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Soluble suppression of tumorigenicity 2 associated with atrial fibrillation detected after stroke: A retrospective study

Wenquan Hou [a,b,1], Yong Li [c,1], Jing Wang [c], Menghua Xu [c], Siwen Wu [c], Wen Li [c], Suhua Qi [a,*]

[a] Xuzhou Medical University, Xuzhou, 221000, Jiangsu, China
[b] Department of Laboratory Medicine, The First People's Hospital of Yuhang District, Hangzhou, 311100, Zhejiang, China
[c] Department of Cardiology, The First People's Hospital of Yuhang District, Hangzhou, 311100, Zhejiang, China

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ABSTRACT

Background: The soluble suppression of tumorigenicity 2 (sST2) is closely associated with stroke and atrial fibrillation (AF). However, no studies on sST2 and AF detected after stroke (AFDAS) have been reported. This study investigated the correlation between sST2 and AFDAS.
Methods: This was a single-center, retrospective, clinical observational study. Patients diagnosed with a transient ischemic attack (TIA) or acute ischemic stroke were enrolled, and all patients underwent sST2 detection and electrocardiogram (ECG) or Holter monitoring for at least 24 h.
Results: In total, 970 patients were enrolled, including 72 (7.4 %) with AFDAS. Multivariate analysis showed that age (OR 1.078; 95 % CI, 1.050–1.107; $p < 0.001$), heart rate (HR) (OR 1.025; 95 % CI, 1.007–1.044; $p = 0.007$), national institutes of health stroke scale (NIHSS) score (OR 1.089; 95 % CI, 1.029–1.152; $p = 0.003$), high sensitivity C-reactive protein (hs-CRP) (OR 1.006; 95 % CI, 1.002–1.009; $p = 0.001$), and sST2 (OR 1.018; 95 % CI, 1.010–1.026; $p < 0.001$) were independent risk factors of AFDAS. The areas under the curve (AUCs) for age, HR, sST2, hs-CRP, and NIHSS were 0.731, 0.599, 0.815, 0.664, and 0.700, respectively. The conventional model included age, HR, NIHSS score, and hs-CRP level based on multivariate results. After adding sST2 to the model, the model's performance in predicting AFDAS increased significantly.
Conclusion: Higher sST2 levels were associated with the occurrence of AFDAS. Thus, sST2 can improve the risk model for AFDAS.

1. Introduction

Reperfusion therapy for ischemic stroke has recently gained significant popularity but remains one of the leading causes of death and disability among adults worldwide [1]. Irreversible nerve damage caused by stroke makes secondary prevention particularly important. Furthermore, correct etiological classification is key to selecting the best plan for secondary prevention. Unfortunately, despite advances in diagnostic techniques, the cause of ischemic stroke remains undetermined in approximately 20–30% of patients [2]. Atrial fibrillation (AF) is known to be closely associated with ischemic stroke [3,4]. In particular, latent AF is a real challenge for the secondary prevention of ischemic stroke because it is asymptomatic or paroxysmal [5]. Previous studies have shown that among

* Corresponding author. Xuzhou Medical University, Xuzhou, 221000, Jiangsu, China.
E-mail address: suhuaqi@xzhmu.edu.cn (S. Qi).
[1] These authors have contributed equally to this work.

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stroke patients with no known history of AF, nearly a quarter was diagnosed with post-stroke atrial fibrillation, also known as "AF detected after stroke (AFDAS)," after continuous electrocardiogram (ECG) monitoring [6]. While wearable or implantable heart monitors can identify more patients with AF [7], they often come at a higher cost [8]. In addition, strokes due to AF have a high rate of disability and death, and there are significant differences in the treatment between strokes caused by AF and other causes [4]. Thus, early identification of AFDAS will contribute to the early diagnosis of stroke caused by AF.

Inflammation is essential in ischemia/reperfusion injury of acute ischemic stroke (AIS) and AF [9,10]. Suppression of tumorigenicity 2 (ST2) is a member of the interleukin-1 receptor family involved in the body's inflammatory response and organ fibrosis [11,12]. Soluble ST2 (sST2) is a form of ST2 present in the body [13], and previous studies have shown that sST2 expression is closely associated with stroke [14], AF [15]. new-onset AF after myocardial infarction [16], and post-stroke depression [17]. However, no studies on sST2 and AFDAS have been conducted. This study aimed to explore the predictive value of sST2 levels for AFDAS in patients with ischemic stroke.

2. Methods

2.1. Study population

This retrospective study was conducted at the Xuzhou Medical University and was approved by the local Ethics Committee, and the written informed consent was exempted due to low risk to patients according to the relevant IRB regulatory guidelines (No. XYFY2022-KL200-13). We retrospectively screened all patients diagnosed with a transient ischemic attack (TIA) or acute ischemic stroke [18] between January 2019 and December 2022. Inclusion criteria: Participants aged ≥18 years, sST2 detection completed upon admission, at least one ECG during the hospital stay, continuous electrocardiographic monitoring or a Holter at least 24 h. The exclusion criteria encompassed the following: Prior known AF before admission, recent (defined in terms of the half-life of the drug) or ongoing use of antiarrhythmic drugs, history of myocardial infarction, history of heart failure, presence of cardiac thrombosis, malignancy, or

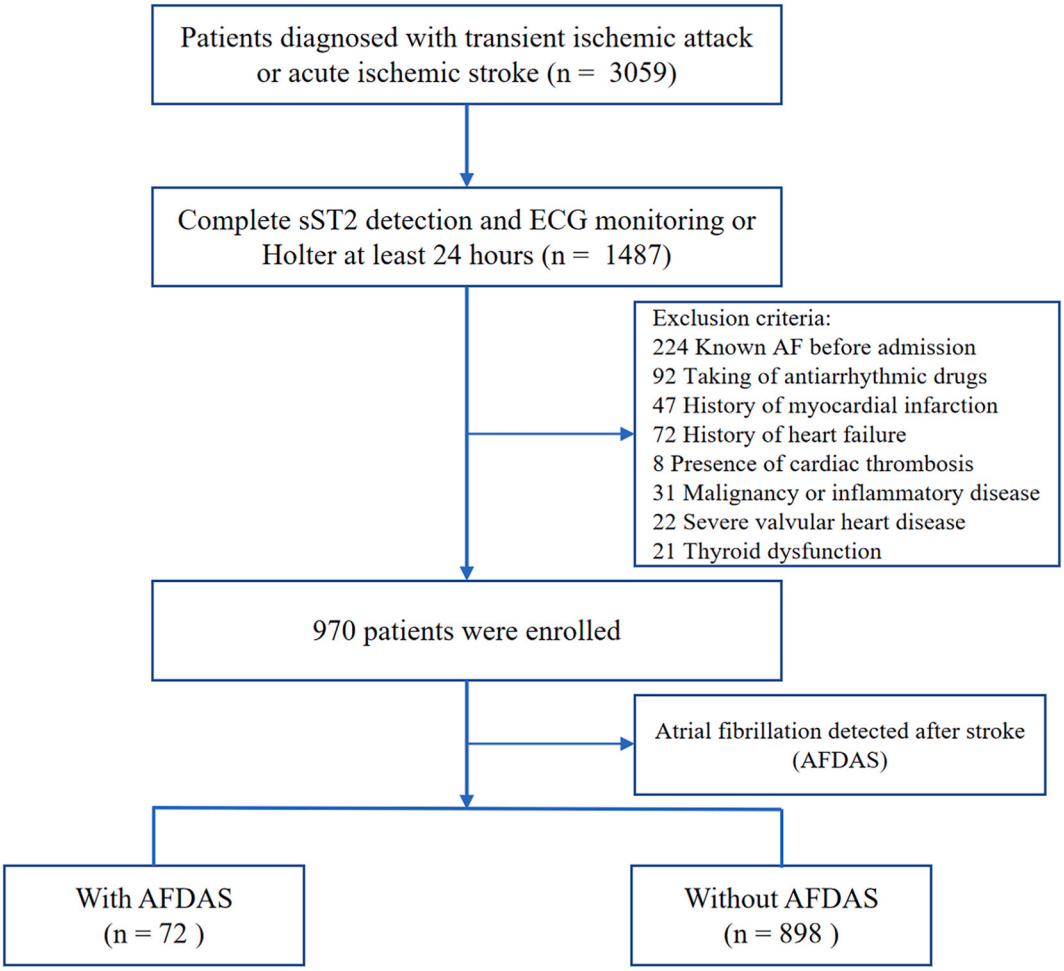

Fig. 1. Study flow chart.

inflammatory disease, severe valvular heart disease, and thyroid dysfunction. In total, 970 patients who met the eligibility criteria were enrolled in this study (Fig. 1).

2.2. Clinical and laboratory data assessment

Baseline clinical data, including sex, age, body mass index (BMI), hypertension, diabetes, left ventricular ejection fraction (LVEF), and National Institutes of Health Stroke Scale (NIHSS) scores, were collected for all cases. NIHSS is a 15-item impairment scale used to measure stroke severity. This includes the level of consciousness, eye movements, the integrity of the visual fields, facial movements, arm and leg muscle strength, sensation, coordination, language, speech, and neglect [19]. After admission, venous blood samples were collected for laboratory analyses. The concentration of sST2 in blood samples was determined using an enzyme-linked immunosorbent assay (ELISA, Elabscience Biotechnology, China). AFDAS was defined as AF after stroke without prior history of AF [20].

2.3. Statistical analysis

SPSS24.0 software and R were used for the statistical analysis. Data conforming to a normal distribution were expressed as mean ± standard deviation (SD) and analyzed using an independent sample *t*-test. Non-normally distributed data were represented by M(Q25, Q75) and analyzed using a non-parametric (Mann–Whitney U) test. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Univariate and multivariate regression analyses were used to identify risk factors for AFDAS, and variables with $p < 0.05$ in univariate analysis or with clinical importance were progressively included in the multivariate analysis. A receiver operating characteristic (ROC) curve was constructed to determine the threshold for the sST2 level prediction of AFDAS. The net reclassification index (NRI) and integrated discrimination improvement (IDI) were used to evaluate additional discriminants of risk factors. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

AFDAS was detected in 72 (7.4 %) patients. Compared with the patients without AFDAS, patients with AFDAS were older (73.58 ± 8.47 vs. 63.65 ± 12.93; $p < 0.001$) and had higher hate rate [81 (71,95) vs. 78 (68,87) bpm; $p = 0.005$], peak of high sensitivity C-reactive protein (hs-CRP) [45.8 (14.8, 134.8) vs. 20.3 (7.5, 56.8) mg/L; $p < 0.001$], NIHSS score [6 [4,16] vs. 4 [3,6]; $p < 0.001$], and

Table 1
Patient Characteristics and the differences between the two groups.

	w/o AFDAS (n = 898)	AFDAS (n = 72)	*P*-Value
Age, years	63.65 ± 12.93	73.58 ± 8.47	< 0.001
Male, n (%)	601 (66.9)	53 (73.6)	0.244
BMI, kg/m2	24.97 ± 3.53	25.26 ± 5.34	0.514
HR, bpm	78 (69, 87)	81 (71, 95)	0.005
SBP, mmHg	130 (115, 145)	124 (105, 145)	0.104
DBP, mmHg	79 (70, 89)	79 (69, 89)	0.859
Current smoker, n (%)	372 (41.4)	27 (37.5)	0.515
Hypertension, n (%)	427 (47.6)	41 (56.9)	0.125
Diabetes mellitus, n (%)	232 (25.8)	20 (27.8)	0.718
LVEF, %	52 (48, 57)	52 (49, 55)	0.593
NIHSS	4 (3,6)	6 (4,16)	< 0.001
Type of stroke			
CI, n (%)	748 (83.3)	66 (91.7)	0.063
TIA, n (%)	150 (16.7)	6 (8.3)	0.063
Medication			
Aspirin, n (%)	801 (89.2)	67 (93.1)	0.305
P2Y12 inhibitors, n (%)	850 (94.7)	69 (95.8)	0.666
Statins, n (%)	849 (94.5)	69 (95.8)	0.640
Laboratory findings			
Peak hs-CRP, mg/L	20.3 (7.5, 56.8)	45.8 (14.8, 134.8)	< 0.001
TSH, mIU/L	2.73 (1.38, 5.19)	2.71 (1.48, 5.42)	0.686
Total cholesterol, mmol/L	4.27 (3.64, 4.99)	4.39 (3.51, 5.16)	0.732
Triglycerides, mmol/L	1.25 (0.92, 1.81)	1.28 (0.98, 2.12)	0.154
LDL cholesterol, mmol/L	2.64 (2.06, 3.20)	2.90 (2.09, 3.40)	0.191
HDL cholesterol, mmol/L	0.98 (0.81, 1.20)	0.97 (0.83, 1.12)	0.507
sST2, ng/mL	30.38 (24.14, 39.16)	54.28 (39.25, 101.52)	< 0.001

AFDAS atrial fibrillation detected after stroke, BMI body mass index, HR heart rate, SBP systolic blood pressure, DBP diastolic blood pressure, NIHSS national institutes of health stroke scale, CI cerebral infarction, TIA transient ischemic attack, TSH thyroid stimulating hormone, HDL high density leptin cholesterol, LDL cholesterol low density leptin cholesterol, hs-CRP high sensitivity C-reactive protein, sST2 soluble ST2, LVEF left ventricular ejection fraction.

sST2 [54.28 (39.25, 101.52) vs. 30.38 (24.14, 39.16) ng/mL; p < 0.001] (Table 1).

3.2. Association between sST2 and AFDAS

Univariate analysis showed that the AFDAS was associated with age, heart rate, NIHSS score, hs-CRP, and sST2. In a multivariable model, age (OR 1.078; 95 % CI, 1.050–1.107; p < 0.001), hate rate (OR 1.025; 95 % CI, 1.007–1.044; p = 0.007), NIHSS score (OR 1.089; 95 % CI, 1.029–1.152; p = 0.003), hs-CRP (OR 1.006; 95 % CI, 1.002–1.009; p = 0.001), and sST2 (OR 1.018; 95 % CI, 1.010–1.026; p < 0.001) were independent risk factors of AFDAS. All these factors were associated with a higher risk of AFDAS in the present study (Table 2).

3.3. Diagnostic performance of sST2 for AFDAS

ROC analysis demonstrated that sST2 had a cut-off value of 37.88 to predict patients with AFDAS and showed an area under the curve (AUC) of 0.815 (95 % CI 0.762–0.868), with a sensitivity of 84.7 % and a specificity of 72.0 %. Therefore, sST2 showed excellent diagnostic performance for AFDAS. The independent risk factors for AFDAS, the AUCs of age, heart rate, hs-CRP level, and NIHSS score were 0.731 (95 % CI, 0.681–0.782), 0.599 (95 % CI, 0.528–0.671), 0.664 (95 % CI, 0.597–0.730), and 0.700 (95 % CI, 0.632–0.768), respectively. The sensitivity and specificity of age, heart rate, hs-CRP, and NIHSS were 86.1 % and 51.9 %; 61.6 % and 56.6 %; 48.6 % and 76.1 %; and 68.1 % and 69.0 %, respectively (Table 3 and Fig. 2).

3.4. Incremental value of sST2 in patients with AFDAS

The conventional model included age, heart rate, NIHSS score, and hs-CRP level based on multivariate results. After adding sST2 to the model, NRI increased by 58.10 % (95 % CI, 0.346–0.816; p = 0.001), and IDI was 3.90 % (95%CI, 0.004–0.075; p = 0.031). sST2 significantly increased the discriminant and reclassification indices, and the model performance for the prediction of AFDAS significantly increased (p < 0.05). When sST2 was dichotomized based on the cutoff value obtained by ROC, the model with sST2 also showed significantly higher discriminant and reclassification abilities [NRI increased by 34.3 % (95 % CI, 0.200–0.485; p < 0.001), and IDI was 10.3 % (95%CI, 0.070–0.136; p < 0.001]) (Table 4).

4. Discussion

To the best of our knowledge, this is the first study investigating the correlation between sST2 and AFDAS expression. The main finding of this study was that higher sST2 concentrations were associated with the occurrence of AFDAS after adjusting for several confounding factors. Additionally, the ability to discriminate and reclassify AFDAS was greatly enhanced by integrating sST2 into the models with clinical risk factors.

4.1. The occurrence of AFDAS

AFDAS is present in many patients with acute ischemic stroke or TIA [6,21]. Giralt-Steinhauer et al. measured the incidence of AF in patients at different stages of stroke. Approximately 7.5 % of the patients with a normal initial ECG were diagnosed with AF during hospitalization [22]. Furthermore, Anetta et al. found that AF was present in 33 % of stroke patients based on 24-h ECG monitoring during hospitalization, and 6 % of the subjects were diagnosed with AF for the first time [23]. Consistent with these studies, AFDAS was found in 72 of the 970 patients (7.4 %) in this study.

Table 2
Univariate and multivariable logistic regression for the association of variables with atrial fibrillation detected after stroke.

Univariate			Multivariable	
Variables	OR (95%CI)	*P*-Value	OR (95%CI)	*P*-Value
Age, years	1.078 (1.052–1.104)	< 0.001	1.078 (1.050–1.107)	< 0.001
Male, n (%)	1.000(0.580–1.724)	1		
BMI, kg/m2	1.022(0.958–1.090)	0.514		
SBP, mmHg	0.991(0.980–1.002)	0.095		
Hypertension, n (%)	1.459(0.899–2.368)	0.127		
Diabetes mellitus, n (%)	1.104(0.645–1.889)	0.718		
LVEF, %	0.987(0.951–1.024)	0.474		
HR, bpm	1.027 (1.010–1.043)	0.002	1.025 (1.007–1.044)	0.007
Peak hs-CRP, mg/L	1.007 (1.005–1.010)	< 0.001	1.006 (1.002–1.009)	0.001
NIHSS	1.155 (1.106–1.206)	< 0.001	1.089 (1.029–1.152)	0.003
sST2, ng/mL	1.024 (1.017–1.031)	< 0.001	1.018 (1.010–1.026)	< 0.001

HR heart rate, NIHSS national institutes of health stroke scale, hs-CRP high sensitivity C-reactive protein, sST2 soluble ST2.

Table 3
Cutoffs for prediction of AFDAS in patients.

	AUC	95%CI	Cut-off Value	Sensitivity (%)	Specificity (%)
sST2	0.815	0.762–0.868	37.88	84.7	72.0
Age	0.731	0.681–0.782	65.5	86.1	51.9
HR	0.599	0.528–0.671	79.5	61.1	56.6
NIHSS	0.700	0.632–0.768	4.5	68.1	69.0
Peak hs-CRP	0.664	0.597–0.730	61.1	48.6	76.1

HR heart rate, NIHSS national institutes of health stroke scale, hs-CRP high sensitivity C-reactive protein, sST2 soluble ST2.

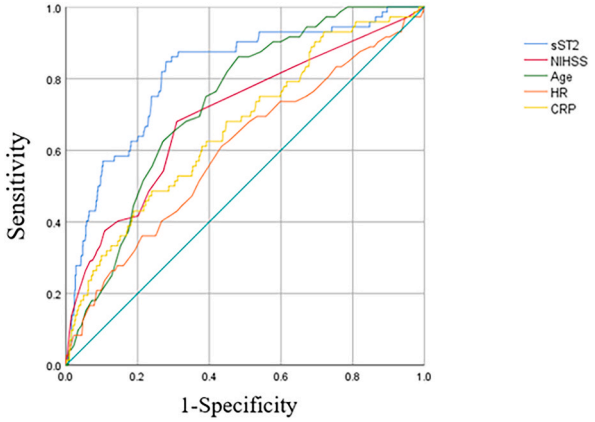

Fig. 2. ROC curve analysis association of HR, NIHSS, hs-CRP, and sST2 with the risk of atrial fibrillation detected after stroke.

Table 4
Reclassification statistics (95 % CI) for depression by sST2 among patients.

	NRI		IDI	
	Estimate (95 % CI)	P value	Estimate (95 % CI)	P value
Conventional model	Reference	–	Reference	–
Conventional model + sST2, continuous	0.581 (0.346–0.816)	0.001	0.039 (0.004–0.075)	0.031
Conventional model + sST2, dichotomized	0.343 (0.200–0.485)	<0.001	0.103 (0.070–0.136)	<0.001

CI confidence interval, IDI integrated discrimination index, NRI net reclassification improvement, sST2 soluble suppression of tumorigenicity 2. Conventional model included age, HR, hs-CRP, and NIHSS. sST2 was dichotomized based on Cutoff Value obtained by the receiver operating characteristics.

4.2. The traditional risk factors for AFDAS

In recent years, considerable research has focused on clinical factors that may predict AFDAS. Several scoring systems have been developed to stratify the risk of AFDAS in patients with ischemic stroke or TIA [22,24,25]. Similarly, this study found that older age and faster heart rate were associated with AF. Moreover, baseline neurological deficits were more severe in the AFDAS group than in the w/o AFDAS group. Notably, higher NIHSS scores have been found to predict AFDAS(22). AFDAS distinguishes pre-existing atrial fibrillation (cardiac AFDAS) from atrial fibrillation secondary to neurogenic heart injury (neurogenic AFDAS), and patients with AF tend to have more severe strokes and higher NIHSS scores [26,27]. From an outcome perspective, more severe nerve injury is often accompanied by a more severe inflammatory response and organ damage, leading to a higher risk of AFDAS(22). Therefore, patients with higher NIHSS scores may have a higher risk of cardiac or neurogenic AFDAS.

4.3. The association between sST2 and AFDAS

sST2 plays essential roles in inflammation, tissue fibrosis, post-stroke secondary injury, and myocardial cell injury [28–30]. After adjusting for major confounding factors, Laura et al. confirmed the predictive value of sST2 for all-cause mortality in patients with AIS [31]. Two population studies from the Framingham Offspring Cohort and Finland showed that sST2 was significantly associated with stroke events [14,32]. In addition, elevated sST2 levels are strongly associated with an increased risk of poor prognosis in patients with a transient ischemic attack or ischemic stroke [33]. Interestingly, in addition to stroke, ST2 is also associated with atrial fibrillation. A previous study reported that sST2 was an independent risk factor for predicting AF recurrence of atrial fibrillation after catheter

ablation in patients with paroxysmal atrial fibrillation [34]. Chen et al. found that elevated sST2 levels were associated with an increased risk of new-onset AF after acute myocardial infarction [16]. However, studies on sST2 and AFDAS have rarely been conducted. In this study, after adjusting for major confounding factors, it was found that sST2 (OR 1.018; 95 % CI, 1.010–1.026) is an independent predictor of AFDAS. There are several potential explanations for this phenomenon. Firstly, as described in this study, the hs-CRP level in the AFDAS group was significantly higher than that in the w/o AFDAS group [45.8 (14.8, 134.8) vs. 20.3 (7.5, 56.8) mg/L]. The inflammatory response plays a vital role in stroke patients and is associated with AF development of atrial fibrillation [35, 36]. Secondly, stroke can also produce selective myocardial cell damage and fibrosis during sympathetic nervous system activation, leading to new arrhythmias, including AF[37]. There is growing evidence that the IL-33/ST2 signaling pathway is essential for these processes. The IL-33/ST2 signaling pathway not only drives the M2 polarization of microglia and macrophages from a pro-inflammatory to an anti-inflammatory phenotype and reduces astrocyte activation [38,39] but also exerts cardioprotective effects in vivo through antifibrosis, reduced hypertrophy, and reduced macrophage infiltration [40]. sST2 acts as a decoy receptor in vivo to sequester free IL-33 in competition with transmembrane ST2, promoting the development of inflammation and inhibiting cardioprotective and neuroprotective effects [41], thereby potentially promoting the development of AFDAS. Chen et al. found that the AUC value of sST2 for new-onset AF was 0.827 in acute myocardial infarction patients with AMI. Whether as a continuous or dichotomized variable, sST2 significantly improves the IDI and INI of the model for new-onset AF(16). In this study, the ROC curve consistently showed that the AUC value of sST2 was 0.815. After adding sST2 to the model, NRI increased by 58.10 % (95 % CI, 0.346–0.816; $p = 0.001$), IDI increased by 3.90 % (95%CI, 0.004–0.075; $p = 0.031$), and the model performance for the prediction of AFDAS increased significantly. These results indicated that sST2 could identify AFDAS and should be considered in predictive models of clinical risk factors. Therefore, it may be a valuable biomarker for the risk stratification of patients with AFDAS. The current guidelines recommend using oral anticoagulants for stroke prevention in patients with AFDAS [42]. Defining new factors for AFDAS could help identify patients at risk of recurrent stroke, improve anticoagulant patient selection, and potentially identify modifiable risk factors for AFDAS.

5. Limitations

This study has some limitations. First, this was a single-center retrospective study with limited sample size and selected population, and there may have been bias. Second, we did not provide continuous ECG monitoring for all patients admitted to the hospital, which may have led to some patients with AFDAS being missed. Third, this was a clinical observational study conducted during admission. If regular post-hospital follow-ups can be conducted to detect AFDAS in patients in the chronic stage of stroke, it may have better clinical value.

6. Conclusion

Higher sST2 concentrations were associated with the occurrence of AFDAS. Thus, sST2 can improve the risk model for AFDAS.

Ethics statement

The study was reviewed by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University.

Data availability statement

The datasets generated during and/or analyzed during the current study are available by request.

Additional information

No additional information is available for this paper.

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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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