Prediction score for clinical outcome of Chinese patients with cerebral venous thrombosis

Min Li  
Xuanwu Hospital, Capital Medical University

Binlong Zhang  
Guang'anmen Hospital, Chinese academy of Chinese Medical Sciences

Jiangbo Xie  
Weifang Traditional Chinese Hospital

Ran Meng  
ranmeng2011@126.com  
Xuanwu Hospital, Capital Medical University

Xunming Ji  
Beijing Institute for Brain Disorders, Capital Medical University

Research Article

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Abstract

**Background:** Despite a series of reported prognostic markers, there is no prediction score for clinical outcome of Chinese patients with cerebral venous thrombosis (CVT). This study is aimed to develop a CVT outcome score for Chinese.

**Methods:** The study sample came from CCC cohort, which is a multicenter study participated by 26 top tertiary hospitals in China Mainland. 170 CVT patients were prospectively recruited from January 2021 to May 2022. The potential prognostic markers were extracted from CCC database and analyzed.

**Results:** Age, diastolic blood pressure (DBP), neutrophil-to-lymphocyte ratio (NLR) and neuron specific enolase (NSE) were identified as prognostic markers for CVT after multivariate logistic analysis. Age > 27.5 years, DBP > 79.5mmHg, NLR > 6.6 and NSE >16.5 ng/ml were identified as cutoff values. One point was assigned to age and NSE, two points were assigned to DBP and three points were assigned to NLR based on adjusted odds ratio. CVT outcome score at baseline was positively correlated with mRS at 6 months of follow-up. CVT outcome score effectively predicted the clinical outcome of CVT with a cutoff value of 3.5. Further analysis showed that patients with CVT outcome score > 3 had significantly higher mRS than those with CVT outcome score ≤3.

**Conclusions:** CVT outcome score consists of age, DBP, NLR, and NSE for Chinese CVT patients was developed in this study. CVT outcome score at baseline positively correlated with mRS at 6 months of follow-up. CVT outcome score > 3 helps to identify CVT patients with high risk of poor clinical outcome and take early interventions to prevent deteriorations.

Introduction

Cerebral venous thrombosis (CVT) account for 0.5-1% of strokes with an incidence ranging from 1.3–1.6/100,000 population [1, 2]. Although CVT patients exhibits various clinical manifestations, diagnosis of CVT has become more accurate due to recent progression in neuroimaging [2, 3, 4]. However, a high proportion of poor clinical outcome and a high mortality rate had been reported [5, 6]. A multicenter study by Ferro et al [5] revealed that 13.4% of CVT patients from 21 Western countries had poor clinical outcome and 8.3% had died. Wasay et al [6] also supported that 12.7% of CVT patients from 9 Asian countries had poor clinical outcome and 8% had died. Furthermore, 56.1% of severe CVT patients in Germany had poor clinical outcome and 34.2% had died [7]. Therefore, a predictive method for the clinical outcome of CVT is in urgent need.

Our previous studies demonstrated that neutrophil-to-lymphocyte ratio (NLR), neuron specific enolase (NSE), and diastolic blood pressure (DBP) predicted outcome of CVT patients [8, 9, 10]. Results from other studies also reported a series of prognostic markers of CVT [5, 11, 12]. However, it is confusing when predictions by distinctive prognostic markers were inconsistent. Thus, developing a CVT outcome score based on identified prognostic markers may exhibit a stronger predictive power for the clinical outcome of CVT.
CVT outcome scores had been put up by Ferro et al [13] in 2009 and Bushnaq et al [14] in 2018. Notably, a considerable difference was observed in two versions of the CVT outcome score. Ferro et al [13] recruited CVT patients in Portugal, France, and Brazil whereas Bushnaq et al [14] recruited CVT patients in New Mexico of United States. It is suggested that CVT outcome score differed in distinctive countries and races. Thus, this study was aimed to establish a CVT outcome score for Chinese CVT patients.

**Methods**

**Study sample**

The study sample came from the CCC cohort (NCT03919305), which is a multicenter study participated by 26 top tertiary hospitals in China Mainland [15]. CVT patients were prospectively recruited from January 2021 to May 2022. The diagnosis of CVT was made based on clinical symptoms and neuroimaging as previously described [10].

**Data extraction**

The potential prognostic markers such as age, gender, level of consciousness (LOC) [16], new-onset epilepsy [17], mental disorders [13], malignancy [18], central nervous system (CNS) infections [5], deep venous system thrombosis [19], use of oral contraceptive pills (OCPs) [20], DBP [10], papilledema [17], number of sinuses involved [17], the occurrence of parenchymal lesions [21], C-reactive protein (CRP) [12], fasting blood glucose [11], NLR [8], NSE [9], platelet count (PLT) [17] and serum sodium level [17] were extracted from CCC database and were further analyzed.

**Outcome measurement**

The outcome of CVT was evaluated by Modified Rankin Scale (mRS) at 6 months post-onset. Similar to previous studies, mRS ≤ 1 was defined as good outcome and mRS > 1 was defined as poor outcome [8, 12]. The binarized mRS outcome was used for further analysis.

**Statistical analysis**

All the statistical analyses were conducted using SPSS version 19.0 (SPSS Inc., Chicago, IL). Two sample t-tests were used to compare the difference of continuous variables between the two groups, and Chi-square tests were used for categorical variables. Cut-off values was identified by the maximum value of Youden index (the sum of sensitivity and specificity minus one) in the receiver operating characteristic (ROC) curve [22]. Univariate logistic regression analysis followed by multivariate logistic regression modeling was conducted to identify the prognostic markers for Chinese CVT patients. Identified prognostic markers were used to build a CVT outcome score. 1 point was assigned to the lowest OR and multiple points based on multiplicities of the lowest OR [23]. The performance of the CVT risk score was evaluated by the classification accuracy as measured by area under the ROC curve (AUC) [24], the distribution of mRS score according to the CVT risk score, as well as a two-sample t-test. Statistical significance was defined as a 2-sided p-value < 0.05.
Results

A total of 170 CVT patients (75 males and 95 females) were recruited with mean age (standard error of mean, SEM) of 35.71 (1.03). Papilledema (55.88%), new-onset epilepsy (32.35%), and decreased LOC (14.12%) occurred most frequently. Among the 170 patients, 95 (55.88%) had three or more sinuses involved and 60 (35.29%) had parenchymal lesions. Detailed data of the reported prognostic markers were presented in Table 1.
Table 1
The detailed data of reported prognostic markers. CNS, central nervous system; CRP, C-reactive protein; CVT, cerebral venous thrombosis; DBP, diastolic blood pressure; LOC, level of consciousness; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron specific enolase; OCPs, oral contraceptive pills.

<table>
<thead>
<tr>
<th>Prognostic markers</th>
<th>Total (N = 170)</th>
<th>Good outcome (N = 141)</th>
<th>Poor outcome (N = 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.71 ± 1.03</td>
<td>34.73 ± 1.14</td>
<td>40.58 ± 2.20</td>
<td>0.0331*</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>75 (44.12%)</td>
<td>61 (43.26%)</td>
<td>14 (48.27%)</td>
<td>0.6205</td>
</tr>
<tr>
<td>Decreased LOC, n (%)</td>
<td>24 (14.12%)</td>
<td>16 (11.35%)</td>
<td>8 (27.59%)</td>
<td>0.0222*</td>
</tr>
<tr>
<td>New-onset epilepsy, n (%)</td>
<td>55 (32.35%)</td>
<td>40 (28.39%)</td>
<td>15 (51.72%)</td>
<td>0.0143*</td>
</tr>
<tr>
<td>Mental disorders, n (%)</td>
<td>2 (1.18%)</td>
<td>1 (0.71%)</td>
<td>1 (3.45%)</td>
<td>0.2128</td>
</tr>
<tr>
<td>Malignancy, n (%)</td>
<td>2 (1.18%)</td>
<td>2 (1.42%)</td>
<td>0 (0.00%)</td>
<td>0.5188</td>
</tr>
<tr>
<td>CNS infection, n (%)</td>
<td>3 (1.76%)</td>
<td>3 (2.13%)</td>
<td>0 (0.00%)</td>
<td>0.4281</td>
</tr>
<tr>
<td>Deep venous system thrombosis, n (%)</td>
<td>7 (4.12%)</td>
<td>6 (4.17%)</td>
<td>1 (3.45%)</td>
<td>0.8421</td>
</tr>
<tr>
<td>Use of OCPs, n (%)</td>
<td>14 (8.24%)</td>
<td>10 (7.09%)</td>
<td>4 (15.38%)</td>
<td>0.2319</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.17 ± 0.97</td>
<td>77.22 ± 1.09</td>
<td>82.21 ± 1.98</td>
<td>0.0436*</td>
</tr>
<tr>
<td>Papilledema, n (%)</td>
<td>95 (55.88%)</td>
<td>75 (53.19%)</td>
<td>20 (68.97%)</td>
<td>0.1192</td>
</tr>
<tr>
<td>Number of sinuses involved &gt; 3, n (%)</td>
<td>95 (55.88%)</td>
<td>82 (58.16%)</td>
<td>13 (44.83%)</td>
<td>0.1880</td>
</tr>
<tr>
<td>Parenchymal lesions, n (%)</td>
<td>60 (35.29%)</td>
<td>42 (29.79%)</td>
<td>18 (62.07%)</td>
<td>0.0009*</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>20.58 ± 2.70</td>
<td>18.23 ± 2.78</td>
<td>31.93 ± 7.96</td>
<td>0.0559</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>7.66 ± 2.27</td>
<td>8.07 ± 2.73</td>
<td>5.64 ± 0.24</td>
<td>0.6883</td>
</tr>
<tr>
<td>NLR</td>
<td>6.02 ± 1.11</td>
<td>4.32 ± 0.59</td>
<td>14.05 ± 5.27</td>
<td>0.0006*</td>
</tr>
<tr>
<td>NSE (ng/mL)</td>
<td>16.26 ± 1.18</td>
<td>14.24 ± 0.62</td>
<td>26.06 ± 5.79</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Platelet (10⁹/L)</td>
<td>256.50 ± 8.91</td>
<td>255.50 ± 9.17</td>
<td>261.00 ± 28.03</td>
<td>0.8191</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>139.60 ± 0.45</td>
<td>139.70 ± 0.49</td>
<td>139.00 ± 1.20</td>
<td>0.5659</td>
</tr>
</tbody>
</table>

The patients were subsequently divided into good outcome (n = 129) and poor outcome (n = 26) based on mRS scores at 6 months of follow-up. Age (p = 0.0331), DBP (p = 0.0436), NLR (p = 0.0006), NSE (p = 0.0001), the number of patients with decreased LOC (p = 0.0415), new-onset epilepsy (0.0339), and parenchymal lesions (p = 0.0005) showed significant difference between the patients with good outcome and those with poor outcome (Table 1).
Univariate logistic regression identified age (p = 0.036), decreased LOC (p = 0.048), new-onset epilepsy (p = 0.038), DBP (p = 0.047), parenchymal lesions (p = 0.001), CRP (p = 0.002), NLR (p = 0.012), and NSE (p = 0.008) as significant prognostic markers in Chinese CVT patients (Table 2).

<table>
<thead>
<tr>
<th>Prognostic markers</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.036</td>
<td>0.036*</td>
</tr>
<tr>
<td>Male</td>
<td>1.117</td>
<td>0.797</td>
</tr>
<tr>
<td>Decreased LOC</td>
<td>2.800</td>
<td>0.048*</td>
</tr>
<tr>
<td>New-onset epilepsy</td>
<td>2.486</td>
<td>0.038*</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>5.120</td>
<td>0.254</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0.000</td>
<td>0.999</td>
</tr>
<tr>
<td>CNS infection</td>
<td>0.000</td>
<td>0.999</td>
</tr>
<tr>
<td>Deep venous system thrombosis</td>
<td>0.000</td>
<td>0.999</td>
</tr>
<tr>
<td>Use of OCPs</td>
<td>2.424</td>
<td>0.169</td>
</tr>
<tr>
<td>DBP</td>
<td>1.043</td>
<td>0.047*</td>
</tr>
<tr>
<td>Papilledema</td>
<td>1.481</td>
<td>0.372</td>
</tr>
<tr>
<td>Number of sinuses involved &gt; 3</td>
<td>0.617</td>
<td>0.264</td>
</tr>
<tr>
<td>Parenchymal lesions</td>
<td>4.523</td>
<td>0.001*</td>
</tr>
<tr>
<td>CRP</td>
<td>4.160</td>
<td>0.002*</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>0.994</td>
<td>0.743</td>
</tr>
<tr>
<td>NLR</td>
<td>1.149</td>
<td>0.012*</td>
</tr>
<tr>
<td>NSE</td>
<td>1.073</td>
<td>0.008*</td>
</tr>
<tr>
<td>Platelet</td>
<td>1.000</td>
<td>0.818</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>0.959</td>
<td>0.562</td>
</tr>
</tbody>
</table>

The cut-off values of age (27.5 years), DBP (79.5 mmHg), CRP (30 mg/L), NLR (6.6) and NSE (16.5 ng/ml) were determined by the maximum value of Youden index (Fig. 1). Using the cut-off values, these
continuous variables were converted to binary variables for further multivariate modeling. AUC analysis also showed that age (AUC = 0.6263, p = 0.0426), DBP (AUC = 0.6434, p = 0.0291), NLR (AUC = 0.7667, p = 0.0027), and NSE (AUC = 0.6545, p = 0.0346) independently predicted the clinical outcome of CVT with high sensitivity and specificity. However, the predictive effect of CRP (AUC = 0.5875, p = 0.2441) exhibited low sensitivity and specificity.

A multivariate model including age, decreased LOC, new-onset epilepsy, DBP, parenchymal lesions, CRP, NLR and NSE was conducted (Table 3). Age > 27.5 years (p = 0.036), DBP > 79.5 mmHg (p = 0.003), NLR > 6.6 (p < 0.001), and NSE > 16.5 ng/ml (p = 0.015) were identified as significant variables to predict the clinical outcome of Chinese CVT patients.

A CVT outcome score was established using four prognostic markers (age, DBP, NLR, NSE) identified from the multivariate logistic analysis. One point was assigned to NSE > 16.5 ng/ml and age > 27.5 years; two points were assigned to DBP > 79.5 mmHg; three points were assigned to NLR > 6.6 (Table 4). A positive correlation between CVT outcome score at baseline and mRS at 6 months of follow-up was observed (p < 0.001, Fig. 2A). ROC analysis showed that CVT outcome score effectively predict the clinical outcome of CVT (AUC = 0.8785, p = 0.0001, Fig. 2B). In addition, the Youden index identified 3.5 as the cutoff value for CVT outcome score. Since CVT outcome score is an integer, patients were divided into CVT outcome score > 3 and ≤ 3. A two-sample t-test showed that the mRS score in patients with CVT outcome score > 3 is significantly lower than those with CVT outcome score ≤ 3 (Fig. 2C).
Table 4
Determination of CVT outcome score for Chinese patients. CVT, cerebral venous thrombosis; DBP, diastolic blood pressure; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron specific enolase.

<table>
<thead>
<tr>
<th>Prognostic markers</th>
<th>Risk point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt; 27.5 years</td>
</tr>
<tr>
<td></td>
<td>≤ 27.5 years</td>
</tr>
<tr>
<td>NSE</td>
<td>&gt; 16.5 ng/mL</td>
</tr>
<tr>
<td></td>
<td>≤ 16.5 ng/mL</td>
</tr>
<tr>
<td>DBP</td>
<td>&gt; 79.5 mmHg</td>
</tr>
<tr>
<td></td>
<td>≤ 79.5 mmHg</td>
</tr>
<tr>
<td>NLR</td>
<td>&gt; 6.6</td>
</tr>
<tr>
<td></td>
<td>≤ 6.6</td>
</tr>
</tbody>
</table>

**Discussion**

Combining results from univariate logistic analysis and multivariate logistic analysis, age, DBP, NLR, and NSE were identified as prognostic markers for CVT. A CVT outcome score which consists of the 4 items mentioned above was established in this study to evaluate the clinical outcome of Chinese CVT patients.

Based on results from two previous multicenter CVT cohort (ISCVT and VENOST), older age was found to be associated with a worse outcome of CVT [5, 25]. The identified cut-off age was 27.5 years in our study, 37 years in the ISCVT study, and 50 years in the VENOST study [5, 25]. The explanation to this observation was probably due to distinctive study population. ISCVT and VENOST did not enroll CVT patients from clinical centers in China Mainland.

NSE is a biomarker of brain damage released when the cell membrane of a neuron is injured [26]. Based on results from our previous study, NSE was identified as an effective marker to predict the severity and outcome of CVT [9]. In this study, the prognostic effect of NSE was confirmed after multivariate logistic analysis. In addition, DBP > 79.5mmHg was also identified as an important prognostic marker for CVT after multivariate logistic analysis. The increase of DBP is correlated with the increase of intracranial pressure, which may cause augmented inflammatory responses, oxidative stress, damage of the blood-brain barrier, and even cerebral herniation [27, 28].

It is accepted that inflammation plays a critical role in CVT. NLR is a simple parameter to assess the inflammatory status and believed to be more stable than single changes in neutrophil or lymphocyte [29, 30]. In previous studies, NLR was found to be correlated with poor clinical outcome of CVT [8, 12]. Results
from the present study confirmed the role of NLR in predicting the clinical outcome of CVT. SII, defined as PLT × NLR, is a novel inflammatory indicator of host immune and inflammatory status. It is reported that SII also served as a prognostic marker for CVT [31]. In this study, we demonstrated that NLR, rather than PLT, predicted the clinical outcome of CVT patients. It is suggested that NLR contributed to the prognostic effect of SII in CVT patients.

The CVT outcome score at baseline was positively correlated with mRS score at 6 months post-onset. In addition, the CVT outcome score effectively predicted the clinical outcome of CVT with a cutoff value of 3.5. Since CVT outcome score is an integer, the score > 3 indicated poor clinical outcome whereas the score ≤ 3 indicated good clinical outcome. Endovascular therapy is currently considered to be used when patients showed deterioration despite anticoagulation [2]. It is reported that CVT patients with high risk of poor clinical outcome may benefit from early endovascular therapy by preventing the growth of the thrombus [32]. CVT outcome score may help to identify CVT patients with high risk of poor clinical outcome and facilitate the early application of endovascular therapy.

The power of this study was limited by the relatively small sample size. However, we will verify this CVT outcome score with a larger cohort in the future.

**Conclusions**

A CVT outcome score which consists of age, DBP, NLR, and NSE for Chinese CVT patients was developed in this study. CVT outcome score at baseline positively correlated with mRS at 6 months of follow-up. CVT outcome score > 3 may help to identify CVT patients with high risk of poor clinical outcome and take early interventions to prevent deteriorations.

**Abbreviations**

CVT

cerebral venous thrombosis

DBP
diastolic blood pressure

NLR
neutrophil-to-lymphocyte ratio

NSE
neuron specific enolase

LOC
level of consciousness

CNS
central nervous system

OCPs
oral contraceptive pills
CRP
C-reactive protein
PLT
platelet count
mRS
modified Rankin Scale
ROC
receiver operating characteristic
AUC
area under the ROC curve
SEM
standard error of mean

Declarations

Ethical approval: This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the ethnic committee of Xuanwu Hospital (2019[006]).

Consent to participate: All participants signed a letter of consent for participation.

Consent to publish: All participants signed a letter of consent for publication.

Competing interests: All authors declare that they have no competing interests.

Author's contributions:

Dr. Min Li: contributed to study design, literature review, data analysis and drafting the manuscript;

Dr. Binlong Zhang: contributed to data collection and drafting the manuscript;

Dr. Jiangbo Xie: contributed to literature review and data collection;

Dr. Ran Meng: contributed to acquisition of study funding, study design and critical revision of the manuscript;

Dr. Xunming Ji: contributed to data interpretation and critical revision of the manuscript.

All authors reviewed and approved the final version of the manuscript.

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Availability of data and materials: The data and materials that support the findings of this study are available from the corresponding author upon reasonable request.

References


**Figures**
ROC analysis was performed to find out the cut-off values of age, DBP, CRP, NLR, and NSE. Abbreviations: ROC, receiver operating characteristic; AUC, area under the ROC curve; DBP, diastolic blood pressure; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron specific enolase.

Figure 1
Figure 2

Validation of CVT outcome score. A. CVT outcome score at baseline showed a positive correlation with mRS at 6 months of follow-up. B. CVT outcome score of 3.5 was identified as a cut-off value to predict the clinical outcome of CVT. C. Patients with CVT risk score > 3 showed a significantly higher mRS score than those ≤ 3. Abbreviations: ROC, receiver operating characteristic; AUC, area under the ROC curve; CVT, cerebral venous thrombosis; mRS, modified Rankin scale.