THERAPEUTIC ADVANCES in
Neurological Disorders

Original Research

Early neurological deterioration in patients with acute ischemic stroke: a prospective multicenter cohort study

Ther Adv Neurol Disord

2023, Vol. 16: 1–13

DOI: 10.1177/17562864221147743

Hongbing Liu, Kai Liu, Ke Zhang, Ce Zong, Hongxun Yang, Yapeng Li, Shen Li, Xin Wang, Jiawei Zhao, Zongping Xia*, Bo Song*, Xuming Xu* and Yuan Gao*

Abstract

Background: There is still no precise knowledge of the causes of progression in patients with acute ischemic stroke (AIS), and we are unable to predict patients at risk.

Objective: To explore the frequency, predictive factors, and the prognosis of early neurological deterioration (END) in patients with AIS

Methods: In this prospective multicenter observational study, we assessed patients with AIS admitted to 18 hospitals in Henan, China. We defined END as an increase of ⩾2 points in total National Institutes of Health Stroke Scale (NIHSS) score or ⩾1 point in the motor items of the NIHSS within 7 days after admission. Risk factors were analyzed using multivariate logistic regression models. Prognosis was evaluated using the modified Rankin Scale (mRS), with poor prognosis defined as mRS 3–6.

Results: A total of 9114 patients with AIS within 24 h of symptom onset were enrolled in the study. END occurred in 1286 (14.1%) patients. The highest incidence (62.5%) of END occurred within 24 h after admission. After adjusting potential confounders, age, body mass index, waist–hip ratio, systolic blood pressure, baseline NIHSS, disabled at baseline, history of atrial fibrillation, diabetes mellitus, intracranial arterial stenosis, infarct location in the lenticulostriate artery area and cerebral watershed, neutrophils, lymphocytes, uric acid, and triglycerides were identified as independent predictors for END. END was significantly associated with poor prognosis at 90 days, and the adjusted OR was 1.74 (95% CI: 1.53–1.97).

Conclusion: One in seven hospitalized patients with AIS may experience END within 24 h of onset. The highest incidence of END occurred within 24 h of admission and decreased steeply with time. Easily identifiable risk factors predict END and could help understand the causal mechanisms and thereby prevent END.

Keywords: incidence, ischemic stroke, neurological deterioration, prognosis, risk factor

Received: 18 August 2022; revised manuscript accepted: 8 December 2022.

Correspondence to:
Yuan Gao
Department of Neurology, The First Affiliated Hospital of Zhengzhou University, No. 1 East Jianshe Road, Zhengzhou 450052, Henan, China.
fccgaoy1@zzu.edu.cn

Xuming Xu
Department of Neurology, The First Affiliated Hospital of Zhengzhou University, No. 1 East Jianshe Road, Zhengzhou 450052, Henan, China.
xuyuming@zzu.edu.cn

Hongbing Liu
Kai Liu
Ke Zhang
Ce Zong
Hongxun Yang
Yapeng Li
Shen Li
Xin Wang
Jiawei Zhao
Zongping Xia
Bo Song
Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

*These authors contributed equally to this work.

Introduction

Early neurological deterioration (END) usually refers to the decline in neurological function that occurs within a few hours or days of the onset of acute ischemic stroke (AIS).[1] Studies have reported END frequencies ranging from 5% to 40%, which could have resulted from different evaluation methods and inclusion criteria.[2,3] Previous studies have indicated that END may affect the prognosis of patients with AIS.[4] However, the etiology and pathogenesis of END in AIS are complex, and clear descriptions, accurate and reliable early prediction indicators, and effective prevention and treatment strategies are lacking.[5] Therefore, it is important to explore END development in patients with AIS.

Although previous studies have reported on AIS with END, most were retrospective and focused on specific populations with stroke, such as

patients receiving intravenous thrombolysis and endovascular therapy or patients with mild stroke.[6–8] In addition, most studies were single-center, small-sample studies; therefore, large multicenter prospective cohort data on END are lacking. We aimed to improve END awareness by exploring the frequency, risk factors, and functional outcomes in patients with AIS using multicenter stroke registry data in Henan, China.

Patients and methods

This study enrolled patients from database of clinical research for Henan Province Multicenter Stroke Registry (Chinese Clinical Trial Registry, ChiCTR2100045258) from January 2021 to January 2022. This prospective, multicenter, web-based registry established in January 2021 is a part of the major science and technology project in Henan Province. Consecutive patients with AIS within 7 days after onset admitted to regional stroke centers were registered. Patient data regarding demographics, medical history, previous therapy, hospitalized treatment, and prognosis were prospectively collected from the registry using standardized protocols. Special quality control personnel, dispatched by the center leader, monitored the integrity of the data every month throughout the study.

The 18 participating hospitals, which passed the assessment as tertiary stroke centers, provide stroke care in Henan Province, and the patients at these centers comprised the participants. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. All patients received conventional treatment in accordance with established guidelines on pharmacological interventions for long-term secondary prevention.[9]

The inclusion criteria were as follows: (1) patients who visited within 7 days after symptom onset and had AIS confirmed by diffusion-weighted imaging; (2) those aged ⩾18 years, and (3) those who provided signed informed consent.

There exclusion criteria were as follows: (1) patients with onset to admission time >24 h; (2) those receiving thrombolysis or endovascular treatment; (3) those with a history of hematologic disease, cancer, or surgery; (4) those with incomplete clinical data or those who could not be evaluated over the subsequent 7 days following admission; (5) those with severe renal or hepatic diseases; and (6) those who were lost to follow-up.

Data collection

The Henan Stroke Registry prospectively collected information on predefined variables using electronic case report forms and a secure web-based databank. Patient baseline data were recorded on the Henan Stroke Data Management Platform website (http://crf.henanstroke.net). Demographic characteristics included age, sex, waist–hip ratio (WHR), body mass index (BMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), and baseline National Institutes of Health Stroke Scale (NIHSS) score. Risk factors for stroke included a history of smoking (defined as continuous or cumulative smoking ⩾6 months or smoking every day for at least 6 months)[10] and drinking [defined as drinking alcohol at least 5 days per week (>30 g/day) for at least 6 months],[11] history of transient ischemic attack/stroke, diabetes, atrial fibrillation, hypertension, coronary heart disease, antiplatelet therapy, anticoagulant therapy, and lipid-lowering therapy. Laboratory tests were performed within 24 h of admission, including white blood cell (WBC), neutrophil, lymphocyte, monocyte, red cell distribution width, mean platelet volume, glucose, HbAlc, uric acid, triglyceride (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), homocysteine, and C-reactive protein (CRP) measurements. Brain magnetic resonance imaging and magnetic resonance angiography were performed within 24 h of admission using a 3.0 T MR scanner in all patients. All data were standardized. Two trained neuroradiologists reviewed all imaging procedures and performed the analysis. The infarct location was rated according to visual assessment as follows: cerebral watershed, thalamus, cerebral lobe, brainstem, cerebellum, and lenticulostriate artery area. Symptomatic intracranial and extracranial atherosclerotic stenoses were defined as the presence of removal of an artery or multiple lesions with 50–99% stenosis.[12,13]

Definition of END and follow-up

The NIHSS score was used to evaluate the AIS severity on the day of admission. After admission, NIHSS scores were assessed by two certified neurologists 1–2 times each day. All certified

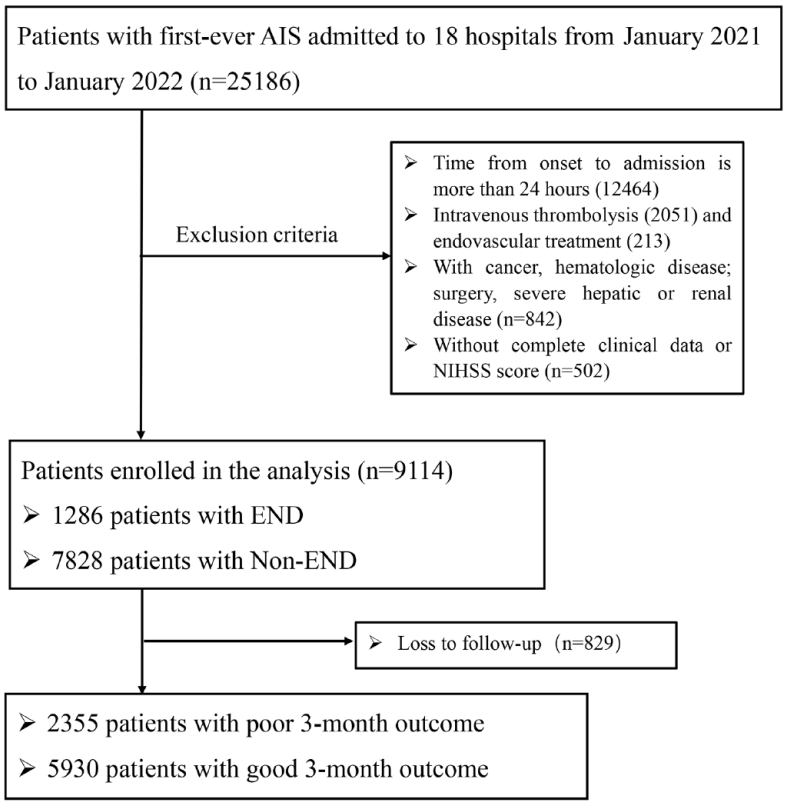

Figure 1. Patients flow-chart of the cohort.

neurologists at the 18 centers underwent unified training for NIHSS score evaluation and were blinded to the study. Patients were divided into three groups based on their NIHSS scores on admission, mild stroke (NIHSS score $\leqslant$5), moderate stroke (NIHSS score 6–15), and severe stroke (NIHSS score $\geqslant$16). END was defined as an increase of $\geqslant$2 points in the total NIHSS score or $\geqslant$1 point in the motor items of the NIHSS within 7 days of hospital admission. Most patients were subsequently followed up *via* telephone. The modified Rankin Scale (mRS) was used to evaluate patient outcomes. Good and poor outcomes were defined as mRS $\leqslant$ 2 and mRS $>$ 2, respectively.

Statistical analysis

SPSS software version 25.0 (IBM Corp., Armonk, NY) was used for statistical analysis. Continuous variables, presented as mean $\pm$ standard deviation, were analyzed using the independent Student's *t*-test or Mann–Whitney *U*-test. Categorical variables, presented as proportions, were analyzed using the χ^2 test. The patient's post-onset END was the dependent variable. Variables with $p < 0.05$ on univariate analysis or those clinically relevant (e.g. sex, age, time from onset to admission, BMI, WHR, SBP, DBP, baseline NIHSS score, disabled at baseline, history of diabetes mellitus, atrial fibrillation, intracranial arterial stenosis, infarction location, and some laboratory parameters) were included in the multivariate logistic regression model with END. Ordinal log regression analysis was performed and adjusted for potential confounders (variables in the univariate analysis [$p < 0.05$] or those considered to be of clinical significance) for the association between END and the mRS score at day 90. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are expressed in the results. A two-tailed $p < 0.05$ was considered significant.

Results

Characteristics of baseline data

A total of 25,186 patients with AIS were consecutively recruited from 18 hospitals (Figure 1). In

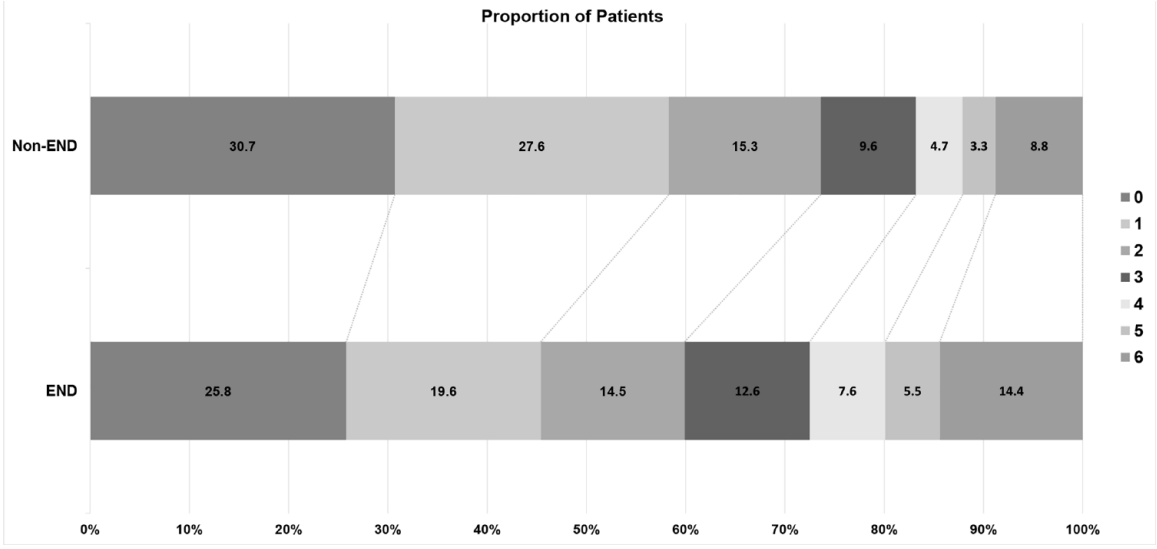

Figure 2. Distribution of modified Rankin Scale (mRS) score at 90 days for no early neurological deterioration (END) *vs* END.

total, 12,722 patients were admitted within 24 h of symptom onset. Of the remaining patients, 3608 patients were excluded as follows: 2051 received thrombolysis, 213 received endovascular treatment, 502 had missing laboratory data, and 842 had other diseases or underwent cancer treatment or surgery. Finally, 9114 patients (median age: 67.20 ± 11.46 years, female: 3716 [40.8%]) were enrolled in the study, and END occurred in 1286 (14.1%) patients. The median [interquartile range (IQR)] hospital arrival time was 7.67 (3.19–17.24) h from the onset. The distribution of infarct locations is shown in Figure 3. The infarct sites in patients with END were mostly distributed in the cerebral watershed (22%) and lenticulostriate artery (43%) areas.

Risk factors for END

The baseline characteristics of the two groups of patients are presented in Table 1. The results of univariate analysis demonstrated that patients with END were prominently older than those without END (68.02 ± 12.71 *vs* 67.11 ± 11.23 years; $p = 0.005$); had a shorter time from onset to admission [6.01 (3.01–15.4) *vs* 8.87 (3.27–17.61) h]; $p < 0.001$); and had higher median NIHSS scores on admission [4.00 (2.00–6.00) *vs* 3.00 [1.00–5.00]; (1.00–5.00); $p < 0$),], WHR (0.87 ± 0.08 *vs* 0.86 ± 0.08; $p = 0.004$), BMI (24.85 ± 3.09 *vs* 24.48 ± 2.68; $p = 0.001$), and SBP (152.86 ± 24.86 *vs* 150.9 ± 23.06; $p = 0.001$). The following variables were significantly associated with patients with END compared with those without END: the proportion of disabled at baseline (62.1% *vs* 36.1%; $p < 0.001$), history of atrial fibrillation (9.9% *vs* 7.5%; $p = 0.004$), diabetes mellitus (31.1% *vs* 26.3%; $p < 0.001$), infarction location ($p < 0.001$), intracranial artery stenosis (45.4% *vs* 39.2%; $p < 0.001$), WBC (7.64 ± 2.36 *vs* 6.94 ± 2.48; $p < 0.001$), lymphocytes (1.62 ± 0.74 *vs* 1.72 ± 0.79; $p < 0.001$), neutrophils (5.36 ± 1.96 *vs* 4.52 ± 1.38; $p < 0.001$), monocytes (0.79 ± 1.46 *vs* 0.69 ± 1.34; $p = 0.017$), glucose (6.61 ± 2.76 *vs* 6.42 ± 2.61; $p = 0.014$), uric acid (285.15 ± 97.42 *vs* 277.86 ± 91.42, $p = 0.009$), TG (1.53 ± 1.09 *vs* 1.43 ± 0.97, $p = 0.001$), homocysteine (14.91 ± 9.43 *vs* 14.28 ± 8.84, $p = 0.023$), and CRP (5.09 ± 3.93 *vs* 3.75 ± 3.81, $p = 0.004$).

Clinical and radiological predictors of END

The results of multivariate analyses for risk factors relevant to END are shown in Table 2. After adjusting all potential confounders, BMI (OR: 1.05, 95% CI: 1.03–1.07; $p < 0.001$), age (OR: 1.01, 95% CI: 1.00–1.02; $p < 0.001$), WHR (OR: 2.68, 95% CI: 1.28–5.59; $p = 0.009$), SBP (OR: 1.01, 95% CI: 1.00–1.01; $p = 0.010$), baseline NIHSS (OR: 1.01, 95% CI: 1.00–1.02; $p = 0.019$), Disabled at baseline (OR: 2.03, 95% CI: 2.68–3.43; $p < 0.001$), history of atrial fibrillation (OR: 1.32, 95% CI: 1.12–1.56; $p = 0.001$), diabetes mellitus (OR: 1.22, 95% CI: 1.07–1.39;

Table 1. Characteristics of patients included according to END.

Characteristic	Total	Non-END	END	*P* value
		N **= 7828 (85.9%)**	***N*** **= 1286 (14.1%)**	
Age, y, mean ± SD	67.20 ± 11.46	67.11 ± 11.23	68.02 ± 12.71	0.005
Male, *n* (%)	5398 (59.2)	4628 (59.1)	770 (59.9)	0.610
Time, h	7.67 (3.19–17.24)	8.87 (3.27–17.61)	6.01 (3.01–15.4)	0.001
BMI	24.54 ± 2.74	24.48 ± 2.68	24.85 ± 3.09	0.001
WHR	0.86 ± 0.85	0.86 ± 0.08	0.87 ± 0.08	0.004
SBP (mmHg)	151.21 ± 0.85	150.9 ± 23.06	152.86 ± 24.86	0.001
DBP (mmHg)	87.76 ± 14.34	87.66 ± 14.21	88.36 ± 15.10	0.108
Baseline NIHSS	3.00 (1.00–5.00)	3.00 (1.00–5.00)	4.00 (2.00–6.00)	<0.001
Disabled at baseline	3620 (39.7)	2823 (36.1%)	797 (62.1%)	<0.001
Medical history, *n* (%)				
Hypertension	5471(60.1)	4669 (59.6)	802 (62.4)	0.065
Stroke/TIA	3130 (34.3)	2670 (34.1)	460 (35.8)	0.245
CHD	1929 (21.2)	1643 (21.0)	286 (22.2)	0.309
Atrial fibrillation	708 (7.7)	581 (7.5)	127 (9.9)	0.004
Diabetes mellitus	2458 (27.1)	2059 (26.3)	399 (31.1)	<0.001
Smoking	2832 (31.1)	2432 (31.1)	400 (30.1)	0.979
Drinking	1978 (21.7)	1683 (21.5)	295 (22.9)	0.510
Previous therapy, *n* (%)				
Antiplatelet	2123 (23.3)	1810 (23.1)	313 (24.3)	0.339
Anticoagulant	501 (5.5)	434 (5.6)	67 (5.2)	0.115
Lipid-lowering	1963 (21.5)	1672 (21.4)	291 (22.6)	0.305
Vascular imaging, *n* (%)				
Extracranial artery stenosis	1622 (17.8)	1384 (17.7)	238 (18.5)	0.472
Intracranial arterial stenosis	3655 (40.1)	3071 (39.2)	584 (45.4)	<0.001
Infarction location, *n* (%)				
Lenticulostriate artery area	2975 (32.6)	2422 (30.9)	553 (43.0)	<0.001
Cerebral watershed	1832 (20.1)	1549 (19.8)	283 (22.0)	
Thalamus	1118 (12.3)	1002 (12.8)	116 (9.01)	
Cerebral lobe	1458 (16.0)	1265 (16.2)	193 (15.0)	

(Continued)

Table 1. (Continued)

Characteristic	Total	Non-END	END	*P* value
		N **= 7828 (85.9%)**	***N*** **= 1286 (14.1%)**	
Brainstem	811 (8.9)	721 (9.2)	90 (7.0)	
Cerebellum	920 (10.1)	869 (11.1)	51 (4.1)	
Anterior infarction	4745 (52.1)	4067 (51.9)	678 (52.7)	0.383
Posterior Infarction	3122 (34.2)	2673 (34.1)	449 (34.9)	
Both anterior and posterior	1247 (13.7)	1088 (14.0)	159 (12.4)	
Laboratory				
WBC (10^9/L)	7.04 ± 2.47	6.94 ± 2.48	7.64 ± 2.36	<0.001
Neutrophil (10^9/L)	4.64 ± 1.50	5.36 ± 1.96	4.52 ± 1.38	<0.001
Lymphocyte (10^9/L)	1.71 ± 0.79	1.72 ± 0.79	1.62 ± 0.74	<0.001
Monocyte (10^9/L)	0.71 ± 1.36	0.69 ± 1.34	0.79 ± 1.46	0.017
RDW (10^9/L)	22.75 ± 14.25	22.80 ± 14.27	22.48 ± 14.16	0.459
MPV (10^9/L)	10.06 ± 1.62	10.07 ± 1.62	9.98 ± 1.65	0.081
Glucose (mmolL)	6.44 ± 2.63	6.42 ± 2.61	6.61 ± 2.76	0.014
HbAlc (mmolL)	6.61 ± 1.70	6.59 ± 1.64	6.67 ± 2.05	0.194
Uric Acid (μmolL)	278.89 ± 92.31	277.86 ± 91.42	285.15 ± 97.42	0.009
TC (mmol/L)	4.31 ± 1.24	4.31 ± 1.23	4.31 ± 1.30	0.915
TG (mmol/L)	1.45 ± 0.99	1.43 ± 0.97	1.53 ± 1.09	0.001
HDL-C (mmol/L)	1.19 ± 0.35	1.19 ± 0.35	1.16 ± 0.36	0.053
LDL-C (mmol/L)	2.44 ± 0.89	2.44 ± 0.88	2.43 ± 0.93	0.806
Hcy (umol/L)	14.38 ± 8.93	14.28 ± 8.84	14.91 ± 9.43	0.023
CRP (mg/L)	3.81 ± 3.83	3.75 ± 3.81	5.09 ± 3.93	0.004

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; Disabled at baseline, baseline mRS ⩽ 2; END, early neurological deterioration; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MPV, mean platelet volume; NIHSS, National Institutes of Health Stroke Scale; RDW, red cell distribution width; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TIA, transient ischemic attack; Time, time from onset to admission; WBC, white blood cell; WHR, waist–hip ratio.

$p = 0.003$), intracranial arterial stenosis (OR: 1.29, 95% CI: 1.14–1.45; $p < 0.001$) and infarct location in the lenticulostriate artery area (OR: 3.84, 95% CI: 2.78–5.28; $p < 0.001$) and cerebral watershed (OR: 3.05, 95% CI: 2.22–4.18; $p = 0.005$) were identified as independent predictors for END. The patients' laboratory parameters were also included. Neutrophils (OR: 1.39, 95% CI: 1.34–1.45; $p < 0.001$), lymphocytes (OR: 0.82, 95% CI: 0.76–0.89; $p < 0.001$), uric acid (OR: 1.01, 95% CI: 1.00–1.01; $p = 0.047$), and TG (OR: 1.11, 95% CI: 1.04–1.17; $p = 0.001$) remained independently predictive of END.

Table 2. Multivariate logistic regression analysis predicting END after AIS.

Characteristic	Adjusted OR (95% CI)	*P* value
Age, y, mean ± SD	1.01 (1.00–1.02)	<0.001
Male, *n* (%)	0.92 (0.81–1.05)	0.225
Time, h	0.94 (0.89–1.03)	0.157
BMI	1.05 (1.03–1.07)	<0.001
WHR	2.68 (1.28–5.59)	0.009
SBP (mmHg)	1.01 (1.00–1.01)	0.010
DBP (mmHg)	0.99 (0.99–1.01)	0.292
Baseline NIHSS	1.01 (1.00–1.02)	0.019
Disabled at baseline	2.03 (2.68–3.43)	<0.001
Atrial fibrillation	1.32 (1.12–1.56)	0.001
Diabetes mellitus	1.22 (1.07–1.39)	0.003
Intracranial arterial stenosis	1.29 (1.14–1.45)	<0.001
Lenticulostriate artery area	3.84 (2.78–5.28)	<0.001
Cerebral watershed	3.05 (2.22–4.18)	0.005
WBC (10^9/L)	1.03 (0.96–1.05)	0.092
Neutrophil (10^9/L)	1.39 (1.34–1.45)	<0.001
Lymphocyte (10^9/L)	0.82 (0.76–0.89)	<0.001
Monocyte (10^9/L)	1.04 (0.99–1.08)	0.079
Glucose (mmol/L)	0.98 (0.96–1.01)	0.187
Uric Acid (μmol/L)	1.01 (1.00–1.01)	0.047
TG (mmol/L)	1.11 (1.04–1.17)	0.001
Hcy (umol/L)	1.01 (0.96–1.03)	0.489
CRP (mg/L)	1.03 (0.98–1.09)	0.524

AIS, acute ischemic stroke; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; Disabled at baseline, baseline mRS ⩽ 2; END, early neurological deterioration; Hcy, homocysteine; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation; TG, triglyceride; Time, time from onset to admission; WBC, white blood cell; WHR, waist–hip ratio.

END and functional outcome

The relationship between END and prognosis is shown in Figure 2. After 3-month follow-up, 829 patients were lost, and a total of 8285 patients were included in the follow-up analysis. The proportion of poor outcomes patients at 90 days was 40.1% in the END group and 26.4% in the non-END group. Good prognosis was observed in 59.9% and 73.6% patients, respectively. Compared to patients without END, those with END had higher median mRS scores at 90 days (2.00 [1.00–4.00] *vs* 1.00 [0.00–3.00]; $p < 0.001$; Figure 2). The results of the multivariate logistic regression analysis predicting outcomes after AIS

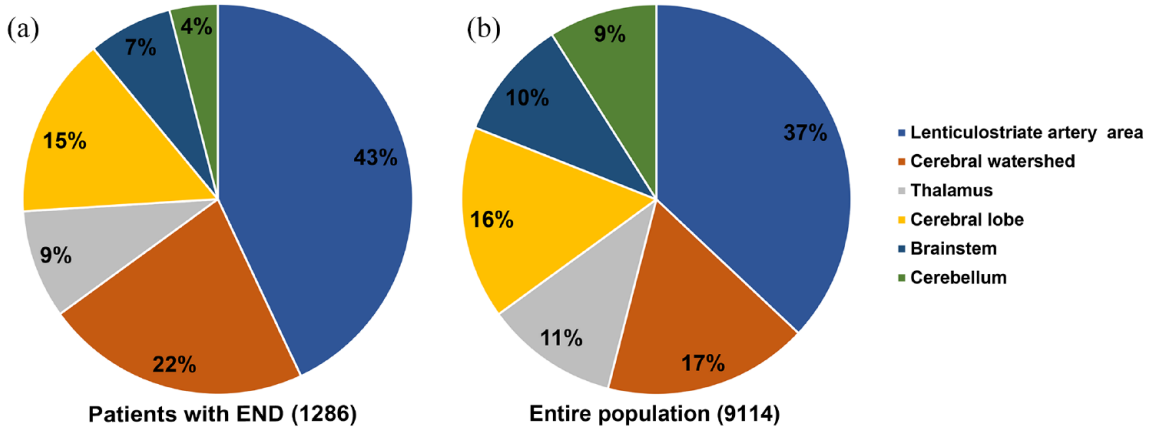

Figure 3. Distribution of infarct location: (a) the entire population and (b) patients with END are depicted.

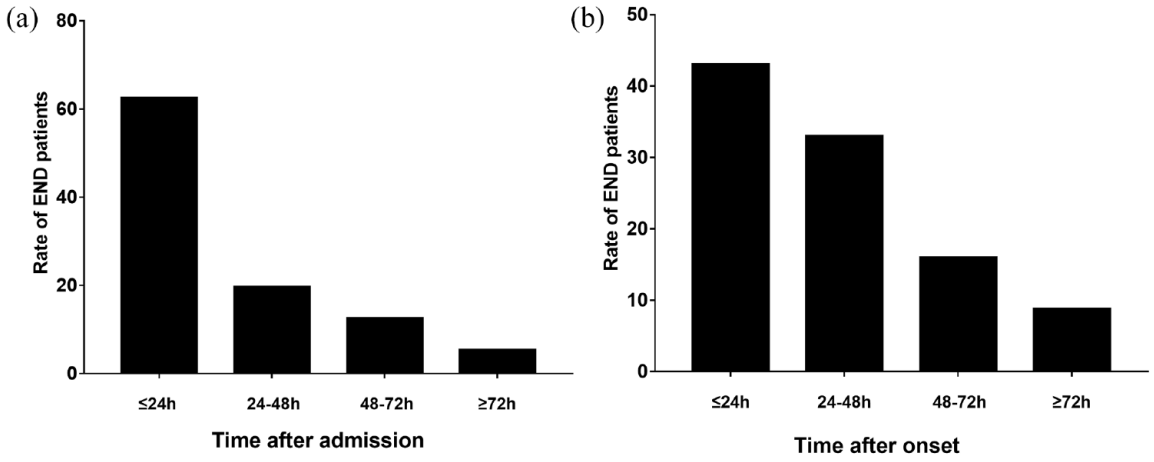

Figure 4. Time-dependent changes in the incidence rates of early neurological deterioration: (a) time after admission and (b) time after onset.

are shown in the Supplementary Table 1. After adjusting for confounding factors, END was significantly associated with poor prognosis at 90 days, and the adjusted common OR was 1.74 (95% CI: 1.53–1.97). Subgroup analyses were performed according to the mRS Score at admission (Supplementary Figure 1). The association of 3-month outcomes of AIS with END appeared more obvious in patients with higher baseline mRS score (OR 3.06; 95% CI: 2.26–4.03, p for interaction = 0.007).

Incidence and trends of END

Figure 4 shows the time variation trend of END. The highest incidence (62.5%) of END occurred within 24 h after admission. The estimated incidence of END decreased steeply after 1 day. The incidence decreased to approximately 19.6% the day after the patient was admitted. By 72 h after admission, the incidence decreased to <10%. Similar results were observed after AIS onset. Therefore, END risk was five times higher in patients who were admitted to hospital within 24 h (43.5%) than those who were admitted after 72 h (8.8%). Furthermore, the highest incidence (20.2%) of END observed in the severe stroke group and remained at 13.1% among patients with minor stroke (Supplemental Figure 2). Multivariate logistic regression analysis revealed that moderate and severe stroke (OR: 1.49, 95% CI: 1.25–1.79) were more likely to be associated with END compared to mild stroke (Supplementary Table 2).

Discussion

In the prospective multicenter observational study, we assessed patients who visited the hospital within 24 h of onset and defined progression as deterioration of clinical presentation after initiation of treatment. END was prospectively recorded and registered according to predetermined protocols, whereas most previous researches identified END retrospectively. Our study revealed following main findings: (1) END was observed in approximately one in seven patients hospitalized with AIS. (2) The highest incidence of END occurred within 24 h of admission and decreased steeply as time progressed. (3) Higher age, BMI, WHR, SBP, baseline NIHSS, neutrophil, uric acid, and TG levels, lower lymphocyte count, history of diabetes mellitus and atrial fibrillation, and infarct location in the lenticulostriate artery area and cerebral watershed were predictive of END. (4) END was associated with a risk of poor outcome at 3 months in patients with AIS.

A recent meta-analysis including 11 independent studies involving patients with AIS reported that the percentage of END occurring after endovascular treatment ranged from 3.4% to 28.8%, an overall rate of approximately 11.0%.[2] Another study performed a retrospective analysis of individual patient data obtained from the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry, and results showed that the rate of END was 6.7% in patients who underwent intravenous alteplase treatment.[14] Most of these studies were retrospective and were limited by the selection of specific populations with stroke. An inconsistent definition of END could also lead to differences in the results. In addition to thrombolytic patients, we focused on worsening of patients with AIS receiving conventional treatment at hospital. There is a lack of epidemiological data from large samples of this population. In our study, the incidence of END was determined by daily neurological function assessment of patients within 7 days of hospitalization, and the rate decreased significantly with increased duration of hospitalization. This result is consistent with those of previous studies.[15,16] The difference between the progression and recurrence of END and its clinical significance remains unclear. Previous studies reported that most END causes are due to the expansion and progression of existing infarct lesions, suggesting the need for effective treatments to prevent END.[17,18] Our results indicate that clinicians should focus on symptom fluctuations in patients with AIS at presentation or early stage of disease to avoid disease progression. Furthermore, our results revealed that moderate and severe stroke are more likely to be associated with END compared to mild stroke. Meanwhile, a review of a previous study also confirmed our findings.[19] Another previous study found that NIHSS score was associated with END in AIS and NIHSS score >14 points was an independent predictor of END.[20] We speculate that higher NIHSS scores at admission may indicate larger infarct size and extent, as well as higher rates of events of hemorrhagic transformation and cerebral edema.

Univariate and multivariate regression analyses revealed that patients with infarcts in the lenticulostriate artery and cerebral watershed areas exhibited a higher incidence of END than those with infarcts at any other location. These infarct locations can also predict the occurrence of END during hospitalization. Regional infarction of the lenticulostriate artery is a cerebral tissue infarction caused by a lesion in the deep perforating branch of the middle cerebral artery.[21] Owing to the poor circulation of collateral branches in the terminal area of the perforating branch, the outflow brain tissue is softened after infarction.[22] In our study, infarcts in the lenticulostriate artery region were mostly located near the basal ganglia and lateral ventricles, which are rich in motor and sensory nerve bundles and are the dominant area of the corticospinal tract. Patients with lenticulostriate arteries involvement are prone to motor function progression due to enlarged infarcts or cerebral edema.[23] Watershed infarction is an ischemic stroke occurring in the marginal zone dominated by intracranial adjacent blood vessels.[24] Previous studies have shown that watershed infarction often leads to cerebral hemodynamic damage and micro-thrombi formation due to intracranial and extracranial vascular stenosis, resulting in stroke progression.[25,26]

Our results revealed that BMI and WHR were predictors of END. It was well known that obesity increases the risk of AIS in the normal population.[27] However, the influence of obesity on the progression of AIS required further study. We hypothesized that the effective increase in abdominal fat accumulation, represented by the increase in abdominal circumference regardless of the increase in body mass, might disturb lipid and

glucose metabolism and resulted in adverse effects.[28,29] In addition, we revealed a significant association between the occurrence of END and higher neutrophil and lower lymphocyte counts.[30] A study in South Korea evaluated 438 patients with single subcortical infarctions and showed that the neutrophil-to-lymphocyte ratio (NLR) was positively associated with END.[31] Another observational study revealed that the NLR was associated with END in patients who received thrombolytic therapy, and the biomarker was of moderate diagnostic value.[32] Some studies have reported that inflammatory mechanisms play a key role in the pathogenesis and progression of AIS.[33] Peripheral WBC were guided by chemokines and inflammatory cytokines released from ischemic tissues and conversely might affect infarcted tissue as well.[34,35] Lymphocyte were considered to have neuroprotective effects and contribute to improvements in neurological function.[36,37] Peripheral neutrophils can be a source of matrix metalloproteinase-9, leading to hemorrhagic transformation and END.[38] Furthermore, it was reported that neutrophils induced free oxygen radicals and cause symptomatic deterioration.[39]

Our results demonstrated that patients with END exhibited worse functional outcomes and were more frequently dependent at 90 days, confirming the findings of previous studies.[40,41] We propose that most patients with AIS will exhibit milder symptoms after conventional treatment (except for a few death cases). Patients who were already disabled on admission were more likely to develop END. It is more difficult for these patients to recover from their neurological deficit after discharge. Although the association did not equate to causality between END and poor functional outcomes at 3 months, our results revealed that one in seven patients with END who received conventional anti-platelet therapy died within 3 months after discharge. To date, there have been no large-sample studies demonstrating effective treatment for patients with END. Previous studies have reported that compared with ordinary wards, stroke units can shorten the length of stay and reduce the incidence, mortality, and disability rate of END, and the effect was better than that of drug therapy alone.[42,43] Further studies are required to focus on END treatment in the future.

There are several limitations in this study. First, the Henan Stroke Registry used in our study was solely based on AIS patients from 18 regional hospitals in Asian population; therefore, the results may not be extrapolated in Caucasians. Second, although we minimized the time between onset and admission, detailed information on the pre-hospital course was not available, and we could not exclude effects of pre-hospital management on outcomes. Third, we did not evaluate changes in imaging and test results before and after END, which may potentially partly explain the mechanism of END. Fourth, the study focuses on worsening of patients with AIS receiving conventional treatment at hospital and patients who underwent intravenous thrombolysis (IVT) or endovascular treatment (EVT) were excluded. Future studies will separately explore patients with IVT or EVT. Finally, although our study confirms that history of atrial fibrillation is strongly associated with the occurrence of END in patients with AIS, other data on acute heart disease are still lacking. These may be potential risk factors for END. Further studies are required to provide greater insights regarding the underlying mechanism of END.

Conclusion

This large-scale prospective study revealed that one in seven patients with AIS experienced END. The highest incidence of END occurred within 24 h of admission and decreased steeply with time. Our findings also showed that older age, BMI, WHR, SBP, baseline NIHSS, neutrophil, uric acid, TG, lower lymphocyte count, history of atrial fibrillation and diabetes mellitus, infarct location in the lenticulostriate artery and cerebral watershed areas were predictive of END, and END may be associated with poor prognosis. Patients with AIS at high risk for END on admission should be included in future targeted trials of novel acute treatment options.

Declarations

Ethics approval and consent to participate

The study was approved by the Research and Clinical Trial Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2021-KY-0067-001). All procedures performed in studies involving human participants complied with institutional and/or National Research Council ethical standards. Only participants who provided a written informed consent were included in the study.

Consent for publication
Not applicable.

Author contributions
Hongbing Liu: Conceptualization; Data curation.

Kai Liu: Formal analysis.

Ke Zhang: Resources; Software.

Ce Zong: Formal analysis.

Hongxun Yang: Resources; Software.

Yapeng Li: Resources; Software; Supervision.

Shen Li: Supervision; Validation; Visualization.

Xin Wang: Resources; Software; Supervision.

Jiawei Zhao: Resources; Software; Supervision.

Zongping Xia: Resources; Software; Supervision.

Bo Song: Resources; Software; Supervision.

Xuming Xu: Resources; Software; Supervision.

Yuan Gao: Conceptualization; Data curation; Resources; Software; Supervision.

Acknowledgements
The authors acknowledge the Changge People's Hospital, Dengfeng People's Hospital, Dengzhou People's Hospital, Fanxian People's Hospital, Gongyi People's Hospital, Guangshan County People's Hospital, Huaxian People's Hospital, Luyi County People's Hospital, Linzhou People's Hospital, Ruyang County People's Hospital, The People's Hospital of Luyi, Wugang People's Hospital, Xixia County People's Hospital, Xixian County People's Hospital, Xiping County People's Hospital, Zhengzhou Zhongkang Hospital, and Zhenping People's Hospital.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the NHC Key Laboratory of Prevention and Treatment of Cerebrovascular Disease, Henan Key Laboratory of Cerebrovascular Diseases (Zhengzhou University), the Non-profit Central Research Institute and Major Science to Yuming Xu (grant no. 2020-PT310-01), and Technology Projects of Henan Province in 2020 to Yuming Xu (grant no. 201300310300).

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
Not applicable.

ORCID iD
Hongbing Liu https://orcid.org/0000-0001-7718-3288

Supplemental material
Supplemental material for this article is available online.

References

1. Boulenoir N, Turc G, Henon H, *et al.* Early neurological deterioration following thrombolysis for minor stroke with isolated internal carotid artery occlusion. *Eur J Neurol* 2021; 28: 479–490.
2. Hou X, Chen W, Xu H, *et al.* The rate of early neurological deterioration occurring after thrombolytic therapy: a meta-analysis. *Brain Behav* 2019; 9: e01210.
3. Bhole R, Nouer SS, Tolley EA, *et al.* Predictors of early neurologic deterioration (END) following stroke thrombectomy. *J Neurointerv Surg*. Epub ahead of print 18 May 2022. DOI: 10.1136/neurintsurg-2022-018844.
4. Kwan J and Hand P. Early neurological deterioration in acute stroke: clinical characteristics and impact on outcome. *QJM* 2006; 99: 625–633.
5. Vila N, Castillo J, Davalos A, *et al.* Proinflammatory cytokines and early neurological worsening in ischemic stroke. *Stroke* 2000; 31: 2325–2329.
6. Seners P, Ben Hassen W, Lapergue B, *et al.* Prediction of early neurological deterioration in individuals with minor stroke and large vessel occlusion intended for intravenous thrombolysis alone. *JAMA Neurol* 2021; 78: 321–328.
7. Bourcier R, Goyal M, Muir KW, *et al.* Risk factors of unexplained early neurological deterioration after treatment for ischemic stroke due to large vessel occlusion: a post hoc analysis of the HERMES study. *J Neurointerv Surg*. Epub ahead of print 15 February 2022. DOI: 10.1136/neurintsurg-2021-018214.
8. Gwak DS, Kwon JA, Shim DH, *et al.* Perfusion and diffusion variables predict early neurological deterioration in minor stroke and large vessel occlusion. *J Stroke* 2021; 23: 61–68.
9. Dawson J, Béjot Y, Christensen LM, *et al.* European Stroke Organisation (ESO) guideline

on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack. *Eur Stroke J* 2022; 7: I–II.

10. Liu H, Liu K, Pei L, *et al.* Atherogenic index of plasma predicts outcomes in acute ischemic stroke. *Front Neurol* 2021; 12: 741754.
11. Liu H, Liu K, Pei L, *et al.* Monocyte-to-high-density lipoprotein ratio predicts the outcome of acute ischemic stroke. *J Atheroscler Thromb* 2020; 27: 959–968.
12. Aburahma AF, Avgerinos ED, Chang RW, *et al.* Society for Vascular Surgery clinical practice guidelines for management of extracranial cerebrovascular disease. *J Vasc Surg* 2022; 75: 4S–22S.
13. Turan TN, Zaidat OO, Gronseth GS, *et al.* Stroke prevention in symptomatic large artery intracranial atherosclerosis practice advisory: report of the AAN guideline subcommittee. *Neurology* 2022; 98: 486–498.
14. Yu WM, Abdul-Rahim AH, Cameron AC, *et al.* The incidence and associated factors of early neurological deterioration after thrombolysis: results from SITS registry. *Stroke* 2020; 51: 2705–2714.
15. Park TH, Lee JK, Park MS, *et al.* Neurologic deterioration in patients with acute ischemic stroke or transient ischemic attack. *Neurology* 2020; 95: e2178–e2191.
16. Ryu WS, Hong KS, Jeong SW, *et al.* Association of ischemic stroke onset time with presenting severity, acute progression, and long-term outcome: a cohort study. *PLoS Med* 2022; 19: e1003910.
17. Terasawa Y, Iguchi Y, Kimura K, *et al.* Neurological deterioration in small vessel disease may be associated with increase of infarct volume. *J Neurol Sci* 2008; 269: 35–40.
18. Kalowska E, Rostrup E, Rosenbaum S, *et al.* Acute MRI changes in progressive ischemic stroke. *Eur Neurol* 2008; 59: 229–236.
19. Kim Y, Choi H, Jung Y, *et al.* The ischemic stroke predictive risk score predicts early neurological deterioration. *J Stroke Cerebrovasc Dis* 2016; 25: 819–824.
20. Siegler J, Boehme A, Kumar A, *et al.* Identification of modifiable and nonmodifiable risk factors for neurologic deterioration after acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2013; 22: e207–e213.
21. Zhou Y, Zhong W, Wang A, *et al.* Hypoperfusion in lenticulostriate arteries territory related to unexplained early neurological deterioration after intravenous thrombolysis. *Int J Stroke* 2019; 14: 306–309.
22. Yan Y, Jiang S, Yang T, *et al.* Lenticulostriate artery length and middle cerebral artery plaque as predictors of early neurological deterioration in single subcortical infarction. *Int J Stroke*. Epub ahead of print 17 March 2022. DOI: 10.1177/17474930221081639.
23. Umemura T, Senda J, Fukami Y, *et al.* Impact of albuminuria on early neurological deterioration and lesion volume expansion in lenticulostriate small infarcts. *Stroke* 2014; 45: 587–590.
24. Momjian-Mayor I and Baron JC. The pathophysiology of watershed infarction in internal carotid artery disease: review of cerebral perfusion studies. *Stroke* 2005; 36: 567–577.
25. Hayashi T, Shirane R, Fujimura M, *et al.* Postoperative neurological deterioration in pediatric moyamoya disease: watershed shift and hyperperfusion. *J Neurosurg Pediatr* 2010; 6: 73–81.
26. Matsukawa H, Tanikawa R, Kamiyama H, *et al.* Risk factors for neurological worsening and symptomatic watershed infarction in internal carotid artery aneurysm treated by extracranial-intracranial bypass using radial artery graft. *J Neurosurg* 2016; 125: 239–246.
27. Ohlsson C, Bygdell M, Sonden A, *et al.* BMI increase through puberty and adolescence is associated with risk of adult stroke. *Neurology* 2017; 89: 363–369.
28. Kurth T and Leitzmann MF. Awakening of the sleeping giant: obesity and stroke in China. *Ann Neurol* 2010; 67: 1–2.
29. Kim Y, Kim CK, Jung S, *et al.* Obesity-stroke paradox and initial neurological severity. *J Neurol Neurosurg Psychiatry* 2015; 86: 743–747.
30. Ferro D, Matias M, Neto J, *et al.* Neutrophil-to-lymphocyte ratio predicts cerebral edema and clinical worsening early after reperfusion therapy in stroke. *Stroke* 2021; 52: 859–867.
31. Nam KW, Kwon HM and Lee YS. Different predictive factors for early neurological deterioration based on the location of single subcortical infarction: early prognosis in single subcortical infarction. *Stroke* 2021; 52: 3191–3198.
32. Gong P, Liu Y, Gong Y, *et al.* The association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio with post-thrombolysis early neurological outcomes in patients with acute ischemic stroke. *J Neuroinflammation* 2021; 18: 51.

33. Deng QW, Huang S, Li S, *et al.* Inflammatory factors as potential markers of early neurological deterioration in acute ischemic stroke patients receiving endovascular therapy – the AISRNA study. *J Inflamm Res* 2021; 14: 4399–4407.
34. Gronberg NV, Johansen FF, Kristiansen U, *et al.* Leukocyte infiltration in experimental stroke. *J Neuroinflammation* 2013; 10: 115.
35. Rodrigues SF and Granger DN. Leukocyte-mediated tissue injury in ischemic stroke. *Curr Med Chem* 2014; 21: 2130–2137.
36. Xiao J, Qiu QW, Qin C, *et al.* Dynamic changes of peripheral blood lymphocyte subsets in acute ischemic stroke and prognostic value. *Brain Behav* 2021; 11: e01919.
37. Baird AE. The forgotten lymphocyte: immunity and stroke. *Circulation* 2006; 113: 2035–2036.
38. Walz W and Cayabyab FS. Neutrophil infiltration and matrix metalloproteinase-9 in lacunar infarction. *Neurochem Res* 2017; 42: 2560–2565.
39. Schabitz WR and Minnerup J. Neutrophils in acute stroke pathophysiology. *Stroke* 2019; 50: e44–e45.
40. Che F, Wang A, Ju Y, *et al.* Early neurological deterioration in acute ischemic stroke patients after intravenous thrombolysis with alteplase predicts poor 3-month functional prognosis – data from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China). *BMC Neurol* 2022; 22: 212.
41. Zhang M, Xing P, Tang J, *et al.* Predictors and outcome of early neurological deterioration after endovascular thrombectomy: a secondary analysis of the DIRECT-MT trial. *J Neurointerv Surg*. Epub ahead of print 10 June 2022. DOI: 10.1136/neurintsurg-2022-018976.
42. Roquer J, Rodriguez-Campello A, Gomis M, *et al.* Acute stroke unit care and early neurological deterioration in ischemic stroke. *J Neurol* 2008; 255: 1012–1017.
43. Shkirkova K, Saver JL, Starkman S, *et al.* Frequency, predictors, and outcomes of prehospital and early postarrival neurological deterioration in acute stroke: exploratory analysis of the FAST-MAG randomized clinical trial. *JAMA Neurol* 2018; 75: 1364–1374.