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Prognostic value of systemic immune–inflammation index in acute/subacute patients with cerebral venous sinus thrombosis

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ABSTRACT

Objective To evaluate the prognosis values of systemic immune–inflammation index (SII) in non-chronic cerebral venous sinus thrombosis (CVST).

Methods patients with CVST, admitted to the First Affiliated Hospital of Zhengzhou University, were retrospectively identified from January 2013 to December 2018. We selected patients in acute/subacute phase from database. Functional outcomes of patients were evaluated with the modified Rankin Scale (mRS)—mRS 3–6 as poor outcomes and mRS 6 as death. The overall survival time was defined as the date of onset to the date of death or last follow-up date. Survival analysis was described by the Kaplan-Meier curve and Cox regression analysis. Multivariate logistic regression analysis assessed the relationship between SII and poor functional outcome. The area under the Receiver Operating Curve curve (AUC) was estimated to evaluate the ability of SII in prediction.

Results A total of 270 patients were included and their duration of follow-up was 22 months (6–66 months), of whom 31 patients had poor outcomes and 24 patients dead. Cox regression analysis showed that SII (HR=1.304, 95% CI: 1.101 to 1.703, p=0.001) was a predictor of death in non-chronic CVST. Patients with higher SII presented lower survival rates (p=0.003). The AUC of SII was 0.792 (95% CI: 0.695 to 0.888, p=0.040) with a sensitivity of 69.6% and specificity of 80.1%. Subgroups analysis demonstrated that SII was an important predictor of poor outcomes in male (OR=1.303, 95% CI: 1.102 to 1.501, p=0.011) and pregnancy/puerperium female (OR=1.407, 95% CI: 1.204 to 1.703, p=0.034).

Conclusions SII was a potential predictor in the poor prognosis of patients with acute/subacute CVST, especially in male and pregnancy/puerperium female.

Highlights

- Systemic immune–inflammation index (SII) was first analysed in cerebral venous sinus thrombosis (CVST) patients.
- SII may be significantly related to the poor prognosis of patients with CVST whose time from onset to addition was less than 30 days.

INTRODUCTION

Cerebral venous sinus thrombosis (CVST), is a rare type of stroke, accounting for 0.5%–1% of all strokes.[1] The disease is more likely to occur in young people, in particular women more regularly.[2] CVST has variable pathogenic factors and complex clinical symptoms, which lack specificity and tend to be misdiagnosed.[3] Therefore, it is very significant to find some biomarkers to help us predict the prognosis in the early phase.

Some factors, such as D-dimer, C-reactive protein, red cell distribution width and mean platelet volume, provided potential values regarding the presence of patients with CVST,[4 5] but due to the ethnic and quantitative differences of the subjects, the results were not consistent and reliable in some researches. Although 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 have been used in prognosis of Patients with CVST, some studies indicated that the scales were not proper for Chinese patients.[8] Thus, it is necessary to find some more stable and representative parameters to predict the prognosis.

Systemic immune–inflammation index (SII) is a novel inflammatory index to comprehensively reflect the balance of host immune and inflammatory status.[9] It was defined as follows: platelet (/L)×neutrophil (/L)/lymphocyte (/L). Up to now, SII has been reported to be associated with survival in patients with various cancers,[9–11] such as gastric cancer and prostate cancer. However, there were no reports concerned with the roles of SII in patients with CVST. Inflammation plays an important role in the risk of CVST and the inflammation response activated by the brain lesion is regarded as a fatal response that provokes secondary brain injury.[12] Also, due to a lack of understanding about the mechanism of the early phase, people are unable to judge the

prognosis of acute/subacute patients with CVST as soon as possible. Compared with platelet to lymphocyte ratio (PLR)[13] and neutrophil to lymphocyte ratio (NLR)[14] which have been identified in the prognosis of patients with CVST, SII is more stable and representative in reflecting the balance of host immune and inflammatory status because it combines one more factor than them. Therefore, we aim to analyse the association between SII and prognosis in non-chronic patients with CVST whose time from onset to addition was less than 30 days.

METHODS

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 2018 were identified. We selected acute/subacute patients from our database. Inclusion criteria were as follows: (1) meeting the diagnostic criteria for CVST and patients with direct or indirect signs of CVST in the MRI; (2) presence of filling defect or obstruction of cerebral sinus in the magnetic resonance venogram, digital subtraction angiography or operation searching; (3) exhibiting 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,[15 16] 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 other unrelated serious brain lesions, serious lung disease or heart disease; (2) patients with undesirable follow-up, including refusal or loss to follow-up; (3) patients younger than 18 years old; (4) patients without complete clinical data and (5) chronic patients whose time from onset to addition was more than 30 days.

Data collection

Clinical data such as age, gender, clinical presentation, laboratory and imaging tests were collected. The inter-rater reliability for involvement of intracranial venous sinus between two investigators was assessed in some cases.

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 as 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 onset to the date of death from any cause, or to the last follow-up date.

Statistical analysis

All statistical analyses were performed using SPSS V.21.0 software. Continuous variables were expressed as mean±SD or median, which were analysed by independent Student's t-test or Mann-Whitney test as appropriate. Categorical variables were presented as numbers which were analysed using χ^2 test or Fisher exact test. Multivariate logistic regression analysis was used to analysis the association between factors and prognosis. And the association between SII and the survival outcome was explored by Cox regression analysis. The area under the Receiver Operating Curve (AUC) was estimated to evaluate the ability of the SII in predicting clinical prognosis. Survival curves were described by the Kaplan-Meier analysis and compared with Log-rank test. Two-tailed p<0.05 were considered significant.

RESULTS

We included 297 patients who confirmed acute and subacute CVST admitted during the study period from database. We excluded eight patients because of incomplete clinical data, four patients because they were lost to follow-up and 15 patients because they were younger than 18 years. A total of 270 patients were enrolled into this study.

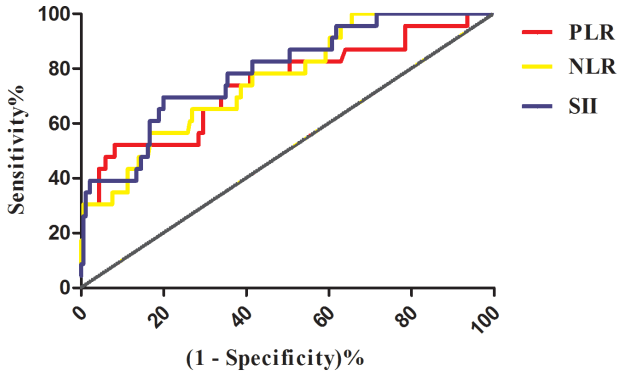
The duration of follow-up was 22 months (6–66 months) and 31 patients were defined as poor prognosis, including 24 patients dead. The baseline clinical data of two groups are shown in table 1. SII (1151.71±1085.54 vs 2893.31±3680.81, p<0.001) was significantly higher in the poor outcome group. And it was higher in the acute and subacute patients than chronic patients (online supplementary table 1). Older patients were identified more frequently in the poor outcome group than good outcome group (33.36±12.49 vs 42.00±14.84, p=0.002). Also, coma was more common among patients with poor outcome (p<0.001). As for laboratory parameters, lymphocyte count reached statistical significance (p<0.001). Additionally, gender (p=0.044) was also regarded as a risk factor. Straight sinus was involved in the poor outcomes group (p=0.011).

In figure 1, we indicated that the discriminatory capability of SII using AUC was 0.792 (95% CI: 0.695 to 0.888, p=0.040) for patients and using a cut-off level of 1525.04. And it predicted the presence of poor outcome with a sensitivity of 69.6% and specificity of 80.1%. Because SII was defined as platelet (/L)×neutrophil (/L)/lymphocyte (/L), we also compared it with other two related prognostic factors, including PLR and NLR. The results demonstrated that SII was the relatively good prognostic factor of these patients whose time from onset to addition was less than 30 days, but not in patients whose time from onset to addition was more than 30 days (online supplementary figure 1). Subgroup analysis demonstrated that SII was an important predictor of poor outcome in male (OR=1.303, 95% CI: 1.102 to 1.501, p=0.011) and pregnancy/puerperium female (OR=1.407, 95% CI: 1.204 to 1.703, p=0.034), after adjusting for age, coma and straight sinus (table 2).

Table 1 Demographic and clinical characteristics of the two outcomes groups in acute/subacute patients with CVST

Variable	Total	Good (239, 89.0%)	Poor (31, 11.0 %)	P value
Age	34.50±13.12	33.36±12.49	42.00±14.84	0.002*
Gender	270	239	31	0.044*
Female	156	134	22	
Male	114	105	9	
Malignancy	4	3	1	0.575
Infection	57	48	9	0.511
Pregnancy or puerperium	65	53	12	0.518
Intracerebral haemorrhage	62	53	9	0.674
Coma	72	50	22	<0.001*
Mental disorder	15	10	5	0.303
Lymphocyte	1.67±0.84	1.74±0.85	1.19±0.62	<0.001*
Granulocyte	7.27±4.73	7.04±4.63	8.79±5.15	0.066
Platelet	244.12±124.21	243.15±122.08	250.54±139.23	0.768
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*
SII	1380.86±1763.22	1151.71±1085.54	2893.31±3680.81	<0.001*
Left sigmoid sinus	70	47	23	0.629
Right sigmoid sinus	75	57	18	0.218
Left transverse sinus	98	63	35	0.147
Right transverse sinus	97	73	24	0.188
Straight sinus	21	14	7	0.011*
Superior sagittal sinus	159	119	40	0.243
Inferior sagittal sinus	25	13	12	0.061
Torcular	28	18	10	0.510
Deep cerebral venous	8	6	2	0.284

*Statistically significant.
CVST, cerebral venous sinus thrombosis; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune–inflammation index.



	AUC	95%CI	P value	Sensitivity(%)	Specificity(%)
PLR	0.760	0.660-0.860	0.050	52.2	90.1
NLR	0.743	0.621-0.864	0.062	56.5	83.3
SII	0.792	0.695-0.888	0.040	69.6	80.1

Figure 1 ROC curve of SII, PLR and NLR in acute/subacute Patients with CVST. CVST, cerebral venous sinus thrombosis; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ROC, Receiver Operating Curve; SII, systemic immune–inflammation index.

We used Kaplan-Meier analysis method to assess SIIin figure 2. According to the threshold values of SII, we divided the patients into two groups, higher SII group and lower SII group. Patients with higher SII had higher mortality than lower SII (p=0.003). In addition, Cox regression analysis showed that SII (HR=1.304, 95% CI: 1.101 to 1.703, p=0.001) was also a significant predictor in death of non-chronic patients with CVST (figure 3).

DISCUSSION

Our study mainly investigated the association between SII and the prognosis with patients with CVST, and tried to find new factors for prognosis. The major finding was higher SII at admission independently and strongly related to the poor prognosis of non-chronic Patients with CVST, especially in male and pregnancy/puerperium female.

The basis of cerebral sinus venous thrombosis can be linked to Virchow's triad, which includes injury to the vessel walls, a hypercoagulable state and stasis.[17]

Table 2 Multivariable logistic regression analysis in different subgroups with acute/subacute patients with CVST

Groups	Variable	OR	95% CI	P value
Subgroup 1	Age	1.055	1.027 to 1.083	<0.001*
	SII	1.303	1.102 to 1.501	0.011*
	Coma	2.726	1.547 to 3.963	0.026*
	Straight sinus	2.485	1.142 to 5.409	0.022*
Subgroup 2	Age	1.100	1.027 to 1.177	0.006*
	SII	1.104	0.998 to 1.209	0.251
	Coma	2.667	1.196 to 5.209	0.001*
	Straight sinus	5.104	1.998 to 12.209	0.009*
Subgroup 3	Age	1.216	0.862 to 1.715	0.266
	SII	1.407	1.204 to 1.703	0.034*
	Coma	1.101	0.997 to 1.501	0.061
	Straight sinus	5.412	0.769 to 11.436	0.120
Subgroup 4	Age	1.064	1.016 to 1.115	0.009*
	SII	1.207	0.986 to 1.505	0.119
	Coma	4.753	2.082 to 6.834	0.003*
	Straight sinus	4.086	1.031 to 8.696	0.046*

*Statistically significant. Subgroup analysis was carried out in male (subgroup 1), female (subgroup 2), pregnancy/puerperium (subgroup 3) and non-pregnancy/puerperium (subgroup 4) Patients with CVST.
CVST, cerebral venous sinus thrombosis; SII, systemic immune–inflammation index.

Recognised predisposing risk factors for thrombosis are known to include inflammation and infection.[18] In human studies, the predictive values of PLR and NLR have been analysed in patients with CVST,[13 19 20] but phase studies were not carried out. And our studies have also proved that lymphocyte to monocyte ratio, as an inflammation factor, was a potential predictor of poor prognosis in patients with CVST.[14] As for SII, it combined the platelet, neutrophil and lymphocyte count, reflecting the inflammation and thrombosis. Therefore, SII was more stable and representative, compared with these factors above.

Recently, it has emerged as a powerful prognostic index in various malignant diseases, including renal cell cancer,[21] gastric cancer[22] and prostate cancer.[23] Evidence is accumulating that neutrophils, apart from their well-known inflammatory function, also promote intravascular thrombus formation. Neutrophils have been shown to be an essential source of tissue factor in the early phase of thrombus formation.[24 25] Brain ischaemia is followed by the activation of the immune system in a sterile inflammatory reaction, resulting in the change of cell adhesion molecules, cytokines, as well as infiltration of leukocytes in the ischaemic tissue. Lymphocytes, as an important subtype of the leucocyte family, are also involved in inflammation. Previous studies have demonstrated the association between the low lymphocyte count and increased cardiovascular disease.[26] Furthermore, trials have shown

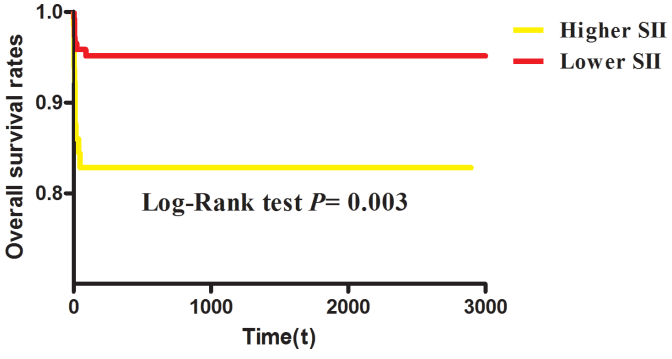


Figure 2 Kaplan-Meier analysis for acute/subacute patients with CVST with higher/lower SII. CVST, cerebral venous sinus thrombosis; SII, systemic immune–inflammation index.

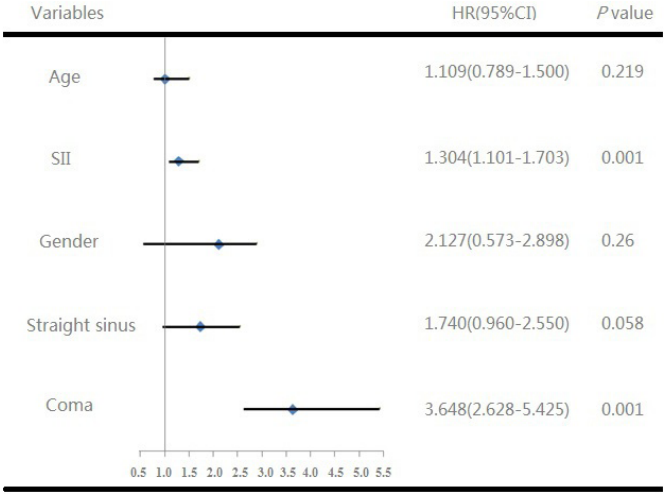


Figure 3 Cox regression analysis of overall survival in acute/subacute patients with CVST. CVST, cerebral venous sinus thrombosis; SII, systemic immune–inflammation index.

an increased association between platelets and development of vascular events.[27 28] Platelets are involved in the early stage of atherosclerosis-associated chronic vascular pathology and plaque rupture. Platelets inside the atherosclerotic plaque ensure replication of leukocytes via direct receptor–ligand interactions and increase the leucocyte activity.[29] Because these factors play an important role in the early stage of related pathophysiological changes, we used this combination index and have confirmed that SII can predictive prognosis in non-chronic patients with CVST. And we found that patients with higher SII showed poorer prognosis conditions in non-chronic phase. However, we still require more randomised controlled trials to clarify the potential benefits.

As we all know, CVST may occur at any age and in both sexes, but it has a three to one female preponderance.[30] It is more common in women of childbearing age,[31] because of the use of oral contraceptives (80% of cases) and pregnancy/puerperium (5%–20% of cases).[32] In our subgroup analysis, we aimed to explore the association between SII and outcomes in different genders. The results showed that SII was more effective in prognosis of CVST with male and pregnancy/puerperium female. This is an important finding, because previous studies have reported gender-specific pathophysiological differences in CVST, based on the fact that men more often have a chronic onset of symptoms.[30] But in our study, we collected the patients whose time from onset to addition was less than 30 days, which was a good addition to the previous facts. Furthermore, SII can be used to inducate the systemic immune and inflammation, so we will suggest a new and different hypothesis that the mechanism of CVST in male and special female is more involved in inflammatory aspects than other groups.

In addition, the previously validated risk score derived from the ISCVT study and Cerebral Venous Thrombosis Portuguese Collaborative Study (VENOPORT) research has been used in prognosis with CVST,[6] including gender, mental disorder, coma, venous thrombosis, intracerebral haemorrhage and malignancy. Whereas, more and more evidences showed that ISCVT-RS scores have some limitations. A Chinese retrospective study found that the accuracy is not ideal, and the AUC is only 0.65 (95% CI: 0.53 to 0.77, p<0.01),[8] which may be due to the heterogeneity of the research population.[33] And we believe that this scale needs to be further improved, especially for the Chinese population. Our findings about SII might provide a way or clue to explore.

Our study was a single-centre study and selection bias was unavoidable. Additional well-designed and larger prospective cohort multicenter studies are required to evaluate this association. In addition, heterogeneity of the research population could not be ignored. It is required to evaluate potential values by further evidence.

CONCLUSION

Our findings suggested that SII was a potential predictor in the poor prognosis of patients with acute/subacute CVST, especially in male and pregnancy/puerperium female.

Contributors SL is the first author. BS, YX and ZX provided funding and designed the study. YT, HL and JZ collected the data. YG, LZ, RZ and HF were involved in data cleaning, follow-up and verification. KL revised the article. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The retrospective cohort study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article or uploaded as supplementary information.

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