

# Predictors of Early Neurological Deterioration and Functional Outcome in Acute Ischemic Stroke: The Importance of Large Artery Disease, Hyperglycemia and Inflammatory Blood Biomarkers

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**Background:** Early neurological deterioration (END) in acute ischemic stroke (AIS) can be associated with poor outcome. The aim of this study was to investigate the association between infarction subtypes, biomarkers and END, and to identify patients with risk of unfavorable functional outcome.

**Materials and Methods:** This prospective study enrolled 101 patients with AIS. Neurological status was evaluated according to NIHSS at acute onset, on days 2, 3, and 90. END was defined as  $\geq 2$ -point increase of NIHSS within 72 hours. Functional outcome was assessed using NIHSS and the modified Rankin Scale (mRS) at day 90.

**Results:** END was observed in 20, 8%. Patients with large artery disease had higher risk of developing END compared with patients with cardioembolism or small vessel disease ( $p < 0.01$ ). Significant higher blood glucose level and leukocytes were observed in the END group. Patients with END had higher scores of mRS at day 90 ( $p < 0.01$ ). Levels of NSE, IL-6, hsCRP and NT-proBNP were higher in the patients with unfavorable compared with favorable functional outcome.

**Conclusion:** Large artery disease, high blood glucose and leukocytes levels are associated with END. Elevated levels of blood markers NSE, IL-6, HsCRP and NT-proBNP indicate poor functional outcome at 90 days after AIS. These patients must be identified and be offered treatment immediately in order to improve the functional outcome after AIS.

**Keywords:** acute ischemic stroke, early neurological deterioration, large artery disease, blood biomarkers, functional outcome

## Introduction

Early neurological deterioration (END) after stroke is described as worsening of symptoms after acute ischemic stroke (AIS), which occurs in 5–40% of patients.<sup>1–5</sup> The time interval in which END occurs is not standardized but is commonly described as neurological deterioration within 24–72 hours following AIS.<sup>6</sup> Several studies define END as an increase in the National Institutes of Health Stroke Scale (NIHSS) score by two or more points.<sup>3,4,7</sup> Due to the varying definition of END the incidence is difficult to determine. Proposed clinical predictors of END include initial stroke severity, diabetes mellitus, hypertension, atrial fibrillation, and stroke subtypes.<sup>5,8</sup> END has been observed in one of five patients with large artery disease and AIS.<sup>9</sup> Initial NIHSS score, MCA stenosis, and carotid stenosis of  $\geq 50\%$  were independently associated with END.<sup>10</sup> A meta-analysis showed that biomarkers such as glucose, total cholesterol, triglycerides, and leukocytes were associated with an increased risk of developing END.<sup>11</sup> END is also observed in patients with symptomatic intracerebral hemorrhages and malignant cerebral edema.<sup>2,12–14</sup> Seizures at the onset, pneumonia or early recurrent AIS may also be associated with END.<sup>2,15</sup>

However, for most patients with END it is not possible to identify these underlying mechanisms, and those patients are referred to as unexplained END.<sup>13,16</sup> The other pathophysiological mechanisms behind END remain elusive and may

involve multiple factors. Seners et al describe in their review of predictors of unexplained END that infarct growth beyond the core extending into the penumbra or even beyond the penumbra could be a possible explanation, but re-thrombosis or re-embolism may cause END as well.<sup>2,6</sup>

To enable identification and treatment of END, patients with risk of deterioration should be monitored at acute stroke surveillance units (ASSU).<sup>17</sup>

Hyperglycemia in non-diabetics was also shown to be related to END.<sup>18</sup> END has been associated with worse outcomes including a higher risk of mortality and increased functional disability.<sup>2,7,19</sup>

Biomarkers are supposed to be suitable to identify pathological processes of END after AIS. A collection of biomarkers may be effective to identify patients at risk of END thereby preventing unfavorable outcome.<sup>20</sup>

Increased levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a biomarker of heart failure, and neuron-specific enolase (NSE), a brain damage biomarker in the blood, have been observed to be associated with poor outcome after AIS.<sup>21,22</sup> AIS activates a storm of pro-inflammatory cytokines as a crisis response and these cytokines have also been associated with END.<sup>20,23</sup> Moreover, elevated interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) were also observed during AIS and may be associated with poor outcome.<sup>21,22,24</sup>

However, it has not always been possible to identify these underlying mentioned factors.<sup>25</sup> Thus it is important to identify risk factors that contribute to END in order to improve treatment and prevention and hence better outcome for patients with AIS.<sup>17</sup>

In this prospective study, 101 patients with AIS were consecutively included. Neurological status was closely monitored and END was identified. Associations between END, levels of biomarkers, clinical parameters and functional outcome were investigated.

## Individuals and Methods

### Study Groups

This study was a single center prospective longitudinal cohort study performed at a comprehensive stroke unit from July 2017 to July 2021. The patients with AIS were after symptom onset consecutively admitted to the Department of Neurology at Linköping University Hospital in Sweden. Management of AIS for all patients followed current national guidelines.<sup>26</sup> A neurologist assessed the patients including NIHSS at admission and a CT-scan was immediately performed to exclude hemorrhage. The treatment was started as quickly as possible by a well-trained stroke team. Inclusion criteria were: (1) AIS with a minimum of two points according to the NIHSS; (2) hospital admission within 24 h after AIS onset.

The exclusion criteria were: (1) hemorrhage on CT of the brain; (2) severe comorbidities such as central nervous system infection or brain tumor; (3) patients <18 years old; (4) suspected stroke mimics; (5) severe aphasia or impaired cognitive function that interfered with the possibility to give informed consent.

### Collection of Demographic and Clinical Data

Demographic data such as gender, age, and lifestyle factors such as smoking habits were collected from medical files. Information regarding treatment including drug prescriptions, comorbidities, history of hypertension, diabetes, coronary artery disease were also collected. Sub-grouping of AIS was performed according to the TOAST classification.<sup>27</sup> AIS was divided into (1) large-artery disease; (2) cardioembolism; (3) small-vessel disease; (4) stroke of undetermined etiology or stroke of other determined etiology.

The neurological deficit was scored according to NIHSS<sup>28</sup> at day 1 (at admission), day 2, day 3 and day 90 after onset. Functional outcome was also assessed at day 90 using the modified Rankin Scale (mRS).

### Blood Samples

Blood samples were obtained within the first 24 hours after admission. The laboratory variables were interleukin 6 (IL-6), high sensitivity C-reactive protein (hs-CRP), neuron-specific enolase (NSE), glucose and N-terminal pro-brain natriuretic peptide (NT-proBNP).

NSE was analyzed by electrochemiluminescence (ECL) using Cobas 8000, reference interval:  $<16 \mu\text{g/L}$ ; range 0.05–370  $\mu\text{g/L}$ . NT-proBNP was analyzed by ECL using Cobas e602, reference interval age  $<75$  years:  $<900 \text{ ng/L}$ ; age  $<60$  years:  $<450 \text{ ng/L}$ ; age  $>75$  years:  $<1800 \text{ ng/L}$ . Range 10–35,000  $\text{ng/L}$ . Hs-CRP was analyzed by particle-enhanced turbidimetric assay using Cobas e502, reference interval:  $<10 \mu\text{g/L}$ . Range 0.15–20  $\text{mg/L}$ . Results  $>20 \text{ mg/L}$  were analyzed with routine CRP. IL-6 was analyzed by ECL using Cobas 602, reference interval:  $<7 \text{ nanogram/L}$ . Range 1, 5–5000  $\text{ng/L}$ . Glucose was analyzed using ACCU-CHEK Inform II from capillary blood sample and reference interval is 4, 2–6.0; range 0.6–33.3  $\text{mmol/L}$ .

## Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 27. Descriptive statistics were used to summarize the baseline demographic and clinical data. Normality was analyzed using Shapiro–Wilk test. Normally distributed variables were presented as a mean (standard deviation) and non-normality distributed variables as median (25th–75th percentile). Categorical data were expressed as frequency (percentage). The Chi-square test was conducted for inter-group comparison. Mann-Whitney *U*-test was used to determine a difference in disability score and laboratory data between END and Non-END. Binary logistic regressions analyses were performed in order to examine the association between END and stroke subtypes using large artery disease as a referent.

*P* value less than 0.05 was considered as statistically significant. In addition, a multiple logistic regression analysis was performed to confirm the results from the binary logistic regression analyses.

## Ethical Considerations

This study was approved by the Ethics Committee for clinical research at Linköping University (2017-/182-31) and was performed according to the Declaration of Helsinki. There was no delay in the therapeutic intervention due to participation in the study. The patients gave their verbal and written informed consent. The patients could end the study without any interference of the treatment.

## Results

### Demographic and Clinical Data

A total of 179 patients were initially screened in this study. Seventy-eight patients were excluded due to the following reasons: 31 due to aphasia, 20 due to unconsciousness, 16 due to delayed admission of over 24 hours, and 11 due to severe comorbidities. One hundred and one patients were included in the study (Table 1). The mean age was  $71.5 \pm 13.7$  years, 46 of them were female. Of 101 patients, 21 patients (20.8%) showed neurological deterioration within the first 72 hours, representing END. Seventeen patients deteriorated on day 2 and a further four patients deteriorated on day 3. Seven of 101 patients (6.9%) died within 90 days: two because of pneumonia, two because of cardiac arrest, one because of heart and kidney failure, one because of ruptured basilar artery aneurysm, and one because of cerebral infarction. Laboratory data and medication at baseline are shown in Table 1. Some data of blood biomarkers were missing due to transport problems and/or hemolysed blood samples. NSE was analysed in 70 of 101 patients, hs-CRP in 78, IL-6 in 95. Among END group only one NSE sample was missing.

### Clinical Differences Between END and Non-END Groups

There were no significant differences regarding age, gender, acute treatment, comorbidities or medication between the END and the Non-END groups. There was neither any statistical difference regarding acute reperfusion therapy with thrombolysis ( $p = 0.24$ ) nor with mechanical thrombectomy ( $p = 0.78$ ) between these two groups (Table 2).

On day one, NIHSS was higher in the non-END group compared with END ( $p = 0.05$ ). Significant differences of stroke severity with higher NIHSS scores in the END group on days 2 and 3 were observed ( $p < 0.001$  for both). Similarly, higher NIHSS ( $p < 0.01$ ) and mRS ( $p < 0.01$ ) on day 90 were also observed in END group compared with non-END (Table 2).

**Table 1** Baseline Characteristics of 101 Patients with Acute Ischemic Stroke

Demographic characteristics	
Age, years, mean (SD)	71.5 (13.7)
Gender, female n (%)	46 (45.5)
Clinical data	
END, n (%)	21 (20.8)
END female n (% of END)	10 (47.6)
NIHSS, mean score after 90 days (range)	1.79 (0–16)
mRS, mean score after 90 days (range)	1.82 (0–6)
Deceased within 90 days after admission, n (%)	7 (6.9)
Comorbidities, n (%)	
Hypertension	79 (78.2)
Ischemic heart disease	22 (21.8)
Heart failure	20 (19.8)
Valve disease	6 (5.9)
Atrial fibrillation	32 (31.7)
Hyperlipidemia	43 (58.1)
Diabetes mellitus	20 (19.8)
Laboratory data, median (IQR)	
Glucose, mmol/L	6.2 (5.4–7.5)
Leukocytes	8.1 (6.4–10.6)
NSE, µg/L	16 (13.0–21.5)
Hs-CRP, mg/L	5 (2.7–15.0)
IL-6, ng/L	9.8 (4.7–28.0)
NT-proBNP, ng/L	370 (142–1322)
Platelets, ng/L	217 (183–275)
HDL, mmol/L	1.2 (1.0–1.5)
LDL, mmol/L	2.3 (1.7–3.0)
Medication at admission, n (%)	
Antihypertensive	85 (84.2)
Warfarin	9 (8.9)
NOAC	25 (24.8)
Thrombocyte inhibitors	61 (60.4)
Lipid lowering drugs	79 (78.2)
Hyperglycemic drugs	19 (18.8)

**Abbreviations:** END, early neurological deterioration; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; NSE, neuron-specific enolase; Hs-CRP, High-sensitive C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NOAC, new oral anticoagulant drugs; IQR, interquartile range; SD, standard deviation.

## Biomarkers Associated with END

The median blood glucose level was 6.2 mmol/L in the whole group. A significant higher blood glucose level was observed in END (8.10 mmol/L) group compared with Non-END (6.15 mmol/L) ( $p = 0.02$ ) (Table 2).

Leukocyte counts at admission were also significantly higher in the patients with END compared with those without ( $p = 0.04$ ).

There were no differences between the two groups regarding NSE, Hs-CRP, IL-6 and NT-proBNP.

**Table 2** Baseline Characteristics in Patients with or Without Early Neurological Deterioration

	<b>END N = 21</b>	<b>Non-END N = 80</b>	<b>P value</b>
<b>Demographic characteristics</b>			
Age, years, mean (SD)	74.3 (11,35)	70.75 (14,27)	0.37
Gender			0.83
Gender, male n (%)	11 (52.28)	44 (55)	
Gender, female n (%)	10 (47.6)	36 (45)	
<b>Clinical data, n (%)</b>			
Reperfusion therapy (use of tPA)	8 (38)	42 (52.5)	0.24
Reperfusion therapy (use of thrombectomy)	1 (4.8)	10 (12.5)	0.31
NIHSS, mean score day 1 (range)	6.3 (1–16)	8.4 (1–22)	0.05
NIHSS, mean score day 2 (range)	9.2 (2–18)	4.3 (0–18)	0.00
NIHSS, mean score day 3 (range)	10.5 (3–20)	3.3 (0–18)	0.00
NIHSS, mean score after 90 days (range)	5.1 (0–15)	1.0 (0–16)	0.00
mRS, mean score after 90 days (range)	3.6 (2–6)	1.5 (0–6)	0.00
Deceased within 90 days after admission, n (%)	2 (9.52)	5 (6.25)	0.18
<b>Comorbidities, n (%)</b>			
Hypertension	16 (76.2)	63 (748.8)	0.80
Ischemic heart disease	2 (9.5)	20 (25.0)	0.13
Heart failure	3 (19.8)	17 (21.5)	0.48
Valve disease	1 (4.8)	5 (6.3)	0.80
Atrial fibrillation	4 (19.0)	28 (35.0)	0.16
Hyperlipidemia	14 (66.7)	51 (63.8)	0.80
Diabetes mellitus	4 (19.0)	16 (20)	0.92
<b>Laboratory data, median (IQR)</b>			
Glucose, mmol/L	8.10 (5.9–11.6)	6.15 (5.4–7.4)	0.02
Leukocytes	8.00 (3.0–14.4)	9.5 (3.9–19.3)	0.04
NSE, µg/L	17.50 (13.3–24.5)	16.0 (12.0–21)	0.38
Hs-CRP, mg/L	12.0 (1.90–25.0)	5.0 (3.0–13.0)	0.58
IL-6, ng/L	9.70 (2.50–60.0)	9.90 (5.0–26.6)	0.73
NT-proBNP, ng/L	380 (145–1155)	360 (140–1470)	0.94
Platelets, ng/L	235 (177–318)	215 (187–258)	0.29
HDL, mmol/L	1.20 (1.05–1.55)	1.2 (0.97–1.47)	0.68
LDL, mmol/L	2.66 (1.80–3.1)	2.3 (1.62–3.07)	0.51
Troponin, ng/L	16 (8.70–26.5)	13 (8.0–23)	0.68
<b>Medication after admission, n (%)</b>			
Antihypertensive	19 (90.5)	66 (82.5)	0.38
Warfarin	2 (9.5)	7 (8.8)	0.91
NOAC	2 (9.5)	23(28.8)	0.07
Thrombocyte inhibitors	16 (76.2)	45 (56.3)	0.11
Lipid lowering drugs	16 (76.2)	63 (78.8)	0.80
Hyperglycemic drugs	5 (23.8)	14 (17.5)	0.51

**Abbreviations:** END, early neurological deterioration; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; NSE, neuron-specific enolase; Hs-CRP, High-sensitive C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NOAC, new oral anticoagulant drugs; IQR, interquartile range; SD, standard deviation.

**Table 3** Subtypes of Cerebral Infarctions According to TOAST Criteria in Patients with or Without END

Stroke Subtype n (%)	END	OR (95%)	P value*	Non-End	Total
Large artery disease	12 (57.2)			13 (16.2)	25 (24.8)
Cardioembolism	5 (23.8)	0.135 (0.04–0.50)	0.00	40 (50.0)	45 (44.6)
Small vessel disease	4 (19.0)	0.206 (0.06–0.80)	0.02	21 (26.2)	25 (24.8)
Undetermined	0			6 (7.5)	6 (5.9)

**Note:** \*Logistic regression analyses showed significant differences of 3 stroke subtypes in developing END ( $p = 0.003$ ).

**Abbreviations:** OR, odds ratio; CI, 95% confidence interval.

**Table 4** Levels of Blood Biomarkers in the Favorable and Unfavorable Functional Outcome Groups According to mRS

Parameter	Unfavorable Functional Outcome Median (IQR)	Favorable Functional Outcome Median (IQR)	P value
Glucose, mmol/L	6.7 (5.8–9.7)	6.1 (5.4–7.4)	0.06
Leukocytes	8.4 (6.9–12.8)	8.0 (6.15–9.5)	0.14
NSE, $\mu\text{g/L}$	21 (13–30)	16 (13.0–19.5)	0.02
Hs-CRP, mg/L	13 (4.7–34.0)	4.4 (2.2–4.4)	0.00
IL-6, ng/L	18 (8.6–44.5)	8.3 (3.9–23.5)	0.01
NT-proBNP, ng/L	1170 (325–4101)	275 (140–910)	0.00

**Note:** Favorable functional outcome  $\leq 2$  points; Unfavorable functional outcome  $> 2$  points according to mRS.

**Abbreviations:** NSE, neuron-specific enolase; Hs-CRP, High-sensitive C-reactive protein; mRS, modified Rankin Scale; IQR, interquartile range.

## Large Artery Disease as a Possible Predictor of END

Based on clinical and radiological findings using CT and/or MRI with angiography the participants were sub-grouped according to the TOAST classification system. Of all patients, 44.6% had cardioembolism, 24.8% had large artery disease, 24.8% had small vessel disease and 5.9% had undetermined etiology. A higher percentage of large artery disease was observed in END compared with the non-END group (57.2% vs 16.2%). A lower percentage of cardioembolism and small vessel disease was shown in END compared with non-END group. Logistic regression analyses showed significant differences of the three stroke subtypes among the END group ( $p < 0.01$ ). Compared with those with large artery disease, patients with cardioembolism had a lower risk for END (OR = 0.135,  $p < 0.01$ ). The multiple logistic regression analysis confirmed this result ( $p < 0.01$ ). Similarly, patients with small vessel disease demonstrated a lower risk compared with those with large artery disease (OR = 0.206,  $p = 0.02$ ). These results indicate that large artery disease is a significant risk factor for developing END (Table 3).

## Functional Outcome

The END group showed poor functional outcome on day 90 compared with the non-END group (Table 2). Poor outcome was defined as mRS  $> 2$  on day 90 (unfavorable outcome). The unfavorable outcome group showed significantly different levels of blood biomarkers at admission compared with the favorable outcome group (Table 4). The levels of NSE, NT-proBNP, Hs-CRP and IL-6 were significantly higher in the unfavorable outcome group compared with the favorable group. Blood glucose was close to significant high level in the unfavorable group ( $p = 0.06$ ) by binary logistic analysis. But multiple logistic regression could not confirm blood glucose as a predictor of poor outcome. Instead, age was significantly associated with outcome after three months ( $p < 0.01$ ).

## Discussion

END was an important independent predictor for poor outcomes at 90 days and one year after stroke shown in a study by Liu.<sup>29</sup> In the present study, we investigated predictors of END after AIS. The rate of END was 20.8%, which was in line with results in previous studies.<sup>3,7,17</sup> At admission, the END group had lower NIHSS compared with non-END

( $p = 0.05$ ). But on days 2 and 3, NIHSS increased consistently in END group in contrast to non-END group ( $p < 0.01$ ). More patients with non-END received reperfusion therapies, although the difference was not statistically significant, but could have contributed to decreased NIHSS as well as mRS in non-END group. Simonsen et al also studied patients who received treatment with intravenous tPA and only 5.8% of patients in their study developed END, which is in agreement with the present study.<sup>14</sup> Unfavorable outcome was observed in END group on day 90 compared with non-END group measured by both NIHSS ( $p < 0.01$ ) and mRS ( $p < 0.01$ ). Our results showed that subgroups of stroke according to the TOAST criteria could predict END. We found that patients with large artery disease had higher risk to develop END than those with cardioembolism or small vessel disease. There are a few previous studies that have shown similar results, indicating that large artery disease could be an important risk factor for developing END.<sup>10,30</sup>

In addition, a panel of blood biomarkers was evaluated in the present study. The levels of NSE, IL-6 and NT-proBNP were similar between the END and non-END groups. In the END group higher Hs-CRP was detected compared with non-END group (12 mg/L vs 5 mg/L), but did not reach statistical significance. This could be due to small samples, especially in END group. Leukocyte counts were significantly higher in patients with END compared with the non-END group ( $p = 0.04$ ). Higher level of glucose was also observed in patients with END compared with patients without END with statistical significance ( $p = 0.02$ ).<sup>14</sup> Hyperglycemia and leukocytosis seem to be the most important predictors for END and our result is in line with previous studies.<sup>13,14</sup> High levels of glucose lead to brain lactate increase, which may cause infarction in hypo-perfused brain tissue.<sup>31</sup> On the other hand, insulin treatment for hyperglycemia in AIS may give sudden hypoglycemia which causes neuronal cell death in hypoperfused brain tissue.<sup>32</sup> Hyperglycemia has also prothrombotic effects, leading to extension of the infarction.<sup>33</sup> In the present study blood glucose was measured fasting at day 2 as clinical routine in all patients with or without a history of diabetes mellitus. It would be of value to closely monitor blood glucose, not just before the administration of insulin but also shortly after administration to assess the impact of hypoglycemia on END.

The collateral circulation is also important to preserve the penumbra and subsequently prohibit the expansion of the infarction. There are theories on collateral failure as an additive explanation for END. In animal models a slight intracranial pressure elevation following an AIS has been observed which may lead to reduction in the collateral flow.<sup>34</sup> This pathophysiological mechanism may be an explanation for END, but has yet not been confirmed in humans.

Many authors have called for better tools to be able to predict which patients are at risk for developing END. There are several predictive models that have been proposed, but none of these is used in clinical praxis today. An assessment of several mechanisms may give more information than a single biomarker. A recent publication by Xie includes NIHSS score, middle cerebral artery stenosis and carotid stenosis in their model, which may identify around 50% of patients at risk of developing END.<sup>10</sup> This is in line with the findings in the present study, that large artery disease is important for the risk of developing END.

Despite lower NIHSS at admission, patients with END had worse outcome on day 90 after the onset evaluated with NIHSS and mRS, which was consistent with previous reports.<sup>29,35,36</sup> We found that there were no significant differences regarding demographic characteristics, other vascular risk factors, comorbidities or therapies before AIS between END and non-END groups. Statistical analyses including logistic regression showed that large artery disease and higher level of blood glucose and leukocytosis in the acute phase were important predictors for END.

When analysing blood biomarkers in relation to outcome on day 90 assessed with mRS, significantly higher levels of NSE, Hs-CRP, IL-6 and NT-proBNP were observed in the unfavorable than in the favorable group which can indicate increased inflammation at the acute phase of stroke and may predict the long-term functional outcome after AIS. Several studies have shown that elevated NT-proBNP is a predictor of worse functional outcome,<sup>37–39</sup> but in this study also NSE, IL-6, and Hs-CRP predicted worse outcome. Inflammation has been proposed as a predictor of poor prognosis in other conditions as well.<sup>40–42</sup> Proinflammatory cytokines are increased in brain ischemia. In the present study we found a correlation between leukocytosis and END but not between IL-6 and END. A recent review has identified prognostic biomarkers in AIS.<sup>43</sup> The authors found studies on 97 different biomarkers which indicate the diversity of different etiologies believed to affect prognosis in AIS. The authors of the review conclude that the quality of research in this area is poor and there is still no consensus on how to use biomarkers for prognosis in AIS.

NSE had a positive correlation with NIHSS in AIS according to a previous study.<sup>44</sup> However, we found that NSE in the acute phase was associated with worse functional outcome after three months. Higher levels of NSE may be associated with greater neuronal damage leading to poor functional outcome.

Based on the findings of this study, we consider it essential to monitor and treat patients at high risk of developing END at an ASSU to use resources in the best way. Roquer et al have shown that the best prevention of END is frequent inspections of patients at ASSU.<sup>17</sup> We conclude that patients with large artery disease and patients with hyperglycemia or leukocytosis tend to develop END and should be offered close monitoring and rapid interventions.

## Strengths and Limitations

The strengths of the study are as follows: daily assessment of neurological status by neurologist allowed accurate NIHSS evaluation and timing of END. All laboratory tests were accredited, ensuring the quality of the results. Extensive investigations of risk factors and complications after AIS were carefully performed and monitored at our comprehensive stroke unit. Almost all patients came for follow-up, indicating good compliance.

However, there are several limitations in this study. First, the patients with aphasia and impaired cognitive function were excluded due to ethical issues, which may have influenced the proportion of patients with END versus non-END. Second, all the blood samples were taken within 24 hours, but not taken at the exact time point. Third, a total of 49.5% of the study population was treated with thrombolysis (Alteplase), potentially leading to a decreased risk of developing END. This could be a possible confounder factor. Finally, the study population was relatively small since the project was carried out in a single stroke centre.

## Conclusion

Our study demonstrates an independent association between large artery disease and END, likely to be caused by extension of infarction or brain edema. Blood glucose levels and leukocytes at admission were higher in the END group compared with the non-END group. Further elevated levels of blood NSE, IL-6 and NT-proBNP indicate poor functional outcome at 90 days after AIS. Patients with END had worse functional outcome after 90 days compared with patients without END. These findings strengthen the need to identify patients with large artery disease as well as patients with high levels of the blood biomarkers, glucose, leukocytes, NSE, IL-6 and NT-proBNP and to carefully monitor these patients in order to prevent END and poor functional outcome. Close surveillance and immediate treatment is essential to improve the functional outcome after AIS. Future studies with larger cohorts are warranted to improve the understanding of END.

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## Disclosure

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