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Predictive role of ABCD2, ABCD3I, C-reactive protein, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and systemic immune-inflammation index in 90-day and long-term stroke after transient ischemic attack

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ABSTRACT

Objectives: Transient ischemic attack (TIA) is a neurological emergency and a precursor of ischemic stroke. ABCD2 and ABCD3I scores predict stroke after TIA, and clinicians use preclinical, clinical, and radiological parameters for calculating these scores. Our study aimed to investigate the efficacy of peripheral blood markers in predicting 90-day and long-term stroke risk after TIA.

Methods: This retrospective study was conducted in Kastamonu Training and Research Hospital between January 2015 and November 2022. The demographic data of 99 patients who applied with the diagnosis of TIA and peripheral blood markers at the time of first admission to the hospital were used in the study. These parameters was evaluated in 90-day and long-term (> 12 months) stroke after TIAs.

Results: Of the 99 patients in our study, 59% (n = 58) were male. The mean age of the patients was 70 ± 13 years. ABCD2 (age, blood pressure, clinical features, duration of symptoms, and presence of diabetes mellitus) and ABCD3I (age, blood pressure, clinical features, duration of symptoms, presence of diabetes mellitus, dual TIA, and ipsilatheral carotis stenosis) scores and C-reactive protein (CRP) were statistically significant in predicting 90-day stroke. ABCD2 and ABCD3I were not effective in predicting long-term stroke. In addition, CRP, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) parameters were statistically significant in long-term stroke. CRP (AUC=793, sensitivity = 82%, and specificity = 81%) values were higher than ABCD2 (AUC = 779, sensitivity = 73%, and specificity = 76%) and ABCD3I (AUC = 755, sensitivity = 82%, and specificity = 70%) scores in predicting 90-day stroke.

Conclusions: Our study showed that ABCD2, ABCD3I, and CRP effectively predict 90-day stroke after TIA. Furthermore, CRP was more effective than ABCD2 and ABCD3I scores in predicting 90-day stroke after TIA. CRP, NLR, PLR, and SII also effectively predicted long-term stroke after TIA.

Keywords: Transient ischemic attack, ABCD2, ABCD3I, C-reactive protein

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Transient ischemic attack (TIA) is a neurological emergency characterized by a focal neurological deficit lasting less than 24 hours. Clinically, it most commonly presents as dysarthria, aphasia, hemiparesis, hemihypoesthesia, and amaurosis fugax. Atrial fibrillation (AF), hypertension (HT), and diabetes mellitus (DM) are the most common etiologies. TIA is a critical clinical condition as it is a precursor of ischemic stroke that may develop in the future. Studies reported the risk of stroke following TIA between 1.7% and 20.6% at day 90 [1]. A reasonable etiological investigation and identification of risk factors can minimize the risk of ischemic stroke. Several scales were developed to estimate risk of stroke after TIA. ABCD2 (age, blood pressure, clinical features, duration of symptoms, and presence of diabetes mellitus) and ABCD3I (age, blood pressure, clinical features, duration of symptoms, presence of diabetes mellitus, dual TIA, and ipsilatheral carotis stenosis) scores are the most commonly used scores that predict 90-day stroke after TIA [2-4]. However, markers that are calculated and easily predicted based on laboratory data are still needed. In addition, it is important to differentiate patients with a poor prognosis with peripheral inflammatory markers, especially in cases where magnetic resonance imaging (MRI) is not accessible or takes time to be obtained in the emergency department, to start more effective treatments quickly. C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) parameters are used to predict stroke severity [5, 6]. However, few studies have investigated the role of these inflammatory parameters in predicting ischemic stroke after TIA. Moreover, as far as we know, there is no study investigating the efficacy of these parameters in predicting long-term stroke after TIA [7, 8].

In this study, we aimed to investigate the efficacy of peripheral inflammatory markers in predicting 90-day and long-term stroke after TIA.

METHODS

This retrospective study was conducted in Kastamonu Training and Research Hospital between January 2015 and November 2022. The study was started after the approval of the Kastamonu University Faculty of Medicine Clinical Research Ethics Committee with decision number 2023- KAEK - 12 and dated 30.01.2023. The Demographic data of 99 patients who applied with the diagnosis of TIA and hematological and biochemistry data at the time of first admission to the hospital were used in the study. ABCD2 and ABCD3I scores were calculated according to all patients' demographic, clinical, and radiological data. ABCD2 score was calculated as follows: A = age, 1 point for > 60 years; B = blood pressure, 1 point for > 140/90 mmHg; C = clinical feature, 2 points for unilateral weakness or 1 point for speech impairment without liability; D1 = duration, 2 points for > 60 minutes, 1 point for < 60 minutes; D2 = 1 point for the presence of diabetes mellitus). According to this scoring system, 1-3 points indicate low, 4-5 points indicate moderate, and 6-7 points indicate high stroke risk. ABCD3I score was calculated by adding dual TIA and vascular findings to ABCD2 [2, 3].

Patients under 18 years old, pregnant women, trauma patients, patients with malignancy, liver and kidney failure, and patients without hemogram and biochemistry data were excluded from the study. Hemogram and CRP tests were performed on Sysmex XN-1000 (Sysmex, Kobe, Japan) hematology and Beckman Coulter AU 5800 (Beckman Coulter, Brea, CA, USA) clinical chemistry auto analyzers, respectively. In addition, the D-dimer test was performed on CS 2500 (Sysmex, Kobe, Japan). The NLR, MLR, PLR, SII, and SIRI were calculated as follows:

NLR = Neutrophil count ($\times 10^9$/L)/ Lymphocyte count ($\times 10^9$/L)

MLR = Monocyte count ($\times 10^9$/L)/ Lymphocyte count ($\times 10^9$/L)

PLR = Platelet count ($\times 10^9$/L)/ Lymphocyte count ($\times 10^9$/L)

SII = Platelet count ($\times 10^9$/L) × Neutrophil count ($\times 10^9$/L)/ Lymphocyte count ($\times 10^9$/L)

SIRI = Neutrophil count ($\times 10^9$/L) × Monocyte count ($\times 10^9$/L)/ Lymphocyte count ($\times 10^9$/L).

Statistical Analysis

The "Statistical Package for Social Sciences 18.0 for Windows" (SPSS Inc., Chicago, USA) program was used for statistical analysis of the data. Descriptive statistics of the data obtained were given as numbers and percentages for categorical variables and as median (25, 75 Percentiles) for numerical variables.

Since the groups showed a nonparametric distribution, the Mann-Whitney U test was used to test the significance between the groups. A chi-square test was performed to see if there was a significant difference between the groups regarding gender, DM, HT, and HL. The receiver operating characteristic (ROC) analysis was performed, and Youden's index was used to determine the area under the curve (AUC), sensitivity, specificity, and optimal cut-off values. A p - value of < 0.05 was considered statistically significant.

RESULTS

Of the 99 patients in our study, 59% (n = 58) were male. The mean age of the patients was 70 ± 13 years (Table 1). ABCD2 and ABCD3I scores and CRP were statistically significant in predicting 90-day stroke (Table 2). ABCD2 and ABCD3I were not effective in predicting long-term stroke (Table 3). CRP (AUC = 793, sensitivity = 82%, and specificity = 81%) values were higher than ABCD2 (AUC = 779, sensitivity = 73%, and specificity = 76%) and ABCD3I (AUC = 755, sensitivity = 82, and specificity = 70) scores in predicting 90-day stroke (Table 4) (Fig. 1). Notably, CRP AUC, sensitivity, and specificity values were higher than ABCD2 and ABCD3I scores in predicting 90-day stroke.

Table 1. Demographic and clinical data of TIA patients

	Data
Age (years)	70 ± 13
Gender (male), n (%)	58 (59)
AF, n (%)	20 (20)
HVD, n (%)	37 (37)
DM, n (%)	56 (56)
HT, n (%)	56 (56)
CRP (mg/L)	6.76 ± 11
D-DIMER (ng/dL)	1.1 ± 5.5
NLR	4.6 ± 5.4
PLR	150 ± 105
MLR	0.44 ± 0.75
SII	1081 ± 1368
SIRI	3 ± 4.4

Data are shown as mean±standard deviation or n (%). AF = atrial fibrillation, HVD = heart valve disease, DM = diabetes mellitus, HT = hypertension, CRP = C-reactive protein, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, MLR = monocyte-lymphocyte ratio, SII = systemic immune-inflammation index (neutrophil × platelet/ lenfosit), SIRI = systemic inflammation response index (neutrophil × monocyte/ lenfosit)

In addition, CRP, NLR, PLR, and SII parameters were statistically significant in long-term stroke (Table 3). In the ROC analysis performed in patients with long-term stroke (12 months and above), SII (cut off: 505, AUC: 0.742), NLR (cut off: 3.7, AUC: 0.726), CRP (cut off: 4.8, AUC: 0.722) moderate-high predictive properties were detected in the tests (Fig 1).

In predicting 90-day stroke, ABCD2 and ABCD3I obtained from patients' data at admission to the hospital were statistically significantly different, as expected. However, CRP was also significantly different (Table 2).

ABCD2 and ABCD3I scores were not effective in predicting long-term stroke. However, CRP was again statistically significant in predicting long-term stroke. In addition, NLR, PLR, and SII parameters were significantly different (Table 3).

DISCUSSION

The ABCD2 score was developed for primary care and emergency physicians to predict TIA patients at high risk of stroke and significantly differentiate patients for hospitalization. Nevertheless, in some studies, it was thought to help identify patients with an increased risk of stroke after TIA, whereas this result could not be demonstrated in some studies [9]. These inconsistent results were attributed to methodological differences in the studies. Some of these studies were population-based, while others included only hospitalized patients. In addition, some studies were conducted by stroke specialists, while others were executed by primary care physicians. In our study, in which we examined patients evaluated in the emergency department and hospitalized in the neurology department, we found a significant association between high ABCD2 scores and 90-day stroke.

The clinicians developed the ABCD3I score for more sensitive scoring stroke risk after TIA. However, its disadvantage is that it is not suitable for use by pri-

Table 2. Comparison of hematological and biochemical parameters in predicting 90-day stroke after TIA

	Stroke Group (n = 11)	Non-stroke Group (n = 88)	*p* value
Age (years)	80 (55;83)	73 (58;81)	0.407
Male Gender, n (%)	5 (45.5)	53 (60.2)	0.348
ABCD2	5 (4;6)	4 (3;4)	**0.002**
ABCD3I	5 (5;6)	4 (3;5)	**0.005**
CRP (mg/L)	7.8 (5.26;20.4)	3.25 (1.22;5)	**0.002**
D-DIMER (ng/dL)	0.9 (0.3;1.21)	0.40 (0.26;0.53)	0.067
NLR	2.75 (1.90;1.20)	2.81 (1.86;4.82)	0.551
PLR	115 (101;158)	120 (91;164)	0.920
MLR	0.24 (0.20;0.45)	0.28 (0.19;042)	0.928
SII	608 (471;786)	629 (417;1090)	0.640
SIRI	1.61 (0.60;2.05)	1.62 (0.89;2.64)	0.577

Data are shown as median (25;75 percentiles) or numbers and percentages. ABCD2 scoring system (A = age, 1 point for > 60 years; B = blood pressure, 1 point for >140/90 mmHg; C = clinical feature, 2 points for unilateral weakness or 1 point for speech impairment without liability; D1 = duration, 2 points for > 60 minutes, 1 point for < 60 minutes; D2 = 1 point for the presence of diabetes mellitus), ABCD3I scoring system (A = age, 1 point for > 60 years; B = blood pressure, 1 point for >140/90 mmHg; C = clinical feature, 2 points for unilateral weakness or 1 point for speech impairment without liability; D1 = duration, 2 points for > 60 minutes, 1 point for < 60 minutes; D2 = 1 point for the presence of diabetes mellitus; D3 = dual TIA; I = ipsilatheral carotis stenosis), AF = atrial fibrillation, HVD = heart valve disease, DM, =diabetes mellitus, HT = hypertension, CRP = C-reactive protein, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, MLR = monocyte-lymphocyte ratio, SII = systemic immune-inflammation index (neutrophil × platelet/ lenfosit), SIRI = systemic inflammation response index (neutrophil × monocyte/ lenfosit)

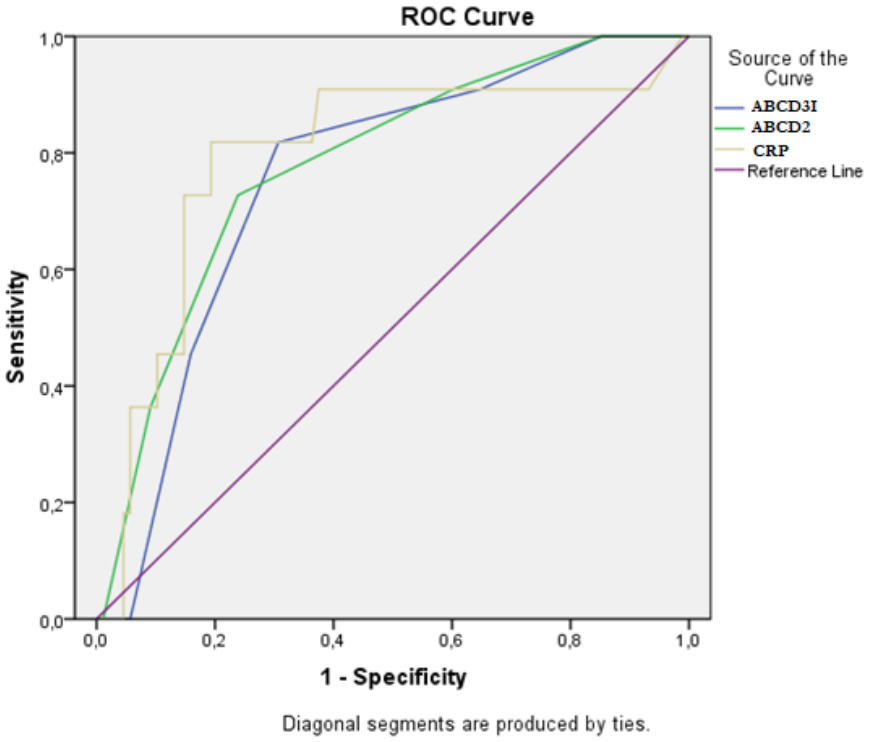

Fig. 1. ROC curve analysis of ABCD2, ABCD3I, and CRP data in TIA patients.

Tablo 3. Comparison of hematological and biochemical parameters in predicting long-term stroke after TIA

	Stroke Group (n = 9)	Non-Stroke Group (n = 90)	*p* value
Age (years)	76 (69;85)	73 (56;81)	0.315
Male Gender, n (%)	5 (55.6)	53 (58.9)	0.848
ABCD2	5 (4;5)	4 (3;5)	0.070
ABCD3I	5 (4;5)	4 (3;5)	0.143
CRP	5 (4;35)	3.4 (1.2;5.2)	**0.029**
D-DIMER	0.46 (0.29;0.50)	0.40 (0.26;0.60)	0.817
NLR	2.75 (1.90;1.20)	2.74 (1.81;4.39)	**0.026**
PLR	180 (119;347)	117 (91;157)	**0.041**
MLR	0.24 (0.20;0.45)	0.27 (0.19;0.39)	0.061
SII	1042 (614;4214)	600 (407;1007)	**0.017**
SIRI	2.47 (1.22;8.27)	1.48 (0.86;2.54)	0.070

Data are shown as median (25; 75 percentiles) or numbers and percentages. ABCD2 scoring system (A = age, 1 point for > 60 years; B = blood pressure, 1 point for >140/90 mmHg; C = clinical feature, 2 points for unilateral weakness or 1 point for speech impairment without liability; D1 = duration, 2 points for > 60 minutes, 1 point for < 60 minutes; D2 = 1 point for the presence of diabetes mellitus), ABCD3I scoring system (A = age, 1 point for > 60 years; B = blood pressure, 1 point for > 140/90 mmHg; C = clinical feature, 2 points for unilateral weakness or 1 point for speech impairment without liability; D1 = duration, 2 points for > 60 minutes, 1 point for < 60 minutes; D2 = 1 point for the presence of diabetes mellitus; D3 = dual TIA; I = ipsilatheral carotis stenosis), AF = atrial fibrillation, HVD = heart valve disease, DM, =diabetes mellitus, HT = hypertension, CRP = C-reactive protein, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, MLR = monocyte-lymphocyte ratio, SII = systemic immune-inflammation index (neutrophil × platelet/ lenfosit), SIRI = systemic inflammation response index (neutrophil × monocyte/ lenfosit)

mary care physicians as carotid artery imaging is required for complete scoring. An emergency department study revealed the ABCD3I score is to be helpful in long-term stroke prevention [10]. Studies showed that the ABCD3I score is superior to the ABCD2 score in predicting stroke. Interestingly, the ABCD2 score was more predictively than the ABCD3I score in our study.

Inflammatory mechanisms in ischemic stroke have been investigated in studies. Proinflammatory factors are activated in the damaged brain region in the first minutes of a stroke. After ischemic stroke, migration of immune system mediators and release of cytokines occur, leading to impaired permeability of the blood-brain barrier, resulting in brain edema, increased infarct volume, and neuronal damage [11, 12]. In the

Table 4. ROC curve analysis of ABCD2, ABCD3I, and CRP data in TIA patients

	Cut-off	AUC	95%CI	*p* value	Sensitivity (%)	Specificity (%)
CRP	5.23	0.793	0.63-0.95	**0.002**	82	81
ABCD2	4.5	0.779	0.64-0.92	**0.003**	73	76
ABCD3I	4.5	0.755	0.62-0.89	**0.006**	82	70

ABCD2 scoring system (A = age, 1 point for > 60 years; B = blood pressure, 1 point for > 140/90 mmHg; C = clinical feature, 2 points for unilateral weakness or 1 point for speech impairment without liability; D1 = duration, 2 points for > 60 minutes, 1 point for < 60 minutes; D2 = 1 point for the presence of diabetes mellitus), ABCD3I scoring system (A = age, 1 point for > 60 years; B = blood pressure, 1 point for > 140/90 mmHg; C = clinical feature, 2 points for unilateral weakness or 1 point for speech impairment without liability; D1 = duration, 2 points for > 60 minutes, 1 point for < 60 minutes; D2 = 1 point for the presence of diabetes mellitus; D3 = dual TIA; I = ipsilatheral carotis stenosis), CRP = C-reactive protein.

early phase of stroke, neutrophils are the first inflammatory mediators to migrate to the damaged brain region. Clinical studies show that the severity of the inflammatory response is important in acute and chronic prognosis and the extent of brain damage [13]. Available data suggest that inflammation increases atherosclerosis, and the ongoing thrombotic process aggravates inflammation. Continued obstruction leads to inflammation and migration of other inflammatory mediators to the site [14].

Hematologic markers such as NLR are used in the diagnosis and prognosis monitoring of many diseases. In addition, these markers have recently been used in the prognosis prediction of many neurological disorders because they are easily accessible and inexpensive. However, there are conflicting results among studies. For example, Ross *et al*. [15] found that neutrophil counts were higher in patients with TIA and acute ischemic stroke (AIS) compared to control groups. Also, Gokhan *et al*. [16] showed that the NLR rate was significantly higher in AIS patients than in TIA patients. Cavrak *et al*. [17] found no significant difference in NLR value between these groups, including TIA, mild ischemic stroke, and stroke mimics. In addition, another study conducted on young patients showed that elevated NLR was a marker of poor prognosis in ischemic stroke and TIA [18]. In our research, NLR and PLR didn't predict 90-day stroke after TIA but predicted long-term stroke after TIA.

Effect of SII and SIRI on prognosis prediction in ischemic stroke was investigated in various studies. Hou *et al*. [19] found that SII was associated with ischemic stroke severity independently of all parameters. Furthermore, Lii *et al*. [20] showed that SII may be a prognostic marker in patients undergoing mechanical thrombectomy (MT) for large artery occlusion. However, another study found that higher SII was associated with greater stroke severity after AIS [21]. Besides, a study revealed that SII and SIRI is closely related to the short- and long-term prognosis of patients with AIS [22]. Moreover, similar to previous studies, Zhou *et al*. [23] showed that SII could predict the risk of adverse outcomes in patients with AIS with an accuracy of 80.2%). However, a prospective study showed that although SII showed significant differences during the first two weeks following stroke, the discrimination capacity of these changes was limited [24]. In our study, SII and SIRI did not predict 90-day stroke after TIA but SII predicted long-term stroke.

C-reaktive protein (CRP) is an important marker used in treatment follow-up in inflammatory diseases. In addition, it is an important prognostic marker in cardiovascular diseases due to the inflammatory mechanisms of these diseases. It is effective in prognosis prediction, especially in cardiovascular diseases, and associated with poor prognosis in ischemic stroke. (It is effective in prognosis prediction, especially in cardiovascular diseases, and associated with poor prognosis in ischemic stroke.) In one study, highly sensitive CRP predicted stroke after TIA [25]. Moreover, in a recent study, H-sensitive CRP (hs-CRP) was an independent indicator of recurrent cerebrovascular events [26]. In our study, CRP predicted 90-day and long-term stroke after TIA and was more effective than ABCD2 and ABCD3I in predicting a 90-day stroke after TIA. This was one of the most striking finding of our research.

The relationship between D-dimer levels and stroke is not consistent across studies. In contrast, some studies have found high D-dimer levels to be significantly associated with stroke [27, 28]. Zakai *et al*. [29] found a weak association between D-dimer levels and stroke. In addition, D-dimer levels were grouped according to different criteria between studies, which may explain the inconsistency in the results of the studies. However, a definitive association between D-dimer levels and stroke has not been found based on the limited available data. Increased D-dimer levels may reflect ongoing thrombosis in cerebral blood vessels [30]. D-dimer is reported to activate the inflammatory process, which may include the activation of monocytes and the release of proinflammatory cytokines such as interleukin-6 (IL-6) [30]. However, the D-dimer levels were ineffective in predicting 90-day and long-term stroke after TIA in our study.

Limitations

Our study had some limitations: It is a single-center and retrospective analysis. We didn't perform serial hemogram measurements. Another limitation is the absence of tumor necrosis factor and interleukin-6 levels, which we could not test in the emergency department.

CONCLUSION

Our study showed that ABCD2, ABCD3I, and C-reactive protein (CRP) effectively predict 90-day stroke after TIA. Furthermore, CRP was more effective than ABCD2 and ABCD3I in predicting 90-day stroke after TIA. CRP, NLR, PLR, and SII also effectively predicted long-term stroke after TIA.

Authors' Contribution

Study Conception: İK, SG; Study Design: İK, SG; Supervision: İK, SG; Funding: İK, SG; Materials: İK, SG; Data Collection and/or Processing: İK, SG; Statistical Analysis and/or Data Interpretation: SG; Literature Review: İK, SG; Manuscript Preparation: İK, SG and Critical Review: İK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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