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Research Article

Association between Red Blood Cell Distribution Width and Neutrophil-to-lymphocyte Ratio and the Incidence of Recurrent Ischemic Events in Patients with Transient Ischemic Attack

Surasak Komonchan, Sahaphum Taemeeyapradit and Saharat Aungsumart*

Department of Neurology, Neurological Institute of Thailand, Bangkok, Thailand

***Corresponding Author:** Saharat Aungusmart, Department of Neurology, Neurological Institute of Thailand, Bangkok, Thailand.

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Abstract

Background: Transient ischemic attack (TIA) is a predisposing factor for ischemic stroke. This study aimed to identify an alternative prognostic indicator for predicting ischemic events after TIA. Red blood cell distribution width (RDW) and neutrophil-to-lymphocyte ratio (NLR) have emerged as potential candidates.

Objective: This study aimed to determine the correlation between RDW and NLR and the risk of recurrent ischemic events in patients with TIA.

Methods: Patients hospitalized with a TIA diagnosis within 24 h from January 2015 to December 2022 were retrospectively analyzed for demographic and laboratory data. Recurrent ischemic events within 7 and 90 days were assessed by comparing RDW and NLR. Logistic regression was used to analyze the association between RDW and NLR and recurrent events.

Results: In total, 283 patients were included in this study. The RDW in patients with recurrent ischemic events within 7 days was 13.35, which was not significantly different from that in the non-ischemic group (13.7). NLRs were 2.03 and 2.24 for patients with TIA with and without recurrent events within 7 days, respectively. For the 90-day follow-up period, patients with TIA with recurrent ischemic events and those without ischemia in 90 days had RDWs of 13.55 and 13.7, respectively, which were not significantly different. The NLR in patients with TIA with recurrent ischemic events in 90 days was also not different from that of the non-ischemic group. The area under the receiver operating characteristic curve obtained from RDW or NLR did not demonstrate a correlation with recurrent ischemic stroke in patients with TIA at either 7 or 90 days.

Conclusions: RDW and NLR are not associated with the occurrence of recurrent ischemic events 7 and 90 days after TIA diagnosis.

Keywords: Transient Ischaemic Attack; Red Blood Cell Distribution Width; TIA; RDW; Neutrophil-to-lymphocyte Ratio; NLR

Abbreviations

CT: Computed Tomography; DWI: Diffusion-Weighted Imaging; IQR: Interquartile Range; MRI: Magnetic Resonance Imaging; NLR: Neutrophil-To-Lymphocyte Ratio; RDW: Red Blood Cell Distribution Width; ROC: Receiver Operating Characteristic; TIA: Transient Ischemic Attack

Introduction

Cerebrovascular disease poses a significant challenge to public health care in Thailand and worldwide, given its increased

mortality rates and substantial burden on disability-adjusted life years [1]. Various conditions, including noncommunicable diseases and atrial fibrillation, are risk factors for acute ischemic stroke. Moreover, individuals experiencing transient ischemic attack (TIA) are at a considerable risk of progressing to ischemic stroke [2].

Among the diverse risk stratification tools for ischemic stroke, the ABCD2 score is the most widely used in patients with TIA. Its widespread use is attributed to its feasibility and simplicity, particularly in emergency department settings. A higher ABCD2 score correlates with a higher risk of developing ischemic stroke compared with individuals with lower scores [3]. However, the ABCD2 score showed an unsatisfactory result in a large prospective study. This prospective cohort study found that with a cutoff point of > 5, only 31.6% sensitivity for stroke within 7 days was observed [4]. Therefore, novel biomarkers for predicting stroke in patients with TIA are crucial.

Several biomarkers associated with the pathophysiological changes in ischemic stroke have been studied as predictive tools for subsequent ischemic stroke in patients with TIA [5], particularly inflammatory biomarkers, such as red blood cell distribution width (RDW) and neutrophil-to-lymphocyte ratio (NLR). These two biomarkers are considered predictors of stroke in patients with TIA because they are routinely obtained from a simple complete blood count. Several studies have reported the use of either RDW or NLR as a good predictor of stroke in patients with TIA [5-11].

RDW is a measure of the variability in erythrocyte size. It is conventionally used to evaluate the cause of anemia. RDW has recently been considered a surrogate marker of inflammatory conditions, consistent with C-reactive protein [12]. Several studies have found an association between a high RDW and worsening outcomes in various diseases. In addition, in systemic lupus erythematosus, higher RDW values have been found in active patients than in inactive patients or controls [12]. According to a previous study, the RDW was higher in patients with inflammatory joint disease than in those with osteoarthritis [13]. Additionally, various studies have found an association between elevated RDW and poor prognosis in cardiovascular diseases, such as myocardial infarction, heart failure, angina, peripheral vascular disease, and cerebrovascular disease [14]. Higher RDW has also been found in patients with ischemic stroke compared with healthy individuals [6-8]. Meanwhile, a high level of RDW is also associated with National Institutes of Health Stroke Scale score and the severity of acute ischemic stroke [15,16].

Another crucial biomarker associated with poor prognosis in various diseases is the NLR [17]. In acute ischemic stroke, a high NLR is associated with stroke severity on admission and unfavorable outcomes [18], especially in patients with symptomatic intracranial atherosclerotic stenosis [19] and large vessel occlusion who receive endovascular therapy [20]. Few studies have explored the roles of RDW and NLR as prognostic markers in patients with TIA. One study showed that RDW higher than 13.95% could help predict acute ischemic stroke following a TIA in 7 days with acceptable sensitivity and specificity [10]. NLR is also valuable in predicting composite cardiovascular events in patients with TIA and minor stroke [9]. However, the variations in RDW and NLR are dependent on various factors not specific to inflammatory situations, such as nutritional status or underlying disease.

Despite the recognition of both RDW and NLR as robust predictors of acute ischemic stroke in patients with TIA in previous studies, it is imperative to acknowledge the influence of various RDW and NLR factors. Therefore, we aimed to evaluate whether RDW and NLR could effectively serve as predictors of acute ischemic stroke in patients with TIA.

Materials and Methods

Patients and study design

The authors declare that all supporting data originated from the Neurological Institute of Thailand. The study design adhered to a retrospective cohort approach within the Thai population, comprising 299 patients diagnosed with TIA and admitted to the inpatient department between January 2015 and December 2022.

The inclusion criteria were as follows: age of TIA onset of at least 18 years, a clinical diagnosis of TIA supported by transient neurological deficits lasting < 24 h, and non-contrast computed tomography (CT) or magnetic resonance imaging (MRI) results indicating no definite cerebral infarction, with patients visiting the hospital within 24 h. The exclusion criteria were incomplete medical records, insufficient laboratory results for complete blood

count, concurrent hematological diseases (excluding anemia), autoimmune diseases, ongoing infections, and corticosteroid use.

The baseline characteristics included sex; age of TIA onset; body mass index; history of hypertension, dyslipidemia, diabetes, and cardiac arrhythmia; previous cerebral infarction and coronary heart disease; and current antiplatelet/anticoagulant medications. Clinical data included the following manifestations: one-sided weakness, dysarthria, sensory symptoms, and episode duration (< 10 min, 11-60 min, > 60 min). The RDW, hemoglobin level, platelet count, and NLR were measured using automated machines.

Recurrent ischemic events, defined as neurological deficits within 7-90 days post-TIA, were assessed. Comparative analyses were performed between patients with and without recurrent events, considering both clinical data and laboratory result. s.

This study was approved by the Ethics Committee of Prasat Neurological Institute (approval number: 67012).

Statistical analyses

For normally distributed quantitative data, mean ± standard deviation was used, and groups were compared using the independent t-test. Alternatively, for data with abnormal distribution, median ± interquartile range (IQR) was presented, and the Mann-Whitney U test was used for analysis. Categorical variables are expressed as proportions and analyzed using Fisher's exact test. The model discrimination was evaluated using the area under the receiver operating characteristic (ROC) curve. A p-value < 0.05 was considered statistically significant. All statistical data were analyzed using STATA13.0.

Results

Demographic data

This study included data from 283 patients from 299 chart reviews. Sixteen patients were excluded from this study, including nine patients with alternative diagnoses, five with concurrent infection, and two with active infection (Figure 1).

A comparison of demographic data between patients with TIA with and without recurrent ischemic events within 7 days is shown in Table 1. There were no significant differences in baseline data or comorbidities, including prior diagnosis of cerebrovascular disease. There were no significant differences in the duration of neurological deficits or characteristics of neurological symptoms between the two groups. The median RDWs in patients with TIA with and without recurrent ischemic events within 7 days were 13.35 (IQR, 1.85) and 13.7 (IQR, 1.50), respectively (p = 0.176). Statistical analysis also revealed no significant differences in NLR between these patient groups.

	TIA without recurrent ischemic events (N = 259)	TIA with recurrent ischemic events within 7 days (N = 24)	p-value
Age (years; mean, SD)	61.41 (14.15)	58.17 (12.23)	0.279
Sex (male, %)	130 (50.20)	12 (50.00)	0.986
BMI (kg/m^2; median, IQR)	24.568 (5.21)	25.396 (5.89)	0.646
Comorbidity			
Diabetes mellitus (%)	59 (22.80)	8 (33.30)	0.426
Hypertension (%)	147 (56.80)	16 (66.70)	0.347
Dyslipidemia (%)	137 (52.90)	9 (37.50)	0.149
Coronary heart disease (%)	20 (7.70)	1 (4.20)	1.000
Previous cerebrovascular disease/TIA (%)	92 (35.80)	9 (37.50)	0.868
Cardiac arrhythmia (%)	21 (8.10)	3 (12.50)	0.441
Anemia (%)	77 (29.70)	6 (25.00)	0.626
Active smoking (%)	37 (14.30)	5 (20.80)	0.373

Medication history			
Antiplatelets (%)	92 (35.50)	8 (33.30)	0.830
Aspirin 81 mg (%)	45 (48.90)	4 (50.00)	0.346
Aspirin 325 mg (%)	5 (5.40)	2 (25.00)	
Clopidogrel 75 mg (%)	20 (21.70)	1 (12.50)	
Aspirin and clopidogrel (%)	13 (14.10)	1 (12.50)	
Other antiplatelets (%)	9 (9.80)	0 (0.00)	
Anticoagulant (%)	13 (5.00)	1 (4.20)	1.000
ABCD2 score			
0-3 (%)	108 (41.70)	10 (41.70)	0.925
4-5 (%)	123 (47.50)	12 (50.00)	
6-7 (%)	28 (10.80)	2 (8.30)	
Duration			
Less than 10 min (%)	57 (22.00)	4 (16.70)	0.370
10 min-1 h (%)	102 (39.40)	13 (54.20)	
More than 1 h (%)	100 (38.60)	7 (29.20)	
Baseline blood pressure			
Systolic blood pressure (mmHg; mean, SD)	149.47 (21.53)	155.29 (24.79)	0.212
Diastolic blood pressure (mmHg; mean, SD)	85.48 (13.30)	83.67 (11.74)	0.520
Laboratory results			
Hb level (g/dL; median, IQR)	13.0 (1.70)	13.85 (2.33)	0.075
White blood cell count (× 10 9/L; median, IQR)	7.40 (3.00)	7.25 (1.38)	0.991
Neutrophil-to-lymphocyte ratio, NLR (median, IQR)	2.24 (1.41)	2.03 (1.31)	0.619
Red blood cell distribution width, RDW (%; median, IQR)	13.7 (1.50)	13.35 (1.85)	0.176
Platelets count (× 10 9/L; median, IQR)	253.50 (93.5)	259.50 (87.5)	0.836

Table 1: Comparison of demographic data, clinical characteristics, and laboratory results of patients with transient ischemic attack with and without recurrent ischemic events within 7 days.

Table 2 shows a comparison of the patient characteristics and laboratory results between patients with and without recurrent ischemic events within 90 days. In terms of complete blood count results, the median RDWs were 13.55 (IQR, 1.58) and 13.7 (IQR, 1.43) in the two groups, respectively, showing no significant difference (p = 0.176). Furthermore, the NLR in patients with TIA with and without recurrent ischemic events within 90 days was not significantly different between the two groups (p = 0.619).

	TIA without recurrent ischemic events (N = 235)	TIA with recurrent ischemic events in 90 days (N = 48)	p-value
Age (years; mean, SD)	61.27 (14.08)	60.46 (13.78)	0.279
Sex (male, %)	117 (49.80)	118 (50.20)	0.772
BMI (kg/m^2; median, IQR)	24.676 (5.42)	23.984 (4.74)	0.646
Comorbidity			
Diabetes mellitus (%)	53 (22.60)	14 (29.20)	0.326
Hypertension (%)	135 (57.40)	28 (58.30)	0.910
Dyslipidemia (%)	125 (53.20)	21 (43.80)	0.233
Coronary heart disease (%)	18 (7.70)	3 (6.30)	1.000
Previous cerebrovascular disease/TIA (%)	85 (36.50)	16 (33.30)	0.679
Cardiac arrhythmia (%)	19 (8.10)	5 (10.40)	0.574
Anemia (%)	69 (29.40)	14 (29.20)	0.978
Active smoking (%)	32 (13.60)	10 (20.80)	0.200
Medication history			
Antiplatelets (%)	87 (37.00)	13 (27.10)	0.189
Aspirin 81 mg (%)	44 (50.60)	5 (38.50)	0.027
Aspirin 325 mg (%)	4 (4.60)	3 (23.10)	
Clopidogrel 75 mg (%)	20 (23.00)	1 (7.70)	
Aspirin and clopidogrel (%)	10 (11.50)	4 (30.80)	
Other antiplatelets (%)	9 (10.30)	0 (0.00)	
Anticoagulant (%)	11 (4.70)	3 (6.30)	0.713
ABCD2 score			
0-3 (%)	99 (42.10)	19 (39.60)	0.616
4-5 (%)	113 (48.10)	22 (45.80)	
6-7 (%)	23 (9.80)	7 (14.60)	
Duration			
Less than 10 min (%)	51 (21.70)	10 (20.80)	0.703
10 min-1 h (%)	93 (39.60)	22 (45.80)	
More than 1 h (%)	91 (38.70)	16 (33.30)	
Baseline blood pressure			
Systolic blood pressure (mmHg; mean, SD)	148.77 (21.35)	155.77 (23.43)	0.212
Diastolic blood pressure (mmHg; mean, SD)	85.58 (13.08)	84.08 (13.64)	0.520
Laboratory results			
Hb level (g/dL; median, IQR)	13.0 (1.70)	13.40 (2.23)	0.075
White blood cell count (× 10 9/L; median, IQR)	7.40 (3.10)	7.15 (1.95)	0.991
Neutrophil-to-lymphocyte ratio, NLR (median, IQR)	2.22 (1.30)	2.23 (2.28)	0.619
Red blood cell distribution width, RDW (%; median, IQR)	13.7 (1.43)	13.55 (1.58)	0.176
Platelets count (× 10 9/L; median, IQR)	253.00 (94.25)	258.0 (88.50)	0.836

Table 2: Comparison of demographic data, clinical characteristics, and laboratory results of patients with transient ischemic attack with and without recurrent ischemic events within 90 days.

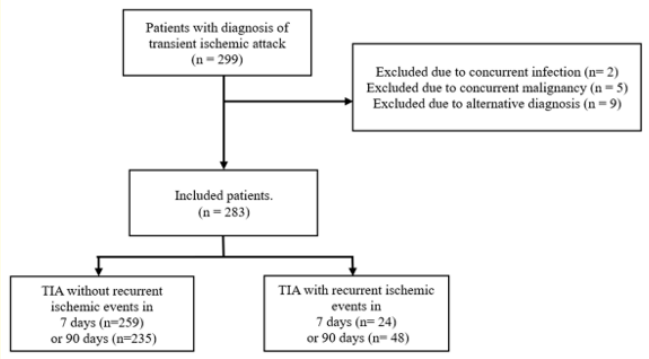

Figure 1: Flowchart of the patients enrolled in the study. Ischemic events occurred in 24 and 48 patients after 7 and 90 days.

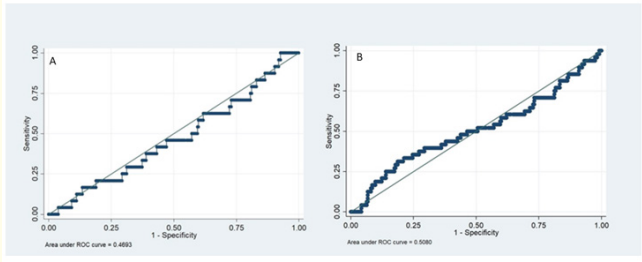

Figure 3: The receiving operating characteristic between neutrophil-to-lymphocyte ratio (NLR) and ischemic stroke events in patients with TIA within 7 (A) and 90 (B) days. The areas under the receiver operating characteristic curve obtained from NLR and ischemic stroke events at 7 and 90 days were 0.469 and 0.508, respectively.

Red blood cell distribution width and the risk of ischemic stroke in patients with transient ischemic attack (TIA)

RDW has a high positive predictive value for predicting ischemic events in patients with TIA [12-14] or is associated with stroke severity [15,16]. Thus, we assessed the value of RDW in predicting stroke in patients with TIA in our cohort. As shown in Figure 2, no correlation was found between RDW and ischemic stroke events.

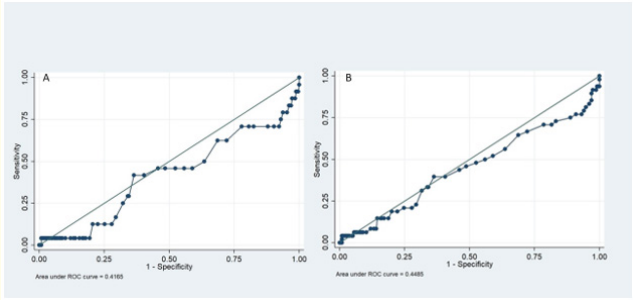

Figure 2: The receiving operating characteristic between red blood cell distribution wide (RDW) and ischemic stroke events in patients with TIA at 7 (A) and 90 (B) days. The areas under the receiver operating characteristic curve obtained from RDW and ischemic stroke events at 7 and 90 days were 0.417 and 0.449, respectively.

Neutrophil-to-lymphocyte ratio as a predictor of ischemic stroke in patients with TIA

According to a previous study, a high NLR was associated with stroke severity on admission and unfavorable outcomes [19]. However, our results (Figure 3) did not demonstrate the predictive value of ischemic stroke in patients with TIA at either 7 or 90 days. The areas under the receiver operating characteristic curve were 0.469 and 0.508, respectively.

Classical ABCD2 score in predicting stroke after TIA

In our study, the patients were categorized into two groups based on the conventional ABCD2 score. The low-risk group scored 0-3, whereas the high-risk group scored 4-7. Notably, 165 of 283 patients were classified as high-risk. Among the 24 patients who experienced recurrent ischemic events, 14 were in the high-risk group and 10 were in the low-risk group. Among patients with TIA without recurrent events, the high-risk group had a higher prevalence (151 patients) than the low-risk group (108 patients).

The sensitivity and specificity of the conventional ABCD2 score for predicting ischemic events within 7 days were 58.3% and 41.7%, respectively. For predicting events within 90 days, the score's sensitivity and specificity were 60.4% and 42.1%, respectively.

Discussion

TIA is considered a medical emergency, with 10% of patients with TIA developing ischemic stroke and 80% cases being treatable to prevent further infarctions [21]. Thus, predictive clinical scores or biomarkers are important for early assessments to prevent further infarctions. Various parameters related to complete blood count, such as RDW and its related parameters, have been demonstrated as good indicators for predicting ischemic events after TIA [6-8,11]. Additionally, elevated NLR is considered a novel predictor of ischemic events in patients with TIA [9]. In the current study, we aimed to evaluate the predictive value of RDW and NLR for the occurrence of ischemic events in patients with TIA. The results showed no association between RDW and the occurrence of recurrent ischemic events, including recurrent TIA and ischemic stroke, regardless of the timing of the ischemic events at 7 and 90 days. The findings of our study deviate from those reported in earlier studies, which showed an association between higher RDW and the risk of ischemic stroke development in patients with TIA [10]. Nevertheless, in our study, high NLR was not associated with ischemic stroke occurrence in patients with TIA. Our results showed that both parameters tended to have an inverse correlation with recurrent ischemic events, as indicated by the ROC curves.

Several assumptions underlie the interpretation of the results of our study that have been debated in the context of previously published literature. The diagnosis of TIA in our study diverged from that employed in earlier studies [6,9,11,20]. In our study, we utilized a clinical diagnostic methodology based on symptoms indicative of acute transient neurological deficits and the absence of new infarctions on CT or MRI scans. In contrast, prior studies have exclusively included patients with negative results on both CT and MRI, including the diffusion-weighted imaging (DWI) sequence, which is considered more accurate for diagnosis based on newly established tissue-based criteria [6,18]. A substantial cohort study demonstrated that 11.1% of 1910 patients diagnosed with TIA according to the World Health Organization criteria who underwent MRI exhibited acute infarctions [19]. Some studies have reported a higher incidence of infarctions on MRI in patients diagnosed with TIA [20]. However, only a limited number of patients diagnosed with TIA underwent MRI as a diagnostic tool owing to its high cost and limited availability. As mentioned, the variance in the diagnostic criteria may have affected the outcomes of our study, as the markers are contingent on the extent of ischemia. Furthermore, the rate of ischemic stroke occurrence in this study was significantly lower than that in a published study, with only 24 of 283 patients who experienced recurrent TIA or ischemic stroke within 7 days. Finally, these two simple blood biomarkers are affected by various conditions, such as nutritional status, chronic infection, or underlying hematological conditions. Therefore, the use of RDW and NLR for the prediction of stroke requires validation before use in routine clinical practice.

Regarding the predictive value of the ABCD2 score, our study observed a lower sensitivity and specificity than those of a prior investigation. This variance could be attributed to differences in both sample size and study protocol. For instance, an earlier study prospectively enrolled 2056 patients from eight emergency departments across Canada [4]. In contrast, our study was exclusively conducted at a single institute, and only 283 patients were included. Disparities in study protocols may also have contributed to the differences in the results. The previous cohort study encompassed both hospitalized patients and outpatients, whereas our study predominantly focused on inpatient cases because of the availability of laboratory results.

Findings from the experimental stroke models revealed an elevation in inflammatory marker levels, including high mobility group box 1 protein serum concentration, within a few hours of vessel occlusion. However, the extent of the inflammatory response to ischemic events appears to be contingent on infarct volume. The study found that only large infarct volumes exceeding 30 mL exhibited significantly higher levels of inflammatory markers compared with smaller infarctions and control groups [8].

Recruitment of neutrophils to the ischemic brain tissue occurs within 30 min and reaches its peak in the first 3 days. In addition to local inflammation, a previous study showed that total leukocyte and neutrophil counts increased in the first 3 days in patients with stroke and were associated with larger infarct volume and severity of symptoms [24]. These findings support the hypothesis that the inflammatory processes play a significant role in ischemic stroke.

However, as detailed earlier, the intensity of the inflammatory process, as indicated by various inflammatory markers and increased neutrophil count, is typically associated with the extent of

neural tissue damage. Our study also focused on patients diagnosed with a TIA, a condition characterized by transient occurrence. TIAs tend to manifest in patients with less severe occlusive lesions and smaller areas of ischemia compared with those with other vascular events, such as ischemic stroke or myocardial infarction. The characteristics of the TIAs may explain the insignificant differences between the two groups. The relatively short duration of ischemia in TIA may induce a lower degree of neuronal inflammatory response, which may be insufficiently severe to cause detectable alterations in red blood cell production or leukocyte ratio.

Additionally, our study stratified patients according to their ABCD2 score. With a score of ≥ 4 as the cutoff point, the sensitivity and specificity for prediction were only 58.3% and 41.7%, respectively. The sensitivity was lower compared with that of the previous validation study, which achieved a sensitivity of 92.1%. However, the specificity was comparable with that of a previous study at 32.7% [5].

Based on the results of this study, neither complete blood count parameters nor conventional ABCD2 scores are potent predictors of the risk of recurrent ischemic events in patients with TIA. This assertion is grounded in sensitivity and specificity. Our study has some limitations. First, the number of patients who experienced ischemic stroke or recurrent TIA was lower than anticipated. Moreover, the included patient population was exclusively sourced from a single-center hospital, which potentially limits the generalizability of our findings to a broader population.

To enhance the robustness of future studies and investigations, a larger and more diverse population is recommended to obtain clearer and more generalizable results. Therefore, the adoption of precise TIA diagnostic criteria involving evidence of no new infarctions, as defined by DWI sequences on MRI, is advocated for more conclusive findings. Additionally, the implementation of a prospective study design can yield more reliable results.

Conclusion

This study demonstrates that RDW and NLR obtained during the first admission of patients are not associated with the occurrence of recurrent ischemic events (recurrent TIA and ischemic stroke) within 7 and 90 days.

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Conflicts of Interest

Authors declare no conflict of interest.

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