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The effect of the mean platelet volume on short-term prognosis in acute ischemic stroke patients who underwent intravenous thrombolytic therapy

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ABSTRACT

Objective: To evaluate the effect of the mean platelet volume (MPV), on the short-term prognosis and bleeding complications of acute ischemic stroke patients who underwent intravenous tissue plasminogen activator (IV-tPA) treatment.

Patients and Methods: Between 01.01.2018 and 01.06.2021, 314 ischemic stroke patients who applied to our clinic with acute neurological deficit were included in the study retrospectively. Alteplase was administered as IV-tPA treatment for 1 hour. MPV value was measured before the treatment and was evaluated as the main parameter. The patients were examined under 4 groups (≤8.8fL, >8.8 – ≤9.9, >9.9-≤10.8, >10.8fL) according to their MPV values, and age, gender, comorbidities, and treatment initiation parameters were standardized by statistical methods. It was compared whether there was a significant difference between the MPV groups in terms of short-term prognosis according to the admission National Institutes of Health Stroke Scale (NIHSS) scores and discharge NIHSS scores and also bleeding complications.

Results: A total of 314 patients, 145 women with a mean age of 76.7±13.0, and 169 men with a mean age of 66.3±13.1, were included in the study. 31 patients (9.9%) died before discharge. The mean MPV value was 9.64±1.15fL and the mean NIHSS score was 9.1±4.9 at admission, and the mean NIHSS score was 4.3±4.7 at discharge. When the NIHSS difference between admission and discharge was compared in the 4 groups, it was found that the prognosis was better in Group 3 with MPV >9.9-≤10.8 compared to Groups 1 and 4. (p=0.002; p<0.01). Despite this, it was seen that low or high MPV values could not be considered as a prognostic factor alone in patients who received IV-tPA treatment, since, there was no significant difference between the 3rd group and the 2nd group in terms of NIHSS decrease and the 4th group had a worse prognosis than the 3rd group.

There was no statistical significance between MPV groups in terms of hemorrhage complications (p value for intracerebral, gastrointestinal, urogenital hemorrhage complications were 0.540, 0.980, 0.783, respectively).

Conclusion: In our study, it was revealed that MPV value, is not an independent risk factor in patients with acute ischemic stroke receiving IV-tPA treatment and cannot be used as a prognostic marker.

Keywords: Stroke, Prognosis, MPV, IV-tPA

1.INTRODUCTION

Stroke ranks third among the causes of loss of function worldwide, according to Disability Adjusted Life Years (DALY) measurements [1,2]. Nowadays, it is aimed to reduce the mortality and morbidity of stroke patients. Improvement in the prognosis of stroke is increased with intravenous tissue plasminogen activator (IV – tPA) therapy and mechanical thrombectomy (MT) treatments. The mechanism of thrombus formation and risk factors in ischemic stroke are a matter of interest for researchers both for primary prevention and for treatment planning. Due to the easy accessibility of blood parameters, many publications investigating the relationship with stroke draw attention. It is thought that hyperactive platelets play an important role in thrombus formation and the Mean Platelet Volume (MPV) value is associated with platelet activation [3]. The MPV is an indicator of the size of the platelets, and "increase in MPV value" means an increase in platelet diameters. The reference value is 7.4-12 fl (femtoliter:µm3) on average, and it can be checked during complete blood count without additional cost. It has been shown in various publications that as MPV increases, platelet activation increases (due to aggregation, thromboxane A2, platelet factor 4 and β-thromboglobulin release) [4,5]. The MPV value was found to be higher in all stroke types compared to the healthy population [6]. The elevated MPV may predict the disabling of the fatal ischemic stroke in the patients treated with tPA [7]. Additionally; the value of MPV in predicting the risk of the secondary hemorrhage in stroke patients receiving the reperfusion therapy remains unclear [8]. The aim of this study

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was to evaluate the effect of MPV on the short-term prognosis and bleeding complications of acute ischemic stroke patients who underwent IV-tPA treatment.

2. PATIENTS and METHODS

We conducted a single-center, retrospective analysis of the patients who applied to Health and Sciences University Fatih Sultan Mehmet Training and Research Hospital emergency between 01.01.2018 and 01.06.2021 with acute stroke presentation. The patients who were in the first 4.5 hours of the onset of their complaints and got reperfusion therapy were informed about all risks and possible complications of the study, including death before treatment. MPV value, found in the routine hemogram taken before the reperfusion treatment was evaluated as the main parameter. Alteplase was used as a thrombolytic agent. The total dose recommended in stroke guidelines was 0.9 mg/kg for the treatment of alteplase. 10% of the calculated total dose was administered as a bolus and the remaining dose was administered as a 1-hour infusion. The max dosage was 90 mg in total. The National Institutes of Health Stroke Scale (NIHSS) was used for all patients included in the study before treatment (initial NIHSS) and at discharge inorder to evaluate their response to the treatment. Age, gender, comorbidities (diabetes, hypertension, atrial fibrillation), IV-tPA onset time were standardized by statistical methods, and it was evaluated whether the MPV value, which was measured at the time of admission, was effective on the NIHSS change and on the major bleeding complications that developed within the first 24 hours after IV – tPA treatment. Patients were divided into 4 groups according to the MPV cut-off values in the study of Debiec et al., in which they investigated the effect of MPV on prognosis [3]. In the 1st group MPV≤8.8fL (N:82), 2nd group >8.8 – ≤9.9 fL (N:123), 3rd group >9.9-≤10.8 fL (N:61), and 4th group >10.8 fL (N:48) was planned. It was evaluated whether there was a statistically significant difference between the groups in terms of age, gender, tPA onset time, admission NIHSS, discharge NIHSS, admission and discharge NIHSS difference, comorbidities, antiaggregant/anticoagulant use, bleeding complications and death rates during hospitalization.

ROC analysis was performed to predict the cut-off point of the MPV value for any bleeding complications. Patients under 18 years of age, patients who do not get anticoagulants but whose IV-tPA treatment was interrupted due to high INR, patients who underwent mechanical thrombectomy after thrombolytic therapy or known hematological pathology – malignancies, patients whose treatment could not be completed due to any allergic reaction, patients whose treatment could not be completed due to acute hemorrhagic complications while IV-tPA was continued were not included in the study.

Ethics committee approval was received from Health Sciences University Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee on 27.05.2021.

Statistical Analysis

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, the distribution of the data was evaluated with the Shapiro-Wilk Test, as well as the descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum). Kruskall-Wallis test for comparison of quantitative data of three or more groups; Mann-Whitney U Test was used for comparison of two groups. Chi-square analysis was used to determine the relationship between qualitative data. Spearman's correlation analysis was used to determine the relationship between quantitative data. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

3. RESULTS

The study included 314 patients, 169 men with a mean age of 66.3± 13.1 years and 145 women with a mean age of 76.7± 12.9 years. It was found statistically significant that the mean age of the male group was lower than that of the females ($p=0.001$; $p<0.05$). It was found that 9.9% (n=31) of 314 patients included in the study died in the hospital. Of the patients who died, 32.3% (n:10) were male and 67.7% (n:21) were female. The mean MPV and platelet in the cohort were 9.64 ±1.15 fL and 269.7 ± 73.7 x 10^3/μL respectively. Age, gender, tPA onset time, medical history (diabetes, hypertension, atrial fibrillation), antiplatelet / anticoagulant use according to MPV groups were evaluated. (Table I).

According to the MPV groups; age, tPA onset time, gender and comorbidities did not show any statistically significant differences. Although there was no difference in terms of antiplatelet use ($p>0.05$); it was found statistically significant that the anticoagulant use in the 1st group was lower than in the 4th group ($p=0.001$; $p<0.01$) (Table I).

Admission NIHSS, discharge NIHSS, admission and discharge NIHSS difference, intracerebral hemorrhage, gastrointestinal system hemorrhage, urogenital hemorrhage, other bleeding complications and their relationship with MPV groups were evaluated in Table II.

No statistically significant difference was observed between MPV groups in terms of bleeding complications and death rates. However; it was statistically significant that the initial-discharge difference of NIHSS in the 1st group is lower than that of groups 2 and 3 and ($p=0.001$; $p<0.01$) that the initial-discharge difference of NIHSS in the 3rd group is higher than that of group 1 and group 4 ($p=0.001$; $p<0.01$). No statistical significance was observed between groups 2 and 3 ($p>0.05$).

ROC analysis was performed to predict the cut-off point of the MPV value for any bleeding complications. When the MPV cut-off taken as 8.85, the sensitivity was 76%; the specificity was 69.1%. It was found statistically significant that all patients with other bleeding complications (epistaxis, gingival, hemoptysis otorrhagia, and subcutaneous hematoma) were observed in the second group which MPV higher than 8.85 fL ($p=0.034$, $p>0.05$). However, no statistical significance was observed in terms of intracranial, gastrointestinal and urogenital bleeding complications ($p>0.05$) (Table III).

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Table I. *Comparison of prognostic factors according to MPV groups*

MPV (fL)	Group 1 8.8 (82)	Group 2 8.8< 9.9 (123)	Group 3 9.9< 10.8 (61)	Group 4 >10.8 (48)	P*	Post Hoc**
Age	70.8 (14.8)	70.5 (12.3)	72.4 (15.5)	71.6 (14.9)	0.490	
Gender (Female)	38 (26.2%)	58 (40%)	28 (19.3%)	21 (14.5%)	0.983	
Atrial Fibrillation	15 (19.5%)	31 (40.3%)	13 (16.9%)	18 (23.4%)	0.091	
Hypertension	58 (25.7%)	89 (39.4%)	41 (18.1%)	38 (16.8%)	0.575	
Antiaggregant Use	33 (26%)	52 (40.9%)	26 (20.5%)	16 (12.6%)	0.729	
Anticoagulant Use	1 (6.3%)	7(43.8%)	2(12.5%)	6 (37.5%)	0.037*	1 vs 4
IV-tPA Onset Time (Minute)	185.0 (57.7)	180.2 (52.9)	176.7 (54.3)	193.0 (54.1)	0.394	

*Values are mean ± SD for quantitative variables and % for qualitative variables. MPV: mean platelet volume; fL: femtolitre; IV-tPA: intravenous tissue plasminogen activator *p <0.05, **Post Hoc: statistically significant results*

Table II. *NIHSS changes and bleeding complications according to MPV groups*

MPV (fL)	Group 1 8.8 (82)	Group 2 8.8< 9.9 (123)	Group 3 9.9< 10.8 (61)	Group 4 >10.8 (48)	P*	Post Hoc**
Initial NIHSS	8.5 (4.7)	9.0 (4.9)	10.0 (4.9)	9.1 (5.1)	0.243	
Discharge NIHSS	5.2 (5.3)	4.05 (4.8)	3.1 (3.2)	4.8 (4.8)	0.084	
Initial- Discharge NIHSS	2.7 (5.0)	4.5 (4.8)	5.9 (4.6)	3.8 (5.2)	0.002**	1vs 2.3 3vs 1.4
Intracranial Hemorrhage	9 (19.1%)	21 (44.7%)	8 (17%)	9 (19.1%)	0.540	
Urogenital Hemorrhage	3 (42.9%)	2 (28.6%)	1 (14.3%)	1 (%14,3)	0,783	
GIS Hemorrhage	2 (25%)	3 (37.5%)	2 (25%)	1 (12.5%)	0.980	
Other bleeding Complications	0 (0%)	6 (54.5%)	3 (27.3%)	2 (18.2%)	0.252	
Death	6 (19.4%)	12(38.7%)	9 (29%)	4 (12.9%)	0.876	

*MPV: mean platelet volume; fL: femtolitre; NIHSS : National Institute of Health Stroke Scale; GIS; gastrointestinal system, *p <0.05, **Post Hoc: statistically significant results*

Table III. *ROC analysis for bleeding complications*

MPV (fL)	<8.85 (82)	8.85> (232)	P*
Age	70.8 (14.8)	71.2 (14.8)	0.946
Gender (Female)	38 (26.2%)	107 (73.8%)	0.973
IV-tPA Onset Time (Minute)	185.0 (57.7)	181.9 (53.6)	0.716
Initial NIHSS	8.5 (4.7)	9.3 (4.9)	0.112
Discharge NIHSS	5.2 (5.3)	3.9 (4.5)	0.055
Initial- Discharge NIHSS	2.7(5.0)	4.7 (4.9)	0.941
Atrial Fibrillation	15 (19.5%)	62 (80.5%)	0.127
Hypertension	58 (25.7%)	168 (74.3%)	0.771
Diabetes Mellitus	25 (23.1%)	83 (76.9%)	0.386
Antiaggregant Use	33 (26.0%)	94 (74.0%)	0.965
Anticoagulant Use	1 (6.3%)	15 (93.8%)	0.079
Intracranial Hemorrhage	9 (19.1%)	38 (80.9%)	0.238
Urogenital Hemorrhage	3 (42.9%)	4 (57.1%)	0.308
Gastrointestinal Hemorrhage	2 (25.0%)	6 (75.0%)	0.942
Other Bleeding Complications	0 (0%)	11 (100%)	0.034*

MPV:Mean platelet volume; fL: Femtolitre; NIHSS: National Institute of Health Stroke Scale; IV-tPA: intravenous tissue plasminogen acti

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4. DISCUSSION

Stroke is considered as one of the leading causes of morbidity and mortality all over the world. Considering that one quarter of all strokes are predicted to recur, modifiable risk factors such as DM, hypertension, dyslipidemia, obesity, smoking, and AF fibrillation must be controlled [9]. Although, studies on risk factors are still on the agenda, publications investigating stroke pathogenesis and prognosis of patients are increasing with new developing treatment methods.

The contribution of platelets to the pathogenesis of thrombus formation is undeniable [10]. Aggregation has a positive association with indicators of platelet activity, including Tx A2, PF 4 and β-TG release. Larger platelets are more reactive, produce more prothrombotic factors, and can aggregate more easily [11,12]. In this study, it was hypothesized that the prognosis of the patient group with an acute ischemic stroke and receiving iv tPA treatment and having a higher MPV value may have a worse prognosis; However, in a retrospective evaluation of 314 patients, it was found that MPV value alone could not be a prognostic factor.

Debiec et al., in their study, it was observed that patients with MPV above 10.8 fL had higher discharge NIHSS values and a worse prognosis [13]. In our study, in which the same MPV groups were used, no statistical significance was observed in terms of death, arrival NIHSS, discharge NIHSS or bleeding complications in all 4 MPV groups. However, when the groups were evaluated according to the decrease in NIHSS (arrival-discharge), it was observed that the NIHSS decrease, that is, the prognosis, in the 3rd group (MPV>9.9 and ≤10.8) was statistically better than the 1st and 4th groups. However, since there was no significant difference between the 3rd group and the 2nd group in terms of NIHSS decrease and the prognosis of the 4th group was worse than the 3rd group, it was observed that low or high MPV values could not be considered a prognostic factor alone in patients receiving iv-tPA treatment.

Arevalo-Lorido et al., in their study on 379 patients who were followed up for ischemic stroke but did not receive iv tPA treatment, it was found that at the end of first year higher MPV values (>11.5fL) were related with worse prognosis [13]. In our study, since the majority of the patients did not continue their follow-up, 3-month-6-month and 1-year MRS scores could not be evaluated, and no comment could be made regarding the effect of MPV on long-term prognosis.

In the PROGRESS study, which included 3134 people with a history of cerebrovascular disease, it was stated that high MPV was associated with an increased risk of stroke, and even every 1 fL increase in MPV value could cause an 11% increase in stroke risk [14]. In studies comparing ischemic stroke patients with control groups, it was observed that the MPV values of the stroke groups were higher than the healthy population [15,16]. In the study administered by Ntaios et al. on 623 patients, it was shown that MPV did not statistically affect stroke severity and prognosis, as in our study, in both 137 patients receiving iv tPA treatment and 486 patients who were not candidates for iv-tPA [17].

In our study, in addition to evaluating the effect of MPV on the short-term prognosis of patients, its relationship with intracranial, urogenital, GI and other bleeding complications after IV-tPA was also evaluated. When the patients were examined in 4 groups according to MPV values, no significant difference was found regarding bleeding complications. However, in ROC analysis it was found statistically significant that all other bleeding complications were in the higher MPV group (>8.85 fL). Nevertheless; it would not be totally correct to determine a clear MPV cut-off point since the number of patients with this complication was only 11.

Hemorrhage complications of iv-tPA other than intracerebral, GIS, and urogenital system are written on a case-by-case basis, but no data were found in the literature regarding other bleeding complications seen in patients receiving tPA in which the effect of MPV on prognosis was investigated. Khandelwal et al., They published the massive epistaxis, seen in 2 patients who were Covid-19 + and received IV-tPA as a case report and explained the epistaxis as the potentiation of coagulopathy due to Covid-19 infection by tPA, but they did not share any data about MPV in their study [18].

Conclusion

In this study, where it is hypothesized that short-term prognosis will worsen as MPV value increases, no statistically significant relationship can be found between increasing MPV values and prognosis. There is no difference in bleeding complications and death rates between MPV groups.

The increasing prevalence of IV-tPA treatment will allow studies to be conducted with a larger patient population. Studies that will contribute to the literature will increase day by day by diversifying prognostic evaluations, enabling long-term follow-up, and increasing the patient population.

Compliance with Ethical Standards

Ethical approval: The study protocol was approved by Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (approval number: 2021/56). Informed consent was obtained from all patients.

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Conflict of interest: The authors have no potential conflicts to declare.

Authors' contributions: CIOB: Literature search, EG, CIOB,: Study design, CIOB, IKA: Data collection, EK, IKA: Supervision and quality control, EG: Statistical advice, EG: Statistical data analysis, CIOB: Data interpretation, IKA, EG, CIOB: Drafting the manuscript. All authors read and approved the final version of the article.

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