Research Square

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Serum soluble ST2 is a predictor for poor long-term prognosis after transient ischemic attack and ischemic stroke: a cohort study

Xuan Tian
Zhengzhou University First Affiliated Hospital
Yinan Guo
Zhengzhou University First Affiliated Hospital
Xiao Wang
Zhengzhou University First Affiliated Hospital
Lulu Pei
Zhengzhou University First Affiliated Hospital
Xin Wang
Zhengzhou University First Affiliated Hospital
Jun Wu
Zhengzhou University First Affiliated Hospital
Shilei Sun
Zhengzhou University First Affiliated Hospital
Yusheng Li
Zhengzhou University First Affiliated Hospital
Mingming Ning
Massachusetts General Hospital Department of Neurology
Ferdinando S. Buonanno
Massachusetts General Hospital Department of Neurology
Yuming Xu
Zhengzhou University First Affiliated Hospital
Bo Song (fccsongb@zzu.edu.cn)
Zhengzhou University First Affiliated Hospital https://orcid.org/0000-0002-4563-0781

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Abstract

Background

Soluble ST2 (sST2) is a novel inflammation marker for the prediction of adverse outcomes in patients with cardiovascular disease and diabetes mellitus. The aim of the present study was to examine the predictive value of serum sST2 for prognostic outcomes in patients with transient ischemic attack (TIA)/ischemic stroke.

Methods

Patients within 24 h after symptom onset were prospectively enrolled based on the TIA/ischemic stroke database of the First Affiliated Hospital of Zhengzhou University. The 1-year prognostic outcomes were composite adverse events (including ischemic and hemorrhagic stroke, myocardial infarction, and all-cause death) and a combination of major disability and death [modified Rankin Scale (mRS), 3-6]. Cox proportional hazard and logistic regression models were used to evaluate the association between serum sST2 and TIA/ischemic stroke prognosis. The C statistic, net reclassification index (NRI), and integrated discrimination index (IDI) were used to present improvement in risk classification.

Results

Serum sST2 levels were positively correlated with National Institutes of Health Stroke Scale (NIHSS) scores. Kaplan-Meier analysis indicated a significantly different risk in composite adverse events between patients with higher and those with lower levels of sST2 (P=0.006). Serum sST2 was an independent predictor for composite adverse events (HR: 2.517, 95% CI: 1.279-4.956, P=0.008) and major disability or death (OR: 3.126, 95% CI: 1.452-6.728, P=0.004) after multivariate adjustment. The addition of the sST2 to the NIHSS score significantly improved the predictive value for prognostic outcomes in patients with TIA/ischemic stroke (C statistic: 0.021, IDI: 1.91%, P=0.042 for composite adverse events; NRI: 32.82%, P=0.042 for major disability or death).

Conclusions

Serum sST2 levels were positively associated with the severity of TIA/ischemic stroke and could independently predict composite adverse events and major disability or death, indicating that sST2 may be a potential prognostic marker for TIA/ischemic stroke.

Background

The high incidence, recurrence, disability, and mortality associated with transient ischemic attack (TIA)/ischemic stroke impose a heavy burden on families and society [1]. It is essential to make an early diagnosis and establish reliable markers and indices for predicting prognosis in patients with TIA/ischemic stroke.

Soluble ST2 (sST2) is one such inflammation marker candidate, which functions as a decoy receptor for interleukin (IL)-33 and thus prevents cellular IL-33 signaling mediated by the transmembrane receptor (ST2L) [2]. Further, sST2 is associated with cardiac diseases [3] and atherosclerosis [4]. Elevated circulating sST2 is also an effective prognostic marker for adverse outcomes in myocardial infarction, coronary artery disease, heart failure, atrial fibrillation, and type 2 diabetes [5, 6].

The relationship between sST2 and TIA/ischemic stroke and its long-term prognostic value after TIA/ischemic stroke remain unclear. Studies have found that higher sST2 levels increase risk for incident stroke/TIA in the Framingham Offspring cohort [7]. Elevated sST2 is also associated with increased risk of hemorrhagic transformation, 90-day poor functional outcomes, and higher mortality after acute ischemic stroke (AIS) [8, 9]. However, results have been mixed, with another study reporting that sST2 offered no prognostic value for 90-day all-cause mortality after AIS in multivariate analysis [10]. The present study aimed to investigate the predictive value of serum sST2 for long-term prognostic outcomes in a cohort of patients with TIA/ischemic stroke.

Methods

Study design and patient selection

Patients included in this study were from the TIA/ischemic stroke database of the First Affiliated Hospital of Zhengzhou University, which is a prospective hospital-based cohort registry enrolled consecutive patients with TIA/ischemic stroke. Details regarding the database recruitment and assessment have been described previously [11–13]. The present study involved and analyzed the patients enrolled in the database from October 2015 to June 2018.

The inclusion criteria were: TIA/ischemic stroke within 24 h after symptom onset and aged 18 years or older. TIA and ischemic stroke were diagnosed based on computed tomography/magnetic resonance imaging-based guidelines outlined in a scientific statement by the American Heart Association/American Stroke Association in 2009 [14]. The exclusion criteria were: failure to collect blood samples or interval between symptom onset and blood sample collection > 24 h; active inflammation; severe renal or liver dysfunction, heart failure, or malignant tumor; history of surgery, trauma, or cardiovascular and cerebrovascular diseases within the last year; and incomplete data collection at baseline or at follow-up.

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. All patients or their designated proxies provided written informed consent.

Blood sample collection and serum sST2 measurement

Venous blood samples of 4 mL per person were collected from patients within 24 h after symptom onset. Blood was centrifuged at 4000 rpm for 4 min within 1 h after collection and serum was separated and stored at -80℃ until further testing. Serum sST2 levels were measured using a human sST2 enzyme-

linked immunosorbent assay (ELISA) kit (Elabscience Co, Wuhan, China) according to the manufacturer's instructions. Serum samples in plates were diluted at 1:60, and all results are expressed in ng/mL.

Clinical data collection and outcome assessment

The following baseline clinical characteristics were collected for all patients: demographic data, smoking status, and medical history (hypertension, diabetes mellitus, hyperlipidemia, prior ischemic stroke, coronary heart disease, and atrial fibrillation). Stroke severity on admission was assessed using the National Institutes of Health Stroke Scale (NIHSS) administered by trained neurologists blinded to the sST2 levels.

All patients were followed up at 3, 6 months and 1 year after TIA/ischemic stroke via face-to-face/telephone interviews. The follow-up was performed by trained and qualified neurologists who were not involved in the registry and blinded to any baseline data or the sST2 levels. The prognostic outcomes were composite adverse events (including ischemic and hemorrhagic stroke, myocardial infarction, and all-cause death) and a combination of major disability and death [modified Rankin Scale (mRS), 3–6] within the 1-year follow-up period. Scores on the mRS ranged from 0 to 6, with a score of 0 indicating no symptoms, 5 indicating severe disability, and 6 indicating death [15].

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) for normal distribution or as medians [interquartile range (IQR)] for skewed distribution. Univariate analyses were conducted using Student's t and Mann-Whitney U tests for continuous variables. Categorical data are expressed as frequencies with percentages and compared using chi-square test. Spearman correlation was calculated to assess the relationship between NIHSS scores and sST2 levels. We established a cohort to explore the association between sST2 levels and prognosis after TIA/ischemic stroke, censoring patients at the 1-year follow-up or upon prespecified events. Optimal sST2 cut-off values for outcomes were obtained using receiver operating characteristic (ROC) curve analysis. The cumulative event risks were calculated by Kaplan-Meier survival analysis, and the log-rank test was performed to compare cumulative event curves. A Cox proportional hazards model was conducted to investigate the predictive value of sST2 for composite adverse events. The association between sST2 and a combination of major disability and death was examined with a logistic regression model. All multivariate analyses were adjusted for age, sex, smoking status, medical history, and NIHSS scores. Associations are presented as hazard ratios (HRs) or odds ratios (ORs) with corresponding 95% confidence intervals (CIs). C statistic, the net reclassification index (NRI), and integrated discrimination index (IDI) were calculated to evaluate the discriminative and risk stratification abilities by sST2 beyond the NIHSS score.

Overall, a two-sided $P < 0.05$ was considered as a significance level. All analyses were performed with SPSS 24.0 (IBM Corp., Armonk, NY) and R Studio 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

From October 2015 to June 2018, 452 consecutive patients with TIA/ischemic stroke were eligible for prospective enrollment. After excluding 15 patients without blood samples, 3 with active inflammation, 2 with malignant tumor, 2 with history of trauma or surgery within the last year, and 17 lost to the 1-year follow-up, a total of 413 patients were included in the final analysis (Fig. 1).

Baseline characteristics are shown in Table 1. Among the 413 patients, the average age was 60.34 ± 11.48 years and 128 patients (30.99%) were female. The median NIHSS score on admission and serum sST2 levels of the cohort were 2 (0–4) and 17.74 (9.16–28.72) ng/mL, respectively.

Table 1
Baseline characteristics of TIA/ischemic stroke patients included according to 1-year prognostic outcomes

Baseline characteristics	Total (n = 413)	1-year prognostic outcomes after TIA/ischemic stroke					
		Composite adverse outcomes (n = 38)	Non-composite adverse outcomes (n = 375)	P value	mRS, 3–6 (n = 40)	mRS, 0–2 (n = 373)	P value
Female, n (%)	128 (30.99)	12 (31.58)	116 (30.93)	0.935	16 (40.00)	112 (30.03)	0.195
Age, mean ± SD	60.34 ± 11.48	64.55 ± 11.56	59.92 ± 11.40	0.018	66.20 ± 11.89	59.72 ± 11.27	0.001
Current smoking, n (%)	121 (29.30)	11 (28.95)	110 (29.33)	0.960	10 (25.00)	111 (29.76)	0.530
Medical history, n (%)							
Hypertension	283 (68.52)	26 (68.42)	257 (68.53)	0.989	34 (85.00)	249 (66.76)	0.018
Diabetes mellitus	113 (27.36)	10 (26.32)	103 (27.47)	0.879	15 (37.50)	98 (26.27)	0.130
Hyperlipidemia	101 (24.46)	7 (18.42)	94 (25.07)	0.364	6 (15.00)	95 (25.47)	0.143
Prior ischemic stroke	91 (22.03)	15 (39.47)	76 (20.27)	0.006	14 (35.00)	77 (20.64)	0.037
Coronary heart disease	69 (16.71)	9 (23.68)	60 (16.00)	0.226	9 (22.50)	60 (16.09)	0.301
Atrial fibrillation	26 (6.30)	3 (7.89)	23 (6.13)	0.940	6 (15.00)	20 (5.36)	0.041
NIHSS on admission, median (IQR)	2 (0–4)	2 (0–3)	2 (0–4)	0.593	4 (2–9)	2 (0–4)	< 0.0001
sST2 (ng/mL), median (IQR)	17.74 (9.16–28.72)	24.02 (12.99–43.06)	16.97 (8.98–27.57)	0.035	24.82 (13.93–43.74)	16.70 (8.99–26.70)	0.003

IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; sST2, soluble ST2; TIA, transient ischemic stroke.

Association of serum sST2 with the severity of TIA/ischemic stroke

Serum sST2 levels were positively correlated with the NIHSS score on admission ($r = 0.247$ $P < 0.0001$). Stratified by a NIHSS score of 3 [16], the patients were divided into the mild group (NIHSS ≤ 3, $n = 293$) and severe group (NIHSS > 3, $n = 120$). The sST2 levels were significantly higher in the severe group than in the mild group ($P < 0.001$, Fig. 2a). Among the 413 patients, 312 had ischemic stroke and 101 had TIA according to the tissue-based definitions. Serum sST2 levels were markedly higher in patients with ischemic stroke than in those with TIA ($P < 0.0001$, Fig. 2b).

Association between serum sST2 and prognostic outcomes after TIA/ischemic stroke

During the 1-year follow-up period, 38 (9.20%) patients experienced composite adverse events (Table 1). Serum sST2 levels were higher in patients with composite adverse events. ($P = 0.035$, Fig. 2c). Kaplan-Meier analysis according to the optimal sST2 cut-off value of 22.97 ng/mL revealed that patients with higher sST2 levels had higher incidence of composite adverse events at 1 year (log-rank test $P = 0.006$, Fig. 3a). Using sST2 dichotomized by the cut-off value, the univariate Cox proportional hazards regression showed that elevated sST2 levels were associated with increased risk of composite adverse events (HR = 2.356, 95% CI: 1.246–4.453, $P = 0.008$). After adjusting for age, sex, smoking status, medical history (hypertension, diabetes mellitus, hyperlipidemia, prior ischemic stroke, coronary heart disease, and atrial fibrillation) and baseline NIHSS score, serum sST2 levels could still independently predict 1-year composite adverse events (HR: 2.517, 95% CI: 1.279–4.956, $P = 0.008$, Table 2). Additional significant predictors were age (HR: 1.041, 95% CI: 1.006–1.077, $P = 0.022$) and prior ischemic stroke (HR: 2.182, 95% CI: 1.100-4.332, $P = 0.026$).

Table 2

Multivariate analyses for the association between serum sST2 and prognostic outcomes at 1 year

Variables	Composite adverse events			A combination of major disability and death		
	HR[a]	95% CI	P value	OR[b]	95% CI	P value
Sex (female)	1.235	0.571–2.670	0.592	1.569	0.670–3.674	0.299
Age	1.041	1.006–1.077	0.022	1.060	1.018–1.103	0.005
Current smoking	1.246	0.554–2.802	0.594	0.915	0.336–2.492	0.862
Hypertension	0.777	0.379–1.589	0.489	2.340	0.888–6.165	0.085
Diabetes mellitus	0.737	0.350–1.551	0.421	1.337	0.607–2.948	0.471
Hyperlipidemia	1.021	0.424–2.456	0.964	1.033	0.370–2.883	0.951
Prior ischemic stroke	2.182	1.100-4.332	0.026	2.197	0.994–4.857	0.052
Coronary heart disease	1.052	0.472–2.341	0.902	0.681	0.258–1.794	0.436
Atrial fibrillation	0.845	0.238–2.997	0.794	0.963	0.264–3.519	0.955
NIHSS on admission	0.932	0.825–1.052	0.255	1.263	1.140–1.399	< 0.0001
sST2 (> cut-off value ng/mL)[c]	2.517	1.279–4.956	0.008	3.126	1.452–6.728	0.004

[a]HR was adjusted ratio calculated by multivariate Cox proportional hazards regression.

[b]OR was adjusted ratio calculated by multivariate logistic regression.

[c]sST2 was dichotomized according to optimal cut-off values obtained by ROC curve analysis.

CI, confidence interval; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; sST2, soluble ST2.

Within 1 year after TIA/ischemic stroke, composite outcomes of major disability and death occurred in 40 (9.69%) patients (Table 1). Higher sST2 levels were observed in patients with mRS of 3–6 (P = 0.003,

Fig. 2d). Unadjusted logistic regression, dichotomizing sST2 levels with a cut-off value of 24.61 ng/mL, showed that serum sST2 levels were associated with a combination of major disability and death within 1 year (OR: 3.408, 95% CI: 1.751–6.634, P < 0.001). The association remained significant in multivariate logistic regression. The adjusted OR for the higher versus lower sST2 levels was 3.126 (95% CI: 1.452–6.728, P = 0.004, Table 2). In addition, age (OR: 1.060, 95% CI: 1.018–1.103, P = 0.005) and baseline NIHSS scores (OR: 1.263, 95% CI: 1.140–1.399, P < 0.0001) were also significantly associated with major disability or death.

We also examined the association between sST2 and 1-year stroke recurrence (including ischemic and hemorrhagic stroke, n = 30). There was a significant difference in the risk of recurrent stroke between the low-level (≤ 7.92 ng/mL) and high-level (> 7.92 mg/mL) categories (log-rank test P = 0.049, Fig. 3b). However, after adjusting for confounders, there was no significance but only a trend toward an association between higher sST2 levels and higher risk of stroke recurrence (P = 0.055).

Incremental predictive value of sST2 for TIA/ischemic stroke outcomes

Adding serum sST2 to the NIHSS score, we evaluated whether sST2 would further increase the predictive value for TIA/ischemic stroke outcomes (Table 3). For the composite adverse events, the C statistic by sST2 combined with NIHSS showed a significant improvement (from 0.526 to 0.669, P = 0.021) and the IDI was 1.91% (P = 0.042). Only the NRI of 32.82% by NIHSS with the addition of sST2 appeared to be substantially better than NIHSS alone (P = 0.042) for major disability or death.

Table 3

Reclassification and discrimination statistics for prognostic outcomes within 1 year by serum sST2

Outcomes within 1 year	C statistic		NRI (continuous), %		IDI, %	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Composite adverse events						
NIHSS	0.526 (0.438–0.613)		Reference		Reference	
NIHSS + sST2	0.669 (0.598–0.740)	0.021	31.48 (-0.77-63.73)	0.056	1.91 (0.07–3.75)	0.042
A combination of major disability and death (mRS, 3–6)						
NIHSS	0.710 (0.628–0.793)		Reference		Reference	
NIHSS + sST2	0.726 (0.641–0.810)	0.378	32.82 (1.25–64.38)	0.042	1.61 (-0.42-3.65)	0.120

CI, confidence interval; IDI, integrated discrimination index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NRI, net reclassification index; sST2, soluble ST2.

Discussion

In this study, we investigated the association between serum sST2 and prognostic outcomes in patients with TIA/ischemic stroke within 24 h after onset. Our results revealed that serum sST2 levels were positively correlated with the severity of TIA/ischemic stroke and sST2 was shown to be an independently prognostic marker for composite adverse events and major disability or death at the 1-year follow-up.

The IL-33/ST2 signaling pathway plays a crucial role in the pathogenesis of cerebrovascular diseases and associated inflammation [5, 8, 17–19]. ST2, which acts as the only receptor for IL-33, is a member of the toll-like/IL-1-receptor superfamily [20], with the soluble, circulating form (sST2) and transmembrane form (ST2L) occurring due to alternative splicing and 3' processing at the RNA level [21]. IL-33, ST2L, and sST2 are all upregulated with cell damage or necrosis, which occurs after TIA/ischemic stroke onset. Furthermore, the expression of sST2 increases in response to proinflammatory cytokines [22]. Given this, we measured serum IL-33 from patient blood samples using Human IL-33 Quantikine ELISA Kit (R&D Systems, Minneapolis, MN). The results showed that the IL-33 levels were below the ELISA detection limits, which was also found by a prior report [8]. Nevertheless, previous studies have reported a role of sST2 in stroke that indicated some possible underlying mechanism. For instance, one small study found a markedly higher proportion of AIS patients with high sST2 levels compared to healthy controls when

sST2 was dichotomized by a cut point (n = 53 vs. 12, P = 0.037) [8]. Another study reported that serum ST2 levels were markedly upregulated in AIS patients versus controls (n = 112 vs. 78, P < 0.01) [23]. Accordingly, we finally measured and analyzed serum sST2 levels in this study.

We demonstrated that there was a positive correlation between serum sST2 levels and NIHSS scores. This is possibly related to some sST2 pathophysiologic characteristics. IL-33 binding to ST2L drives a shift toward a Th2-type immune response and M2-type macrophages, which are protective in ischemic stroke [8, 17, 18]. Conversely, sST2, a decoy receptor for IL-33, can attenuate IL-33's action by binding and sequestering IL-33 [2]. Accordingly, sST2 should oppose the biological effects of IL-33. A recent study found that sST2 levels were higher when cerebral infarct volumes, NIHSS scores, and high sensitivity C-reactive protein levels were increased [23]. Our results on the association between serum sST2 and the severity of TIA/ischemic stroke agreed with these, further verifying this potential marker in patients with TIA/ischemic stroke and suggesting that sST2 may be an indicator for risk stratification in TIA/ischemic stroke.

sST2 is a prognostic marker in patients with heart failure and myocardial infarction [24, 25] and significantly associated with incident stroke/TIA in previously stroke-free individuals [7]. In cerebrovascular disease, prior work found that sST2 is an independent predictor for poor functional outcomes (mRS > 2) 3 months after AIS [8, 9]. Additionally, sST2 levels were found to independently correlate with 90-day mortality and hemorrhagic transformation after AIS [9]. However, the predictive value of sST2 for all-cause mortality 90 days after ischemic stroke showed no statistical significance after multivariate adjustment [10]. Our data supported and further reported the independent predictive value of sST2 for long-term prognosis after TIA/ischemic stroke (composite adverse events and a combination of major disability and death at 1 year). We also evaluated the association of sST2 with recurrent stroke, although sST2 may not be an independent predictor for stroke recurrence after TIA/ischemic stroke. Moreover, we examined the incremental predictive value of sST2 when added to the NIHSS score and found that sST2 could improve the risk reclassification and discriminatory power for outcomes, indicating that sST2 should be considered a potential marker for TIA/ischemic stroke prognosis.

Several limitations of the present study should be considered. First, we measured the baseline sST2 levels only at the acute stage of TIA/ischemic stroke and did not assess the levels serially, which did not allow evaluation of subsequent change in sST2 levels on prognostic outcomes. Second, this single-center study enrolled patients mostly with mild to moderate severity and selection bias could have occurred. Third, sST2 levels are associated with age, male sex, hypertension, diabetes mellitus, low-density lipoprotein cholesterol [26, 27], and poor prognosis in atrial fibrillation and coronary heart disease [28, 29]. Although we conducted multivariate analyses of these related covariables, confounding bias might still exist despite adjustment. Finally, medications administered to the patients before blood sample collection were not considered. We therefore could not identify any influence of therapeutic interventions on sST2 levels. Thus, additional multicenter and large sample studies with serial measurement of sST2 are warranted to validate our findings.

Conclusions

In summary, higher levels of serum sST2 in TIA/ischemic stroke were independently associated with increased risk of composite adverse events and major disability or death at 1 year. Serum sST2 may have potential predictive value in the risk stratification of TIA/ischemic stroke, which should be confirmed by future studies.

Abbreviations

AIS: Acute ischemic stroke; CI: Confidence interval; ELISA: Enzyme-linked immunosorbent assay; HR: Hazard ratio; IDI: Integrated discrimination index; IL: interleukin; IQR: Interquartile range; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NRI: Net reclassification index; OR: Odds ratio; ROC: Receiver operating characteristic; SD: Standard deviation; sST2: Soluble ST2; TIA: Transient ischemic attack

Declarations

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Authors' contributions

XT performed the ELISA experiments, collected and analyzed the data, and drafted the first version of the manuscript. YG and XW (Xiao Wang) contributed to the data analysis and interpretation. LP contributed to the data analysis and manuscript revision. XW (Xin Wang), JW, SS, and YL contributed to the data collection and analysis. MN, FS contributed to the writing and revision of the manuscript. BS and YX designed and conceptualized the study, supervised the analysis, and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. All patients or their designated proxies provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

A flowchart of the patient selection process. TIA, transient ischemic attack.

Figure 2

Serum sST2 levels in different groups. (a-b) The group with NIHSS>3 had significantly higher sST2 levels than that with NIHSS≤3 [20.58 (11.37-40.65) vs. 16.13 (8.25-25.02) ng/mL]. Ischemic stroke patients had significantly higher sST2 levels than that with TIA [18.75 (10.98-30.96) vs. 12.50 (5.48-20.02) ng/mL]. Mann-Whitney U test, ***P<0.001, ****P<0.0001; (c-d) Serum sST2 levels were notably higher in patients who experienced composite adverse events and major disability or death at 1 year. Mann-Whitney U test, *P<0.05, **P<0.01. mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; sST2, soluble ST2; TIA, transient ischemic attack.

Figure 3

Cumulative incidence of composite adverse events and recurrent stroke by optimal sST2 cut-off values. sST2, soluble ST2; TIA, transient ischemic attack.