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# Mean Platelet Volume, C-Reactive Protein, and Prognosis in Patients with Acute Ischemic Stroke Following Intravenous Thrombolytic Treatment

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**Corresponding Author:** Yılmaz İnanç, e-mail: drinacc@gmail.com**Source of support:** Departmental sources**Background:** The aim of this study was to investigate the association between mean platelet volume (MPV), C-reactive protein (CRP), and prognosis in patients with acute ischemic stroke (AIS) following intravenous (IV) thrombolytic treatment.**Material/Methods:** A retrospective clinical study included 129 patients within 4.5 hours from the onset of AIS, who received IV thrombolytic treatment. Clinical data were retrieved from electronic medical records. MPV, CRP, and National Institutes of Health (NIH) Stroke Scale and the modified Rankin Scale (MRS) scores for physical disability were recorded.**Results:** Of the 129 patients, 65.9% were men, and more than half received IV thrombolytic treatment within between 3–4.5 hours. The NIH Stroke Scale scores at 24 hours and at three months after hospital admission were compared with the NIH Stroke Scale scores on hospital admission. A significant correlation was found between the MPV values at 24 hours ( $r=0.221$ ;  $p=0.012$ ) and at three months after hospital admission ( $r=0.196$ ;  $p=0.026$ ). There was a significant correlation between CRP values at 24 hours ( $r=0.224$ ;  $p=0.021$ ), the difference in NIH Stroke Scale score between 24 hours and three months ( $r=0.249$ ;  $p=0.005$ ), and the MPV score at three months ( $r=0.186$ ;  $p=0.035$ ).**Conclusions:** MPV and CRP values were significantly associated with improvement in the NIH Stroke Scale and MRS scores in AIS when patients were treated with IV thrombolytic therapy within 4.5 hours of the onset of symptoms.**MeSH Keywords:** Brain Ischemia • C-Reactive Protein • Mean Platelet Volume • Prognosis**Full-text PDF:** <https://www.medscimonit.com/abstract/index/idArt/906813> 2518 3 4 29

## Background

Worldwide, stroke is one of the most common causes of death, and may also lead to major disability. In the United States, stroke is reported as the third leading cause of death, and approximately 795,000 people experience a stroke each year, either as a first event or as a recurrent event [1]. Of all strokes, 87% are ischemic, 10% are due to intracerebral hemorrhage (ICH), and 3% are due to subarachnoid hemorrhage (SAH) [1].

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study group recommended that treatment with intravenous (IV) recombinant tissue plasminogen activator (rtPA) within 3 hours of the onset of acute ischemic stroke (AIS) could be beneficial and improve clinical outcome [2]. Based on the results of a study in 2008, reported by Hacke et al., in routine clinical practice, the recommended effective time for initiation of IV rtPA is within 4.5 hours from the onset of symptoms of AIS [3].

Mean platelet volume (MPV) plays a crucial role in the pathogenesis of ischemic stroke, and an elevated MPV has been identified as an independent risk factor in AIS [4]. Previously published studies have shown that increased levels of MPV were found in patients with AIS when compared with control subjects, and measurement of MPV has been proposed as a predictor of outcome in patients with AIS [4,5].

C-reactive protein (CRP) is an acute phase protein and a biomarker of systemic inflammation. High levels of CRP have been found in patients AIS, leading to the possibility that CRP may also be a prognostic factor in AIS [6]. A recently published study has shown that increased CRP levels were associated with short-term functional outcome, stroke severity, long-term mortality, and recurrence in the first year after the onset of AIS [6].

The aim of this study was to investigate the association between MPV, CRP, and prognosis in patients with AIS who received IV thrombolytic treatment within 4.5 hours after the onset of acute cerebrovascular symptoms.

## Material and Methods

This study was a multicenter, retrospective, observational cohort study in patients with AIS, conducted in the emergency unit of three centers in Turkey: the Başkent University Adana Training and Research Hospital, Adana, Turkey, the Medical Faculty of Gaziantep University, Gaziantep, Turkey; and Medical Faculty of Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey. Data of patients who were admitted to the study centers within 4.5 hours after the onset of an acute ischemic stroke (AIS) and who received intravenous thrombolytic

treatment between January 2012 and December 2015 were included in the study. Ethical approval was obtained from the Local Ethics Committee.

Patient recovery following AIS was assessed and quantified using the National Institutes of Health (NIH) Stroke scale:  $\leq 1$  point at 24 hours or a decrease of  $\geq 10$  points within 24 hours. Improved recovery was considered to be an increase of 4 points, and reduced recovery was defined as a decrease of 4 points using the NIH Stroke Scale score. Clinical outcome was measured using the Modified Rankin Scale (MRS) scores with two categories: 1=very good outcome (MRS score 0–1); 2=good outcome (MRS score 0–2) [7].

MPV was measured in femtolitre (fL) (normal range, 7.5–11.5 fL), and CRP was measured in mg/L (normal range, 0–10 mg/dL) for each patient on presentation with symptoms of AIS, using a Sysmex XN-3000 automated hematology analyzer. The same analytical system for MPV and CRP was used in the three different centers.

Statistical analysis was carried out using SPSS version 22.0 (IBM Corporation, Armonk, New York, USA). The Shapiro-Wilk test was used to test univariate normality, and variance homogeneity was evaluated with the Levene test. When comparing two independent groups in terms of quantitative data, the Mann-Whitney U test with Monte Carlo simulation was used as a non-parametric test. Correlations between variables were evaluated by using Spearman's rank correlation coefficient ( $\rho$ ) test. A value of  $p < 0.05$  was accepted as statistically significant.

## Results

A total of 129 patients with acute ischemic stroke (AIS) were included in this study, and 65.9% of the patients were men, with a male-to-female ratio of 1.9. The mean ( $\pm$ SD) age of the patients was  $61.7 \pm 12.8$  years with a range of 24–79 years. Cardio-embolic stroke was the most frequent cause of AIS (48.1%), and more than half of the patients received thrombolytic treatment within 3–4.5 hours (Table 1). The mean National Institutes of Health (NIH) Stroke Scale scores were 13.9, 6.9, and 4.4 on hospital admission, at 24 hours, and at three months post-admission, respectively.

Significant correlations were detected between MPV values and changes in NIH Stroke Scale scores, as shown in Table 2. The change in functional ability using the NIH Stroke Scale score at 24 hours and at three months after admission were compared with the NIH Stroke Scale score at admission. A positive correlation was found between patient functional ability and MPV values at 24 hours ( $r=0.221$ ;  $p=0.012$ ), and at three months after admission ( $r=0.196$ ;  $p=0.026$ ) (Figures 1, 2). Similar

**Table 1.** Baseline characteristics of the study population of patients with acute ischemic stroke (AIS) at the time of hospital admission.

		n	%
Gender	Female	44	34.1%
	Male	85	65.9%
Ischemic stroke subtype	Atherosclerotic	24	18.6%
	Cardioembolic	62	48.1%
	Small-artery occlusion	15	11.6%
	Other	5	3.9%
	Cryptogenic	23	17.8%
Thrombolytic treatment time	0–1 Hour	0	0.0%
	1–2 Hours	16	12.4%
	2–3 Hours	43	33.3%
	3–4.5 Hours	70	54.3%
Hemispheric stroke side	Right	58	45.0%
	Left	71	55.0%
Circulation	Posterior	104	80.6%
	Anterior	25	19.4%

**Table 2.** Correlation between patient age, mean platelet volume (MPV), and C-reactive protein (CRP) levels.

Correlations		r	p Value
MPV	NIHSS (admission–24 hours)	0.221	0.012
MPV	NIHSS (admission–3 months)	0.196	0.026
CRP	NIHSS 24 Hours	0.204	0.021
CRP	NIHSS (24 hours–3 months)	0.249	0.005
CRP	MRS 3 months	0.186	0.035

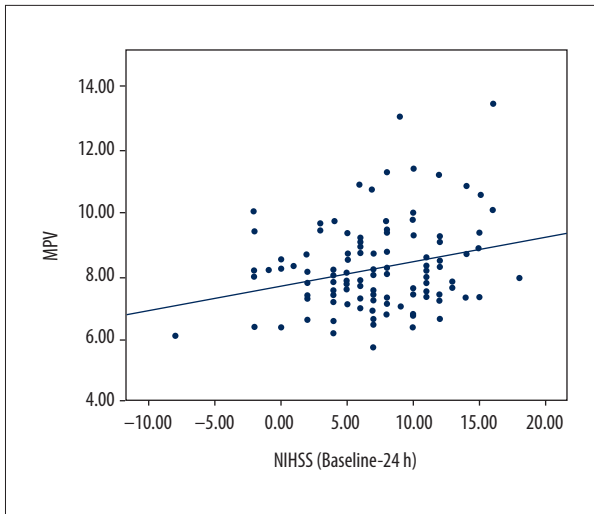
Spearman’s rho test, r – correlation coefficient. MPV was measured in femtolitre (fL) (normal range, 7.5–11.5 fL), and CRP was measured in mg/L (normal range, 0–10 mg/dL).

significant correlations were also found for CRP values. CRP levels were correlated with the NIH Stroke Scale score at 24 hours (r=0.224; p=0.021); there was a significant difference in NIH Stroke Scale score between 24 hours and three months (r=0.249; p=0.005); there was a significant difference in NIH Stroke Scale score and MRS score at three months (r=0.186; p=0.035) (Figures 3, 4).

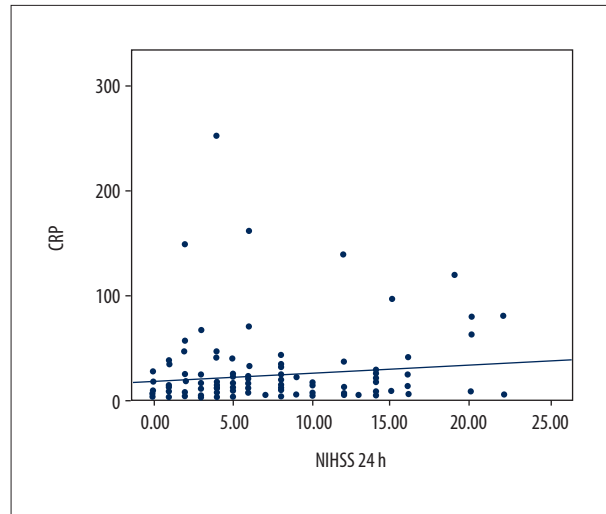
The mean MPV was 8.21±1.35 fL, and the mean CRP was 22.52±34.75 mg/dL, respectively (Table 2). The median (maximum–minimum) MPV values of the patient subgroups with or without stroke resolution were 8.25 fL (13.41–6.38 fL) and 7.88 fL (13.0–5.71 fL), respectively. There was a significant difference between the patients with and without recovery in 24 hours in terms of MPV (p=0.025).

Median (maximum–minimum) CRP values were 9 mg/dL (162–2 mg/dL) and 13.5 mg/dL (252–2 mg/dL) in the patients with and without recovery in 24 hours. Similarly, a statistical significant difference (p=0.008) was found between the CRP values of patients with recovery at 24 hours and the CRP values of the patients for whom no functional recovery at 24 hours following the onset of AIS (Table 3). The presence or absence of functional neurological deterioration, very good outcome, good outcome and patient mortality were also evaluated. No significant differences were found between these categories in terms of MPV or CRP values (p>0.005).

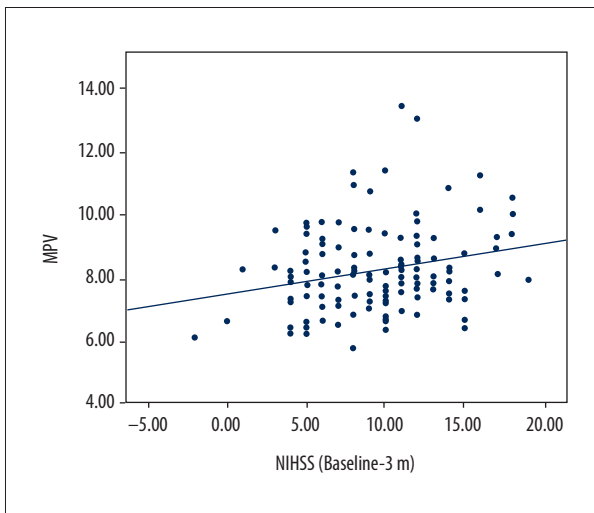
Female gender was determined as a predictor of significant patients recovery from AIS within 24 hours of the onset of symptoms (OR, 2.5; 95% CI, 1.2–5.3; p=0.016). The study findings



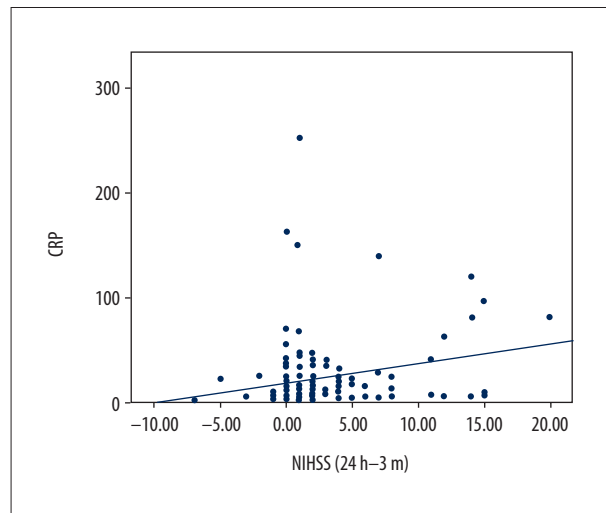
**Figure 1.** Correlation of MPV and change in NIHSS score at 24 hour.



**Figure 3.** Correlation of CRP and NIHSS score at 24 hour.



**Figure 2.** Correlation of MPV and change in NIHSS score at 3 months.



**Figure 4.** Correlation of CRP and change in NIHSS score between 24 hour and 3 months.

**Table 3.** Mean MPV and CRP values of patients.

	Total (N=129)	Not dramatical recovery (n=72)	Dramatical recovery (n=57)	P value
	Mean $\pm$ S.D./Median (Max.-Min.)	Median (Max.-Min.)	Median (Max.-Min.)	
MPV	8.21 $\pm$ 1.35/8.06 (13.41-5.71)	7.88 (13-5.71)	8.25 (13.41-6.38)	0.025
CRP	22.52 $\pm$ 34.75/11 (252-2)	13.5 (252-2)	9 (162-2)	0.185

Mann Whitney U test (Monte Carlo); Max. – Maximum; Min. – Minimum; S.D. – standard deviation.

showed that the absence of heart failure was another predictor of significant recovery (OR, 4.4; 95% CI, 1.4–13.9;  $p=0.009$ ), and also a predictor of recovery within 24 hours (OR, 3.0; 95% CI 1.1–8.0;  $p=0.029$ ). The absence of symptomatic intracerebral

hemorrhage was correlated with recovery (OR, 15.9; 95% CI 1.7–142.8;  $p=0.009$ ), whereas the presence of intracerebral hemorrhage was a strong predictor of worsening patient recovery (OR, 45.6; 95% CI 4.6–447.9,  $p<0.001$ ).

The occurrence of a previous stroke was significantly associated with a very good clinical outcome (OR, 2.5; 95% CI 1.1–5.7;  $p=0.047$ ). Predictors of good outcome were absence of symptomatic intracerebral hemorrhage (OR, 18.6; 95% CI, 1.1–343.5;  $p=0.009$ ), absence of hemorrhagic transformation (OR, 3.1; 95% CI, 1.3–7.6;  $p=0.014$ ), and absence of a previous stroke (OR, 3.5; 95% CI, 1.3–9.4;  $p=0.011$ ).

The mean difference of NIH Stroke Scale scores between admission and at three months after admission and also MRS scores at three months were evaluated in terms of clinical parameters. Significant differences were identified for gender, stroke subtype, symptomatic hemorrhage, previous stroke, previous antiplatelet therapy use, and the presence of cardiac failure.

The mean difference of NIH Stroke Scale score between admission and at three months was greater in women than in men (10.6 vs. 8.8;  $p=0.023$ ) indicating an improved recovery in AIS in women.

A statistically significant difference was found between acute ischemic subtypes in terms of the change in NIH Stroke Scale scores. Patients with cardio-embolic stroke had a significant reduction in NIH Stroke Scale scores between admission and at three months compared with patients with small vessel occlusion (10.3 vs. 6.5;  $p=0.001$ ). A similar difference was also detected between patient groups with small vessel occlusion and cryptogenic stroke (6.5 vs. 9.3;  $p=0.037$ ). The patients with cardio-embolic had higher significantly greater MRS values compared with patients with cryptogenic stroke (2.9 vs. 1.7;  $p=0.001$ ).

Increased MRS values were found in patients who had symptomatic hemorrhage compared with those without hemorrhage (5.8 vs. 2.4;  $p=0.001$ ). Increased MRS values were found in patients who had previous antiplatelet treatment compared with patients who were not treated with antiplatelet therapy (2.9 vs. 2.2;  $p=0.035$ ). Increased MRS values were found in patients who had cardiac failure compared with patients without cardiac failure (3.7 vs. 2.3;  $p=0.010$ ).

## Discussion

This study investigated the association between mean platelet volume (MPV), C-reactive protein (CRP), and prognosis in patients with acute ischemic stroke (AIS) following intravenous (IV) thrombolytic treatment. The findings showed that the mean difference between the National Institutes of Health (NIH) Stroke Scale scores for functional ability in patients with between admission and the third month following admission was greater in female patients. A significant correlation was found between MPV and CRP, and the difference of NIH Stroke Scale scores at 24 hours or three months following AIS. The

study findings also showed a significant correlation between CRP and MRS at three months following AIS and a significantly increased MPV in patients with recovery in functional ability. Both MPV and CRP were not associated with impaired neurological function or patient outcome following AIS.

The findings of this study showed that female gender, the absence of heart failure or symptomatic intracerebral hemorrhage were found to be associated with significant patient recovery following AIS. Previous stroke, the absence of hemorrhage or hemorrhagic transformation, were related to good patient outcome. The patients with cardioembolic stroke, symptomatic hemorrhage, or who had previous antiplatelet treatment or cardiac failure had increased MRS values compared with patients with cryptogenic stroke.

Gender difference in stroke outcome has been studied in previous local and multinational clinical studies, and stroke has been found to be more common in men, but women have been reported to have a higher risk of stroke, are more likely to experience recurrent stroke, and to suffer from more severe strokes compared with men [1]. Data from 19 countries and five continents were reviewed in a previous study and the results showed that the male-to-female ratio ranged between 0.95 and 2.13 with a pooled ratio of 1.33 [8]. In the current study, the male-to-female ratio was 1.9, which is supported by previously published studies.

According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST), acute ischemic stroke (AIS) can be classified into five etiological subtypes: large-artery atherosclerosis; cardiac thrombo-embolism; small-vessel occlusion; stroke of other determined etiology; and stroke of undetermined etiology [9]. In the current study, the most frequently detected stroke subtype was cardio-embolic stroke, which had a frequency of 48.1%, which was greater than other studies, including that of Al-Rajeh et al. who reported a frequency of cardioembolic stroke of 14% [9], and of 16% by Bogousslavsky et al. [11], of 18% by Arboix et al. [12], of 19.4% by Timsit et al. [13], of 22% by Rothrock et al. [14], of 26% by Oruc et al. [15], and of 30.6% by Norrvig and Löwenhielm [16].

The relationship between MPV and AIS has previously been well studied, and increased MPV values in ischemic stroke patients have been reported in previous studies [17–21]. An increased CRP level has also been shown to be a strong predictor of AIS [22]. In the current study, an evaluation was made of the correlations between MPV and CRP values and changes in NIH Stroke Scale and MRS scores. The study findings were that MPV and CRP values were significantly positively correlated with changes in NIH Stroke Scale and MRS scores. Also, significant correlations between MPV values and NIH Stroke Scale scores were previously reported [23].

In support of the findings of the present study, Gill et al. found that changes in CRP levels were correlated with NIH Stroke Scale scores, which may support CRP as a prognostic marker for clinical outcome in patients with AIS [24]. However, different results have also been published. Ntaios et al. evaluated the associations between MPV values and NIH Stroke Scale scores but did not detect any significant correlations [25]. In another recently published study, Ciancarelli et al. reported that no significant correlation was found between MPV values and NIH Stroke Scale and MRS scores [26]. Chen et al., investigated thrombocyte microparticles and MPV values in 112 patients with AIS, in which patients were divided into two groups, as large artery occlusion, and small artery occlusion group, but in both groups, MPV was found to be increased [27]. In another study that included 215 patients with atherothrombotic stroke, MPV was found to be increased in patients with severe carotid stenosis [28]. Greisenegger et al. showed that increased MPV was associated with poor patient outcome in a study that included 776 patients with AIS or transient ischemic attack (TIA) [4].

Increase in platelet volume results in increased numbers of platelet granules, and so an increase in MPV may be regarded as being associated with more reactive platelets compared with smaller volume platelets [29]. Therefore, an increased MPV may be regarded as an indicator of increased thrombocyte reactivity, and as shown in previously reported studies, platelets with an increased MPV may contribute to the formation of ischemic stroke due to carotid stenosis or embolic causes, due to their increased reactivity that is associated with an increase in platelet volume.

This study had several limitations. There were only 129 patients identified from three centers. A larger patient sample size should be studied in future. In this study, the NIH Stroke Scale scores were used for functional patient assessment only, but in future studies, these scores could be combined with the evaluation of other serum markers, as could the MRS scale. The addition of imaging studies to evaluate the size of the cerebral infarcts and changes in cerebral infarction and ischemia would also be of value in evaluating the meaning of changes in serum and platelet markers. Finally, in future studies the additional measurement of high-sensitivity CRP (hsCRP) that detects low levels of CRP in the blood can also identify low levels of inflammation and may be of value in the study of patient outcome following AIS.

## Conclusions

The findings of this study showed that mean platelet volume (MPV) and C-reactive protein (CRP) values were positively correlated with changes in National Institutes of Health (NIH) Stroke Scales and modified Rankin Scale (MRS) scores for physical disability and prognosis in patients with acute ischemic stroke (AIS) following intravenous (IV) thrombolytic treatment. However, this was a small retrospective clinical study, and because of the conflicting results from previous studies, further large-scale, controlled, prospective studies are recommended to determine the prognostic role for MPV and CRP levels in the outcome of AIS treated with IV thrombolytic agents.

## Competing interests

None.

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