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RESEARCH ARTICLE

Effects of PCSK9 Inhibitors on Early Neurologic Deterioration in Patients with Acute Non-Cardioembolism without Hemorrhagic Transformation After Intravenous Thrombolysis

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Abstract: ***Background*:** END (Early Neurologic Deterioration) significantly elevates the risk of morbidity and mortality. While numerous studies have investigated END following hemorrhagic transformation post-thrombolysis in acute cerebral infarction research on END without hemorrhagic transformations in patients with acute cerebral infarction due to non-cardiogenic embolism remains scarce.

***Aim*::** This study aimed to elucidate the impact of PCSK9 inhibitors on early neurological deterioration (END) in patients with acute non-cardioembolism cerebral infarction without hemorrhagic transformation post-intravenous thrombolysis. Additionally it aimed to identify risk factors associated with END in patients suffering from this type of stroke.

***Objective*::** The objective of this study is to investigate the effect of PCSK9 inhibitors on early neurologic deterioration (END) in patients with acute non-cardiogenic cerebral infarction without hemorrhagic transformation after intravenous thrombolysis and identify associated risk factors for END in this patient population.

***Methods*:** In this retrospective case-control study the data of consecutive patients who underwent intravenous thrombolysis after AIS (acute ischemic stroke) without hemorrhagic transformation during hospitalization at the Stroke Center of The Fifth Affiliated Hospital of Sun Yat-sen University between January 2018 to February 2023 were retrieved and assessed. An increase of ≥2 in the National Institutes of Health Stroke Scale (NIHSS) within 7 days after admission was defined as END.

***Results*:** This study included 250 patients (56 males 22.4%) they were 63.344±12.901 years old. There were 41 patients in the END group and 209 in the non-END group. The usage rate of PCSK9 inhibitors was significantly different between the END group and non-END group (29.268% *vs* 58.852% $P<0.001$). The White blood cell count (WBC) and homocysteine levels showed a significant difference between the two groups (all $P<0.05$). Patients not using PCSK9 inhibitors (OR=0.282 95%CI: 0.127-0.593) and white blood cell count (OR=1.197, 95%CI: 1.085-1.325) were independently associated with END. Receiver-operating characteristic curve analysis suggested that the sensitivity specificity and area under the curve for PCSK9 inhibitors used for END were 88.9%, 80.7% and 0.648 respectively.

***Conclusion*:** The use of PCSK9 inhibitors can reduce the incidence of early neurological deterioration in patients with acute non-cardioembolism and non-hemorrhagic transformation after intravenous thrombolysis.

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1. INTRODUCTION

Acute ischemic stroke constitutes a principal cause of mortality and morbidity globally [1]. Current therapeutic strategies are primarily limited to intravenous thrombolysis and endovascular treatments in the initial stages of stroke management [2]. However, the applicability of reperfusion therapy is constrained by a stringent temporal window, resulting in less than 10% of patients receiving such treatment [3]. Early neurological deterioration (END), a significant complication of stroke, is characterized by an increase in the National Institutes of Health Stroke Scale (NIHSS) score of more than 2 within 72 hours from the initial NIHSS assessment, although definitions vary [4, 5]. Despite its relatively low incidence, END significantly elevates the risk of morbidity and mortality. While numerous studies have investigated END following hemorrhagic transformation post-thrombolysis in acute cerebral infarction, research on END without hemorrhagic transformations in patients with acute cerebral infarction due to non-cardiogenic embolism remains scarce [6]. Hence, this study aimed to investigate the effect of PCSK9 inhibitors on END in patients with acute non-cardiogenic cerebral infarction without hemorrhagic transformation after intravenous thrombolysis and sought to identify risk factors for END in this population.

2. METHOD

2.1. Patients

This study included 250 patients (56 males, 22.4%), they were 63.344 ± 12.901 years old. There were 41 patients in the END group and 209 in the non-END group. The patients who experienced END during hospitalization were grouped as the END group; otherwise, they were grouped as the non-END group. END was defined as an NIHSS score increase of >2 within 7 days after admission [5]. Inclusion criteria included adults over 18 years of age. They presented symptoms of AIS within 72 hours of admission. AIS was confirmed by computed tomography (CT) scan or magnetic resonance imaging (MRI). They received intravenous thrombolytic therapy without hemorrhagic transformation during hospitalization. Exclusion criteria were patients with a history of psychiatric disorders, conditions impeding NIHSS assessment, traumatic brain injury, or cases that died before assessment.

This study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (K557). The requirement for individual consent was waived by the committee owing to the retrospective nature of the study. All procedures performed in this study involving human participants were in accordance with the ethical standards of The Fifth Affiliated Hospital of Sun Yat-Sen University committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

2.2. The Study Design

In this retrospective case-control study, the data of consecutive patients who underwent intravenous thrombolysis after AIS (acute ischemic stroke) without hemorrhagic transformation during hospitalization at the Stroke Center of The Fifth Affiliated Hospital of Sun Yat-sen University between January 2018 to February 2023 were retrieved and assessed. All cases were diagnosed and managed based on a standardized protocol and care pathway in adherence to guidelines. The patients were categorized into two groups based on the presence or absence of END. Clinical data, medication usage, and laboratory results were collected and compared between the two groups. Significant variables that demonstrated clinical relevance and significant differences between the END and non-END groups were identified and subsequently included in a multivariate logistic regression analysis. Receiver Operating Characteristic (ROC) curve analysis was used to assess the predictive accuracy of the identified risk factors in determining END.

In the present research, demographic, clinical, and laboratory data were extracted from the hospital records of stroke patients. Information about age, sex, smoking status, alcohol use, medical history (hypertension, diabetes, hyperlipidemia, previous transient ischemic attack, ischemic stroke, ischemic heart disease, atrial fibrillation, heart failure,), and various laboratory measures (white blood cells (WBC), platelets (PLT), fibrinogen, creatinine, uric acid, blood pressures, platelets, blood glucose, glycated hemoglobin (HbA1c), lipids, homocysteine, total protein, and albumin) were gathered for the analysis. The use of PCSK9 inhibitors after admission was collected. The classification of stroke was carried out according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [7], affected cerebral areas, and National Institutes of Health Stroke Scale (NIHSS) score upon admission. The impact of stroke on cerebral circulation was categorized as anterior, posterior, or both. Stroke type was grouped as large-artery atherosclerosis, cardioembolism, small-artery occlusion, stroke of another determined etiology, or stroke of undetermined etiology. Dyslipidemia was established by lipid profile, such as cholesterol or triglyceride levels, or by the use of medications, such as statins. Smoking was defined as consistent smoking if it lasted for the last six months [8].

Neuroimaging data were comprehensively assessed by both a radiologist and a neurologist, and the results were confirmed through mutual consensus. The recorded neuroimaging information comprised details about the affected cerebral circulation, location of infarction, and stroke subtype. The impact of stroke on cerebral circulation was categorized as anterior, posterior, or affecting both. The type of stroke was categorized as large-artery atherosclerosis, cardioembolism, small-artery occlusion, stroke of another determined etiology, or stroke of undetermined etiology, following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification criteria [7]. The criteria for carotid unstable plaque with ultrasound include the following features: A plaque is defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-media thickness (IMT) value or demonstrates a thickness of 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface [9].

2.3. Statistical Analysis

Statistical analyses were performed with SPSS (IBM Corp, Armonk, NY, USA) and the R programming language (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous data were expressed as mean ± SD or median (interquartile range) and categorical data as frequencies (%) depending on their distribution. Group comparisons utilized t-tests, Mann-Whitney U-tests, chi-square, or Fisher's exact tests as appropriate. Factors associated with END were identified by multivariable logistic regression, which included significant univariate variables. The model provided adjusted odds ratios with 95% confidence intervals. The area under the curve (AUC) was calculated as a measurement of the accuracy of the test. $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Characteristics of the Patients

This study included 250 patients (56 males, 22.4%). They were 63.344 ± 12.901 years old. There were 41 patients in the END group and 209 in the non-END group. The mean age of patients with END was 63.537 ± 12.529 years, while the mean age of patients with non-END was 63.306 ± 12.972 years. The baseline clinical characteristics of patients with and without early neurological deterioration (END) are shown in Table **1**. There were no significant differences in demographic data, such as age, sex, smoking, and drinking status, between the two groups.

Regarding medical history, the prevalence of hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, atrial fibrillation, history of heart failure, and history of stroke/TIA were comparable between patients with and without END. Systolic and diastolic blood pressure, as well as NIHSS scores at admission, were also similar in both groups. DNT and ONT showed no significant differences. TOAST classification of stroke subtypes was comparable, and the majority of patients had large artery atherosclerosis in both groups. The proportion of patients with unstable carotid plaque was also not significantly different.

In summary, baseline clinical characteristics were well balanced between patients with or without developing END. However, the usage rate of PCSK9 inhibitors was significantly different between the END group and non-END group

Table 1. Comparison of baseline clinical characteristics between the END and Non-END groups.

Clinical Characteristic	(n=250)	Non-END (n=209)	END (n=41)	t/z/χ2	*p* Value
Male, n (%)	56 (22.400)	48 (22.967)	8 (19.512)	0.235	0.628
Age, mean (±SD)	63.344 ± 12.901	63.306 ± 12.972	63.537 ± 12.529	-0.104	0.917
Smoker, n (%)	116 (46.400)	92 (44.019)	24 (58.537)	2.905	0.088
Alcohol Use, n(%)	51 (20.400)	39 (18.660)	12 (29.268)	2.375	0.123
Hypertension, n(%)	169 (67.600)	142 (67.943)	27 (65.854)	0.068	0.794
Diabetes Mellitus, n(%)	74 (29.600)	57 (27.273)	17 (41.463)	3.312	0.069
Hyperlipidemia, n(%)	89 (35.600)	73 (34.928)	16 (39.024)	0.251	0.616
Ischemic Heart Disease, n(%)	44 (17.600)	36 (17.225)	8 (19.512)	0.124	0.725
Atrial Fibrillation, n(%)	26 (10.400)	23 (11.005)	3 (7.317)	0.500	0.479
History of Heart Failure, n(%)	7 (2.800)	4 (1.914)	3 (7.317)	3.677	0.055
History of Stroke or TIA, n(%)	81 (32.400)	68 (32.536)	13 (31.707)	0.011	0.917
SBP at Admission (mmHg), Median [IQR]	162.000 [145.000, 176.000]	159.000 [145.000, 175.000]	167.000 [142.000, 179.000]	-1.182	0.238
DBP at Admission (mmHg), Median [IQR]	88.000 [80.000, 98.000]	89.000 [80.000, 98.000]	84.000 [78.000, 98.000]	1.492	0.136
NIHSS at Admission, Median [IQR]	3.000 [1.000, 7.000]	3.000 [1.000, 6.000]	3.000 [1.000, 7.000]	-0.518	0.601
DNT (min), Median [IQR]	38.000 [29.000, 52.000]	37.000 [29.000, 52.000]	39.000 [26.000, 53.000]	0.136	0.893
ONT (min), Median [IQR]	160.000 [110.000, 210.000]	160.000 [108.000, 208.000]	160.000 [115.000, 211.000]	-0.598	0.551
TOAST Subtype, n(%)	-	-	-	3.843	0.279
LAA	108 (43.200)	85 (40.670)	23 (56.098)	-	-
SOE	32 (12.800)	27 (12.919)	5 (12.195)	-	-
SAA	105 (42.000)	93 (44.498)	12 (29.268)	-	-
SUE	5 (2.000)	4 (1.914)	1 (2.439)	-	-
Carotid Unstable Plaque, n(%)	162 (64.800)	136 (65.072)	26 (63.415)	0.041	0.839
Cerebral Circulation Affected by Stroke, n(%)	-	-	-	0.733	0.693
Anterior Circulation	162 (64.800)	135 (64.593)	27 (65.854)	-	-
Posterior Circulation	53 (21.200)	46 (22.010)	7 (17.073)	-	-
Both	35 (14.000)	28 (13.397)	7 (17.073)	-	-
PCSK9 Inhibitor, n (%)	135 (54.000)	123 (58.852)	12 (29.268)	12.076	<0.001*

Note: * $p < 0.05$; **Abbreviations:** END: early neurological deterioration; SD: standard deviation; TIA: transient ischemic attack; SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale. DNT: door to needle time; ONT: onset to needle time.

Table 2. Comparison of laboratory tests between the END and Non-END groups.

Clinical Characteristic	(n=250)	Non-END (n=209)	END (n=41)	t/z/χ2	*p* Value
WBC (10^9/L), Median [IQR]	7.640 [6.220, 10.170]	7.460 [6.170, 9.600]	9.960 [6.890, 13.030]	-2.728	0.006*
PLT (10^9/L), Median [IQR]	217.000 [180.000, 266.000]	216.000 [179.000, 261.000]	224.000 [184.000, 274.000]	-1.124	0.261
RBC (10^12/L), Median [IQR]	4.630 [4.170, 5.030]	4.630 [4.210, 5.050]	4.590 [4.110, 4.870]	1.043	0.298
Hb (g/L), median [IQR]	138.000 [125.000, 150.000]	138.000 [125.000, 151.000]	138.000 [125.000, 149.000]	0.781	0.436
FBG (mmol/L), median [IQR]	7.100 [6.100, 9.700]	7.040 [6.020, 9.600]	7.700 [6.190, 10.200]	-0.634	0.527
Cr (μmol/L), median [IQR]	77.000 [66.000, 92.700]	77.000 [66.000, 92.000]	79.800 [66.000, 97.000]	-0.931	0.353
TP (g/L), median [IQR]	65.200 [61.600, 69.500]	65.200 [61.600, 69.200]	66.000 [61.000, 70.800]	-0.875	0.382
ALB (g/L), Median [IQR]	40.100 [38.100, 42.600]	40.100 [38.100, 42.500]	41.200 [37.500, 42.700]	-0.443	0.659
Fibrinogen (g/L), Median [IQR]	3.180 [2.680, 3.650]	3.190 [2.690, 3.650]	3.000 [2.530, 3.500]	0.925	0.356
D-dimer (mg/L), Median [IQR]	0.600 [0.330, 1.200]	0.610 [0.350, 1.400]	0.500 [0.250, 1.100]	0.852	0.395
Homocysteine (μmol/L), Median [IQR]	13.380 [10.900, 16.820]	12.980 [10.820, 16.560]	15.450 [13.640, 18.730]	-2.839	0.005*
HbA1c (%), Median [IQR]	5.900 [5.500, 6.600]	5.900 [5.500, 6.500]	6.000 [5.400, 7.200]	-0.034	0.974
TG (mmol/L), Median [IQR]	1.370 [0.980, 1.970]	1.300 [0.980, 1.920]	1.670 [1.180, 2.090]	-1.489	0.137
T-CH (mmol/L), Median [IQR]	4.400 [3.560, 5.230]	4.390 [3.640, 5.250]	4.510 [2.640, 5.060]	1.267	0.205
LDL-C (mmol/L), Median [IQR]	2.760 [2.070, 3.400]	2.760 [2.060, 3.380]	2.930 [2.100, 3.410]	0.021	0.984

Note: * $p < 0.05$. **Abbreviations:** END: early neurological deterioration; SBP: systolic blood pressure; DBP: diastolic blood pressure; TIA: transient ischemic attack. NIHSS: National Institutes of Health Stroke Scale. WBC: White blood cell count; PLT: platelet count; RBC: red blood cell; Hb: hemoglobin; Cr: Creatinine; TP: total protein; ALB: albumin; FBG: fastting blood glucose; GHbA1c%: glycated hemoglobin; TG: triglyceride; T-CH: total cholesterol; LDL-C: low density lipoprotein cholesterin; IQR: interquartile range; SD: standard deviation.

(29.268% *vs* 58.852%, $p < 0.001$). This implies that patients who used PCSK9 inhibitors may have a lower risk of developing END compared to those without PCSK9 inhibitors.

3.2. Comparison of Laboratory Results between END Group and Non-END Group

White blood cell count (WBC) showed a significant difference between the two groups (p =0.006). The median WBC value of the END group was 9.960×10^9/L, higher than the Non-END group's 7.460×10^9/L. Homocysteine levels also exhibited a significant difference between the groups (p =0.005). The END group's median homocysteine level was 15.450 μmol/L, higher than the Non-END group's 12.980 μmol/L. Other laboratory results like FBG, PLT, RBC, Hb, Cr, TP, and ALB showed no significant differences between the two groups (all p <0.05). Additionally, the fibrinogen, D-dimer, HbA1c, TG, total cholesterol, and LDL-C did not differ significantly between the END and non-END groups (all p <0.05). Hence, the results in Table 2 demonstrate that the END group had significantly higher median levels of white blood cell count and homocysteine compared to the non-END group. The differences in these two markers may be related to the occurrence of END. Other laboratory results did not vary significantly between the groups (Table **2** and Fig. **1**).

3.3. Regression Analysis of END and Clinical Factors

After adjusting for potential confounders, logistic regression analysis was performed to identify independent predictors of END, and the results are shown in Table **3** and Fig. (**2**). The usage of PCSK9 inhibitors was significantly associated with non-END, with a p-value of 0.001. Patients who used PCSK9 inhibitors had an odds ratio of 0.282, indicating their odds of developing END were lower by a factor of 0.282 compared to patients who did not use PCSK9 inhibitors. White blood cell count (WBC) was also significantly associated with END, with a p <0.001. The odds ratio for WBC was 1.197. This means that for each unit increase in WBC level, the odds of END increased by 19.7%. No other factors analyzed in the regression model showed a significant association with END. National Institutes of Health Stroke Scale (NIHSS) at admission, door-to-needle time, low-density lipoprotein cholesterol (LDL-C) levels, and unstable plaque presence all had non-significant p-values. The regression analysis identified two factors that were significantly associated with END not using PCSK9 inhibitors, which was associated with lower odds by a factor of 0.282 and higher WBC levels, which increased the odds of END by 19.7% for each unit increase.

3.4. The Receiver Operating Characteristic Curve of Factors in Distinguishing END

The use of PCSK9 inhibitors showed the largest area under the curve (AUC) of 0.648. At a cutoff value of 1.0, it demonstrated a sensitivity of 88.9% and specificity of 80.7%, yielding a Youden index of 0.296. This suggests that PCSK9 inhibitor use has moderate discriminative ability for END. White blood cell count (WBC) produced the second-highest AUC of 0.635. At a cutoff of 11.63×10^9/L, it achieved a sensitivity of 41.5% and specificity of 89%, with a Youden index of 0.305. Thus, WBC also showed a moderate predictive performance. Homocysteine levels generated an AUC of 0.64. With a cutoff of 14.0 μmol/L, it obtained a sensitivity of 70.7% and specificity of 63.6% for a Youden index of 0.344. Homocysteine, therefore, similarly exhibited a moderate predictive accuracy (Table **4** and Fig. **3**). Of note, PCSK9 inhibitors had the highest AUC and, thus, best overall predictive power. This suggests that the use of PCSK9 inhibitors is a valuable indicator for predicting non-END.

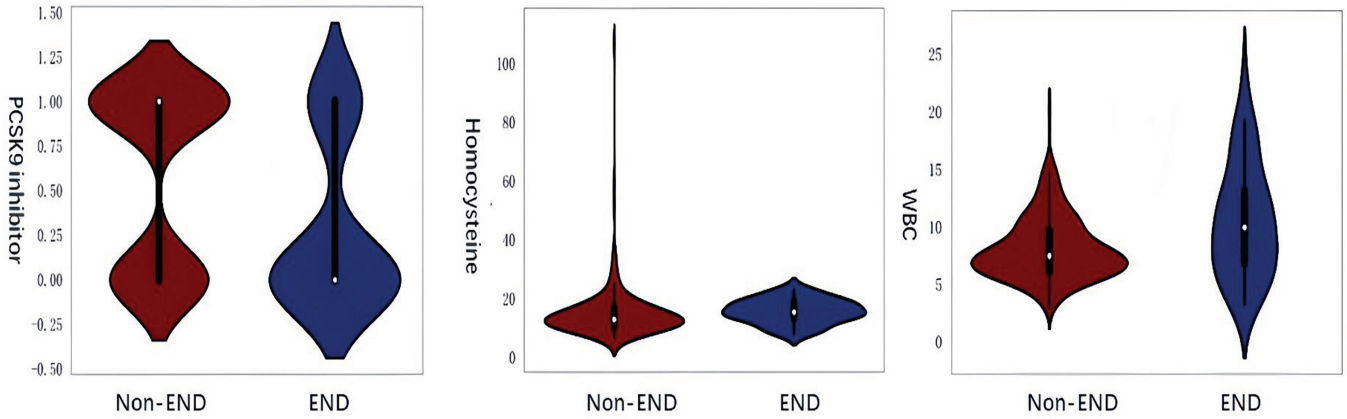

Fig. (1). Comparison of PCSK9 inhibitors, homocysteine and leukocytes between END group and non-end group. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

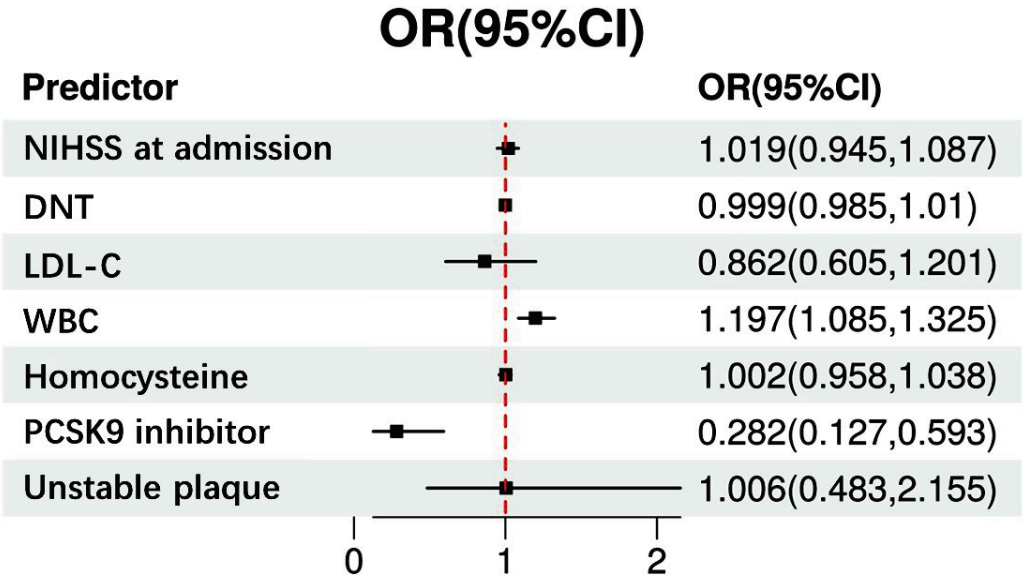

Fig. (2). Forest plot related to END. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 3. Logistic regression analysis of factors associated with END.

Predictor	Estimate	SE	Z	*p*	Odds Ratio	Lower	Upper
(Intercept)	-2.369	0.889	-2.664	0.008	0.094	0.016	0.523
NIHSS at admission	0.019	0.035	0.532	0.595	1.019	0.945	1.087
DNT	-0.001	0.007	-0.203	0.839	0.999	0.985	1.01
LDL-C	-0.149	0.174	-0.855	0.393	0.862	0.605	1.201
WBC	0.18	0.05	3.564	0.0	1.197	1.085	1.325
Homocysteine	0.002	0.019	0.109	0.913	1.002	0.958	1.038
PCSK9 inhibitor	-1.265	0.39	-3.243	0.001	0.282	0.127	0.593
Unstable plaque	0.006	0.379	0.016	0.987	1.006	0.483	2.155

Table 4. The receiver operating characteristic curve of factors in distinguishing END.

Variable	AUC	Sensitivity	Specificity	Youden Index	Cutoff
PCSK9 inhibitor	0.648	0.889	0.807	0.296	1.0

Variable	AUC	Sensitivity	Specificity	Youden Index	Cutoff
WBC	0.635	0.415	0.89	0.305	11.63
Homocysteine	0.64	0.707	0.636	0.344	14.0

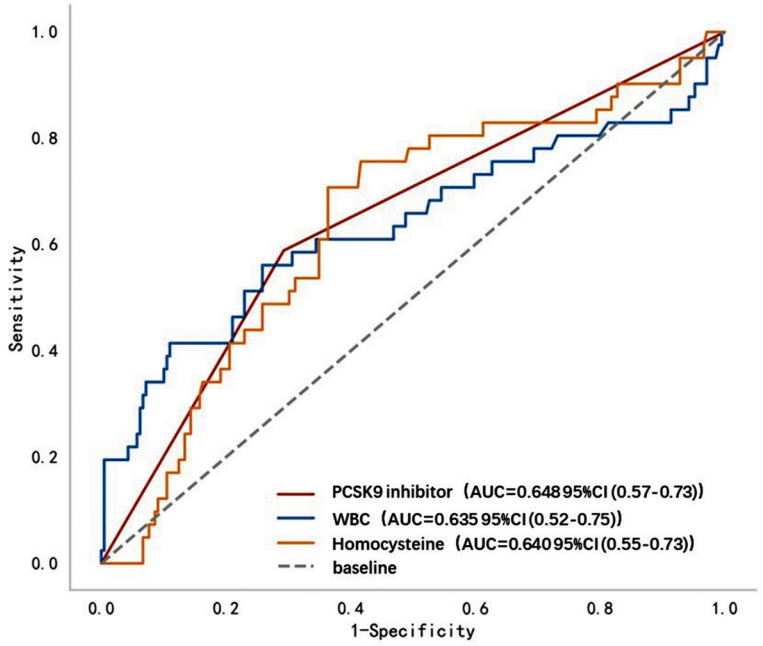

Fig. (3). ROC cure of END. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

4. DISCUSSION

This study aimed to elucidate the impact of PCSK9 inhibitors on early neurological deterioration (END) in patients with acute non-cardiogenic cerebral infarction without hemorrhagic transformation after intravenous thrombolysis. Additionally, it identified risk factors associated with END in patients suffering from different types of stroke. The absence of PCSK9 inhibitor treatment, increased white blood cell counts, and elevated homocysteine levels were found to be significantly associated with a higher incidence of END. These findings may facilitate the early recognition of patients at elevated risk, enabling targeted management and intervention strategies.

Stroke ranks as a major global health challenge, being the second highest cause of death worldwide and substantially contributing to disability. It accounts for about 11% of all deaths, with pronounced geographical and demographic disparities in its prevalence [10]. Notably, stroke incidence is markedly higher in low- to middle-income countries than in high-income ones, with the age-standardized rates in less wealthy regions being almost twice as high. This discrepancy underscores the influence of socioeconomic factors on stroke risk [1].

In China, the stroke burden is exacerbated by notable regional differences, where rural areas report higher stroke rates than urban counterparts. Such disparities are linked to variations in healthcare accessibility, risk factor prevalence, and levels of health literacy [10]. In response, the Chinese government has launched targeted public health initiatives aimed at reducing stroke risk through lifestyle changes, enhancing public awareness, and expanding access to timely stroke treatment [11].

Ischemic stroke, marked by the disruption of blood flow to the brain, urgently requires medical attention to reduce brain damage and improve patient outcomes. The key to acute ischemic stroke management is reperfusion therapy, which includes intravenous thrombolysis using recombinant tissue plasminogen activator (rtPA) and mechanical thrombectomy. These treatments are aimed to reestablish blood flow to the ischemic brain area. However, the efficacy of acute stroke interventions is limited by the short window for treatment, the potential for hemorrhagic transformation, and the diverse causes of stroke. In the RESCUE BT2 study, which included diverse patient groups with recent stroke onset or worsening stroke symptoms and non-occluded large to medium cerebral vessels, intravenous tirofiban was linked to a higher probability of an excellent outcome compared to low-dose aspirin. While occurrences of intracranial hemorrhages were infrequent, they were marginally more common with tirofiban [12].

Complications following a stroke play a significant role in increasing both morbidity and mortality, with stroke-related deaths reaching an estimated 5.5 million globally in 2016 [13]. Early neurological deterioration (END), which is a worsening of neurological function in the initial hours or days after a stroke, occurs in about 10-20% of patients [14].

END is linked to worse functional outcomes, a higher likelihood of disability, and increased mortality. Strategies to prevent END include careful management of hemodynamic stability, blood glucose control, and close monitoring for any signs of worsening conditions. The variability of END highlights the necessity for personalized care and underscores the importance of ongoing research to identify high-risk patients and devise specific interventions [15].

The pathophysiology of early neurological deterioration (END) in ischemic stroke is intricate and remains incompletely understood. END, a complex event, can arise from several pathophysiological processes, such as the progression of the initial infarct due to continued ischemia, unstable plaque, cerebral edema causing elevated intracranial pressure, hemorrhagic transformation within the infarct zone, and further embolic episodes [16, 17]. Additionally, post-ischemic inflammatory responses, which can amplify tissue damage, significantly contribute to END [18].

Despite considerable research efforts, substantial gaps remain in our understanding of the specific triggers and mechanisms underlying END. The diversity in stroke pathology, further complicated by the influence of comorbidities and pre-existing conditions, makes it challenging to identify consistent predictors or therapeutic targets for END. Moreover, the variation in the timing of neurological decline across patients adds complexity to establishing optimal periods for intervention [17].

Current research challenges include swiftly and precisely identifying patients at elevated risk for END, developing therapeutic strategies to prevent or mitigate END, and establishing standardized criteria for defining and evaluating neurological deterioration. Thus, managing END in ischemic stroke continues to be a formidable challenge in stroke care, emphasizing the critical need for ongoing research to decode its underlying processes and forge effective prevention and treatment strategies. Currently, a lot of studies have explored the early neurological deterioration caused by hemorrhage transformation after thrombolysis in acute cerebral infarction, but there are few studies on the early neurological deterioration related to non-hemorrhage transformation after thrombolysis in patients with acute cerebral infarction caused by non-cardiogenic embolism.

Our study showed that the use of PCSK9 inhibitors can reduce the occurrence of early neurological deterioration in patients with acute non-cardiogenic cerebral infarction without hemorrhagic transformation after intravenous thrombolysis. PCSK9 inhibitors reduce low-density lipoprotein cholesterol (LDL-C) levels by inhibiting PCSK9-mediated LDL receptor degradation [19]. Previous studies have demonstrated the neuroprotective effects of PCSK9 inhibitors. One potential mechanism is that lowering LDL-C with PCSK9 inhibitors mitigates oxidative stress and inflammation triggered by ischemia-reperfusion injury [20]. Larger randomized trials are still needed to validate the protective effects of PCSK9 inhibitors against END. In animal models of ischemic stroke, PCSK9 inhibition reduced infarct volume and improved neurological function, potentially *via* anti-inflammatory and antioxidant mechanisms [21]. Clinically, PCSK9 inhibitor treatment prior to acute ischemic stroke was linked to smaller infarct size and better functional outcomes [22]. Recent clinical trials have highlighted the efficacy of PCSK9 inhibitors in reducing the risk of cerebrovascular events. By lowering LDL cholesterol levels, these inhibitors contribute to a decreased incidence of stroke and other related complications [23]. Vulnerable plaques are a critical factor in the progression of stroke. PCSK9 inhibitors have been shown to effectively stabilize these plaques, thereby preventing their rupture and the subsequent risk of stroke [24]. The anti-inflammatory properties of PCSK9 inhibitors play a significant role in their protective effects against stroke progression. These agents have been found to reduce markers of inflammation and slow the progression of atherosclerotic plaques [25]. Moreover, PCSK9 inhibitors may enhance the efficacy of thrombolytic therapy in acute ischemic stroke patients. By improving endothelial function, reducing inflammation, and stabilizing plaques, PCSK9 inhibitors can work synergistically with thrombolytic agents to prevent END [6]. Evidence indicates that PCSK9 inhibitors could impact platelet function and coagulation. Studies on PCSK9 knockout mice have demonstrated a decrease in venous and arterial thrombosis, alongside diminished platelet activation following arterial injury [26]. Plasma PCSK9 directly augments platelet activation and *in vivo* thrombosis by interacting with platelet CD36, subsequently activating downstream signaling pathways. The administration of PCSK9 inhibitors or aspirin mitigates these PCSK9-mediated effects, underscoring the utility of aspirin alongside PCSK9 inhibitors in patients with elevated plasma PCSK9 levels to avert thrombotic complications. PCSK9 binds to platelet CD36 and thus activates Src kinase and MAPK (mitogen-activated protein kinase)-extracellular signal-regulated kinase 5 and c-Jun N-terminal kinase, increases the generation of reactive oxygen species, and activates the p38MAPK/cytosolic phospholipase A2/cyclooxygenase-1/thromboxane A2 signaling pathways downstream of CD36 to enhance platelet activation [27]. Our study underscores the potential of PCSK9 inhibitors in improving outcomes in patients with acute non-cardiogenic cerebral infarction who are not undergoing hemorrhagic transformation after intravenous thrombolysis. Further research is warranted to fully explore their therapeutic potential and integrate them into stroke management protocols.

Elevated white blood cell count (WBC) on admission emerged as another independent predictor of END (Table **3**). Leukocytosis is a marker of systemic inflammation, which plays a key role in secondary brain injury after stroke [28]. The anti-inflammatory properties of PCSK9 inhibitors may play a crucial role in reducing the risk of END in patients undergoing intravenous thrombolysis. Inflammatory cytokines released by activated leukocytes can disrupt the blood-brain barrier, exacerbate edema, and induce neuronal death [29]. Animal data corroborate that leukocyte infiltration into the ischemic brain worsens tissue damage and functional recovery [30]. Elevated white blood cell count levels suggest an inflammatory response. Elevated white blood cell counts

have been associated with a higher risk of neurological deterioration, underscoring the importance of managing inflammatory responses to improve patient outcomes [31]. PCSK9 inhibitors, known for their lipid-lowering properties, have also been shown to exert anti-inflammatory effects. These effects may contribute to their potential in reducing the incidence of END by mitigating the inflammatory response associated with acute ischemic stroke [32]. By decreasing inflammation, these inhibitors could indirectly prevent the worsening of neurological function, offering a novel approach to stroke management [33]. The current study's finding of WBC as a predictor of END is consistent with prior studies [34, 35]. The correlation between elevated white blood cell counts and the risk of END emphasizes the importance of addressing inflammation in these patients. PCSK9 inhibitors offer a promising therapeutic approach to improve outcomes by mitigating inflammatory responses post-thrombolysis. Further research is needed to confirm these findings and explore the clinical implications of PCSK9 inhibitors in the management of acute ischemic stroke.

Higher homocysteine levels also showed a moderate ability to discriminate between patients who did or did not experience END per ROC analysis (Table **4** and Fig. **3**). Homocysteine is a risk factor for stroke, potentially promoting atherosclerosis, oxidative stress, and endothelial dysfunction [36, 37]. Elevated homocysteine has been tied to larger infarct sizes, worse recanalization with thrombolysis, and poorer functional recovery after stroke [38, 39]. The biological mechanisms linking homocysteine to END may involve enhanced oxidative damage, impaired blood-brain barrier integrity, and exacerbated inflammation [40, 41]. Clinical trials are investigating whether B vitamin supplementation, which lowers homocysteine, improves outcomes after acute ischemic stroke [42, 43]. Recent studies have suggested that PCSK9 inhibitors may have pleiotropic effects beyond their lipid-lowering properties, including anti-inflammatory and neuroprotective actions [44]. Homocysteine, a sulfur-containing amino acid, has been identified as an independent risk factor for cardiovascular and cerebrovascular diseases [45]. Elevated homocysteine levels have been associated with increased oxidative stress, endothelial dysfunction, and neuronal excitotoxicity [46]. In the context of AIS and IVT, high homocysteine levels have been linked to an increased risk of hemorrhagic transformation and END [47]. We hypothesize that PCSK9 inhibitors may attenuate END after IVT by synergistically modulating homocysteine levels. PCSK9 inhibitors have been shown to reduce homocysteine levels in patients with hyperlipidemia [48]. This effect may be mediated through the upregulation of the LDL receptor (LDLR) and the subsequent increased uptake of homocysteine-rich lipoproteins [38]. By lowering homocysteine levels, PCSK9 inhibitors may mitigate the deleterious effects of homocysteine on the neurovascular unit, thereby reducing the risk of END.

Furthermore, PCSK9 inhibitors may exert direct neuroprotective effects by reducing neuroinflammation and oxidative stress [49]. These mechanisms may work in concert with the homocysteine-lowering effects to provide comprehensive protection against END after IVT. Future prospective studies should explore whether targeting elevated homocysteine may help prevent neurological worsening early post-stroke.

This study had some limitations. Its observational design precludes determining causality. The sample size was modest, and the study was conducted at a single center. Thus, replication in larger multicenter cohorts is needed and additional biomarkers warrant exploration for their predictive value in END.

CONCLUSION

In conclusion, this study suggests that the use of PCSK9 inhibitors may help reduce the early neurologic deterioration associated with non-hemorrhagic transformation after intravenous thrombolysis in acute cerebral infarction caused by non-cardioembolism. Inflammation and homocysteine levels are associated with early neurological deterioration in patients with different types of cerebral infarction. Further elucidation of the roles of PCSK9 inhibitors, inflammation, and homocysteine in secondary brain injury could provide novel therapeutic targets to mitigate early neurological deterioration. Moreover, larger prospective validation of these findings could help optimize prognostication and management of acute stroke patients.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AIS	=	Acute Ischemic Stroke
AUC	=	Area Under the Curve
CT	=	Computed Tomography
MRI	=	Magnetic Resonance Imaging
PLT	=	Platelet
ROC	=	Receiver Operating Characteristic
WBC	=	White Blood Cell

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (Approval number K557).

HUMAN AND ANIMAL RIGHTS

All procedures performed in this study involving human participants were in accordance with the ethical standards of The Fifth Affiliated Hospital of Sun Yat-Sen University committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

CONSENT FOR PUBLICATION

The requirement for individual consent was waived by the committee owing to the retrospective nature of the study.

STANDARD OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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