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# The relationship between hematological parameters and prognosis of children with acute ischemic stroke

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## Abstract

**Background** Stroke is rarely seen in children, but it is a major cause of morbidity and mortality. Therefore, there is a need for inexpensive and noninvasive diagnostic methods for estimating the prognosis. Although the prognostic importance of hematological parameters in acute ischemic stroke were reported in adult studies, there is a lack in pediatric ages. The aim of the study is to investigate the relationship between hematological parameters and prognosis of acute ischemic stroke in children.

**Methods** Retrospectively scanned in the study were 106 pediatric patients with acute ischemic stroke who managed at the Medical Faculty of Erciyes University, Kayseri, between the years of 2000 and 2014. White blood count (WBC); neutrophil, lymphocyte, and platelet count; mean platelet volume (MPV); platelet distribution width (PDW); neutrophil count/lymphocyte count (N/L) ratio values obtained from the measurements and initial symptoms; demographical features; risk factors; neurological examination; and clinical follow-up were recorded. Their hematological parameters were compared with those of 106 age and sex-matched healthy individuals.

**Results** MPV and PDW values were found similar in patient and control groups, and the platelet count was found significantly low in the control group ($p = 0{,}028$). WBC, neutrophil count, and N/L ratio were found considerably high in the patient group ($p < 0.001$). Lymphocyte count, however, was found significantly low in the control group ($p < 0.001$). No statistically significant difference was detected in WBC, neutrophil count, lymphocyte count, platelet count, N/L ratio, and MPV and PDW values between the group with sequelae and the one without sequelae. In addition, it was determined that WBC, neutrophil count, lymphocyte count, platelet count, N/L ratio, and MPV and PDW values in the univariate Cox-regression analysis of the patient group had no effect on survival and disease-free survival. When receiver operating characteristic curve was applied, it was observed that the area below WBC, N/L ratio curve was important in the patient group in terms of predicting acute ischemic stroke.

**Conclusion** The values of WBC, neutrophil count, and N/L ratio differ significantly from those of the control group. The WBC and N/L ratio may help for an earlier diagnosis in children with acute ischemic stroke. WBC, thrombocyte count, MPV, PDW, and N/L ratio do not constitute a risk in overall survival, disease-free survival, and sequelae development.

**Keywords** Arterial ischemic stroke · Children · Prognosis · Hematological parameters

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## Introduction

The World Health Organization (WHO) defines stroke as "a clinical syndrome of rapidly developing focal or global disturbance of brain function lasting > 24 h or leading to death with no obvious nonvascular cause" [1]. Classically, stroke is divided into two subtypes as ischemic and hemorrhagic stroke. Although the estimated incidence of ischemic stroke in children older than 28 days is variable, in large prospective studies, the incidence of overall stroke is 13/100000, the incidence of ischemic stroke is 7.9/100000, while it is 5.1/100000 for

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hemorrhagic stroke [2–4]. The most common risk factors in stroke for children are congenital heart disease, sickle cell anemia, infections, and various prothrombotic conditions [5, 6]. Pediatric ischemic stroke is an important cause of long-term disability, including seizures in up to 25%, long-term significant neurologic sequelae in more than half of patients, and death in 6–14% [7, 8]. Since its mortality and morbidity are high, there is a need for cheap, practical tests to be used in predicting the course of the disease. In general, since the whole blood count is done for most patients at the time when they reach hospital following the development of symptoms, assessment of hematologic parameters can be a helpful guidance. The authors did not encounter any pediatric studies examining the relationship of hematological parameters and ischemic stroke in English Medical literature review.

In the current study, we have aimed to research the relationship between the platelet parameters at the time of diagnosis (platelet count, MPV, PDW) and peripheral blood cells (WBC, neutrophil and lymphocyte count, N/L ratio and overall survival, disease-free survival, and incidence of sequel development).

## Patients and methods

Retrospectively scanned in the study were 202 patients with acute ischemic stroke who were managed at the Medical Faculty of Kayseri Erciyes University between the years of 2000 and 2014. The patients' age, sex, absence or presence of a chronic disease, history of medication, platelet and peripheral blood cell parameters, outcomes, prognosis, and complications were recorded. Ninety-six patients having one or more of the following conditions were excluded from the study: Those aged less than 1 month and above 18 years, having a benign or malign hematologic disease, having an oncologic disease, receiving chemotherapy, those having inaccessible platelet and peripheral blood data pertaining to the time of diagnosis, having whole blood count studied with a different device were excluded from the study. The control group was comprised of sex- and age-matched, completely healthy individuals with no history of stroke, chosen from among the children applying to the pediatric outpatient clinical for a check-up or vaccination. The data was obtained through computer from the hospital database.

Recorded in the study were the results of the peripheral blood count of all the cases done within the first 2 h from the samples placed in tubes with ethylenediaminetetraacetic acid (EDTA) within the first 6 h of application to hospital (Siemens Advia 2120/Advia 120). WBC, platelet, neutrophil and lymphocyte counts, MPV, PDW values obtained from the measurements and initial symptoms, demographical features, risk factors, neurological examination, and clinical follow-up were recorded. N/L ratio was calculated and recorded.

Ethical permission for a review of all records was granted by the ethics committee of Erciyes University.

## Statistical analyses

Histogram and q-q plots were examined. Shapiro-Wilk's test was applied to assess the data normality. Levene test was used to test variance homogeneity. A logarithmic transformation (base 10) is applied for WBC due to its highly skewed distribution. To compare the differences between groups, either a two-sided independent samples *t* test or Mann-Whitney U test were applied for continuous variables; Pearson's $\chi 2$ test was applied for categorical variables. Univariate COX proportional hazard analysis was performed to identify the risk of WBC, N/L ratio, PDW, platelet count, and MPV on overall survival and disease-free survival. Hazard ratios are calculated with 95% confidence intervals. ROC analysis was applied to identify the predictive ability of log (WBC), N/L ratio, and PDW and MPV markers on ischemic stroke. Area under ROC curves were calculated with 95% confidence intervals and compared each other using DeLong's test. For each marker, cut-off values are determined using Youden index. Using these cut-off values, for each marker, sensitivity, specificity, and positive and negative predictive values are calculated with 95% confidence intervals. Analyses were conducted using R 3.2.1. (www.r-project.org), MVN [9], and easy ROC 1.2 [10] software. A *P* value less than 5% was considered to be statistically significant.

## Results

One hundred six consecutive children with acute ischemic stroke between 2000 and 2014 were retrospectively analyzed. The general characteristics of the patient and control groups have been summarized in Table 1. The patient group was comprised of 106 patients with ages ranging from 1 month to 18 years and a history of experiencing their first ischemic attack. No difference of age and sex was found between the patient group and the control group ($p > 0.05$). Of the platelet parameters, while MPV and PDW were found similar in both groups, the platelet count was found significantly low in the control group ($p = 0.028$). WBC, neutrophil count, and N/L ratio were found considerably high in the patient group ($p < 0.001$). Lymphocyte count, however, was found significantly low in the control group ($p < 0.001$).

Acute ischemic stroke was confirmed by magnetic resonance imaging in all 106 patients, included in the study. Further radiological techniques such as cranial computed tomographic angiography, magnetic resonance angiography, and conventional angiography were used to determine the etiology of ischemia when clinically indicated. Seizure was detected as the most common reason for applying to the

**Table 1** Demographic characteristics and hematological values of the patient and control group

| Variable | Groups | | *p* value |
|---|---|---|---|
| | Control (*n* = 106) | Patient (*n* = 106) | |
| Age (months) | 54.0 (14.5–99.3) | 50.0 (13.0–96.0) | 0.825 |
| Gender (male/female) | 53 (50.0)/53(50.0) | 53 (50.0)/53(50.0) | 0.999 |
| WBC ($10^3$/μL) | 7.9 (6.5–9.4) | 8.6 (6.7–11.9) | 0.015 |
| Neutrophil count ($10^3$/μL) | 3.0 (2.2–3.9) | 4.2 (2.7–6.5) | < 0.001 |
| Lymphocyte count ($10^3$/μL) | 3.7 (2.7–4.9) | 2.7 (1.9–4.2) | < 0.001 |
| N/L ratio | 0.9 (0.5–1.3) | 1.4 (0.8–3.1) | < 0.001 |
| PDW (fL) | 42.29 ± 14.85 | 41.07 ± 13.24 | 0.530 |
| Thrombocyte count ($10^3$/μL) | 345.47 ± 110.73 | 309.97 ± 122.85 | 0.028 |
| MPV (fL) | 7.98 ± 1.31 | 8.18 ± 1.57 | 0.530 |

Values are expressed as *n*(%), mean ± SD, median(1st–3rd quartiles)

*WBC* white blood count, *N/L ratio* neutrophil count/lymphocyte count ratio, *PDW* platelet distribution width, *MPV* mean platelet volume

hospital (58%) (Table 2). Underlying clinical conditions or circumstantial risk factors were detected in 91 patients (86%); 15 patients (14%) did not have known risk factors. The risk factors are listed in Table 3. Fifteen patients (14%) had more than one risk factor.

While sequelae associated with acute ischemic stroke such as hemiparesis and epilepsy occurred in 73 patients, no sequel was detected in 30 patients. We could not gain access to the data related to sequel in three patients. No statistically significant difference was detected in WBC, neutrophil count, lymphocyte count, platelet count, N/L ratio, MPV, and PDW values between the group with sequel and the one without sequelae (Table 4). In addition, it was determined that WBC, neutrophil count, lymphocyte count, platelet count, N/L ratio, MPV, and PDW values in the univariate Cox-regression analysis of the patient group had no effect on survival and disease-free survival (Table 5).

**Table 2** Presenting complaint among 106 children with ischemic stroke

| Symptom and/or sign | Number |
|---|---|
| Fever | 14 |
| Seizure | 62 |
| Diffuse neurological signs | |
| Altered state of consciousness | 31 |
| Headache | 9 |
| Nausea and/or vomiting | 9 |
| Focal neurological Signs | |
| Hemiparesis and/or hemiplegia | 29 |
| Cranial nerve palsy | 9 |
| Speech impairment | 5 |
| Visual impairment | 3 |
| Extremity weakness, other | 2 |
| Gaze palsy | 1 |

When ROC curve was applied, it was observed that the area below log (WBC), N/L ratio curve was important in the patient group in terms of predicting acute ischemic stroke [for log (WBC), the area below the curve = 0.60, $p = 0.014$, 95%CI 0.53–0.66; for N/L, the area below the curve = 0.70, $p < 0.001$, 95%CI 0.63–0.76 (Table 6)]. When the threshold value of log (WBC) for stroke is taken to be 1.00 while the sensitivity was 36%, the specificity was 88%, positive predictive was value 75%, and negative predictive value was 58%. N/L threshold value was found to be 1.64, sensitivity 45%, specificity 86%, positive predictive value 76%, and negative predictive value 61% (Fig. 1). The relationship between log (WBC), N/L ratio, PDW, and MPV could not be established.

All the children were treated with enoxaparin continued with acetylsalicylic acid; none received thrombolytic therapy.

**Table 3** Risk factors of ischemic stroke in 106 children

| Factor | Number |
|---|---|
| Infection disease | 19 |
| Congenital heart disease | 12 (4 after cardiac catheterization) |
| Hyperlipidemia | 1 |
| Trauma | 9 |
| Moyamoya disease | 1 |
| Hypertension | 7 (4 with renal disease and 3 with aortic coarctation) |
| Fibromuscular dysplasia | 2 |
| Congenital adrenal hyperplasia | 1 |
| İmmune deficiency | 1 |
| Homocystinuria | 4 |
| Factor V Leiden mutation | 7 |
| Prothrombin 20210A mutation | 1 |
| MTHFR polymorphism | 35 |
| Undetermined | 18 |

*MTHFR* methyltetrahydrofolate reductase

**Table 4** Effect of hematological parameters on sequelae development in children with ischemic stroke

| Variable | Sequelae | | *p* value |
|---|---|---|---|
| | Absent ($n = 30$) | Present ($n = 73$) | |
| WBC ($10^3/\mu L$) | 9.5 (6.5–13.2) | 8.4 (6.6–11.1) | 0.481 |
| Neutrophil count ($10^3/\mu L$) | 5.7 (3.1–7.0) | 3.8 (2.6–5.9) | 0.052 |
| Lymphocyte count ($10^3/\mu L$) | 2.6 (1.9–4.2) | 2.7 (1.9–4.0) | 0.706 |
| N/L rate | 1.9 (0.9–3.7) | 1.3 (0.7–3.0) | 0.316 |
| PDW (fL) | 42.7 (34.4–49.0) | 41.4 (35.7–48.4) | 0.589 |
| Thrombocyte count ($10^3/\mu L$) | 267.0 (207.8–372.8) | 295.0 (248.5–357.5) | 0.180 |
| MPV (fL) | 7.9 (6.8–8.7) | 8.0 (6.9–9.3) | 0.965 |

Values are expressed as median (1st–3rd quartiles)

*WBC* white blood count, *N/L ratio* neutrophil count/lymphocyte count ratio, *PDW* platelet distribution width, *MPV* mean platelet volume

Six children (6%) died after the episode because of an underlying disease.

## Discussion

In ischemic cerebral damage associated with arterial occlusion, there occur acute local inflammation and changes in the level of inflammatory cytokines in human body [11, 12]. In reaction to inflammation, the leucocytes migrating to ischemic area decelerate blood flow, causing post-ischemic reperfusion stagnancy phenomenon [13, 14]. In few studies in adult patients with acute ischemic stroke, the relationship between leukocyte and neutrophil count and the risk of ischemic development has been studied seriously, and it has been found to be correlated to high leukocyte count and neutrophil count [15–17]. In a study on ischemic stroke subgroups, leukocyte and neutrophil counts have been found higher in jugular vein ischemia group than in small vein ischemia group and the control group. In the same study, a positive correlation has been found between the severity of stroke and the leukocyte and neutrophil counts [18]. It has been seen that the height of N/L ratio could also be used as a prognostic factor in cancer, coronary artery disease, and ischemic cerebrovascular diseases [17, 19, 20]. In agreement with the literature, in the children with the first acute ischemia in our study, WBC, neutrophil count, and N/L ratio studied within the first 6 h of application to hospital were found higher in the patient group. In predicting stroke, while the cut-off point for log (WBC) was 1.0, the cut-off point used for N/L ratio was 1.64. However, at these cut-off points, sensitivity for log (WBC) is 36%, specificity is 88%, positive predictive value is 75%, and negative predictive value is 58%. Similar values were obtained for also N/L ratio. The age-range of the patients being wide, the patients not being divided into age group and the etiological factors not being grouped (as viral or bacterial infections) may have caused us to obtain such results. Although no relationships were observed, it can be speculated that the values of WBC, neutrophil count can gain stoical importance on survival and disease-free survival by increasing the number of the included patients.

Thrombocytes play a crucial part in the pathogenesis of atherosclerotic complications and in the development of thrombus. The size of platelet measured as MPV is a favorable indicator of activities such as thrombocyte aggregation and the release of thrombocyte factor 4 and thromboglobulin. In some studies, it has been reported that cytokines, such as IL 3 and IL6, affect megakaryocyte DNA content, causing the production of larger and more reactive thrombocytes [21, 22]. Proinflammatory process can cause the generation of large thrombocytes prior to

**Table 5** Univariate Cox-regression analysis results indicating the survival risk of variables in children patients with ischemic stroke

| Variable | OS | | DFS | |
|---|---|---|---|---|
| | Univariate HR (95%CI) | *p* value | Univariate HR (95%CI) | *p* value |
| Log (WBC) | 0.86 (0.64–1.16) | 0.314 | 0.82 (0.59–1.15) | 0.254 |
| N/L rate | 0.73 (0.35–1.55) | 0.414 | 0.72 (0.34–1.49) | 0.372 |
| PDW | 1.01 (0.93–1.09) | 0.791 | 1.05 (0.95–1.15) | 0.321 |
| Thrombocyte count | 0.99 (0.98–1.00) | 0.216 | 1.00 (0.99–1.01) | 0.353 |
| MPV | 1.09 (0.64–1.83) | 0.759 | 1.16 (0.71–1.92) | 0.551 |

*OS* overall survival, *DFS* disease-free survival, *HR* hazard ratio, *CI* confidence interval, *WBC* white blood count, *N/L ratio* neutrophil count/lymphocyte count ratio, *PDW* platelet distribution width, *MPV* mean platelet volume

**Table 6** Predictive ability of hematological parameters on acute ischemic stroke

| Variable | ROC curve statistics | | Statistical diagnostic measures | | | |
|---|---|---|---|---|---|---|
| | AUC (95%CI) | *p* value | SEN (95%CI) | SPE (95%CI) | PPV (95%CI) | NPV (95%CI) |
| Log (WBC) (> 1.00) | 0.60 (0.53–0.66) | 0.014 | 0.36 (0.27–0.46) | 0.88 (0.80–0.90) | 0.75 (0.62–0.83) | 0.58 (0.54–0.62) |
| N/L ratio (> 1.64) | 0.70 (0.63–0.76) | < 0.001 | 0.45 (0.36–0.55) | 0.86 (0.78–0.92) | 0.76 (0.66–0.84) | 0.61 (0.57–0.66) |
| PDW (> 45.90) | 0.57 (0.50–0.63) | 0.464 | 0.69 (0.59–0.77) | 0.53 (0.43–0.63) | 0.59 (0.53–0.65) | 0.63 (0.55–0.70) |
| MPV (> 7.80) | 0.53 (0.46–0.60) | 0.097 | 0.53 (0.43–0.63) | 0.58 (0.49–0.68) | 0.56 (0.49–0.62) | 0.55 (0.49–0.62) |

*ROC* receiver operating characteristics, *AUC* area under curve, *SEN* sensitivity, *SPE* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *CI* confidence interval, *WBC* white blood count, *N/L ratio* neutrophil count/lymphocyte count ratio, *PDW* platelet distribution width, *MPV* mean platelet volume

cerebrovascular event. Large thrombocytes are more active and produce more thrombotic factors, and they stick more easily [23, 24]. There are studies which report that the risk of having a stroke, and the prognosis deteriorates with the increase in MPV [25, 26]. In a prospective, multi-centered study focusing on the late phase prognosis with a large number of patients, it has been detected that the size of MPV is an independent risk factor in recurrent strokes [27]. In the study by Du et al. [28], while the increase in MPV in ischemic and hemorrhagic stroke has been detected as independent risk factor, in ischemic stroke a statistically significant increase and in hemorrhagic stroke a significant decrease in thrombocyte count have been detected. It has been propounded that, in pediatric patients followed up with the diagnosis of sickle cell anemia, MPV is one of the factors contributing to increases in vaso-occlusive crisis and cerebrovascular events. In the same study, no relationship has been detected between thrombocyte count and cerebrovascular event [29]. There are also publications in which no relationship between MPV and the severity of stroke has been found [18, 30]. Ntaios et al. [31] have also claimed that no relationship exists between the MPV values in the early phase of acute ischemic stroke and the severity and prognosis of the stroke. In another study with 200 adult patients who had the history of stroke, while no relationship has been detected between MPV and the severity of stroke, a strong relationship has been found between N/L ratio and the severity of stroke [32]. In our study, no relationship has been found between MPV values; thrombocyte counts; and overall survival, disease-free survival, and sequel development. In addition, the thrombocyte count in the patient group was found low compared to the control group, which can be ascribed to viral inhibition associated with viral infections, in particular, when the disease had this etiology.

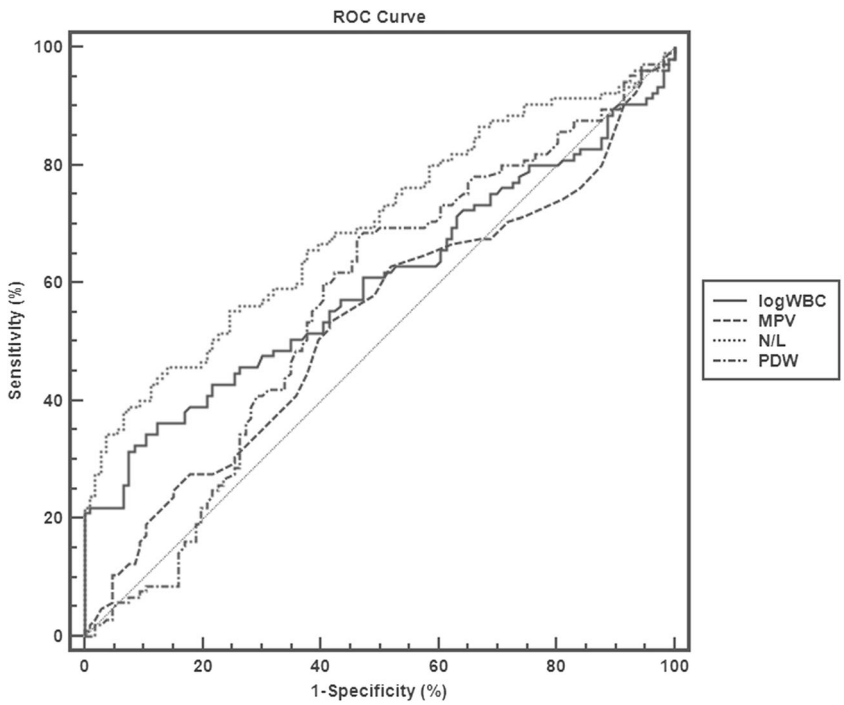


**Fig. 1** Receiver operating characteristic curve for predictive ability of hematological parameters on ischemic stroke

PDW represents the range of variability in platelet size, and it has been suggested that large PDW may be an indicator of prothrombotic status [33]. For this reason, PDW may potentially provide more information than MPV in terms of platelet reactivity and could be a predictor of cerebrovascular events in patients with asymptomatic disease [34, 35]. There are few studies in which PDW values in ischemic patients are researched. Chen et al. [36] reported no difference of PDW between the patient group and the control group as it is reported in the present study. Additionally, no relationship was found between PDW and overall survival, disease-free survival, and sequel development in the present study ($p > 0.05$).

In our study, statistical analyzes were repeated after excluding the patients with infection in the etiology of ischemia that may affect the neutrophil, lymphocyte, and platelet counts due to infection. Nevertheless, we found that WBC, N/L ratio, PDW, platelet count, and MPV values were not affected on overall survival, disease-free survival, and sequelae. WBC, neutrophil count, and N/L ratios were detected higher in the patient group when compared to the control group with the same number, age and gender distribution as similar to the previous evaluation while the platelet count was found insignificantly low in the control group. Like the majority of literature, the value of MPV was found to be significantly higher in the patient group. Retrospectivity of our study, lack of repetitive measurements, the patients not being grouped according to their ages, and etiologic factors are the limitation of our study.

In conclusion, it has been determined in this study that in children with acute ischemic stroke, WBC, neutrophil count, and N/L ratio differ significantly from those of the control group, that log (WBC) and N/L ratio do not constitute a risk in overall survival, disease-free survival, and sequel development, and finally that log (WBC) and N/L ratio could be used in predicting ischemic stroke.

On the other hand, it has been found that thrombocyte count and MPV and PDW values have been determined not to be correlated to overall survival, disease-free survival, and sequel. There is a need for multifocal, prospective studies which enable grouping according to age and etiologic factors so that peripheral blood cells, a cheap and practical test, can be used in monitoring ischemic stroke.

#### Compliance with ethical standards

**Conflict of interest** The authors have declared that there is no conflict of interest in the preparation and publication stages of this manuscript.

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