Construction of a predictive formula according to multivariable logistic regression analysis

According to multivariable logistic regression, we could construct the predictive formula of the model to predict the AKI for multiple wasp sting patients in the training set:

$P(\text{for AKI following wasp stings})$

$$= \frac{1}{1 + e^{4.36 - 1.79X1 - 2.07X2 - 1.65X3 - 1.41X4 - 1.87X5 - 1.18X6}}$$

In the formula, P indicated the predicted AKI probability, X indicated the variables that included in the model (X1-X6 represented that number of stings is 15–50, number of stings > 50, HB < 110 g/dl, TBI > 34 mg/dl, ALT > 40 U/L, APTT > 47 s respectively). X was assigned as 1 while patient was consistent with the variable, otherwise, X was assigned as 0. The probability of AKI following multiple wasp stings could be calculated according to the formula based on the patient's individual clinical characteristics. When calculated probability > 0.338 (the cut off of the model), the AKI was predicted to occur, and when calculated probability \leq 0.338, the AKI might not occur.

Of note, as shown in the Table 3, the model showed a higher predictive value and diagnostic accuracy (area under the curve [AUC] = 0.912, accuracy [ACC] = 0.869) than any other risk factors such as ALT (AUC = 0.745, ACC = 0.772), APTT (AUC = 0.708, ACC = 0.703), HB (AUC = 0.594, ACC = 0.717), number of stings (AUC = 0.778, ACC = 0.774) and TBI (AUC = 0.777, ACC = 0.795) (all P value < 0.05). The cut off of the model was 0.338. In addition, the specificity of the model was 0.882, the sensitivity of the model was 0.856 and the prediction accuracy was 0.869. The similar results were found in the validation set (as shown in the Table 3 and Figure A1 in Additional file 3).

Table 3
Performance of prediction model and independence risk factors

Variables	AUC	95%CI	Specificity	Sensitivity	ACC	P-value ^a	
Prediction model							
Training set	0.912	0.88	0.94	0.882	0.856	0.869	
Validation se	0.936	0.88	0.97	0.922	0.865	0.898	
ALT							
Training set	0.745	0.70	0.79	0.684	0.805	0.772	< 0.001
Validation se	0.755	0.67	0.83	0.644	0.865	0.709	< 0.001
APTT							
Training set	0.708	0.66	0.75	0.696	0.720	0.703	< 0.001
Validation se	0.705	0.62	0.78	0.733	0.676	0.717	< 0.001
HB							
Training set	0.594	0.54	0.64	0.916	0.271	0.717	< 0.001
Validation se	0.532	0.44	0.62	0.956	0.108	0.709	< 0.001
Number of stings							
Training set	0.778	0.73	0.82	0.783	0.754	0.774	< 0.001
Validation se	0.836	0.76	0.90	0.822	0.811	0.819	0.005
TBI							
Training set	0.777	0.73	0.82	0.825	0.729	0.795	< 0.001
Validation se	0.885	0.82	0.94	0.878	0.892	0.882	0.01
a: The P value was obtained by compared the AUC between the prediction model and ALT, APTT, HB, Number of stings or TBI respectively.							
AUC: area under the curve							
CI: confidence interval							
ACC: accuracy							
ALT: alanine transaminase							
APTT: activated partial thromboplastin time							
HB: hemoglobin							
TBI: total bilirubin							

Construction of a Nomogram and Validation

The individual nomogram was constructed based on the result of the multivariable logistic regression analysis to predict AKI for wasp sting patients in the training set too. As shown in the Fig. 2 and Table A3 in Additional file 4, scores were signed for each variable. A total point could be calculated by adding all points based on patient's individual clinical characteristics, which was lower meaning a lower probability of AKI. The nomogram was validated internally in the training set and were validated externally in the validation set. The calibration curves for AKI prediction showed excellently accordance between predictions of the nomogram and the actual observations in the training set (as shown in the Fig. 3) and validation set (see Figure A2 in Additional file 5). DCA verified the net benefit associated with the use of the nomogram-derived probability for AKI following wasp stings in the training set (as shown in the Fig. 3) and validation set (see Figure A3 in Additional file 6).

Discussion

In our study, number of stings, HB < 110 g/dl, TBI > 34 mg/dl, ALT > 40 U/L and APTT > 47 s were identified as independent risk factors for AKI following wasp stings according to univariable and multivariable logistic regression analysis in the training set. And the predictive formula and the individual nomogram that included those independent risk factors was developed and validated to predict the probability of the AKI following wasp stings. Those were demonstrated having the sufficient accuracy and good predictive capability based on the internal validation and external validation in the training set and validation set respectively. In addition, the predictive formula and individual nomogram both have clinical significance to assess the probability of the AKI following wasp stings and make a decision for therapy by those easy, convenient and effective methods.

At present, wasp stings are reported frequently, especially in rural areas where patients may have low incomes[22–24], which is a common challenge to society. In the present study, the incidence rate of AKI is 30.5% (155/508) in patients with wasp stings, which is nearly equal to results in the previous studies that reported the incidence rate of AKI is 20–25%[11, 25, 26]. In addition, the mortality in patients with wasp stings is 5.7% (29/508), however the mortality (17.4% [27/155]) in the AKI group is apparently higher than that (0.6% [2/353]) in the non-AKI group ($P < 0.001$ as shown Figure A4 in Additional file 7). Those indicated that it is significant to understand, risk predict and early diagnose the AKI following wasp stings. Of note, 55.6% (15/27) patients with AKI following wasp stings died within 72 hours after admission, that is similar to the result of previous study[14]. At present, AKI following wasp stings with relatively high mortality rate and rapid onset were called the “Silent Killer” because it threatened to human public health. Therefore, early detection and diagnosis should be performed promptly to help clinicians make therapeutic decisions for obtaining a good prognosis.

However, the prediction model of AKI following wasp stings is rarely reported in previous studies. We established the predictive formula and the individual nomogram based on the independent risk factor,

which predicted the AKI of patients undergoing wasp stings with a good validation. As reported in previous studies, nomogram is extensively used to predict the probability of a disease or a clinical outcome based on multiple variables[27–30]. In the present study, the visual nomogram could calculate the specific probability of AKI following wasp stings based on the sum of the scores of each risk factor, that is the most user-friendly tool to judge the specific situation of each patient[31]. The nomogram is intuitive and easy-to-understand not only clinicians but for patients as well, which might make it easy for communication between clinicians and patients. Of note, nomograms have never been reported for AKI following wasp stings to our knowledge, we conduct the first nomogram to predict the AKI following wasp stings.

Besides, the predictive formula also is conducted to assess whether occur AKI or not in patients with wasp stings, that is judged according to whether the calculated probability > the cut off of the model (0.338) or not. One of the two methods could be selected according to the habits and preferences of clinicians, or both to mutually detect and support the results. Those are composed of common clinical parameters, that are easy to obtain from laboratorial blood tests. In addition, the sufficient accuracy and good predictive capability of the model are verified by AUC of ROC (0.912 in the training set and 0.936 in the validation set), and the net benefit is verified by DCA. Therefore, the model might provide a clinical assistance in early recognition, detection, diagnosis and intervention of AKI following wasp stings.

According to previous studies, AKI is induced in wasp stings based on direct toxicity of the venom components, hypotension, intravascular hemolysis and rhabdomyolysis[32]. The venom components, such as PLA₂ that is mainly included in wasp venom and melittin that is the mainly included in the bee venom, both have strong hemolytic toxicity and direct toxic effect for inducing the apoptosis of renal tubule epithelial cells[16, 33]. Hypotension might lead to ischemic renal lesion, which is induced by main components of bee venom such as hyaluronidase, apamin and substances induced by those venom themselves such as histamine, serotonin, bradykinin.

Besides, rhabdomyolysis and hemolysis induced AKI by renal vasoconstriction, formation of intratubular deposits of myoglobin and direct cytotoxicity of myoglobin and HB that are release from muscle and red blood cells. However, there is no full understanding in the mechanism through which renal damage occurs. Nonetheless, it is certain that rhabdomyolysis and hemolysis are thought play important roles in AKI following wasp stings.

In the present study, compared with non-AKI group, we actually find the levels of CK, ALT, AST elevate in the AKI group, which might be associated with rhabdomyolysis. We also find LDH increase and anemia (HB in the red blood cells decrease) in the AKI group, which might be is concerned with hemolysis. They also are the risk factors of AKI following wasp sting according to univariable logistic regression analysis. Continuous variables are transformed into categorical variables according to their reference range, which is beneficial to full use the results through constructing the model.

According to multivariable logistic regression analysis, number of stings, HB < 110 g/dl, TBI > 34 mg/dl, ALT > 40 U/L and APTT > 47 s are considered as independence risk factors and could help to predict AKI in patients with wasp stings. Rhabdomyolysis and hemolysis could induce the level of indirect bilirubin to elevate, which could be one explanation of the increasing of TBI in AKI following wasp stings. According to the study reported, disseminated intravascular coagulation (DIC) might be a possible factor that contributes to AKI, described in rhabdomyolysis. While DIC occurred, thromboplastin is released and micro thrombi is formed in the glomeruli, which causing the consequent glomerular filtration rate reduction[34]. DIC might induce APTT prolonged by increasing the consumption of coagulation factors. We think those might explain why prolonged APTT is an independence risk factors in AKI following wasp stings. In addition, we also find that wasp compared with other bee species, sting at head and face compared with other locations, the greater number of stings and large area of sting might be associated with AKI following wasp stings.

However, a recent study with a retrospective cohort study involving 112 patients conducted by Hai Yuan et al, which showed that elevated leukocytes, high myoglobin, high urinary monocyte chemotactic protein-1 (MCP-1) are the independence risk factors of AKI induced by multiple wasp stings[25]. In fact, our results also find that, while compared with non-AKI, the level of leukocytes is higher in the patients with AKI following wasp stings. However, we do not think elevated leukocytes is an independence risk factor of AKI following wasp stings based on the multivariable logistic regression analysis. There exists a difference between the two studies. It's worth noting that the results are obtained based on the single center as well as the small sample size in the Hai Yuan's study. In addition, 12 variables included in the multivariable logistic regression analysis to find out the independence risk factors based on only 54 patients who occurred AKI. We think those might restrict external validity and cause the different results in the Hai Yuan's study. Besides, Hai Yuan's study only reported some independence risk factors, which did not construct a model to predict AKI for fully utilization the result. We construct the first model based on a large data from the multicenter prospective cohort study and validate it.

There exist some limitations in the present study. First, there are some variables missing too much so that we have to exclude them such as cystatin -C and urine protein, although we already try our best to collect the complete data of each patient. Second, although data were collected from multicenter, the enrolled patients all were of the same ethnicity, which might limit the scalability of the model. Third, we select the variable by forward stepwise in multivariable logistic regression analysis, that might induce the final model that contain terms of little values. Besides, the validation was performed by bootstrapping technology, however there also need further external validation in further.

Conclusion

In conclusion, we proved that number of stings, HB < 110 g/dl, TBI > 34 mg/dl, ALT > 40 U/L and APTT > 47 s were independence risk factors for AKI following multiple wasp stings. And the predictive formula and the individual nomogram were established and validated based on those predictive factors to predict AKI following wasp stings. Of note, those could serve as promising predictive tools to assess the

probability of the AKI following wasp stings and help make a decision for therapy easily and conveniently.

Declarations

Ethics approval and consent to participate

The study was approved by Institutional Research Ethics Committees of West China Hospital of Sichuan University (Approval No. of the ethics committee: 2014-156).

All enrolled patients approved to participate and written informed consents were obtained from all enrolled patients or their legally authorized representatives.

Consent for publication

All authors approved of publication.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

All authors contributed to the study conception and design. PF and LZ, as the corresponding authors of this paper, were mainly responsible for program design and modification. XT and LL wrote the first draft. XT, LL and YY summarized data from each center. LZ, BW and RH assessed the data and analyzed. And YW, JXu, JXi, DC, ZZ, HX, CL7, WB, YM, HT, ZT, WZ, DX, LinZ, LL, FC, YW all put their hands-on enrolling patients, recording data and completing patient follow-up. All authors commented on previous versions of the manuscript and all authors read and approved the final manuscript.

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