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Research article

# Cerebrospinal fluid soluble growth stimulation expressed gene 2: A potential predictor of outcome for prognosis after aneurysmal subarachnoid hemorrhage

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ABSTRACT

*Background:* Serum concentration of soluble growth stimulation expressed gene 2 (sST2) appears to have prognostic value in patients with aneurysmal subarachnoid hemorrhage (aSAH) by now. This study aimed to investigate the relationship between cerebrospinal fluid (CSF) sST2 concentration and outcome in patients with aSAH.

*Methods:* A total of 65 aSAH patients who met the inclusion criteria in the Neurosurgery Department of Jining No.1 People's Hospital from March 2021 to August 2022 were selected as the research objects. 35 patients with the third month Modified-Rankin-Scale (mRS) score of 0–2 were divided into good prognosis group, and 30 patients with the third month mRS score of 3–5 were divided into poor prognosis group. CSF was collected by lumbar puncture for the first 5 days after aneurysm surgery. CSF sST2 concentration was determined using an enzyme-linked immunosorbent assay.

*Results:* In all patients, CSF sST2 concentrations initially increased, peaked on day 2, and then decreased. Compared with the good prognosis group, the sST2 concentration was significantly increased in the poor prognosis group at 1, 2, 3, 4 and 5 days after aSAH surgery. CSF sST2 concentration exhibited good diagnostic performance for predicting outcome (area under the receiver operating characteristic curve = 0.988). Additionally, CSF sST2 concentration has good performance for predicting cerebral edema, but only in the poor prognosis group (area under the curve = 0.93).

*Conclusions:* Elevated CSF sST2 concentration is associated with poor outcome in aSAH patients. CSF sST2 may have a role as a predictive biomarker in these patients.

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## 1. Introduction

Subarachnoid hemorrhage (SAH) is a cerebrovascular disease characterized by hemorrhage from the cerebral vasculature into the subarachnoid space [1,2]. Approximately 85 % of cases are associated with rupture of an intracranial aneurysm [3]. A meta-analysis showed that there are approximately 500,000 new Aneurysmal SAH (aSAH) patients worldwide each year, and outcomes range widely from complete recovery to death [4]. If the ruptured aneurysms is not treated rapidly, severe complications that can affect quality of life may occur, such as secondary bleeding, hydrocephalus, and cerebral vasospasm Even if the aneurysm and any accompanying hydrocephalus and vasospasm are treated, patients may still experience long-term neurological deficits and epilepsy [5–7]. Therefore, it is important to identify markers that may help predict outcomes in aSAH patients to assist with diagnosis and treatment.

Growth stimulation expressed gene 2 (ST2) is a member of the interleukin (IL) receptor 1 family that binds to Interleukin-33 (IL-33) and has. There are two isoforms: transmembrane ST2 one with has an IL-1 receptor-like structure (ST2L) and a soluble one that lacks a transmembrane domain (sST2) [8]. sST2 has a role in enhancing phagocytosis, which may be an important response to vascular injury [9] , and previous studies have shown that higher concentrations of sST2 are associated with stroke events [10]. IL-33 is a cytokine known to induce a shift to a Th2-type immune response, polarize macrophages/microglia toward the m2 type, and induce the production of anti-inflammatory cytokines [11]. Soluble ST2 acts as a decoy receptor, reducing the interaction of IL-33 with transmembrane ST2 and thus switching to a proinflammatory response [12]. Several studies have shown that the production of sST2 has been associated with various autoimmune diseases [13], heart disease [14], inflammatory bowel disease [15], and type 2 diabetes [16]. Furthermore, serum sST2 concentration is higher in SAH patients who experience delayed cerebral ischemia and death in those who do not [17]. These data suggest that serum sST2 concentrations may have value as a prognostic biomarker for aSAH. However, further research is needed. Although sST2 can penetrate the blood-brain barrier, the prognostic value of sST2 concentration in the cerebrospinal fluid (CSF) has not been examined. We hypothesized that CSF sST2 is associated with outcomes in aSAH patients and performed this study to further investigate.

## 2. Materials and methods

### 2.1. Ethics statement

The study was approved by the Medical Ethics Committee of Jining No.1 People's Hospital (No. JNRM-2021-DW-028), and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

### 2.2. Patient selection

This prospective observational study recruited 125 aSAH patients hospitalized in the Department of Neurosurgery, Jining No.1 People's Hospital from March 2021 to September 2022. All patients received uniform standardized treatment. Those who met the following criteria were included: (1) age 18–80 years; (2) SAH confirmed by cranial computed tomography scan (3) cerebral aneurysm confirmed by digital subtraction angiography; (4) hospital presentation within 24 h of SAH onset; and (5) surgical treatment within 2 days. Patients with traumatic SAH, SAH caused by a vascular malformation other than aneurysm, SAH of unknown cause, previous cerebral hemorrhage or ischemic stroke, autoimmune disease treated with immunosuppression, uremia, cirrhosis, malignant tumor, blood disease, chronic heart disease, chronic lung disease, or other systemic disease were excluded. We also excluded patients with a recent history of surgery, trauma, or infection within the previous month and those who experienced aneurysmal rehemorrhage after treatment.

### 2.3. Collection of SCF and measurement of CSF sST2 concentration

CSF samples (5 mL) were collected daily from all patients on days 1to 5 after surgery via lumbar puncture in a sterile test tube. Samples were centrifuged within 2 h of collection. The supernatant was transferred a sterile Eppendorf tube (1.5 mL) and stored at −80 °C.

CSF sST2 concentration was measured using a commercial human sST2 enzyme-linked immunosorbent assay kit (Boster, China) according to manufacturer instructions.

### 2.4. Statistical analysis

Statistical analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Data with a normal distribution are expressed as means with standard deviation; non-normally distributed data are expressed as medians with (interquartile range). Categorical data are expressed as numbers with percentage. Comparisons were performed using the independent samples *t*-test or Kruskal-Wallis test as appropriate.

Variables with a significant association in univariate analyses were included in a multivariate logistic regression model analysis to further explore the association between aSAH outcome and potential predictor variables. Receiver operating characteristic curve analysis was performed to determine the sensitivity and specificity of ST2 predicting aSAH outcome and complications. $P < 0.05$ was considered significant.

## 3. Results

### 3.1. Patient characteristics

Among the 125 patients with aSAH were screened for inclusion in this study. Of these, 26 did not meet criteria and were excluded. In total, 99 patients met the inclusion criteria and were further screened. A further 9 were excluded because of incomplete data, and 25 were excluded because CSF was not collected in each of the first 5 days after surgery. Therefore, 65 patients were enrolled. Patients were grouped according to modified Rankin scale score measured 3 months after discharge: the good prognosis group comprised patients with mRS score 0–2 (n = 35) and the poor prognosis group comprised those with mRS score 3–5(n = 30). The mRS score was evaluated by two neurosurgeons 3 months after discharge from hospital. Scale details are provided in Supplementary Material 1.

In the good prognosis group, mean age was 54.4 ± 9.28 years and mean weight was 64.74 ± 11.73 kg. Mean age and weight in the poor prognosis group were 66.9 ± 9.7 years and 61.56 ± 13.89 kg, respectively. Although age and weight did not significant differ between the two groups, sex distribution did. There were no significant differences between the good prognosis and poor prognosis groups in terms of smoking, drinking alcohol, and hypertension (Table 1).

World Federation of Neurological Surgeons (WFNS) grade and Hunt and Hess (H–H) grade significantly differ between the good prognosis and poor prognosis groups. When the aneurysm diameter was ≥5 mm, the size of aneurysm was significantly different between the two groups. Aneurysm location was anterior communicating artery in 30 patients (46.25 %) and posterior communicating artery in 35 (53.85 %). Aneurysm location did not significantly differ between the groups. Although total CSF white blood cell count significantly differed between the groups, CSF glucose and protein concentrations did not (Table 1).

Gender, WFNS grade, H–H grade, aneurysm size, and total CSF white blood cell count were included in multivariate logistic regression analysis. Female sex, WFNS grade, H–H grade, and aneurysm size were significantly associated with aSAH outcome (Table 2).

### 3.2. Change in CSF sST2 concentrations over times

In all aSAH patients, CSF sST2 concentration initially increased, peaked on day 2, and then decreased (Fig. 1A). CSF sST2 concentration was significantly higher in the poor prognosis group on all day (Fig. 1B and C).

**Table 1**
Characteristics of aSAH Patients.

| | Overall ( $n = 65$ ) | Good prognosis group($n = 35$) | Poor prognosis group($n = 30$) | $P$ value |
|---|---|---|---|---|
| Demographics | | | | |
| age, years | 60.17 ± 11.31 | 54.4 ± 9.28 | 66.9 ± 9.7 | 0.75 |
| gender, female | 48 (73.85) | 23 (65.71) | 25 (83.33) | < 0.01 |
| weight, kg | 63.28 ± 12.49 | 64.74 ± 11.73 | 61.56 ± 13.89 | 0.15 |
| smoking | 13 (20.00) | 6 (17.14) | 7 (23.33) | 0.23 |
| drinking | 5 (7.69) | 2 (5.71) | 3 (10.00) | 0.20 |
| hypertension | 32 (49.23) | 13 (37.14) | 19 (63.33) | 0.94 |
| Clinical Status on Admission | | | | |
| Hunt-Hess grade | | | | |
| 1 | 1 (1.53) | 0 (0.00) | 2 (6.67) | 0.03 |
| 2 | 33 (50.77) | 22 (62.86) | 11 (36.67) | 0.94 |
| 3 | 29 (44.62) | 13 (37.14) | 16 (53.33) | 0.30 |
| 4 | 2 (3.08) | 0 (0.00) | 2 (6.67) | 0.01 |
| WFNS grade | | | | |
| 1 | 20 (30.77) | 11 (31.43) | 9 (30.00) | 0.81 |
| 2 | 27 (41.54) | 18 (51.43) | 9 (30.00) | 0.02 |
| 3 | 14 (21.53) | 6 (17.14) | 8 (26.66) | 0.07 |
| 4 | 2 (3.08) | 0 (0.00) | 2 (6.67) | 0.001 |
| 5 | 2 (3.08) | 0 (0.00) | 2 (6.67) | 0.001 |
| Aneurysm Location | | | | |
| anterior circulation aneurysm | 30 (46.25) | 18 (51.43) | 12 (40.00) | 0.25 |
| posterior circulation aneurysm | 35 (53.85) | 17 (48.57) | 18 (60.00) | 0.25 |
| Aneurysm Diameter | | | | |
| < 5 mm | 32 (49.23) | 26 (74.28) | 6 (20.00) | 0.28 |
| 5 mm–10mm | 27 (41.54) | 8 (22.86) | 19 (63.33) | 0.022 |
| ≥10 mm | 6 (9.23) | 1 (2.86) | 5 (16.67) | < 0.001 |
| CSF Biochemistry Indicators | | | | |
| TWBC ( $10^6$/L ) | 100.00 (48.00,310.00) | 73.00 (39.00,165.00) | 130.50 (79.25,467.75) | 0.01 |
| glucose ( mmol/L ) | 2.60 (1.99,3.36) | 2.50 (1.83,3.39) | 2.80 (2.25,3.34) | 0.82 |
| protein ( mg/L ) | 1.34 (0.96,2.23) | 1.34 (0.85,2.02) | 1.53 (1.02,2.48) | 0.05 |

Values were expressed as mean ± SD or numbers (% of total).
Hunt-Hess: Hunt and Hess Scales; WFNS: World Federation of Neurological Societies Scale; CSF: cerebrospinal fluid; TWBC: total white blood cell.

**Table 2**
The factors influencing outcome in patients with aSAH by multivariate logistic analysis.

| Factors | B | SE | Wald | P | OR | 95%CI |
|---|---|---|---|---|---|---|
| Gender | 1.53 | 1.03 | 2.18 | 0.14 | 4.59 | 0.61–34.79 |
| Hunt-Hess grade | 0.81 | 0.67 | 1.47 | 0.23 | 2.25 | 0.61–8.27 |
| WFNS grade | 0.10 | 0.48 | 0.05 | 0.84 | 1.11 | 0.43–2.83 |
| TWBC in CSF ( $10^6$/L ) | 0.003 | 0.002 | 2.21 | 0.14 | 1.003 | 0.39–2.91 |
| Aneurysm Diameter ( mm ) | 1.91 | 0.72 | 6.97 | 0.01 | 6.74 | 1.64–27.79 |

Hunt-Hess: Hunt and Hess Scales; WFNS: World Federation of Neurological Societies Scale; CSF: cerebrospinal fluid; TWBC: total white blood cell; 95%CI: 95 % confidence intervals.

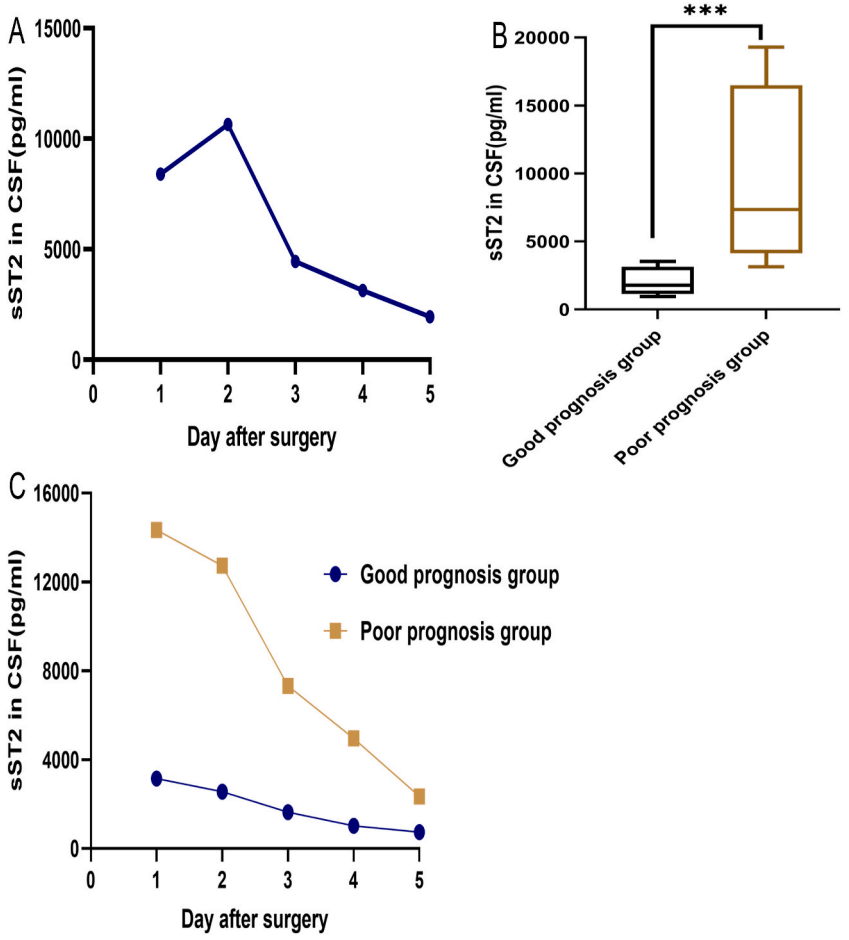


**Fig. 1.** Cerebrospinal fluid (CSF) sST2 concentrations in the first 5 days after surgery. (A) In all patients, CSF sST2 concentration initially increased to reach a peak on day 2; then, it fell sharply. (B) CSF sST2 concentration significantly differed between the good and poor prognosis groups (C) Over the first 5 days at different time points.

### *3.3. Diagnostic performance of CSF sST2 as a predictive marker for aSAH*

In the receiver operating characteristic curve analysis, CSF sST2 concentration >17600.86 pg/mL predicted the prognosis of neurologic function at 3 months after discharge with 90.5 % sensitivity and 95.2 % specificity. The maximum area under the receiver operating characteristic curve (AUC) for sST2 was at 2 days after surgery. The AUC, sensitivity, and specificity were 0.988, 95.7 %, and 95.7 %, respectively (Fig. 2).

### *3.4. Diagnostic performance of CSF sST2 for predicting aSAH complications*

CSF sST2 concentration was significantly associated with the occurrence of cerebral edema in the poor prognosis group (AUC =

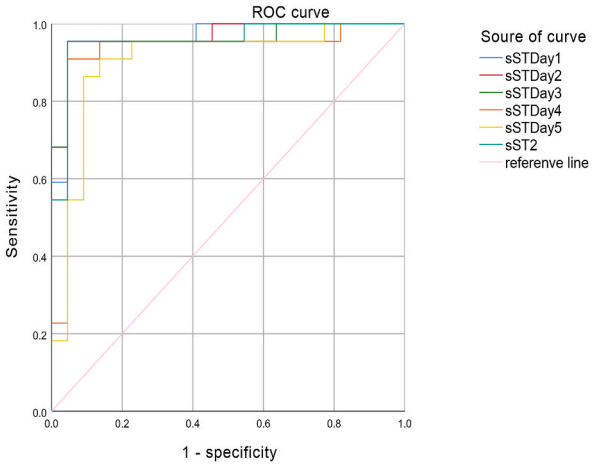


**Fig. 2.** The receiver operating characteristic curve of cerebrospinal fluid sST2 concentration for predicting aSAH outcome. sST2-1-5: Median CSF sST2 concentration on day 1–5 after aSAH surgery; sST2: Median CSF sST2 concentration on days 1–5 after aSAH surgery.

0.93) with a sensitivity of 100 % and specificity of 83.3 %. No such association was demonstrated in the good prognosis group or the entire cohort. Similarly, no significant association was found between CSF sST2 concentration and cerebral infarction in either group or the entire cohort (Table 3 and Fig. 3).

## 4. Discussion

aSAH is a severe disease that negatively impacts patient health and quality of life. Approximately 30 % of aSAH patients die from early brain injury and delayed cerebral ischemia. Most survivors experience various disabilities, which places a heavy burden on patients, their families, and society [18]. The main findings of our aSAH study were as follows: (1) female sex, WFNS grade, H–H grade, and aneurysm size were risk factors for poor outcome; (2) CSF sST2 concentration was higher in patients who experienced a poor outcome; (3) CSF sST2 concentration predicted outcome with high specificity and sensitivity; and (4) CSF sST2 concentration was a significant predictor of cerebral edema in patients who experienced poor outcome. These results suggest that CSF sST2 concentration is strongly associated with outcome in aSAH patients.

The early brain injury of aSAH leads to hypoperfusion of cerebral blood flow, and the body is in a state of ischemia-induced hypoxia, which leads to the activation of astrocytes and microglia and the death of endothelial cells, and then causes inflammatory response and blood-brain barrier dysfunction, cytotoxic edema and cell death [19].The immune response is also thought to play a key role in the pathophysiology of SAH [20], and activation of proinflammatory pathways is involved in a variety of sequelae including cerebral vasospasm and delayed cerebral ischemia [21,22]. In the central nervous system, IL-33 is constitutively expressed in oligodendrocytes [23], while ST2 is mainly expressed in microglia and astrocytes [9].

CSF sST2 concentration peaked 2 days after surgery and then gradually decreased. This concentration was significantly higher in the poor prognosis group than the good prognosis group in the first 5 days after surgery. CSF sST2 concentration was also negatively correlated with the 3-month mRS scores of aSAH patients, suggesting that CSF sST2 concentrations of aSAH patients reflect the severity of disease and the neuroimmune response.

Multivariate logistic regression showed that female sex was a significant predictor of outcome (OR = 4.59), which is likely related to the influence of sex on aSAH incidence. The incidence of aSAH is approximately 20 % higher in females than in males, suggesting that sex hormones may increase the risk of aSAH in women [24,25]. Our results are also consistent with a recent study that reported that WFNS grade and H–H grade are risk factors for aSAH [26]. That study suggested that it is possible to score a patient's condition in the early stages of aSAH to analyze the risk of disease progression and death and give the necessary early intervention. Implementing effective intervention could improve the prognosis of aSAH patients. We found that aneurysm size is an outcome predictor, therefore, it

**Table 3**
The diagnostic efficacy of CSF sST2 for the complications of aSAH.

| | | AUC | *P* | 95%CI | Sensitivity(%) | Specificity(%) |
|---|---|---|---|---|---|---|
| Brain edema | Ungrouped | 0.64 | 0.33 | 0.28–0.99 | 60 | 92.3 |
| | Good prognosis group | 0.26 | 0.28 | 0.74–0.45 | 60 | 92.3 |
| | Poor prognosis group | 0.93 | 0.21 | 0.80–1.00 | 100 | 83.3 |
| Cerebral infarction | Ungrouped | 0.71 | 0.43 | 0.52–0.89 | 78 | 81.8 |
| | Good prognosis group | 0.48 | 0.93 | 0.22–0.75 | 60 | 92.3 |
| | Poor prognosis group | 0.66 | 0.22 | 0.39–0.94 | 60 | 89.7 |

AUC : Area under the curve; 95%CI: 95 % confidence intervals.

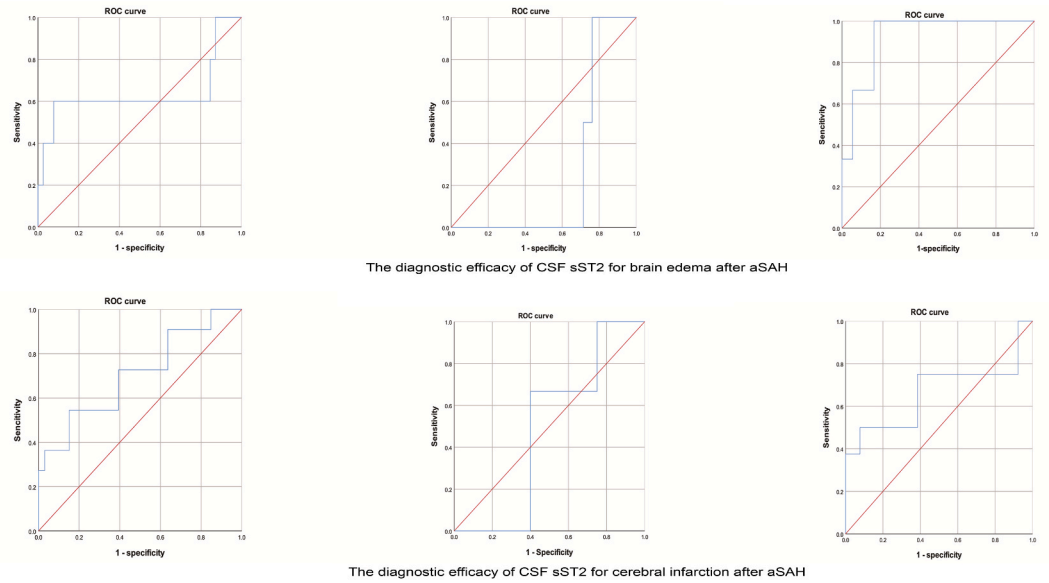


**Fig. 3.** The receiver operating characteristsic curve of CSF sST2 concentration for complications after aSAH. Two columns of figures from left to right are the diagnostic efficacy of CSF sST2 for the brain edema/cerebral infarction of aSAH with ungrouped, good prognosis group and poor prognosis group.

may be particularly important to provide early treatment and rehabilitation for patients harboring an aneurysm with a diameters $> 5$ mm.

A 2023 meta-analysis of serum sST2 in stroke patients showed positive associations between sST-2 concentration and post-stroke mortality, composite adverse events, major disability, cerebral–cardiac syndrome, and cognitive impairment [27]. Abnormal changes of serum IL-33 and sST2 concentration in stroke patients are related to production of inflammatory factors, which affect the prognosis of cerebrovascular disease. These same factors have also been linked to the occurrence and aggravation of depression after stroke [28]. Zhu et al. conducted a prospective study, which showed that elevated plasma sST2 concentration was significantly associated with cognitive impairment after stroke [29]. Many other studies have shown that sST2 is associated with the development of cerebrovascular disease, and diease prognosis. Serum sST2 concentration predicted functional outcome and mortality after SAH as well as delayed cerebral ischemia [17]. Our study has shown that CSF sST2 also has value in predicting outcome in aSAH patients. Several studies have investigated the relationship between inflammation and poor outcome in aSAH patients [30–32]. sST2 and IL33 are involved in numerous pathologic and physiologic processes, and may promote anti or pro-inflammatory signaling, depending on the disease. In humans, sST2 is produced by mast cells activated by IL-33, or by $CD4^+$ and $CD8^+$ T cells [33,34]. Our study did not investigate specific mechanisms of the neuroimmune inflammatory response after aSAH. However, based on the results of previous studies and our data, we speculate that aSAH may promote an increase in IL-33 concentration which trigger production of sST2.

### *4.1. Research limitations and prospects*

Although this study was designed and experimented rigorously, there are still deficiencies and areas for improvement. First, the sample size of the included studies in this study is relatively small and belongs to a single-center experiment, the experimental results may not be representative, which requires us to conduct a large-sample multicenter experiment in the future. Second, we found that sST2 was associated with neuroinflammatory response through clinical experiments, but this conclusion was not verified by establishing an animal experimental model, which did not allow us to further explore in detail the inflammatory mechanism on the cognitive function and prognosis of aSAH in terms of cellular and inflammatory aspects. This requires us to clarify the existing mechanisms by establishing animal models in the next scientific research to better serve the clinic.

## 5. Conclusion

Our study demonstrated that female sex, WFNS grade, H–H grade, and aneurysm size were significantly associated with aSAH outcome. Compared with the good prognosis group, the CSF sST2 concentration of the poor prognosis group was significantly increased throughout the day. We also found that CSF sST2 concentration was significantly associated with the occurrence of cerebral edema in the poor prognosis group. Based on the above studies, we can conclude that elevated CSF sST2 concentration is associated with poor outcome in aSAH patients. CSF sST2 may have a role as a predictive marker in these patients.

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## Data availability statement

The data are available upon reasonable request from the corresponding author.

## CRediT authorship contribution statement

**Qingjian Wu:** Supervision, Resources, Methodology, Funding acquisition. **Xuemei Hu:** Software, Resources, Methodology, Data curation. **Ye Guo:** Resources, Methodology, Investigation. **Mingyang Zhao:** Resources, Methodology, Investigation, Data curation. **Meixue Wang:** Resources, Investigation, Data curation. **Lei Feng:** Resources, Methodology, Formal analysis. **Dongsen Wang:** Writing – review & editing, Writing – original draft, Software, Methodology, Data curation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31745.

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