Association of fibrinogen level with early neurological deterioration among acute ischemic stroke patients with diabetes

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Abstract

Background: Diabetes mellitus (DM) is a risk factor for early neurological deterioration (END) in acute ischemic stroke. The prothrombotic protein fibrinogen is frequently elevated in patients with diabetes, and may be associated with poorer prognoses. We evaluated whether fibrinogen is associated with END in patients with diabetes after acute ischemic stroke.

Methods: We included 3814 patients from a single hospital database admitted within 72 h of onset of ischemic stroke. END was defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) ≥2 within 7 days post-admission. In the total population (END, n = 661; non-END, n = 3153), univariate and multivariate analyses were performed to assess fibrinogen as an independent predictor for END. We then performed propensity score matching and univariate analyses for DM (END, n = 261; non-END, n = 522) and non-DM populations (END, n = 399; non-END, n = 798). Multiple logistic analyses were performed after matching for fibrinogen as a risk factor in each subgroup.

Results: Fibrinogen levels were higher in the END group than in the non-END group (367 ± 156 mg/dL vs. 347 ± 122 mg/dL, p = 0.002), though they were not associated with END in logistic regression analyses. Fibrinogen levels were found to be an independent predictor for END, but only in the DM population (fibrinogen levels 300–599 mg/dL, odds ratio: 1.618, 95% confidence interval: 1.037–2.525, p = 0.034, fibrinogen levels ≥600 mg/dL, 2.575, 1.018–6.514, p = 0.046; non-DM population, p = 0.393). The diabetes-fibrinogen interaction for the entire cohort was p = 0.101.

Conclusions: Elevated fibrinogen is dose-dependently associated with END in patients with diabetes following acute ischemic stroke.

Keywords: Cerebral infarction, Disease progression, Diabetes mellitus, Fibrinogen, Intracranial thrombosis
to it. One possible mechanism linking DM with adverse outcomes of stroke involves fibrinogen, a prothrombotic protein, and acute phase reactant that is consistently elevated in patients with diabetes [13, 14]. In fact, a large body of evidence identifies fibrinogen as a mediator in the development of coronary artery thrombi and future cardiac events [15, 16]. However, the association of hyperfibrinogenemia and END in acute ischemic stroke has not yet been demonstrated. In this study, we evaluated whether elevated fibrinogen levels in patients with diabetes and acute ischemic stroke are associated with END in a large, single-center population.

**Methods**

**Study population**

We performed a retrospective study that was approved by the Institutional Review Board, and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, incorporating consecutive patients enrolled in a hospital stroke database. From this database, we reviewed consecutive patients from Jan. 2000 to Dec. 2015. Among them, we included 3814 patients with acute ischemic stroke within 72 h of onset, and with available National Institutes of Health Stroke Scale (NIHSS) data.

**Data acquisition**

For this study, the diagnosis of DM was defined as either a prior diagnosis of diabetes, or glycated hemoglobin (HbA1c) levels >6.1% at admission, according to a previous study which showed that prediabetic levels of hba1c >6.1% were associated with increased stroke recurrence [17]. Lab data concerning the hemostatic profiles such as fibrinogen, fibrin degradation products (FDP), D-dimer, and classic stroke risk factors were obtained on the day of admission, before initiation of intravenous tissue plasminogen activators for those who were applicable. Acute inflammatory markers, erythrocyte sedimentation rate (ESR), and standard C-reactive protein (CRP) levels were included in the analysis, to compare with fibrinogen. Components of metabolic syndrome were also analyzed. Lab data routinely taken to evaluate diabetic status, such as fasting glucose levels, urine glucose, urine protein, and HbA1c levels were also included in the analysis. Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification, and NIHSS scores on admission and at discharge were also collected from the database.

**Propensity score matching and statistical analysis**

END was defined as a NIHSS score increase of 2 or more within 7 days after admission. A number of studies have, for the definition of END, used an increase of ≥2 points in the total NIHSS score within 7 days [18], as modified from a previous study. We have incorporated such sensitive criteria to define END for such subtle changes call for action in clinical practice. Because END in patients with acute ischemic stroke can be influenced by a greater initial NIHSS and TOAST classification, we used propensity score matching to adjust for well-known confounding factors. First, among the 3814 patients with acute stroke, we performed univariate and multivariate analyses to document the effects of fibrinogen and other predictive factors of END. Multivariate analysis was performed, adjusting for age, sex, presence of hypertension, diabetes mellitus, initial NIHSS score, and TOAST classification. The p value for the diabetes status x fibrinogen level interaction was also calculated in the logistic regression model. For subgroup analysis, the patients were divided into DM (n = 1360) and non-DM (n = 2454) populations. In each subgroup, a 1:2 propensity score matching of END patients and non-END patients was performed, adjusting for age, sex, initial NIHSS score, and TOAST classification (Additional file 1: Figure S1A-B). Differences between the two groups were analyzed before and after propensity score matching, using a χ² test for categorical variables and Student’s t-test for continuous variables. Multiple logistic regression analysis was performed, adjusting for baseline clinical variables known to be associated with END such as age, sex, hypertension, initial NIHSS, and TOAST classification, as well as with potentially significant factors determined in the univariate analysis (p < 0.005), to verify the significance of fibrinogen levels on END. All statistical analyses were performed using IBM SPSS Statistics 20 software (Chicago, IL).

**Results**

Among 3814 patients with acute stroke, 661 cases (17.3%) experienced early neurological deterioration. Patients in the END group were significantly older (65.3 ± 12.6 vs. 63.5 ± 13.5, p = 0.001), and more frequently had a history of DM (39.6% vs. 34.8%, p = 0.019), a history of hypertension (70.0% vs. 65.8%, p = 0.039), a higher initial NIHSS (8.2 ± 6.7 vs. 5.6 ± 6.3, p < 0.001), a higher fasting glucose (151 ± 66 vs. 144 ± 63 mg/dL, p = 0.005), higher uric acid positivity (22.7% vs. 14.6%, p < 0.001), and higher fibrinogen levels (367 ± 156 vs. 347 ± 122 mg/dL, p = 0.002) (Table 1). In the multiple regression analysis of the total population, higher fibrinogen levels were not significantly associated with END after adjusting for confounders (p = 0.195) (Table 2). The interaction between diabetes status and fibrinogen levels regarding END was not statistically significant in the entire cohort (p = 0.101).

There were 1360 diabetic and 2454 non-diabetic patients. In the DM population (END = 262, non-END = 1098), a diagnosis of hypertension (81.6% vs. 74.6%, p = 0.017), initial NIHSS (10.4 ± 10.6 vs. 3.6 ± 5.7,
Table 1 Comparison of baseline data in patients with acute ischemic stroke admitted within 72 h

|                        | END (n = 661) | Non-END (n = 3153) | P    |
|------------------------|--------------|--------------------|------|
| Age                    | 65.3 ± 12.6  | 63.5 ± 13.5        | 0.001|
| Male sex               | 409 (61.9%)  | 2017 (64.0%)       | 0.309|
| Hypertension           | 462 (70.0%)  | 2052 (65.8%)       | 0.039|
| Diabetes mellitus      | 262 (39.6%)  | 1098 (34.8%)       | 0.019|
| Initial NIHSS          | 8.2 ± 6.7    | 5.6 ± 6.3          | <0.001|
| Discharge NIHSS        | 10.5 ± 10.3  | 3.2 ± 5.4          | <0.001|
| TOAST                  |              |                    |      |
| Cardioembolism         | 160 (24.2%)  | 718 (22.8%)        |      |
| Atherosclerosis        | 201 (30.4%)  | 818 (25.9%)        |      |
| Small artery disease   | 159 (24.1%)  | 614 (19.5%)        |      |
| Others                 | 141 (21.3%)  | 1003 (31.8%)       |      |
| Fasting glucose (mg/dL)| 151 ± 66     | 144 ± 63           | 0.005|
| Glycated hemoglobin (%)| 6.65 ± 1.57  | 6.46 ± 1.36        | 0.051|
| Urine protein positivity| 100/441 (22.7%) | 276/1896 (14.6%) | <0.001|
| Fibrinogen (mg/dL)     | 367 ± 156    | 347 ± 122          | 0.002|
| ESR (mm)               | 18.15 ± 17.09| 17.57 ± 17.01      | 0.439|
| CRP (mg/dL)            | 0.81 ± 2.00  | 0.73 ± 2.33        | 0.459|
| BM1                    | 23.8 ± 3.2   | 24.0 ± 3.4         | 0.163|
| Metabolic syndrome     | 288 (43.6%)  | 1295 (41.1%)       | 0.236|
| Lipid panel            |              |                    |      |
| T.chol (mg/dL)         | 179.54 ± 42.07| 179.15 ± 51.46    | 0.857|
| LDL (mg/dL)            | 107.42 ± 37.48| 105.68 ± 35.45    | 0.262|
| HDL (mg/dL)            | 45.65 ± 12.87| 45.94 ± 13.40      | 0.616|
| TG (mg/dL)             | 139.77 ± 122.26| 142.83 ± 117.81   | 0.552|

END early neurological deterioration, NIHSS National Institutes of Health Stroke Scale, TOAST trial of Org 10,172 in acute stroke treatment, ESR erythrocyte sedimentation rate, CRP c-reactive protein, BMI body mass index, T.chol total cholesterol, LDL low density lipoprotein, HDL high density lipoprotein, TG triglyceride

In the non-DM population (END = 399, Non-END = 2055), age (65.3 ± 13.2 vs. 62.7 ± 14.3, p < 0.001), initial NIHSS (8.4 ± 6.8 vs. 5.6 ± 6.3, p < 0.001), and fasting glucose levels (125.6 ± 30.9 vs. 122.1 ± 29.7 mg/dL, p = 0.036) were significantly higher in the END group, as were differences in TOAST classification (p < 0.001) (Additional file 2: Table S1). Propensity score matching was performed for age, sex, initial NIHSS, and TOAST classification, with a relative multivariate imbalance measure L1 of 0.581 before matching, and 0.525 after matching. No covariate exhibited a large imbalance. After matching, TOAST classification (p = 0.003), elevated total cholesterol (179.5 ± 41.3 vs. 173.6 ± 38.4 mg/dL, p = 0.015), and elevated low density lipoprotein (108.2 ± 37.4 vs. 102.8 ± 34.3 mg/dL, p = 0.015) were significantly associated with END (Additional file 2: Table S1). In further regression analysis in the matched population, including age, male sex, presence of hypertension, initial NIHSS, TOAST classification, and total cholesterol levels as covariables, fibrinogen did not remain significant.
Fibrinolysis [25], and decreases α structure that reduces permeability [24], decreases glycated in vivo [23], causing a change in the fibrin clot under diabetic conditions have shown fibrinogen to be syndrome [13]. Prolonged glycation also induces a pro-

patients correlate with insulin resistance and metabolic syndrome, and fibrinogen levels and high drug resistance to be significantly associated with diabetes [36]. Such data suggest that diabetes may be linked to antiplatelet resistance, which may in turn result in END. Previous large scale trials, such as the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAPAD) trial [34], and the Prevention of Progression of Arterial Disease and Diabetes (POPAPAD) trial [35], have shown low efficacy of aspirin monotherapy for prevention of cardiovascular events in patients with diabetes. In addition, recent data show that responses to clopidogrel in patients with diabetes are suboptimal [36]. Such data suggest that diabetes is associated with considerable resistance to aspirin and clopidogrel therapy, and such insufficient antiplatelet responses could be an underlying causal factor for the frequent END observed in this population. In accordance with the elevated fibrinogen levels in our data, a recent study evaluating platelet aggregation characteristics in acute coronary syndrome found antiplatelet drug resistance to be significantly associated with metabolic syndrome, and fibrinogen levels and high sensitivity-CRP were higher in this population [37]. Serum fibrinogen levels appeared to be strongly associated with drug resistance [37]. In this case, elevated fibrinogen levels may call for more radical choices for antiplatelet therapy in such a population.

Apart from the antiplatelet issue, the idea that reduced fibrin, which is formed by fibrinogen in blood, may reduce blood viscosity, improve blood flow, and help re-

| Table 2 | A logistic regression model including potential factors associated with early neurologic deterioration in patients with acute ischemic stroke admitted within 72 h |
|---------|--------------------------------------------------------------------------------------------------|
| **Age** | Odds ratio (95% confidence interval) | P       |
| Male sex | 1.00 (1.00–1.01) | 0.605   |
| Hypertension | 0.94 (0.78–1.14) | 0.551   |
| Diabetes mellitus | 1.11 (0.92–1.33) | 0.268   |
| Initial NIHSS | 1.07 (1.05–1.08) | <0.001  |
| TOAST | <0.001 |  |
| Cardioembolism | Reference | | |
| Atherosclerosis | 1.38 (1.07–1.78) | 0.013 | |
| Small artery disease | 1.97 (1.48–2.63) | <0.001 |
| Others | 0.94 (0.71–1.24) | 0.652 |
| Fibrinogen (mg/dL) | 0.195 | | |
| 0–300 mg/dL | Reference | | |
| 300–600 mg/dL | 1.20 (0.97–1.49) | 0.091 |
| > 600 mg/dL | 1.36 (0.78–2.37) | 0.195 |

NIHSS National Institutes of Health Stroke Scale, TOAST trial of Org 10,172 in acute stroke treatment

not prove to be associated with END (p = 0.393) (Additional file 2: Table S2).

Discussion

The results of this study suggest that hyperfibrinogenemia in patients with acute stroke and DM is associated with END, using both propensity score matching and multiple logistic regression analysis. Whereas the influence of hyperfibrinogenemia on END was consistently seen in the DM subgroup, it disappeared in the non-DM subgroup.

Hyperfibrinogenemia itself may directly induce a higher frequency of END in diabetic individuals through activation of the coagulation cascade. Fibrinogen forms fibrin clots as part of the final common stages of both the extrinsic and intrinsic pathways of the coagulation cascade [19]. Atherogenesis and the growth of atheromatous lesions are also initiated in part by fibrin deposition [20, 21]. Fibrinogen also facilitates platelet aggregation by binding to the glycoprotein IIb/IIIa receptor, increasing its reactivity [22].

Hyperfibrinogenemia may also indirectly reflect a prothrombotic condition induced by hyperinsulinemia and prolonged glycation. Levels of fibrinogen in diabetic patients correlate with insulin resistance and metabolic syndrome [13]. Prolonged glycation also induces a prothrombotic condition. Studies on fibrin clot structure under diabetic conditions have shown fibrinogen to be glycated in vivo [23], causing a change in the fibrin clot structure that reduces permeability [24], decreases fibrinolysis [25], and decreases α-chain crosslinking [26].

Thus, the effects of insulin resistance and prolonged glycation increase the risk of thrombosis, which underpins the development of vascular disease [27]. These studies lead us to assume that fibrinogen levels may represent a marker of platelet aggregation or progression to a prothrombotic phenotype in patients with diabetes [27].

This is the first study to link diabetic hyperfibrinogenemia to a higher frequency of END after ischemic stroke. Epidemiological studies have established that elevated fibrinogen levels are strongly and independently correlated with the risks of coronary arterial disease (CAD), stroke, and peripheral arterial disease [16, 28–31]. In stroke, carotid artery stenosis is significantly associated with elevated fibrinogen levels [32], and placebo data analysis in the Stroke Treatment with Ancrod Trial (STAT) and European Stroke Treatment with Ancrod Trial (ESTAT) has shown that plasma fibrinogen levels at stroke onset are independently associated with a poor functional outcome [33]. However, it has not been reported that hyperfibrinogenemia in patients with diabetes is associated with END in the acute stroke period.

It is conceivable that stronger antiplatelet treatments might be needed for patients with diabetes and hyperfibrinogenemia following acute ischemic stroke. Of note, elevated fibrinogen levels in our group of patients with diabetes may be linked to antiplatelet resistance, which may in turn result in END. Previous large scale trials, such as the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAPAD) trial [34], and the Prevention of Progression of Arterial Disease and Diabetes (POPAPAD) trial [35], have shown low efficacy of aspirin monotherapy for prevention of cardiovascular events in patients with diabetes. In addition, recent data show that responses to clopidogrel in patients with diabetes are suboptimal [36]. Such data suggest that diabetes is associated with considerable resistance to aspirin and clopidogrel therapy, and such insufficient antiplatelet responses could be an underlying causal factor for the frequent END observed in this population. In accordance with the elevated fibrinogen levels in our data, a recent study evaluating platelet aggregation characteristics in acute coronary syndrome found antiplatelet drug resistance to be significantly associated with metabolic syndrome, and fibrinogen levels and high sensitivity-CRP were higher in this population [37]. Serum fibrinogen levels appeared to be strongly associated with drug resistance [37]. In this case, elevated fibrinogen levels may call for more radical choices for antiplatelet therapy in such a population.

Aside from the antiplatelet issue, the idea that reduced fibrin, which is formed by fibrinogen in blood, may reduce blood viscosity, improve blood flow, and help re-

move the blood clot blocking the artery and re-establish
blood flow has inspired clinical trials testing the therapeutic effects of the fibrin-depleting agents ancred and defibrase [38]. In eight trials involving 5701 patients, fibrin-depleting agents marginally reduced the proportion of patients who were dead or disabled at the end of follow-up, and there were fewer stroke recurrences in the treatment group than in the control group. However, symptomatic intracranial hemorrhage was about twice as common in the treatment group compared with the control group [38]. The use of fibrin-depleting agents to reduce blood viscosity in patients with DM and elevated fibrinogen at risk for END holds similar problems. Plasma fibrinogen levels are associated with silent cerebrovascular lesions [39], and although this relationship may be evidence that increased viscosity by fibrinogen is a risk factor for stroke, deep white matter hyperintensities, on the other hand, are a known risk factor for intracerebral hemorrhage [40]. Accordingly, the use of fibrin-depleting agents in patients with DM may confer a higher risk of hemorrhagic complications. Thus, while the selective use of fibrin-depleting agents in patients with DM and END may be considered, further clinical studies to address the risks are needed prior to making such treatment a recommendation.

We acknowledge that our study has limitations. First, due to the retrospective nature of the study, there may be selection bias. We tried to minimize this issue by maximizing the number of patients included in the study and including adequate propensity score matching. Second, our somewhat long temporal definition of END (<7 days) incorporates a range of heterogeneous underlying mechanisms, and different definitions are used in other reports. Due to the retrospective nature and large number of enrolled patients in the study, the heterogeneity of END could not be addressed in this study. Third, because of the focus on lab data in this study, medication factors and imaging variables such as intracranial occlusion, stenosis, or diffusion weighted image volume were not included for analysis. However, variables that may have similar implications such as TOAST classification, and NIHSS

| Table 3 Comparison before and after propensity score matchinga in patients with diabetes and acute ischemic stroke admitted within 72 h |
|---|---|---|---|---|---|
| | Before matching | | After matching | | |
| | END (n = 262) | Non-END (n = 1098) | P | END (n = 261) | Non-END (n = 522) | P |
| Age | 65.3 ± 11.8 | 65.1 ± 11.7 | 0.771 | 65.3 ± 11.8 | 64.8 ± 11.8 | 0.593 |
| Male sex | 160 (61.1%) | 700 (63.8%) | 0.418 | 159 (60.9%) | 315 (60.3%) | 0.877 |
| Hypertension | 213 (81.6%) | 812 (74.6%) | 0.017 | 213 (81.6%) | 431 (82.6%) | 0.741 |
| Initial NIHSS | 8.0 ± 6.6 | 5.7 ± 6.4 | <0.001 | 7.9 ± 6.6 | 7.6 ± 6.8 | 0.562 |
| Discharge NIHSS | 10.4 ± 10.6 | 3.6 ± 5.7 | <0.001 | 10.4 ± 10.5 | 4.8 ± 6.5 | <0.001 |
| TOAST | 0.167 | 76 (23.4%) | 0.169 | 0.619 | 76 (23.4%) | 0.169 |
| Cardioembolism | 52 (19.8%) | 221 (20.1%) | 0.418 | 52 (19.9%) | 111 (21.3%) | 0.418 |
| Atherosclerosis | 88 (33.6%) | 328 (29.8%) | 0.877 | 88 (33.7%) | 163 (31.2%) | 0.877 |
| Small artery disease | 64 (24.4%) | 235 (21.4%) | 0.017 | 64 (24.5%) | 102 (19.5%) | 0.017 |
| Others | 58 (22.1%) | 314 (28.6%) | 0.012 | 57 (21.8%) | 146 (28.0%) | 0.012 |
| Fasting glucose (mg/dL) | 190.9 ± 84.1 | 184.0 ± 85.5 | 0.238 | 190.7 ± 84.2 | 189.5 ± 87.8 | 0.852 |
| Glycated hemoglobin (%) | 7.5 ± 1.7 | 7.3 ± 1.5 | 0.119 | 7.5 ± 1.7 | 7.4 ± 1.6 | 0.392 |
| Urine protein positivity | 59 (35.1%) | 143 (21.2%) | <0.001 | 58 (34.7%) | 76 (23.4%) | 0.007 |
| Fibrinogen (mg/dL) | 392.9 ± 204.2 | 359.0 ± 119.1 | 0.012 | 392.8 ± 204.6 | 361.1 ± 123.1 | 0.009 |
| ESR (mm) | 22.0 ± 20.5 | 21.2 ± 20.1 | 0.547 | 22.0 ± 20.5 | 21.3 ± 18.9 | 0.643 |
| CRP (mg/dL) | 0.9 ± 2.3 | 0.9 ± 2.8 | 0.931 | 0.9 ± 2.3 | 1.1 ± 3.2 | 0.528 |
| BMI | 24.2 ± 3.3 | 24.5 ± 3.2 | 0.317 | 24.2 ± 3.3 | 24.5 ± 3.2 | 0.317 |
| Metabolic syndrome | 149 (56.9%) | 609 (55.5%) | 0.681 | 149 (57.1%) | 305 (58.4%) | 0.720 |
| Lipid panel | | | | | | |
| T.chol (mg/dL) | 179.6 ± 43.2 | 181.7 ± 69.0 | 0.629 | 179.3 ± 43.0 | 182.2 ± 47.4 | 0.396 |
| LDL (mg/dL) | 106.3 ± 37.7 | 106.1 ± 37.4 | 0.919 | 106.0 ± 37.4 | 107.5 ± 38.1 | 0.604 |
| HDL (mg/dL) | 43.7 ± 11.7 | 43.9 ± 15.0 | 0.825 | 43.7 ± 11.7 | 44.0 ± 12.1 | 0.775 |
| TG (mg/dL) | 158.6 ± 113.5 | 163.4 ± 133.4 | 0.600 | 158.7 ± 113.7 | 165.6 ± 153.3 | 0.521 |

END early neurological deterioration, NIHSS National Institutes of Health Stroke Scale, TOAST trial of Org 10,172 in acute stroke treatment, ESR erythrocyte sedimentation rate, CRP c-reactive protein, BMI body mass index, T.chol total cholesterol, LDL low density lipoprotein, HDL high density lipoprotein, TG triglyceride

a Age, sex, initial NIHSS and TOAST were adjusted
Table 4 A logistic regression model for END after propensity score matching* in patients with diabetes mellitus admitted within 72 h of acute ischemic stroke

|                          | Odds ratio (95% confidence interval) | P     |
|--------------------------|-------------------------------------|-------|
| Age                      | 1.01 (0.99–1.03)                    | 0.397 |
| Male sex                 | 1.22 (0.80–1.87)                    | 0.352 |
| Hypertension             | 1.01 (0.584–1.74)                   | 0.982 |
| Initial NIHSS            | 1.01 (0.98–1.05)                    | 0.434 |
| TOAST                    |                                     | 0.098 |
| Cardioembolism           | Reference                            |       |
| Atherosclerosis          | 1.24 (0.71–2.16)                    | 0.445 |
| Small artery disease     | 2.01 (1.00–4.02)                    | 0.049 |
| Others                   | 0.95 (0.51–1.75)                    | 0.858 |
| Positive urine proteins  | 1.40 (0.90–2.17)                    | 0.140 |
| Fibrinogen per 300 mg/dL |                                     | 0.044 |
| 0–300 mg/dL              | Reference                            |       |
| 300–600 mg/dL            | 1.62 (1.04–2.53)                    | 0.034 |
| > 600 mg/dL              | 2.60 (1.02–6.51)                    | 0.046 |

END early neurological deterioration, NIHSS National Institutes of Health Stroke Scale, TOAST trial of Org 10,172 in acute stroke treatment

*Age, sex, initial NIHSS and TOAST were adjusted

scores were included, and the large patient numbers included may supplement such limitations. We hope to address these issues in later prospective studies.

Conclusion
In conclusion, hyperfibrinogenemia at admission in patients with acute ischemic stroke and DM is independently associated with END. This finding suggests that an elevated fibrinogen level is a marker of a prothrombotic or antiplatelet-resistant condition related to DM that could affect the patient’s prognosis. On the other hand, these results also reveal a category of patients wherein fibrin-depleting therapy could be significantly more effective.

Additional files

Additional file 1: Figure S1. A dot plot of standardized mean differences before and after propensity score matching in (A) DM population and (B) non-DM population. (TIFF 261 kb)

Additional file 2: Table S1. Comparison before and after propensity score matching in patients with acute ischemic stroke admitted within 72 h, but without diabetes. Table S2. A logistic regression model for END after propensity score matching in patients without diabetes mellitus admitted within 72 h of acute ischemic stroke. (DOCX 25 kb)

Abbreviations
CAD: Coronary arterial disease; CRP: C-reactive protein; DM: Diabetes mellitus; END: Early neurological deterioration; ESR: Erythrocyte sedimentation rate; FDP: Fibrin degradation products; HbA1c: Glycated hemoglobin; NIHSS: National Institute of Health Stroke Scale; TOAST: Trial of Org 10,172 in acute stroke treatment

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due for they are personal data, but are available from the corresponding author on reasonable request.

Authors’ contributions
JSL contributed to analysis and interpretation of data, preparation and review of the manuscript. JMH contributed to patient data acquisition and review of the manuscript. SEL contributed to patient data acquisition of the manuscript. DRK contributed to statistical analysis of the data. BO contributed to analysis and interpretation of data and review of the manuscript. AMD contributed to analysis and interpretation of data and review of the manuscript. JSL contributed to analysis and interpretation of data, preparation and review of the manuscript. All the authors have read and approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
As this was a retrospective study, consent for publication was waived.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Ajou University Hospital. As this was a retrospective study, consent to participate was waived.

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