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Development and Validation of Nomogram-Based Prediction of Chronic Subdural Hematoma Recurrence after Initial Burr-Hole Surgery

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ABSTRACT

AIM: To establish and validate a practical nomogram to predict recurrence of chronic subdural hematoma (CSDH) in patients after initial burr-hole surgery.

MATERIAL and METHODS: The prediction model was developed from a training set of 272 patients with CSDH who had undergone standard burr hole with irrigation surgery. A separate external validation cohort comprising 112 patients who underwent the same operation was also included. Least absolute shrinkage and selection operator (LASSO) regression was adopted to minimize the high dimension of data and predictor selection. Binary logistic regression was used to develop the present model. Subsequently, a nomogram was established as the ultimate representation of the prediction model. Area under the curve (AUC) was used to identify the discrimination of the designed predictive nomogram. The calibration plot was used to verify the goodness-of-fit of the nomogram. Finally, Decision curve analysis (DCA) was employed to appraise the clinical applicability of the present nomogram.

RESULTS: A total of 3 independent variables were filtered by LASSO analysis from the 22 candidate factors. The AUC of the training and validation sets were 0.833 (95%CI: 0.774-0.894) and 0.817 (95%CI: 0.711-0.922), respectively, which indicated a good discrimination ability. The calibration charts showed that the prediction probability and the actual probability fitted well. The DCA of the prediction model indicated an excellent clinical efficacy.

CONCLUSION: The proposed nomogram can quantitatively and conveniently predict the recurrence rate of CSDH after burr hole with irrigation surgery. Besides it can facilitate customized treatment adjustment and follow-up of patients who are at a high-risk of recurrence.

KEYWORDS: Prediction model, Nomogram, Chronic subdural hematoma, Recurrence

ABBREVIATIONS: AUC: Area under the curve, **AT:** Antithrombotic treatment, **CSDH:** Chronic subdural hematoma, **CT:** Computed tomography, **DCA:** Decision curve analysis, **LASSO:** Least absolute shrinkage and selection operator, **ROC:** Receiver operating characteristic

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INTRODUCTION

In neuroscience, chronic subdural hematoma (CSDH) is a common intracranial hemorrhage which can be easily diagnosed and treated. However, investigators have continued to focus on improving the available treatment options (12). Surgery is the most preferred therapy option for patients with CSDH, especially when there are clinical symptoms that can be attributed to mass effect. Owed to the numerous research studies, surgical methods for CSDH treatment have gradually advanced giving rise to diverse treatment options such as mini or full craniotomy, neuroendoscopy, twist-drill opening, and fully enclosed conus cranial drainage (30). The most effective and preferred operation procedure by neurosurgeons is drilling a burr hole for drainage since it has a postoperative recurrence rate of 2-35% (1). Furthermore, researchers have continued to look into other possible factors affecting the disease that can improve its treatment (22). Subsequently, several conflicting cases about the kinds of elements that can influence the postoperative recurrence of CSDH patients have been encountered. Generally, the main factors that influence CSDH postoperative recurrence are; the patient's history, underlying physical conditions, CSDH imaging features, and treatment options. Therefore, to accurately predict the postoperative recurrence of CSDH based on clinical data, there is a need to quantify the importance of these influencing factors. The objective identification of high-risk patients can facilitate making a targeted follow-up. The purpose of the present study was to establish and verify a nomogram for predicting postoperative recurrence of CSDH as well as to provide a useful and practical tool that can assist in clinical and scientific research.

MATERIAL and METHODS

Study Design and Participants

A total of 384 out of the 457 patients who had undergone a burr hole with irrigation surgery between 2000 and 2019 at the neurosurgery of People's Liberation Army Joint Logistic Support Force 904th Hospital, Wuxi, Jiangsu, China were selected. Only the patients who had complete clinical records and at least half a year of follow-up information were enrolled in the current retrospective research. All cases were divided randomly into the training set (272 patients) and the validation set (112 patients) as per 7:3 ratios.

Diagnosis information was supported by a head computed tomography (CT) scan. Two competent teams reviewed all the data. Recurrence was characterized as a brain CT showing CSDH that requires reoperation, which had spread in the unilateral subdural area within six months after the first burr hole drilling. Additionally, engendered signs and symptoms such as hemiparesis, aphasia, and deterioration of consciousness were considered (5). Exclusion criteria included: (a) patients under 18 years of age; (b) patients with severe complications during the course (such as apparent secondary intracranial infection, puncture site intracranial hemorrhage, etc.); (c) patients on long-term steroids (9); and (d) the CSDH patients who had blood diseases or malignant tumors. The retrospective research received ethical approval from the Institutional Review Board of People's Liberation Army Joint Logistic Support Force 904th Hospital.

Surgery and Comprehensive Administration

A normalized (or two) burr hole was made in the ipsilateral CSDH of all patients, and 0.9% NaCl was used for irrigation. The choice of anesthetic and method of application was based on the patient's tolerance level and fitness. Thus, local, combined (local anesthesia combined with intravenous sedation) or general anesthesia was used. Closed-system subdural drainage was performed in all cases, and the silicon tubes were placed in frontotemporal. The amount and color of drainage and CT scan were used to determine the drainage time.

Clinical and Radiological Feature Selection

In present study, 22 candidate predictors were selected according to a previous report's recommendation (Table I).

During the treatment period, antihypertensive drugs were used in cases where the patient or their representative complained of a history of hypertension. This was considered as being hypertensive in the current study. Similar approaches were used to designate the rest of the related accounts. In this study, "history of head injury" cases were decided in situations where the patient had obtained affirmatory head injury 3 to 12 weeks before the initial surgery (11).

The CT scan was used to assess hematoma volume before initial burr-hole surgery, and one week after the operation (the total volume of bilateral hematoma was estimated). Subsequently, the following equation was used to determine the postoperative brain re-expansion rate: (pre-operative volume of CSDH – post-operative volume of CSDH) / preoperative the volume of CSDH×100(%) (4,15,25). As for satisfactory postoperative in the 1st day, more than 50% hematoma reduction was considered satisfactory, and less than 50% was considered unsatisfactory (16).

Statistical Analysis

Illuminating figures were used to compile the general distinctive features of each factor. Descriptive statistics, that is, median values (25-75% interquartile) was used to summarize non-normal data. Mann Whitney U test was performed to analyze continuous data. Proportions (percentages) were used to summarize categorical statistics through the chi-square test. The least absolute shrinkage and selection operator (LASSO) regression method, an effective mode of selecting variables (26,34), was used to select the optimum indicator elements from all candidate components.

After screening for characteristic predictors by LASSO regression, the prediction model was produced by binary variable regression and presented by the visual nomogram. The area under the curve (AUC), defined as the area under the receiver operating characteristic (ROC) curve was applied to assess the discrimination of the models. In this study, the calibration chart illustrated the goodness-of-fit for the

Table I: Characteristics of Patients of CSDH in the Training Set and Validation Set

	Training Set			Validation Set		
Characteristic	**NRG (n=232)**	**RG (n=40)**	**p**	**NRG (n=93)**	**RG (n=19)**	**p**
Gender, n (%)			0.90			0.557
Male	199 (85.8)	34 (85.0)		75 (80.6)	17 (89.5)	
Female	33 (14.2)	6 (15.0)		18 (19.4)	2 (10.5)	
Age, n (%), years			**< 0.01**			0.061
≤ 65	115 (49.6)	6 (15.0)		41 (44.1)	4 (21.1)	
66 - 79	68 (29.3)	13 (32.5)		34 (36.5)	7 (36.8)	
≥ 80	49 (21.1)	21 (52.5)		18 (19.4)	8 (42.1)	
Head injury, n (%)			0.469			0.680
No	167 (72.0)	31 (77.5)		59 (63.4)	13 (68.4)	
Yes	65 (28.0)	9 (22.5)		34 (36.6)	6 (31.6)	
Hypertension, n (%)			0. 253			0.920
No	144 (62.1)	21 (52.5)		55 (59.1)	11 (57.9)	
Yes	88 (37.9)	19 (47.5)		38 (40.9)	8 (42.1)	
Diabetes, n (%)			0.057			0.974
No	212 (91.4)	32 (80)		80 (86.0)	17 (89.5)	
Yes	20 (8.6)	8 (20)		13 (14.0)	2 (10.5)	
PLT level, n (%), 10^9/L			0.898			1.00
< 100	209 (90.1)	37 (92.5)		88 (94.6)	19 (100)	
100 - 300	18 (7.7)	2 (5)		3 (3.2)	0 (0)	
> 300	5 (2.2)	1 (2.5)		2 (2.2)	0 (0)	
Cerebral infarction, n (%)			0.772			0.889
No	214 (92.2)	38 (95)		87 (93.5)	17 (89.5)	
Yes	18 (7.8)	2 (5)		6 (6.5)	2 (10.5)	
AT, n (%)			0.635			1.00
No	217 (93.5)	36 (90.0)		85 (91.4)	17 (89.5)	
Yes	15 (6.5)	4 (10.0)		8 (8.6)	2 (10.5)	
Course, n (%), month			0.557			1.00
< 1	36 (15.5)	6 (15.0)		19 (20.4)	4 (21.1)	
1 - 2	151 (65.1)	29 (72.5)		57 (61.3)	12 (63.2)	
> 2	45 (19.4)	5 (12.5)		17 (18.3)	3 (15.8)	
Preoperative GCS score			0.792			0.757
13 - 15	215 (92.7)	36 (90.0)		83 (89.2)	18 (94.7)	
3 - 12	17 (7.3)	4 (10.0)		10 (10.8)	1 (5.3)	
Bilateral surgery, n (%)			0.684			0.465
No	164 (70.7)	27 (67.5)		62 (66.7)	11 (57.9)	
Yes	68 (29.3)	13 (32.5)		31 (33.3)	8 (42.1)	
Midline, n (%)			0.772			0.657
No	33 (14.2)	4 (10.0)		10 (10.8)	3 (15.8)	
< 1cm	127 (54.7)	23 (57.5)		59 (63.4)	10 (52.6)	
≥ 1cm	72 (31.1)	13 (32.5)		24 (25.8)	6 (31.6)	
Hematoma density in CT, n (%)			0.775			0.447
Hypodense	63 (27.2)	8 (20.0)		22 (23.7)	2 (10.5)	

Table I: Cont.

	Training Set			Validation Set		
Characteristic	**NRG (n=232)**	**RG (n=40)**	**p**	**NRG (n=93)**	**RG (n=19)**	**p**
Isodense	54 (23.3)	9 (22.5)		21 (22.6)	3 (15.8)	
Hyperdence	66 (28.4)	13 (32.5)		29 (31.4)	8 (42.1)	
Mixed	49 (21.1)	10 (25.0)		21 (22.6)	6 (31.6)	
Preoperative volume, median (IQR), ml	80.0 (40.0)	100.0 (37.5)	**< 0.01**	90.0 (30.0)	100.0 (10.0)	**0.039**
Type of anaesthesia, n (%)			0.340			0.103
Local	185 (79.7)	36 (90.0)		74 (79.6)	11 (57.9)	
Local+Intravenous	11 (4.7)	1 (2.5)		7 (7.5)	3 (15.8)	
General	36 (15.5)	3 (7.5)		12 (12.9)	5 (36.3)	
Unilateral double hole, n (%)			0.106			0.321
No	199 (85.8)	37 (92.5)		80 (86)	14 (73.7)	
Yes	33 (14.2)	3 (7.5)		13 (14)	5 (26.3)	
Duration of catheter, n (%), day			0.137			0.088
≤ 2	80 (34.5)	9 (22.5)		33 (35.5)	3 (15.8)	
3 - 5	135 (58.2)	25 (62.5)		54 (58.1)	16 (84.2)	
> 5	17 (7.3)	6 (15.0)		6 (6.4)	0 (0)	
Encephalatrophy, n (%)			0.088			0.610
NO/Mild	118 (50.9)	13 (32.5)		39 (41.9)	10 (52.6)	
Moderate	89 (38.4)	20 (50.0)		44 (47.3)	8 (42.1)	
Severe	25 (10.8)	7 (17.5)		10 (10.8)	1 (5.3)	
Brain re-expansion, n (%)			**< 0.01**			**0.004**
Good (≥ 50%)	167 (72.0)	13 (32.5)		53 (57.0)	4 (21.1)	
Poor (< 50%)	65 (28.0)	27 (67.5)		40 (43.0)	15 (78.9)	
Satisfaction on 1st postoperative day, n (%)			0.511			**0.048**
No	187 (80.6)	34 (85.0)		72 (77.4)	19 (100)	
Yes	45 (19.4)	6 (15.0)		21 (22.6)	0 (0)	
Statins therapy, n (%)			0.127			**0.032**
No	87 (37.5)	10 (25.0)		39 (41.9)	3 (15.8)	
Yes	145 (62.5)	30 (75.0)		54 (58.1)	16 (84.2)	
Carbazochrome use, n (%)			0.416			0.311
No	129 (55.6)	25 (62.5)		51 (54.8)	8 (42.1)	
Yes	103 (44.4)	15 (37.5)		42 (45.2)	11 (57.9)	

CSDH: *Chronic subdural hematoma,* ***NRG:*** *Non-recurrence group,* ***RG:*** *Recurrence group,* ***AT:*** *Antithrombotic treatment,* ***PLT:*** *Platelets,* ***GCS:*** *Glasgow Coma Scale,* ***CT:*** *Computed tomography,* ***IQR:*** *Interquartile.*

postoperative recurrence risk prediction model of CSDH. The decision curve analysis (DCA) was used to evaluate the analytical practicality of the nomogram by assessing its net benefits at specific threshold possibilities. Data analysis was completed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA), R software version 3.5.1 (http://www.R-project.org), and Stata version 14.0 (StataCorp, College Station, TX, USA). The packages in the R software were 'glmnet' package for LASSO and 'rms' package for nomogram and calibration. The statistical tests applied in the present study were all double-tailed. The significant level was set at $p < 0.05$.

RESULTS

Clinicopathologic Characteristics of the Patients

The relationship between various factors and the recurrence rate post-operation was evaluated using univariable analyses. The relapse rate of the training set (n=272) was 14.7% while the rate of validation set (n=112) was 17.0%. The relapse rate of the validation set was considered similar to that of the training set. The related baseline characteristics of the training and validation cohorts are classified in Table I.

Factor Selection and Development of the Prediction Model

The LASSO regression analysis was used to screen the optimum predictors from the candidate elements in the present study (34). A total of 22 candidate factors of the 272 patients in the training cohort were reduced to 3 predictors (Figure 1A). A non-zero coefficient profile was generated from the LASSO regression analysis (Figure 1A). The cross-validation results of the LASSO regression and the coefficient paths entered in the model are illustrated in Figure 1B. Cross-validation error within one standard error of the minimum (1SE) range received the most appropriate and concise model containing 3 factors.

The model in the present study contained 3 unbiased variables and was established as a nomogram (Figure 2). The entire nomogram presented the list of variable names alongside their weight in the form of scores. In the study, the process of model development and subsequent validation was based on the TRIPOD statement (6).

Discrimination and Calibration of the Nomogram

The AUC of the present training and validation sets were 0.833 (95%CI: 0.774-0.894) and 0.817 (95% CI: 0.711-0.922), respectively (Figure 3A, B). This exceeded 0.70 and thus indicated an excellent performance and favorable predictive efficacy (10).

The calibration chart of the current CSDH recurrence risk model revealed that there was an excellent relationship between the actual incidence and the predicted possibilities in the training set (Figure 4A, P=0.741>0.05). Accordingly, this corresponded well with the validation set (Figure 4B, P=0.662>0.05). Moreover, the statistical value of the Hosmer–Lemeshow test (P= 0.679>0.05) demonstrated that the model did not deviate from the perfect fit.

Decision Curve Analysis of the Nomogram

The DCA was applied to assess the potential of clinical practicability of the postoperative CSDH recurrence by computing the net benefits. The DCA of the prediction model is shown in Figure 5. The model indicates that, at the threshold probability range of 4.3 to 56.6%, using this model to predict

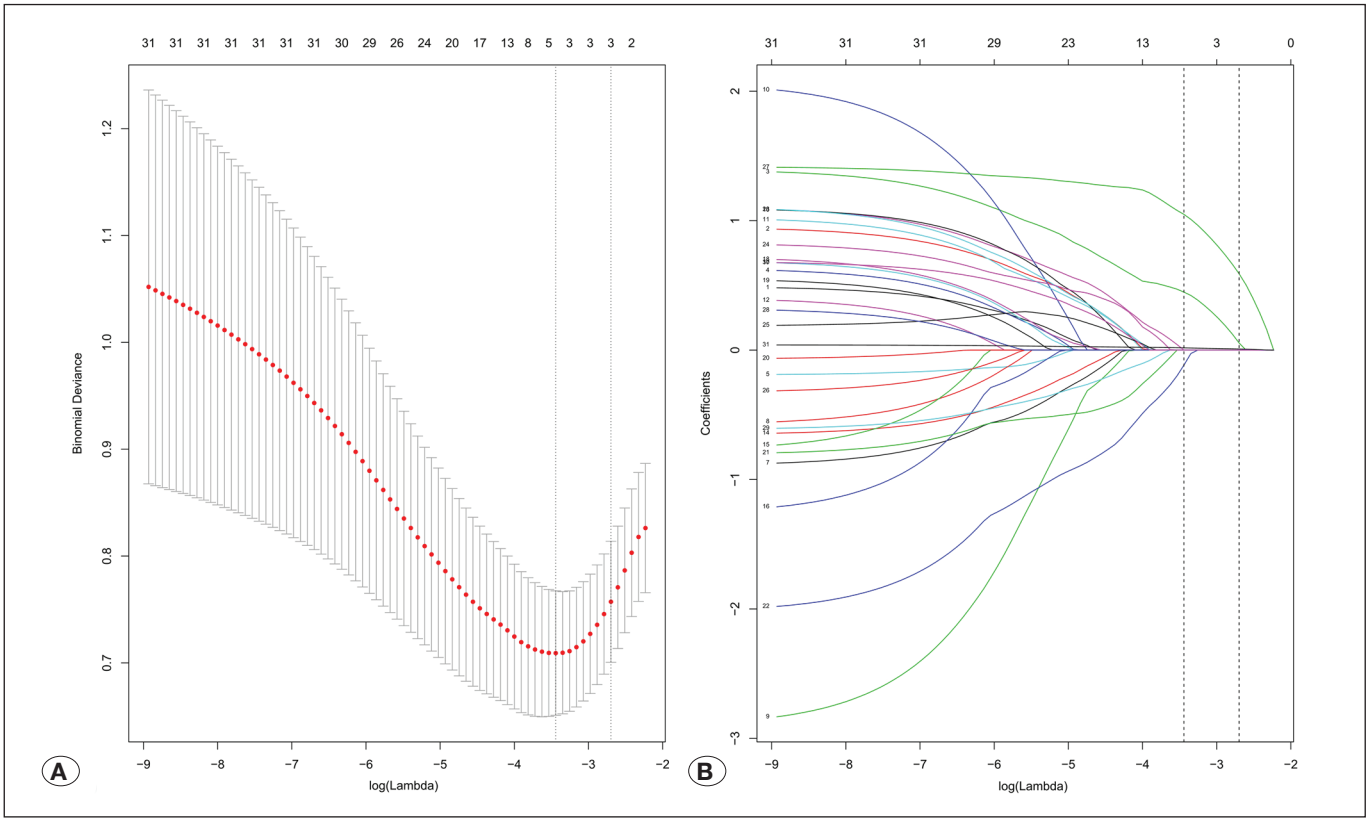

Figure 1: Factors selection using the LASSO logistic regression model. **A)** LASSO coefficients of 22 candidate variables. **B)** Identification of the optimal penalization coefficient (λ) in the LASSO model was achieved through 10-fold cross-validation and the minimum criterion. The left vertical line represents the minimum error, and the right vertical line represents the cross-validated error within 1 standard error of the minimum. **LASSO:** Least absolute shrinkage and selection operator.

Table II: Predictors for Postoperative Recurrence of CSDH

Intercept and Variable	β	Odds Ratio (95% CI)	p
Intercept	-4.381	0.013	-
Age			
≤ 65	-	1	-
66 - 79	0.923	2.517 (0.921-6.885)	0.072
≥ 80	1.366	3.920 (1.351-11.376)	**0.012**
Preoperative volume	0.013	1.013 (1.001-1.025)	**0.040**
Brain re-expansion			
Good(≥ 50%)	-	1	-
Poor(< 50%)	1.332	3.788 (1.824 to 7.867)	**<0.001**

CSDH: *Chronic subdural hematoma.*

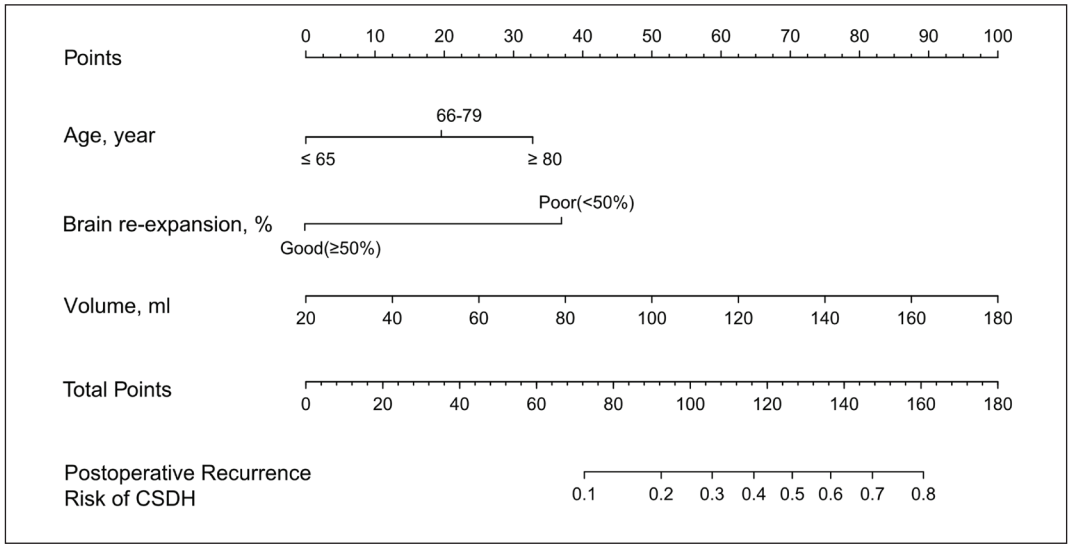

Figure 2: The calibration nomogram for predicting postoperative recurrence in patients with CSDH. The nomogram was developed in the training group by incorporating the following 3 parameters: age, preoperative hematoma volume, brain re-expansion. **CSDH:** Chronic subdural hematoma.

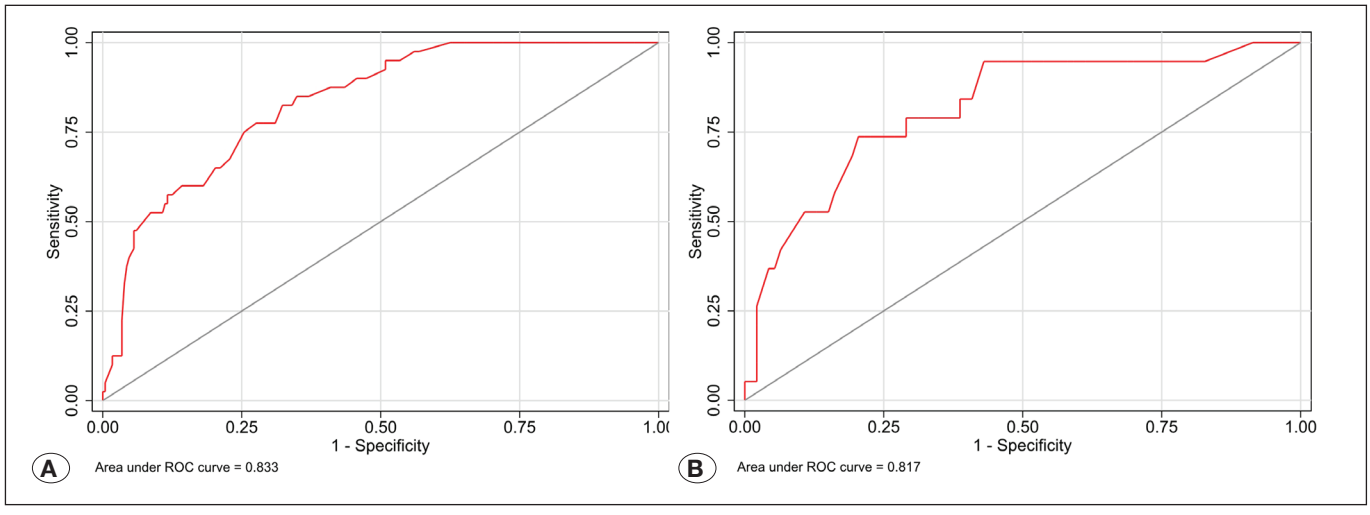

Figure 3: The ROC curves of the postoperative recurrence risk of CSDH nomogram. **A)** The ROC curve in the training set. **B)** The ROC curve in the validation set. **ROC:** Receiver operating characteristic; **CSDH:** Chronic subdural hematoma.

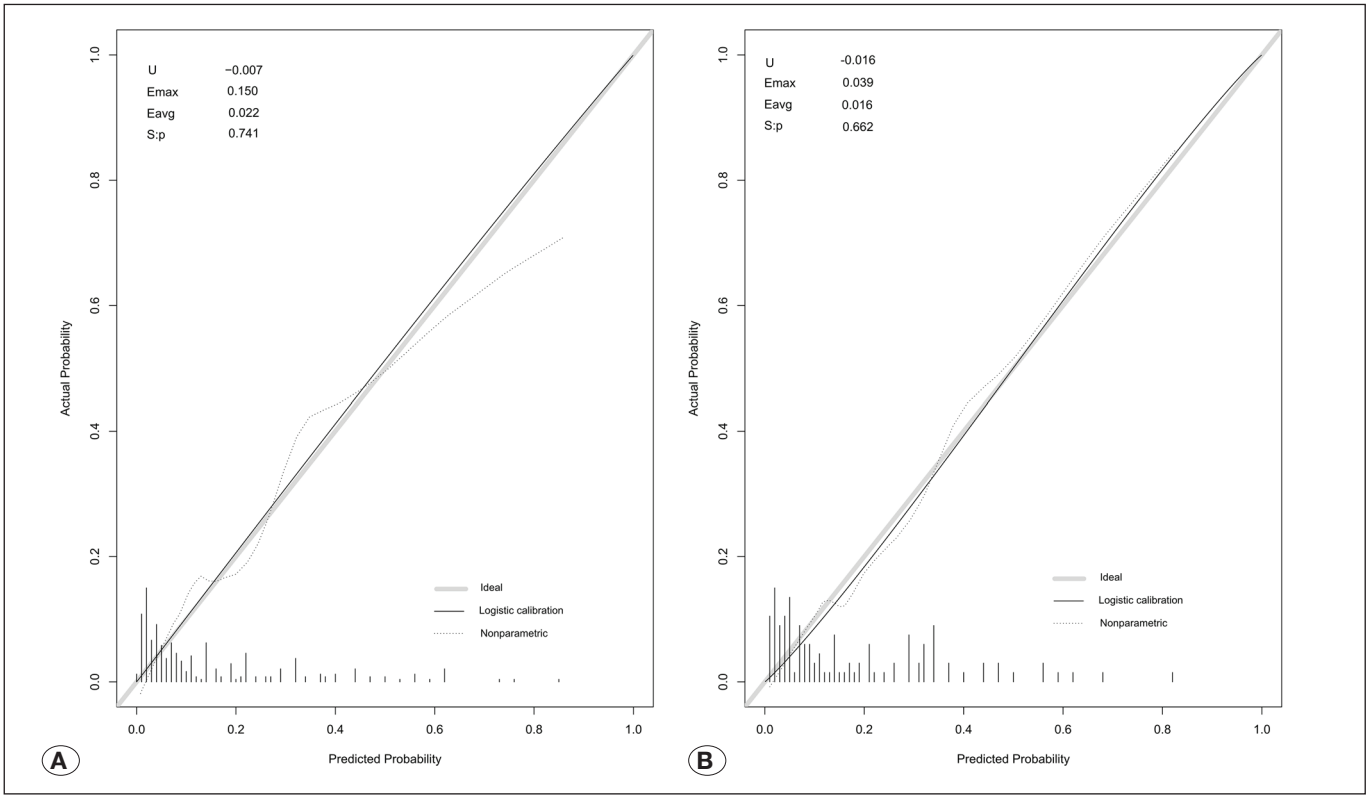

Figure 4: The calibration curves of the postoperative recurrence risk of CSDH nomogram. **A)** The calibration of the nomogram in the training set. **B)** The calibration of the nomogram in the validation set. It shows that logistic calibration is very close to the ideal, thus indicating that the prediction model has a higher degree of calibration. **CSDH:** Chronic subdural hematoma.

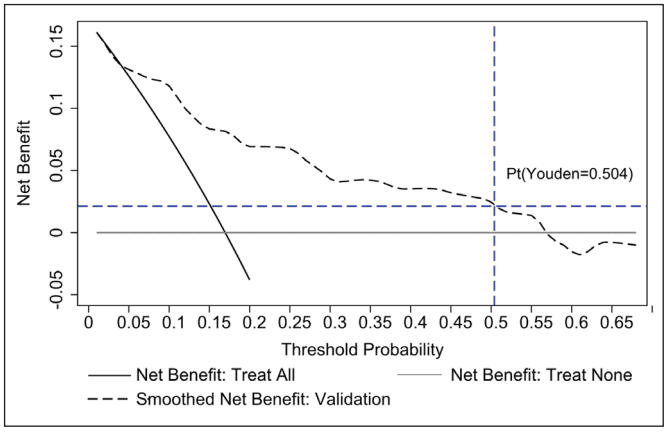

Figure 5: DCA of the postoperative for postoperative recurrence risk of CSDH nomogram. The y-axis determines the net benefit. The dotted line represents the predictive nomogram. **DCA:** Decision curve analysis, **CSDH:** Chronic subdural hematoma.

the recurrence rate was more beneficial than "all treatment" or "no treatment" strategy. The DCA of the model has been shown that even at Pt (point, the cut-off point with the largest Youden index), there is also a satisfactory net benefit.

DISCUSSION

In the past few decades, scholars have proposed a series of factors leading to the recurrence of CSDH through several clinical prospective and retrospective studies (8,31). Besides, numerous related causative factors have been reported. These include: gender (male patients are more prone to the condition), history of patient's lifestyle (such as alcohol and smoking), antithrombotic treatment (AT, such as antiplatelets and anticoagulants), associated chronic diseases (hypertension, diabetes and so on), old age, bilateral hematoma, severe brain atrophy, hematoma density on CT, massive hematoma before operation among other factors (20,21). Although various studies have attempted to elucidate the causes and mechanisms of postoperative recurrence of CSDH, the specific inducement, etiology, and pathogenesis of this condition remains unclear.

Motei-Langroudi et al. pointed out that many studies on the causative factors of incidence or recurrence in CSDH are usually not rigorous, and confounding factors are often omitted during the studies (16). In their study, they speculated that non-objective chief complaints, inappropriate choice of statistical methods, and different definitions for these factors in various studies may have led to the reported conflicting results (32,33). For statistical methods, most of the recent studies have adopted the statistical method for step-by-step screen-

ing of risk factors, which somehow leads to overfitting (27,28). LASSO regression is an excellent solution to this problem.

Recent studies in this area have gradually focused on investigating how to predict recurrence through more systematic statistical methods, rather than only finding out the recurrence factors (2,23). The weight of each influencing factor can be objectively reflected by establishing a forecasting model. This facilitates the accurate calculation of the CSDH recurrence rate, thus helps to identify high-risk patients. The identification of these cases can improve doctor-patient communication and facilitate personalized follow-up by doctors.

It has been long-established that the reliability of univariate analysis is not ideal at a statistical point of view. In the present study, by using the LASSO approach, 22 candidate risk factors were reduced to 3 potential predictors (age, preoperative hematoma volume, and brain re-expansion) in the construction of the predictive model of recurrence. This does not mean that the candidate elements that were not included in the present model are not related to the recurrence of CSDH. As shown in Figure 1, if the minimum mean squared error (lambda. min) was chosen, 5 candidate factors were included in the prediction model and statins therapy as well as duration of catheter were also included. Nevertheless, using one standard error (lambda.1SE) some candidate factors can be removed and the generalization of the model increased while ensuring the integrity of the model (14). This implies that this study did not intend to explore all the risk factors related to CSDH but only to find the most suitable prediction model.

Intuitively, age as a predictor in the model, the weights were different at different age groups (Figure 2). This result is consistent with previous studies (18,19). Among the various factors that influence postoperative recurrence of CSDH, brain re-expansion rate has been unanimously reported in most studies (13). Consistent with these studies, the brain re-expansion occupied the maximum weight in the present nomogram (Figure 2).

In the present study, the model was validated in three levels including AUC, calibration, and DCA after selecting the three prediction factors and presenting the prediction model in the form of a nomogram. The AUC of the model on the training set was 0.833. This indicated the model's capability to discriminate recurrence in a large group of patients. Despite the AUC indicating that the current model yielded a high predictive efficiency, it was verified through the calibration of the validation set. Satisfactorily, through this model, the AUC of the validation set was 0.817. As for the calibration of the predicted and actual risks, the accuracy of a nomogram is best depicted by the calibration chart, which shows the relationship between the two risks (24). The calibration plot of our model on the training set (Figure 4A) revealed a strong association between the nomogram and the data. The validation plot (Figure 4B) was slightly weaker but was still able to show superior calibration for the patients. Since the logistic calibration was also very close to the ideal, the difference between the two lines was not statistically significant ($P=0.662>0.05$). These results showed that the prediction model was an appropriate model for discrimination and calibration.

ROC or calibration chart is considered incapable of demonstrating the clinical validity of the model. Therefore, DCA was conducted to examine the clinical applicability of the model. The DCA is a statistical method that is used to evaluate whether the decision made through the model will enhance the prognosis of cases (29). This approach is established on the threshold probability to observe the clinical applicability and balance the net benefits (3). In the present study, the DCA indicated that using the model to predict the relapse rate in CSDH had an extra benefit. The advantages of the current study are as follows: 1) the selected predictors were selected by lasso regression to avoid over-fitting; 2) This nomogram provided more reliable data for future prospective research. This can help physicians to make judgments and timely advise on the risk of postoperative recurrence, hence build up individual follow-up plans conforming to the risk; 3) This model was validated at three dimensions (discrimination, calibration, and clinical usefulness).

There are some limitations to this study. Although the candidate factors selected in this study were appropriate as reported by previous studies, some other factors that needed further exploration were not included. For instance, a study demonstrated that the correlation between the relapse rate in CSDH patients and seniority of the surgeon was not significantly different ($p<0.05$) (17). The authors pointed out that due to incomplete morbidity and follow-up data, further studies were needed to validate their findings. Since the study was retrospective, selection biases were inevitable. Based on the effects of some factors on CSDH, some results of this study may be strange, such as AT. Our results are consistent with some studies (2,7). Thus far, external verification is the gold standard and should be obtained as much as possible. The present investigation adopted an independent data validation model after the development model. Moreover, a multi-center validation is needed to further evaluate the generalization of the model.

CONCLUSION

In the present study, 3 predictors (age, preoperative volume, and brain re-expansion) were selected from 384 candidate factors using the LASSO method. The predictive model was constructed based on the above predictors and presented in the form of a nomogram, which was verified by the validation group. The nomogram is concise with fewer variables and can be used to predict the recurrence of CSDH in routine clinical activity. However, further studies are required to validate whether it can be adopted for further external validation of patient groups.

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