The Novel Biomarkers-Based HALP (Hemoglobin, Albumin, Lymphocyte and Platelet)-Prognostic Model for Acute and Subacute Patients with Cerebral Venous Sinus Thrombosis: A Retrospective Cohort Study

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Aim: Increasing evidences suggest that HALP is an independent predictor of prognosis in patients with inflammation. However, the relationship between HALP and prognosis in patients with cerebral venous sinus thrombosis (CVST) has not been studied. In this study, we aimed to evaluate the prognosis values of HALP in acute or subacute CVST and explore the new prognostic model for CVST.

Methods: Consecutive patients who were diagnosed as having acute and subacute CVST were retrospectively investigated. We determined the patients’ functional outcomes by modified Rankin Scale (mRS). Multivariate logistic regression analysis was used to assess the relationship between factors and poor functional outcomes. The area under the ROC curve (AUC) was estimated to evaluate the ability of markers and models in predicting clinical prognosis. The prognostic model was presented as nomogram. In addition, the decision curve analysis (DCA) was used to analyze the benefit of this model. Furthermore, survival curves were described by the Kaplan-Meier analysis.

Results: A total of 270 patients were included of which 31 had poor outcome. Multivariable logistic regression analysis demonstrated HALP (OR=0.978, 95%CI: 0.958-0.999, P=0.039) was a protective predictor of outcome. The AUC of HALP was 0.749 (95% CI: 0.633-0.865, P=0.044). DCA demonstrated that this model significantly improved risk prediction at threshold probabilities of CVST at 0 to 85% compared to ISCVT-RS scores. Patients with higher HALP (P=0.006) presented higher overall survival rates.

Conclusion: HALP may be a potential protective marker in acute and subacute CVST patients. The new prognostic model with HALP had potentially better value for acute and subacute CVST patients.

Key words: Stroke; Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP); Acute and subacute cerebral venous sinus thrombosis; Prognostic model; Protective marker

Abbreviations: CVST: Cerebral Venous Sinus Thrombosis; ISCVT: International Study on Cerebral Vein and Dural Sinus Thrombosis; ISCVT-RS: CVST prognostic score based on the International Study on Cerebral Vein and Dural Sinus Thrombosis; CVT-GS: Cerebral Venous Thrombosis grading scale; HALP: hemoglobin (g/L) × albumin (g/L) × lymphocyte (/L)/platelet (/L); PLR: Platelet to Lymphocyte Ratio; NLR: Neutrophil to Lymphocyte Ratio; CRP: C-reactive protein; mRS: modified Rankin Scale; AUC: Area under the ROC curve; CI: Confidence Interval; ROC: Receiver Operating Characteristic; OR: Odds Ratio; VENOPORT: Cerebral Venous Thrombosis Portuguese Collaborative Study; ISCVT-V: Research and Validation sample for ISCVT.

HIGHLIGHTS:
- HALP values firstly were analyzed in prognosis of stroke, especially in acute and subacute CVST
- Higher HALP value may indicate an independent predictor for good prognosis in patients.
- The novel prognostic model with HALP had potential value for Chinese CVST patients.
1. Introduction

Cerebral Venous Sinus Thrombosis (CVST) is a rare type of stroke, accounting for 0.5–1% of all strokes\(^1\). Compared to arterial stroke, CVST has highly variable pathogenic factors and complex clinical symptoms, which lacks of specificity and leads to misdiagnosed\(^2\). There have been many efforts to find useful prognostic markers and models for monitoring CVST patients, such as platelet to lymphocyte ratio (PLR)\(^3\), neutrophil to lymphocyte ratio (NLR)\(^4\), C-reactive protein (CRP) and D-dimer\(^5\). Furthermore, the CVST prognostic score based on the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT-RS)\(^6\) and Cerebral Venous Thrombosis grading scale (CVT-GS)\(^7\) score were useful models in prognosis of CVST patients. However, some studies have indicated that the scales were not proper for Chinese patients\(^8\). Therefore, it is necessary to increase external items or explore some new prognosis models which are suitable for more patients.

The combination of hemoglobin, albumin, lymphocyte and platelet (HALP) was defined as follows: hemoglobin (g/L) × albumin (g/L) × lymphocyte (/L) / platelet (/L)\(^9\). It was the integration of these four indexes and relatively more stable than single blood parameters. Increased HALP score was associated with a decreased risk of recurrent stroke and death within 90 days and 1 year after stroke onset, suggesting that HALP score may serve as a powerful indicator for AIS\(^10\). In addition, the HALP was closely associated with clinical features and was an independent prognostic factor in several types of malignant tumors, including genitourinary cancer, bladder cancer and renal cell carcinoma\(^11, 12\). However, there were no reports concerned with roles of HALP in CVST patients, especially in acute and subacute CVST patients.

In this retrospective study, we aimed to analyze the association between HALP values and prognosis in acute and subacute CVST patients, and to explore the predictive new models for prognosis in these patients.

2. Materials and Methods

2.1. Patient Selection

Patients included in the retrospective cohort study were from the database of the Henan CVST Registry in the First Affiliated Hospital of Zhengzhou University (Henan, China). All patients diagnosed with CVST from January 2013 through December 2020 were identified. We selected acute/subacute patients from our database. Inclusion criteria were as follows: (1) meeting the diagnostic criteria for CVST established by the American Heart Association/American Stroke Association in 2014\(^8\); (2) filling defect or obstruction of cerebral sinus in the magnetic resonance venogram, digital subtraction angiography, or operation searching; (3) clinical features such as vomiting, visual disturbances, focal neurologic deficit, seizure, and other typical symptoms; (4) acute and subacute patients whose time from onset to admission was less than 30 days\(^13, 14\), or named non-chronic patients; (5) an initial blood sample for laboratory testing 12 hours of admission. Exclusion criteria were as follows: (1) patients with unrelated other serious brain lesions, serious lung disease, or heart disease; (2) patients with undesirable follow-up, including refusal or loss to follow-up; (3) patients less than 18 years old; (4) patients without complete clinical data; (5) chronic patients whose time from onset to admission was more than 30 days. The retrospective cohort study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and patients signed the informed consent form.

2.2. Data Collection

Clinical data such as age, gender, clinical presentation, laboratory and imaging tests were collected. Laboratory samples were routinely collected after 12 hours of fasting upon admission to the hospital. The inter-rater reliability for involvement of intracranial venous sinus between two investigators were assessed in some cases.

2.3. Evaluation of Prognosis

We evaluated the modified Rankin Scale (mRS) to determine the patients’ functional outcomes: mRS 0-2 as good outcomes, mRS 3-6 as poor outcomes, and death was defined with mRS score of 6. Follow-up information was recorded by telephone interview. Telephone interviewers were not involved in the registry and were blinded to the baseline data. The overall survival time was defined as the date of admission to the date of death from any cause, or to the last follow up date.
Table 1. Demographic and clinical characteristics of the two outcomes groups in CVST patients

| Variable                        | Total     | Good (n, %) 239 (89.0) | Poor (n, %) 31 (11.0) | P value |
|---------------------------------|-----------|------------------------|-----------------------|---------|
| Age, years old                  | 34.50 ± 13.12 | 33.36 ± 12.49         | 42.00 ± 14.84         | 0.002*  |
| Gender                          | 270       | 239 (89.0)             | 31 (10.0)             | 0.044*  |
| Female                          | 156       | 134 (56.1)             | 22 (71.0)             |         |
| Male                            | 114       | 105 (43.9)             | 9 (19.0)              |         |
| Malignancy                      | 4         | 3 (1.3)                | 1 (3.2)               | 0.575   |
| Infection                       | 57        | 48 (20.1)              | 9 (29.0)              | 0.511   |
| Pregnancy or Puerperium         | 65        | 53 (22.2)              | 12 (38.7)             | 0.518   |
| Intracerebral hemorrhage        | 62        | 53 (22.2)              | 9 (29.0)              | 0.674   |
| Coma                            | 72        | 50 (20.9)              | 22 (9.2)              | <0.001* |
| Mental disorder                 | 15        | 10 (4.2)               | 5 (16.1)              | 0.303   |
| Lymphocyte, × 10⁹/L             | 1.67 ± 0.84 | 1.74 ± 0.85           | 1.19 ± 0.62           | <0.001* |
| Granulocyte, × 10⁹/L            | 7.27 ± 4.73 | 7.04 ± 4.63           | 8.79 ± 5.15           | 0.066   |
| Platelet, × 10⁹/L               | 244.12 ± 124.21 | 243.15 ± 122.08      | 250.54 ± 139.23       | 0.768   |
| Albumin, g/L                    | 40.31 ± 5.23 | 40.41 ± 5.34          | 39.64 ± 4.46          | 0.358   |
| Hemoglobin, g/L                 | 126.96 ± 27.51 | 127.51 ± 27.77       | 123.34 ± 25.89        | 0.384   |
| HALP                            | 42.51 ± 32.09 | 44.46 ± 32.97        | 29.68 ± 21.80         | 0.001*  |
| PLR                             | 179.47 ± 129.72 | 159.61 ± 90.38       | 339.32 ± 257.80       | <0.001* |
| NLR                             | 6.81 ± 7.90 | 5.50 ± 5.15           | 17.05 ± 15.94         | <0.001* |
| Left sigmoid sinus              | 70        | 47 (19.7)              | 23 (74.2)             | 0.629   |
| Right sigmoid sinus             | 75        | 57 (23.8)              | 18 (58.1)             | 0.218   |
| Left transverse sinus           | 93        | 63 (26.4)              | 30 (96.8)             | 0.147   |
| Right transverse sinus          | 97        | 73 (30.5)              | 24 (77.4)             | 0.188   |
| Straight sinus                  | 21        | 14 (5.9)               | 7 (22.6)              | 0.011*  |
| Superior sagittal sinus         | 149       | 119 (49.8)             | 30 (96.8)             | 0.243   |
| Inferior sagittal sinus         | 25        | 13 (5.4)               | 12 (38.7)             | 0.061   |
| Torcular                       | 28        | 18 (7.5)               | 10 (32.3)             | 0.510   |
| Deep cerebral venous            | 8         | 6 (2.5)                | 2 (6.5)               | 0.284   |

*Statistically significant

2.4. Statistical Analysis

All statistical analyses were performed using SPSS 21.0 software. Continuous variables were expressed as mean ± standard deviation or median, which were analyzed by independent student t-test or Mann-Whitney test as appropriate. Categorical variables were presented as numbers which were analyzed using Chi-square test or Fisher exact test. The association between these markers and prognosis was explored using multivariate logistic regression analysis. Additionally, we created a heat map to show these results. The area under the ROC curve (AUC) was estimated to evaluate the ability of markers in predicting clinical prognosis. According to the threshold values of HALP, we divided the patients into two groups, including higher HALP group and lower HALP group. Besides, the prognostic model was presented as nomogram for individual patient. Clinical usefulness and net benefit were estimated with decision curve analysis (DCA). Survival curves were described by the Kaplan-Meier analysis and compared with Log-Rank test in higher HALP group and lower HALP group. Two-tailed P<0.05 were considered significant.

3. Results

We included 297 patients confirmed acute and subacute CVST admitted during the study period from database. We excluded 8 patients because of their incomplete clinical data, 4 patients because of missing of their follow-up data and 15 patients because of their being younger than 18 years old. A total of 270 patients were enrolled into this study.

The follow-up was 6 months and 31 patients were defined as poor prognosis, of which 24 were dead. The baseline clinical data of two groups are shown in Table 1. HALP (44.46 ± 32.97 vs. 29.68 ± 21.80, P<0.001) was significantly higher in the good outcome group, which was clearly illustrated in Fig.1. In Table 1, older patients were identified more frequently in the poor outcome group than in the
good outcome group (33.36 ± 12.49 vs. 42.00 ± 14.84, \( P=0.002 \)). Furthermore, coma was more common among patients with poor outcome (\( P<0.001 \)). As for laboratory parameters, lymphocyte reached statistical significance (\( P<0.001 \)). Additionally, gender (\( P=0.044 \)) was also regarded as a risk factor: female patients had poor outcome more regularly (14.1%). Straight sinus was involved in the poor outcome group (\( P=0.011 \)).

HALP of \( \geq 31.54 \) and age of \( \geq 36.5 \) were found as threshold values by ROC curve. The discriminatory capability of HALP using the area under the ROC curve was 0.749 (95% CI: 0.633-0.865, \( P=0.044 \)), and HALP predicted the presence of good outcome with a sensitivity of 69.7% and specificity of 82.6% (Fig. 2). As illustrated in Table 2, after adjusting for age, gender, coma and straight sinus which reached statistical significance in logistic regression, multivariable logistic regression analysis demonstrated that HALP (OR=0.978, 95%CI: 0.958-0.999, \( P=0.039 \)) was a protective predictor of outcome. The weights and points associated with the five variables are shown in Fig. 3. The nomogram indicated that age \( \geq 36.5 \), female, coma and straight sinus thrombosis location were the poor prognostic factors, but higher HALP was still a potential good prognostic factor. The results of the nomogram were similar to those of aforementioned multivariate analyses in tumor\(^{10-12} \).

As seen in Fig. 4, the decision curve analysis graphically showed the clinical usefulness of the model.
Our study mainly investigated the association between HALP and the prognosis in acute or subacute CVST patients and tried to provide a new model for clinical prognosis in patients. We found HALP to be a potential independent protective predictor of prognosis in acute and subacute CVST patients. Our new prognostic model with HALP had potentially better value for acute and subacute CVST patients.

Previous studies showed that a high HALP score predicted good therapeutic outcomes and prognosis based on a continuum of potential thresholds for poor outcome risk (x axis) and the net benefit of using the model to risk stratify patients (y axis) relative to assuming that all patients will have a poor prognosis. In this analysis, we compared our prognostic model with ISCVT-RS scores. And it was gratifying that our model significantly improved risk prediction at threshold probabilities of CVST at 0 to 85%. Kaplan-Meier analysis was used to determine the prognostic significance of HALP (Fig. 5). Patients with higher HALP presented significantly higher overall survival rates ($P=0.006$) than those with lower HALP.

### Table 2. Multivariable logistic regression analysis in CVST patients

| Variable      | OR      | 95% CI       | $P$ value |
|---------------|---------|--------------|-----------|
| Age           | 1.054   | 1.022-1.086  | 0.001*    |
| Gender        | 3.321   | 0.704-6.661  | 0.129     |
| Coma          | 5.440   | 2.344-8.624  | 0.001*    |
| HALP          | 0.978   | 0.901-0.989  | 0.039*    |
| Straight sinus| 5.683   | 1.702-8.980  | 0.005*    |

*Statistically significant

![Nomogram for the new values-based risk score in CVST patients](image)

**Fig. 3.** Nomogram for the new values-based risk score in CVST patients

![Decision curve analysis for the novel prediction model of CVST patients](image)

**Fig. 4.** Decision curve analysis for the novel prediction model of CVST patients

4. **Discussion**

Our study mainly investigated the association between HALP and the prognosis in acute or subacute CVST patients and tried to provide a new model for clinical prognosis in patients. We found HALP to be a potential independent protective predictor of prognosis in acute and subacute CVST patients. Our new prognostic model with HALP had potentially better value for acute and subacute CVST patients.

Previous studies showed that a high HALP score predicted good therapeutic outcomes and prognosis in
sinus venous thrombosis can be linked to Virchow’s triad, which includes injury to the vessel walls, a hypercoagulable state and stasis \(^{30}\). Platelets are involved in early stage of vascular pathology, which inside the plaque ensure replication of leukocytes via direct receptor interactions and increase the leukocyte activity \(^{31}\). According to the heat map in Fig. 1, it was clear that patients with poor outcome had lower HALP than those with good outcome. But the four single parameters did not show obvious trends. This was one of the reasons that we made the definition of HALP. The results of our study confirmed the significance of HALP, indicating that the patients with higher HALP had better prognosis. Nevertheless, we still required more randomized controlled trials to strengthen the potential benefits.

![Fig. 5. Kaplan-Meier analysis for CVST patients with high/low HALP patients](image)

Such factors, as PLR, NLR, LMR, D-dimer, C-reactive protein, red cell distribution width and mean platelet volume, provided important information regarding the prognosis of CVST patients \(^{5, 32}\). In addition, the previously validated risk score derived from the ISCVT study and the VENOPORT registry (the ISCVT-RS system) has been most commonly accepted \(^{6}\), including gender, mental disorder, coma, venous thrombosis, intracerebral hemorrhage and malignancy. But more and more evidences showed that ISCVT-RS scores have some limitations. A Chinese retrospective study was conducted with this scale. It is found that the accuracy is not ideal, and the AUC is 0.65 (95% CI 0.53-0.77, \(P<0.01\)) \(^{8}\). It may be due to the heterogeneity of the research population \(^{33}\). Our previous studies have similar findings. And we have reasons to believe that this scale needs to be further updated and improved, especially for the Chinese population. Therefore, we evaluated HALP and explored prognosis models which are suitable for our Chinese patients. The DCA was used to analyze the benefit of prognostic model commonly used in clinical
practice in Fig.4. In this analysis, the red line is almost 0 to 1 above the gray line and the black line, and we could think that the prognostic model can benefit more patients.

In our study, to improve the reliability, we figured out the nomogram to visually show the impact of some clinic-pathological parameters on the prognosis of CVST patients. In this nomogram, HALP was included via a stepwise algorithm. According to the nomogram, the prognosis of individual patient could be well predicted. We also noticed HALP and age might play a similarly important role in prognosis, which was a very exciting result.

There were several limitations in our study. First, the study was a single-center study and selection bias was unavoidable. Additional well-designed and larger prospective cohort multicenter studies are required to evaluate this association. Second, HALP was only collected once, thus there was a lack of dynamic data. Further evidence is required to evaluate potential values.

5. Conclusion

Our findings suggested that higher HALP value may indicate an independent predictor for good prognosis in acute and subacute CVST patients. The new prognostic model with HALP had potentially better value for acute and subacute CVST patients.

Data Availability Statement

The dataset that support the results and findings of this research are available from the correspondence author, [YMX] or [BS], on reasonable request.

Ethics Statement

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, China.

Author Contributions

(I) Conception and design: Dr. Bo Song, Dr. Yuming Xu and Dr. Zongping Xia; Dr. Bo Song and Dr. Yuming Xu provided funding, and Dr. Dr. Bo Song and Dr. Zongping Xia designed the study; (II) Provision of study materials or patients: Dr. Kai Liu, Dr. Hongbing Liu and Dr. Jiawei Zhao; (III) Collection and assembly of data: Dr. Hui Fang, Dr. Yongli Tao, Dr. Lulu Pei and Dr. Mengke Tian; (IV) Data analysis and interpretation: Dr. Kai Liu and Dr. Xin Wang; (V) Manuscript writing: Dr. Shen Li and Dr. Yuan Gao; (VI) Final approval of manuscript: All authors.

Consent for Publication

Informed consent was obtained from all subjects.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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