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Active tissue factor and activated factor XI in patients with acute ischemic cerebrovascular events

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Abstract

Background—Elevated factor (F)XI and tissue factor (TF) have been reported to occur in patients with acute ischemic stroke (AIS). We sought to investigate whether circulating activated FXI (FXIa) and TF on admission can predict clinical outcomes in patients with acute cerebrovascular events.

Materials and methods—In the observational study we evaluated 205 consecutive patients aged 70 years or less within the first 72 hours of acute event, including 140 with AIS and 65 with transient ischemic attack (TIA). Plasma TF and FXIa activity were determined on admission in clotting assays by measuring the response to inhibitory monoclonal antibodies.

Results—Active TF and FXIa activity were detected in 58 (28.9%) and 132 (64.4%) patients on admission, respectively. Active TF was detected in 45 of the 136 AIS patients with available TF levels (33.1%) and 13 of the 65 acute TIA patients (20%; p=0.05). Corresponding values for FXIa were 99 of the 140 (70.7%) and 33 of the 65 (50.8%; p=0.006), respectively. Patients with detectable TF were more frequently female and hypertensive, while subjects with detectable FXIa had more often diabetes and higher levels of fibrinogen, C-reactive protein, and interleukin-6 (all p<0.05). Patients with detectable FXIa but not TF had higher NIHSS score, higher modified Rankin scale score and lower Barthel Index at discharge (all p<0.05).

Conclusions—Circulating active TF and FXIa occur frequently in acute cerebrovascular ischemic events. Active FXIa in plasma might be useful as a novel risk marker of worse functional outcomes in patients with acute cerebrovascular events.

Keywords

acute cerebrovascular events; functional outcomes; coagulation; factor XI; stroke; tissue factor

Introduction

Cerebrovascular ischemic events represent heterogeneous syndromes caused by several different underlying pathologies. There is evidence linking ischemic cerebrovascular events and hypercoagulability [1].

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Conflict of Interest
The authors have no conflicts of interest.

Factor (F)XI is a homodimeric coagulation protein produced in the liver that plays a role in the intrinsic coagulation pathway. Activated FXII on negatively charged surfaces activates FXI to FXIa, and FXIa activates FIX leading to thrombin generation. Under physiological circumstances, FXI is activated by thrombin bypassing the contact activation pathway [2]. The feedback loop formed with thrombin activating FXI results in the amplification of thrombin generation predominantly initiated via the tissue factor (TF)-FVIIa pathway. It has been suggested that *in vivo* FXI and FXII can be activated in the presence of extracellular RNA [3]. Recently, polyphosphate derived from activated platelets has been shown to be an activator of FXII [4]. Thrombin-mediated FXI activation contributes to the impairment of fibrinolysis via enhanced activation of thrombin-activatable fibrinolysis inhibitor (TAFI) [5]. FXIa activates FIX leading ultimately to thrombin generation.

Growing evidence indicates that both FXII and FXI play a role in the thrombus formation and stabilization during stroke [5]. Increased FXIa levels are known to confer a higher risk of venous and arterial thrombosis [6]. However, clinical data on the association between FXI or TF and ischemic cerebrovascular events are sparse. A 5-fold increased risk of ischemic stroke has been shown in patients aged less than 55 years with elevated FXI levels above the 95th percentile of the control range [7]. A higher risk of stroke observed at elevated FXI levels (>144% of normal) has been suggested to be linked with dyslipidemia [8]. However, all the available association studies presented FXI antigen, with the results expressed as a percentage, where 100 percent was equivalent to the mean normal FXI antigen level. To our knowledge, no data on plasma coagulant FXIa activity in stroke patients have been published. On the other hand, severe FXI deficiency has been shown to protect against ischemic stroke [9] A blockade of FXI as well as FXII is protective against cerebral ischemia without overtly affecting hemostasis in experimental studies [10]. The aim of this observational study was to investigate whether the presence of active TF and FXIa in circulating blood is associated with worse clinical outcome in patients with acute cerebrovascular events.

Patients and Methods

We enrolled white consecutive patients with acute ischemic cerebrovascular events, aged of 70 years or less, admitted to an acute stroke unit from September 2008 to September 2009 within the first 72 hours from the onset of symptoms (median 12 hours) typical of acute ischemic stroke or transient ischemic attack (TIA). Stroke was defined according to WHO criteria [11] and demonstrated by brain imaging. TIA was defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, lasting <24 hours. All patients had computed tomography (CT) or CT followed by conventional magnetic resonance imaging (MRI) performed during their hospital stay.

Exclusion criteria were: intracerebral or subarachnoid hemorrhage, acute illness, known cancer, hepatic or renal dysfunction, acute coronary syndrome within the preceding 6 months, treatment with oral anticoagulants, heparins or clopidogrel. Patients who were treated with fibrinolytic agents or who had suffered an iatrogenic stroke due to diagnostic and/or therapeutic interventions such as catheter angiography were not included.

The study was approved by the Jagiellonian University Ethical Committee. All participants gave informed written consent.

Stroke subtyping

Stroke and TIA etiology was diagnosed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria as large vessel disease (atherothrombotic) stroke, small vessel disease (lacunar) stroke, cardioembolic (CE) stroke, stroke of other determined etiology (i.e

dissection), and stroke of undetermined etiology (cryptogenic), including subjects with patent foramen ovale or two potential causes [12]. The diagnostic work-up included ultrasound examination of the carotid and vertebral arteries, electrocardiography, transthoracic echocardiography, and screening for antiphospholipid syndrome. Atherothrombotic stroke was defined as carotid and vertebral artery stenosis >50% in the arterial territory of the ischemic event. SVD was defined as a clinical lacunar syndrome with normal imaging or a compatible subcortical or brain stem lesion with a diameter <1.5 cm on CT or MRI. Cardioembolic stroke was defined on the basis of a potential cardiac source of an embolus even if the infarct was of lacunar type [13].

Stroke scales

The severity of an acute ischemic cerebrovascular event was assessed at presentation and at discharge using the National Institutes of Health Stroke Scale (NIHSS) score [14]. Patients were examined by the same raters. Functional status on discharge was recorded using the modified Rankin scale (mRS) [15]. The Barthel index (BI) was also used to measure basic aspects of self-care and mobility on discharge in the acute event group [16].

Laboratory methods

Blood cell counts, biochemical analysis, including lipid profile, creatinine, glucose, were assessed by standard automated laboratory methods. Venous blood samples for clotting assays were taken into 0.11 M trisodium citrate tubes (Becton Dickinson) and centrifuged at 24 °C and 2500 g for 20 minutes within 30 min of collection. Platelet-poor plasma was immediately frozen and stored at −80 °C. Fibrinogen and C-reactive protein (CRP) were assayed by immunonephelometry (Dade Behring). A commercially available immunoenzymatic assay was used to determine serum interleukin-6 (R&D Systems, Abingdon, UK). All intra-assay and inter-assay coefficients of variation were <7%.

Plasma clotting assays were performed as described previously [17]. Briefly, plasma was thawed at 37 °C in the presence of corn trypsin inhibitor (CTI, an inhibitor of the contact pathway of blood coagulation by blocking FXI activation by FXIIa) and either buffer or inhibitory monoclonal anti-FXI (αFXI-2) or anti-TF (αTF-5) antibody (both produced in house) at a final 0.1 mg/ml concentration was followed by the addition of $CaCl_2$ at a final 15 mM concentration. Clotting was initiated by the addition of 2 μM phospholipid vesicles (PCPS) composed of 25% dioleoyl-*sn*-glycero-3-phospho-L-serine and 75% 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (both from Avanti Polar Lipids, Inc; Alabaster, AL). Clotting times were determined using the ST8 clotting instrument (Diagnostica Stago, Parsippany, NJ). FXIa and TF activity in plasma was calculated from calibration curves built by sequential dilutions of human FXIa (a gift from Dr. R. Jenny from Haematologic Technologies, Inc., Essex Junction, VT) or relipidated $TF_{1–242}$ (a gift from Dr. R. Lundblad from Baxter Healthcare Corp., Duarte, CA) in pooled 10-donor plasma. Laboratory personnel were “blinded” to the status of samples. Age- and sex-matched healthy control individuals (n=12) recruited from the hospital staff showed no detectable TF or FXIa.

Reporting of the study conforms to STROBE along with references to STROBE and to broader STROBE guidelines [18].

Statistical analyses

Data are given as mean±SD, median (interquartile range), or percentage unless otherwise stated. Normality of a value distribution was tested using the Kolmogorov-Smirnov test. Intergroup differences for continuous variables were assessed by the Wilcoxon test for non-Gaussian distribution or Student’s t-test for normal distribution. The Spearman correlation coefficient was calculated to test significant associations between variables. The Fisher

exact test was used to assess intergroup difference in categorical variables. A p-value <0.05 was considered significant.

Results

The demographic, clinical, and routine laboratory data are summarized in Table 1. Compared with AIS patients, subjects with acute TIA used more frequently β-blockers and had slightly lower glucose. They were more frequently diagnosed with cryptogenic events and had less frequently cardioembolic events. On discharge TIA patients had lower NIHSS score as well as modified Rankin score.

Plasma TF levels were unavailable in 4 AIS patients. Fifty-eight of the 201 acute patients (28.9%) had detectable TF activity, including 31 subjects with TF below the quantitation limit (<0.5 pM) and 27 subjects with higher TF of a median of 0.8 (IQR 13.6) pM. Active TF was detected in 45 of the 136 AIS patients (33.1%) and 13 of the 65 acute TIA patients (20%; p=0.05).

Circulating FXIa was found in 132 of the 201 (64.4%) acute patients [median, 86 (IQR 507) pM]. Most of TF-positive patients (n=55, 94.8%) had also circulating FXIa. FXIa were found in plasma obtained from 99 of the 140 AIS patients (70.7%) and 33 of the 65 TIA patients (50.8%; p=0.006).

As shown in Table 2, patients with detectable TF were more frequently female and hypertensive compared with those without active TF on admission. Patients having detectable FXIa on admission were more frequently female and had more often diabetes compared with the remaining 73 subjects; none of diabetic subjects displayed the presence of FXIa in plasma. Circulating FXIa on admission was associated with significantly higher levels of fibrinogen, CRP, and IL-6 as compared with FXIa-negative subjects. Analysis of etiology of acute cerebrovascular events showed that the presence of FXIa, but not active TF, was detected less commonly in patients with cryptogenic events and more frequently among patients with the cerebrovascular event of other causes (Table 2).

Patients with detectable FXIa as well as those with active TF had similar NIHSS score on admission (Table 2). Acute patients with detectable amounts of active TF on admission did not differ from the negative patients with regard to the stroke scale scores assessed at discharge, however NIHSS score and modified Rankin score on discharge tended to be higher (p<0.1) in TF-positive patients (Table 2). The presence of circulating FXIa measured on admission was associated with significantly higher NIHSS and mRS scores, together with lower BI at discharge (Table 2).

Discussion

This study shows that a significant proportion of patients with acute ischemic cerebrovascular events have active TF as well as FXIa in circulating blood on admission. Circulating TF and FXIa were more prevalent among the AIS patients than in those diagnosed with acute TIA. Of note, to our knowledge, this is the first study to demonstrate that the presence of FXIa is associated with worse prognosis and more severe neurological deficits in acute cerebrovascular events. This suggests that FXIa could be a novel thrombotic marker of worse short-term clinical outcome in patients with acute ischemic cerebrovascular events. These findings have highlighted a role of enhanced blood coagulation in this clinical setting.

Previous studies showed acute prothrombotic changes in coagulation and fibrinolytic parameters during ischemic stroke [19,20]. Recently, Suri et al. [21] have demonstrated that

elevated FXI is associated with the risk of ischemic stroke. We expanded our knowledge on FXI and TF by showing that their active forms can circulate during the acute phase of cerebral ischemia and their presence worsens functional outcomes assessed on discharge.

Previously, we have shown that 96% of patients with acute myocardial infarction (MI) and 76% of CAD patients with a history of MI have circulating FXIa [17]. 38% of acute MI patients and only 6% of stable CAD patients showed detectable TF activity [17]. In the current study, a proportion of TF-positive acute patients was similar to that observed in acute coronary ischemia, whereas the frequency of patients with FXIa coagulant activity was lower in subjects with acute AIS or TIA compared with MI [17]. This indicates that the pattern of prothrombotic alterations, i.e. a lower proportion of subjects with active TF than those with FXIa (almost all individuals positive for TF exhibit also FXIa usually at higher levels compared with those showing FXIa alone), is similar in acute MI and acute cerebrovascular events.

A source of TF detected in plasma of patients with acute cerebrovascular events remains unclear. Cell-derived microparticles could be the main carriers of circulating TF [22]. The source of TF could be the brain, which may release TF into the circulation when necrosis occurs [23] and this source appears highly probable on this analysis. Moreover, TF present in the plaque may also be released following damage to the atherosclerotic plaque in the carotid artery. This source is unlikely in the present study given lack of differences of the occurrence of atherothrombotic events between TF-positive and -negative patients. TF might be derived from monocytes activated by proinflammatory cytokines; their increased levels were reported in AIS and associated with worse prognosis [24]. However, the current study did not show elevated inflammatory markers in TF-positive subjects.

How high could be levels of functionally active TF present in circulating blood of patients? This issue generates controversy. Our data showed that in a majority of plasma samples from patients with acute cerebrovascular events the concentration of active TF is below 1 pM. This finding is in stark contrast with the data suggesting activity of TF with a mean of 193 pg/mL in patients with AIS [25]. Largely due to the lack of validated and reliable commercial assays for TF antigen and activity [26], there are marked discrepancies in the results of measurements of TF in blood, with high (reaching sub-nanomolar) TF concentrations reported [27,28]. Several lines of evidence clearly indicate that such high functional TF levels would cause plasma or blood clotting within minutes if not seconds [27,28]. Since our assay for TF activity determination in citrated plasma has been validated and used in various clinical settings [17,29], we believe that this analysis provides better quantitation of active TF concentrations in subjects with ischemic cerebrovascular events. The presence of active TF in some patients might predispose to recurrent thrombotic events and enhanced atherosclerosis development given proatherogenic properties of TF [30].

As in the acute MI patients [17], we observed that detectable amounts of active FXIa are permanently present in plasma despite the abundance of numerous inhibitors for serine proteases because none of the physiologic inhibitors can effectively inhibit FXIa. As a consequence, 80 to 90% of FXIa can survive in blood for at least the 30 min required for citrate plasma preparation [17]. There is no *de novo* FXIa generation observed in citrate plasma at room temperature over a period of 75 min either in the presence of contact pathway inhibition or in the absence of it [17]. These data indicate that plasma FXIa in the current study does reflect the *in vivo* levels of this enzyme. Worse clinical outcomes observed in FXIa-positive patients might be attributed to impaired fibrinolysis and increased clot stability, which may attenuate elimination of thrombi in blood vessels [31].

In the study evaluating FXIa and TF activity in CAD patients, there was strong evidence that FXIa was generated by thrombin *via* TF pathway [17]. FXIa in stroke patients is, most likely, generated by the same pathway. The enhanced inflammatory state in the patients with FXIa in blood, reflected by elevated fibrinogen, CRP, and IL-6, raises the possibility of the contribution of inflammation to activation of blood coagulation during acute cerebral ischemia [28].

Interestingly, TF and FXIa were more commonly detected in female patients. It has been shown that FXI is higher in women than in men [32]. We demonstrated that even during the acute phase of ischemia women exhibit higher levels of FXI in its functionally active form. Moreover, we found increased prevalence of diabetes in patients with circulating FXIa on admission, which provides additional evidence for potent prothrombotic mechanisms that operate in this disease [33].

Several limitations of this study should be acknowledged. First, the size of the subpopulations, i.e. subjects with detectable TF or particular stroke subtypes, is limited, and the results of such analyses should be interpreted with caution. Second, all laboratory measurements were performed on a single occasion, i.e. on admission. Third, the current conclusions cannot be extrapolated to excluded groups of patients such as anticoagulated subjects or those aged 75 years or more. Finally, we did not analyze imaging data, therefore we cannot address the issue as to the presence of FXI or TF is associated with stroke volumes or other parameters. Further studies are needed to assess correlations between imaging data and hemostatic variables.

In conclusion, we showed that acute cerebrovascular ischemic events are associated with elevated procoagulant potential reflected by the presence of FXIa and TF activity in the patient plasma. Our results increase our knowledge on a hypercoagulable state in patients with acute stroke or TIA. Given growing evidence supporting FXIa inhibition as a novel method for preventing thromboembolic events [34], our data provide new insights into the role of FXIa and active TF in acute cerebrovascular events. It remains to be established to what extent these variables affect long-term prognosis in patients with cerebrovascular diseases.

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Table 1

Characteristics of patients classified into 2 categories: acute stroke and acute transient ischemic attack (TIA)

Variable	all patients	acute stroke	acute TIA	p
	N=205	n=140	n=65	
Age, y	57 (45–66)	57.5(45–68)	53.6(13.7)	0.18
Male, n(%)	121 (59)	80 (57.1)	41 (63.1)	0.42
BMI, kg/m^2	27.2 (23.5–29.4)	27.2(3.9)	27.1(3.4)	0.94
Smoking, n(%)	62 (30.2)	39 (27.9)	23 (35.4)	0.28
Hypertension, n(%)	140 (68.3)	98 (70)	42 (64.6)	0.44
Diabetes, n(%)	39 (19)	28 (20)	11 (16.9)	0.6
Previous MI, n(%)	63 (30.7)	40 (28.6)	23(35.4)	0.33
Previous stroke, n(%)	39 (19)	28 (20)	11 (16,9)	0.6
Medication				
Statins, n(%)	138 (67.6)	95 (67.9)	43 (67.2)	0.92
β–blockers, n(%)	113 (55.1)	70 (50)	43 (66.2)	0.03
ACEIs, n(%)	145 (70.7)	98 (70)	47 (72.3)	0.74
Aspirin, n(%)	180 (87.8)	121 (86.4)	59 (90.8)	0.38
Laboratory tests				
Creatinine, μmol/l	79 (70–90)	79.6(70–91)	78.4(66–92.2)	0.28
Glucose, mmol/l	5.3 (4.6–6.2)	5.5(4.9–6.4)	5.1(4.6–5.9)	0.033
CRP, mg/l	3.2 (1.7–4.9)	3.3(1.7–5)	3(1.9–4.6)	0.82
IL-6, pg/ml	3.4 (2.1–5.4)	3.7(2.2–5.3)	3.2(2.1–5.5)	0.68
Fibrinogen, g/l	4.2 (3.2–4.9)	4.2(1.2)	4.0(1.2)	0.36
Total cholesterol, mmol/l	4.9 (4.2–6.8)	5.1(4.2–5.1)	4.8(1.0)	0.34
LDL-C, mmol/l	2.9 (2.3–3.5)	3(2.4–3.5)	2.9(0.8)	0.47
HDL-C, mmol/l	1.2 (1–1.5)	1.2(1–1.5)	1.2(1–1.4)	0.95
Triglycerides, mmol/l	1.3 (1–1.7)	1.3 (1–1.8)	1.3(1–1.6)	0.43
Etiology				
cryptogenic, n(%)	63 (31.8)	35 (25)	28 (43.1)	0.001
atherothrombotic, n(%)	37 (18)	27 (19.3)	10 (15.4)	0.5
cardioembolic, n(%)	27 (13.2)	23 (16.4)	4 (6.2)	0.043
small vessel disease, n(%)	54 (26.3)	38 (27.1)	16 (24.6)	0.7
other causes, n(%)	24 (11.7)	17 (12.1)	7 (10.8)	0.78
Scales				
NIHSS 1	5.5 (3–12)	6 (3–13.5)	4 (3–9)	0.17
NIHSS 2	3 (1–6)	3 (1–8.75)	1 (0–2)	0.045
Barthel index 2	90 (50–100)	90 (45–100)	90 (61–100)	0.21
mRS 2	1 (1–4)	2 (1–4)	1 (0–2)	0.001

Values are given as median (interquartile range), or percentage.

BMI, body mass index, MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; CRP, C-reactive protein; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale score; 1 denotes the value obtained on admission; 2 denotes the value obtained at discharge; mRS, modified Rankin score.

Table 2

Comparisons of patients with FXIa and TF activity (+) with those without such activity (0) on admission

Variable	TF 0	TF +	p	FXIa 0	FXIa +	p
	N=143	N=58		N=73	N=132	
Age, y	56 (44–66)	58.5 (45–67.5)	0.47	57 (48–70)	56 (44.2–64)	0.16
Male, n(%)	91 (63.6)	27 (46.6)	0.03	50 (68.5)	71 (53.8)	0.04
BMI, kg/m^2	27.2 (3.8)	27.1 (3.4)	0.61	27.2 (3.9)	27.1 (3.6)	0.86
Smoking, n(%)	48 (33.6)	13 (22.4)	0.12	28 (38.4)	34 (25.8)	0.06
Hypertension, n(%)	92 (64.3)	46 (79.3)	0.04	54 (74)	86 (65.2)	0.19
Diabetes, n(%)	26(18.2)	13 (22.4)	0.48	0 (0)	39 (29.5)	<0.01
Previous MI, n(%)	43 (30.1)	19 (32.8)	0.71	17 (23.3)	46 (34.8)	0.15
Previous stroke, n(%)	25 (17.5)	14 (24.1)	0.28	10 (13.7)	29 (22)	0.15
medication						
statins, n(%)	93 (65.5)	42 (72.4)	0.34	47 (64.4)	91 (69.5)	0.46
β-blockers, n(%)	79 (55.2)	33 (56.9)	0.83	36 (49.3)	77 (58.3)	0.21
ACEIs, n(%)	101 (70.6)	42 (72.4)	0.8	53 (72.6)	92 (69.7)	0.66
aspirin, n(%)	123 (86)	53 (91.4)	0.29	61 (83.6)	119 (90.2)	0.17
Laboratory tests						
creatinine, µmol/l	79.6 (69–89.6)	79 (69.9–87.9)	0.53	79.8 (67.7–94.8)	79 (70.7–88.4)	0.43
glucose, mmol/l	5.3 (4.6–5.3)	5.3 (4.7–5.3)	0.98	5.3 (4.6–6.6)	5.3 (4.6–6.2)	0.89
CRP, mg/l	3 (1.8–4.8)	3.3 (1.6–5.7)	0.4	2.4 (1.7–.3)	3.5 (1.9–5.5)	0.001
IL-6, pg/ml	3.2 (2–5.1)	3.9 (2.3–5.9)	0.19	2.5 (1.9–4.3)	4.1 (2.5–6)	0.0001
fibrinogen, g/l	4.1±1.2	4.1±1.1	0.51	3.8±1.0	4.3±1.3	0.013
total cholesterol, mmol/l	5.1 (4.2–5.1)	4.6 (4–4.6)	0.31	5.1 (4.3–5.8)	4.8 (4.2–5.6)	0.31
LDL-C, mmol/l	3.1 (2.4–3.5)	2.8 (2.3–3.3)	0.33	2.9 (2.2–3.7)	3 (2.4–3.4)	0.73
HDL-C, mmol/l	1.2 (1–1.2)	1.2 (1–1.2)	0.47	1.2 (1–1.5)	1.2 (1–1.5)	0.36
triglycerides, mmol/l	1.3 (1–1.3)	1.3 (1–1.3)	0.96	1.3 (1.1–1.7)	1.3 (1–1.8)	0.35
etiology						
cryptogenic	43 (30.1)	19 (22.8)	0.52	29 (29.7)	34 (24.8)	0.024
atherothrombotic	26 (18.2)	10 (17.2)	0.88	12 (16.4)	25 (18.9)	0.66

Variable	TF 0	TF +	p	FXIa 0	FXIa +	p
	N=143	N=58		N=73	N=132	
cardioembolic	16 (11.2)	10 (17.2)	0.25	7 (9.6)	20 (15.2)	0.26
small vessel disease	43 (30.1)	10 (17.2)	0.06	21 (28.8)	33 (25)	0.56
other causes	15 (10.5)	9 (15.5)	0.32	4 (5.5)	20 (15.2)	0.04
scales						
NIHSS1	5 (3–11)	6.5 (3–12.3)	0.51	5 (3–9)	6 (3–13)	0.3
NIHSS 2	2 (0–5)	3 (1–9)	0.052	2 (0–4)	3 (1–8)	0.038
Barthel index 2	95 (55–100)	85 (44–100)	0.13	100 (65–100)	85 (45–100)	0.023
mRS 2	1.9±1.9	2.5±2	0.07	1 (0–3)	1.5 (1–4)	0.037

Values are given as mean±SD, median (interquartile range), or percentage. Plasma TF levels were unavailable in 4 acute stroke patients.

Abbreviations see Table 1.

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