The relation between mean platelet volume and mortality in critical pediatric patients

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Mean platelet volume (MPV) is a simple and economical test that is easy to interpret and is routinely measured with automatic cell counters. It indicates platelet volume and platelet function and activation. Variations in platelet volume may occur more as a result of varying differentiation of megakaryocytes in association with production agents in bone marrow rather than of ageing of platelets in circulation. The purpose of this study was to evaluate the relation between mortality and changes in MPV values in patients hospitalized in the pediatric intensive care unit.

We evaluated MPV1 levels at the first hour of hospitalization of patients monitored in the pediatric intensive care unit between February 2014 and February 2015, MPV2 levels at the 48th hour, Δ MPV (MPV2-MPV1) values PIM, PRISM, PELOD and PMODS values, diagnosis, age and sex.

Fifty-four patients were female (45.4%) and 65 (54.6%) male. The mean age was 51.2 months m(range, 2-189 months). The mean PIM value was 35.4 ± 27.7, the mean PRISM was 18.5 ± 9.3, the mean was PELOD 21.3 ± 10.5, and the mean PMODS was 5.6 ± 3.0. Mortality was correlated with PIM, PRISM, PELOD and PMODS ($p<0.001$). Sixty-six (55.5%) patients survived. The standardized mortality rate (observed/expected mortality) was 0.99. The mean MPV1 was 9.5 ± 1.05 (range, 6.1-12.4) and mean MPV2 was 9.6 ± 1.15 (range, 6.5-12.5). There was a significant correlation between Δ MPV >0 and mortality ($p<0.001$). Mortality in patients with Δ MPV ≤0 was 21.4%, but 65.1% in those with levels >0. No correlation was determined between MPV1 and MPV2 and mortality ($p= 0.480$ and $p= 0.213$). Δ MPV>0, low levels of albumin and PRISM score were identified as independent risk factors for mortality.

An increase in MPV values following hospitalization in the intensive care unit is correlated with higher hospital mortality.

Key words: mean platelet volume, mortality, pediatric intensive care, child, critical illness.

Mean platelet volume (MPV) is a simple and economical test that is easy to interpret and is routinely measured with automatic cell counters. It indicates platelet volume and platelet function and activation. Variations in platelet volume may occur more as a result of varying differentiation of megakaryocytes in association with production agents in bone marrow rather than of ageing of platelets in circulation. Although platelet volume variables (mean platelet volume [MPV] and platelet distribution width [PDW]) have been calculated in automatic complete blood count profiles since the 1980s, only the platelet number is regarded as important in clinical practice. Normal values are 4.5-8.5 fL (femtoliters). Levels are higher in young adults and children. Large platelets are known as stress platelets, and increased MPV is associated with increased megakaryocyte growth as a response to thrombopoietic stress. Diseases in which production of young platelets increase

are also accompanied by macrothrombocytosis in association with increased destruction and sudden release of newly produced cells. Young platelets are large, dense, and more active[1,3].

Material and Methods

Children aged between 1 month and 17 years who stayed in the 7-bed pediatric intensive care unit (PICU) at a tertiary university hospital and were monitored for more than 48 hours between February 2014 and February 2015 were included in the study. Patients were excluded if their records were insufficient, or if they had idiopathic thrombocytopenic purpura, thrombocyte function disorders, thrombosis, malignancy and hypersplenism, had undergone platelet transfusion, hemorrhage during the study, immune deficiency, and those receiving chemotherapy, aspirin, heparin, or immunosuppressive therapy other than steroids. A low platelet count was not an exclusion criterion. The study was approved by the local ethics committee (No. 71 March 9th 2015).

The patient's age, sex, admission diagnosis,whether mechanical ventilation (MV) support was received, MV time, and length of stay in the intensive care unit were recorded.

Values in the patients' first days of hospitalization of hemoglobin (HGB), hematocrit (HCT), white

Table I. Admission Diagnosis

Diagnosis	N	%
Cardiologic disease	22	18.5
Nephrologic disease	21	17.6
Hemato-oncologic disease	21	17.6
Neurologic disease	18	15.1
Pulmonary disease	14	11.8
Sepsis	7	5.9
Gastroenterologic disease	5	4.3
Inborn errors of metabolism	3	2.5
Others (trauma, intoxication etc.)	8	6.7
Total	119	100

Table II. Distribution of Initial Parameters in Relation to Patients (N=119)

	Av±SD (Range)
WBC(units/mm^3)	13.730±7.300 (1.000-40.00)
HGB(g/dl)	9.84±2.08 (5.3-16)
HTC(%)	29.65±6.33 (14.5-46.1)
PLT(10^{3}units/mm^3)	289±168 (38-891)
PT(s)	20.85±11.14 (10.1-61.4)
PTT(s)	38.43±22.30 (14.5-160)
INR	1.55±0.57 (0.9-4.0)
CRP(mg/L)	48.03±56.59 (0.6-256)
PCT(ng/ml)	16.84±30.46 (0.03-100)
Albumin(g/dl)	3.24±0.72(1.4-5.0)
PICU LOS (days)	11.55±20.81 (1-150)
MV period of use (days)	12.67±24.00 (1-150)

WBC: White blood cell, HGB: Hemoglobin, HTC: Hematocrit, PLT: Platelet, PT: Prothrombin, PTT: Partial thromboplastin time, INR: International normalized ratio, CRP: C-reactive protein, PCT: Procalcitonin, PICU LOS: Pediatric intensive care unit lenght of stay, MV: Mechanical ventilation, SD: Standard deviation

blood cell (WBC), serum albumin, prothrombin time (PT), partial thromboplastin, international normalized ratio (INR), C-reactive protein (CRP), and procalcitonin (PCT) were studied. In addition, MPV1 was investigated in the first hour of hospitalization in the PICU, MPV2 after 48 hours, and Δ MPV (MPV2-MPV1) values were recorded. MPV values of 7.3±1.4 fL were accepted as normal. Patients were divided into two groups –ΔMPV ≤0 and ΔMPV >0. Complete blood counts were performed within 1 hour using K3EDTA anticoagulated blood samples on an Abbott CellDyn 3700 system (Abbott Diagnostics, Santa Clara, CA, USA).

The Pediatric Risk of Mortality score (PRISM III) is one of the most commonly used methods for determining mortality in children. It can be applied to patients for the first 12 or 24 hours from entrance to the intensive care unit, the worst value of 17 physiologic variables in these hours are recorded. Variables that most affect mortality are low blood pressure values, stupor/coma, and the presence of abnormal pupillary response. Another method for determining mortality in children is the Pediatric index of mortality (PIM II). There are 10 variables in this scoring system. Different from the PRISM score, the lowest value within the first hour of the patient's ICU admission is calculated and recorded. The most commonly used scoring system in children with multiple organ failure is the Pediatric Logistic Organ Dysfunction (PELOD). Twelve separate variables from six different scoring systems were scored according to the degree of effect on mortality; the highest possible score was 71. The Pediatric Multiple Organ Dysfunction Score scores the parameters of dysfunction of 5 organ systems made with scores between 0 and 4. Scores range from 0-20.PIM II, PRISM III, PELOD, and P-MODS were used for death rate risk calculation online (http://www.sfar.org/scores).

Statistical analysis was performed using SPSS software version 21.0. Numerical data are expressed as mean±standard deviation and median range (highest-lowest), and categorical data are expressed as percentages (%). Normally distributed numerical data were analyzed using Student's t-test, non-normally distributed data using the Mann-Whitney U test, and categorical data using the Chi square test. Measurements of the first hour and after 48 hours that showed normal distribution were compared using the paired-sample t-test. Pearson's correlation analysis was used to evaluate relations between parameters. $p<0.05$ was regarded as statistically significant. Independent risk factors were determined using logistic regression analysis.

Results

One hundred nineteen patients were enrolled, 54 girls (45.4%) and 65 boys (54.6%). The mean age was 51.2±57.6 months (range, 2-189 months). When assessing the diagnoses on admission to the ICU, the largest group (22 patients) constituted cardiac diseases, followed by nephrologic (21 patients) and hemato-oncologic diseases. The hemato-oncologic group included patients with Thalassemia major, vitamin B12 deficiency, and HLH remission (Table I). The average length of stay in the PICU was 11.6 ± 20.7 days (range, 2-150 days). Eighty-three patients were given mechanical ventilation support. The mean MV period was 12.6±24.0 days (range, 1-150 days).

The mean PIM score was 35.4 ± 27.7 (range, 1.4-99), mean PRISM score was 18.5 ± 9.3 (range, 3-53), mean PELOD score was 21.3 ± 10.5 (range, 1-52), and the mean P-MODS score was 5.6 ± 3.00 (range, 1-15).

The patients' hematologic and biochemical

Table III. Evaluation of the Relationship Between Mortality and MPV1, MPV2, Platelet, and ΔMPV

	Non-survivors	Survivors	
	Mean±SD	Mean±SD	p
MPV1	9.45±1.01	9.58±1.09	0.480
MPV2	9.78±1.25	9.52±1.06	0.213
Δ MPV	0.34±0.85	-0.07±0.59	0.003*
Platelet	285.02±189.71	293.65±151.09	[1]0.788

[1]Student's t-test *p<0.01
MPV:Mean platelet volume, SD:Standard deviation

Table IV. Correlation Between ΔMPV and Hospital Mortality

		Non-survivors	Survivors	Total
ΔMPV≤0	N	12	44	56
	%	21.4	78.6	100
ΔMPV>0	N	41	22	63
	%	65.1	34.9	100
Total	N	53	66	119
	%	44.5	55.5	100

MPV: Mean platelet volume

parameters on the first day of admission to the PICU (min.-max. mean ± SD) are shown in Table II.

Ninety-three (78.2%) of the patients had MPV-1> 8.7 fl, and 28 (23.5%) had MPV 2> 8.7. Fifty-six of the patients (47%) had ΔMPV ≤0, and it was ΔMPV >0 in 63 (53%) (Table III).

Mortality was correlated with PIM, PRISM, PELOD, and P-MODS (p<0.001). Sixty-six patients (55.5%) survived and 53 (44.5%) died. The standardized mortality rate (observed/expected mortality) was 0.99. The mean MPV1 was 9.5 ± 1.05 (range, 6.1-12.4) and the mean MPV2 was 9.6 ± 1.15 (range, 6.5-12.5). There was a significant correlation between ΔMPV >0 and mortality (p<0.001). Mortality was 21.4% in subjects with ΔMPV ≤0 and 65.1% in those with a >0 level (Table IV). No correlation was determined between MPV1 and MPV2 and mortality (p= 0.480 and p= 0.213).A statistically significant relationship was found with a negative correlation between PLT, MPV1, MPV2.There was no statistically significant relationship between PLT levels and ΔMPV (p>0.05) (Table V).

Low serum albumin levels, Δ MPV>0, and PRISM score were identified as independent risk factors for mortality. A 1% rise in PRISM values was associated with a 1.2-fold rise in hospital mortality (95% CI: [1.58-13.39]) and ΔMPV ≤0 with a 4.6-fold increase (95% CI:[1.03-1.33]) and the low albumin level 0.33(95% CI:[0.14-0.75]) was associated with increased hospital mortality.Age, sex, HGB, HTC, PT, INR, CRP, and PCT were not detected as factors that affected mortality.

Discussion

Increased platelet activity is associated with increased platelet volume. Large platelets have denser granules than small platelets, are metabolically and enzymatically more active, and have greater thrombotic potential. Increased MPV reduces platelet aggregation of prostacyclin (PGI2) and its inhibitory effect in secretion reactions. Variations in platelet volume markers are therefore of prophylactic and diagnostic importance in thrombotic and prethrombotic events. Various studies have shown an increase in MPV in acute coronary syndrome, diabetes mellitus, cerebrovascular events, renal artery stenosis, hypercholesterolemia, familial Mediterranean fever, and sepsis[3,6]. A decrease in MPV has been shown to be correlated with disease activity in ulcerative colitis and Crohn's disease. Erhan et al[7]. reported higher MPV in patients with inflammatory bowel disease compared with controls. Some studies in recent years have reported that MPV values did not increase in all situations of inflammation. Kısacık et al.[8]

Table V. Evaluation of the Correlation with PLT and MPV Measurements

	PLT	
	r	p
MPV1	-0.195	0.034*
MPV2	-0.205	0.025*
Δ MPV	-0.043	0.644

Pearson's correlation analysis *p<0.05
MPV: Mean platelet volume

found MPV to be lower during active periods of rheumatoid arthritis and ankylosing spondylitis compared with the control group.

Changes in MPV values have also been investigated in different disease groups. A study of children with rotavirus gastroenteritis in 2014 determined lower values compared with the control group, and suggested that MPV might be capable of use as a negative acute phase reactant in children with rotavirus gastroenteritis[9]. Küçük et al.[10] performed a retrospective analysis of 241 patients with appendicitis and reported a significant decrease in MPV in acute appendicitis and suggested that this could be used as a parameter to support diagnosis.

The MPV values of 44 newborn infants with respiratory distress syndrome were reported higher compared with non-RDS infants, and this situation also focused on young platelet production and also lead to increased platlet consumption due to pulmonary damage[11].

Increased MPV has been described as a risk factor for acute myocardial infarction, coronary artery diseases, and stroke, and is regarded as an independent risk factor for recurring myocardial infarction. Budak et al.[12] reported that patients with acute heart failure had higher MPV values than patients without heart failure and reported a positive correlation between BNP concentration, MPV, and neutrophil/lymphocyte ratio.

Oncel et al.[13] in 2013 reported that MPV may be useful predictor in the diagnosis of community-acquired pneumonia, albeit with low specificity. One study of patients with community-acquired pneumonia who presenting to the emergency department also concluded that MPV might be useful in determining severity of disease and in predicting mortality[14].

Van der Lelie et al.[15] determined normal levels of MPV in cases of localized infection, but reported a significant increase in MPV independent of platelet number in cases of sepsis. The authors suggested that this increase in MPV might indicate the presence of both a developing invasive infection and the presence of an infection not responding to antibiotic therapy.

The rise in MPV values in the initial stage of sepsis is not solely an increase in the production of large platelets, it may also be associated with other factors affecting platelets in the circulation. One study of 214 adult patients with sepsis in 2014 identified a significant increase in MPV on the 3rd day in patients with Gram-positive sepsis and on the 5th day in patients with fungal sepsis, and reported a more powerful correlation between MPV elevation and fungal sepsis in particular[16]. Sepsis was only present in 7 patients in our study, and no sepsis subgroup could therefore be established.

Studies have also considered the relation between MPV and changes in MPV values and mortality MPV.In a retrospective study involving 124 adult patients with septic shock, while an increase in MPV was detected during follow-up in the non-survivor group, a decrease in PLT values was noted. The absence of high or increased MPV during the first three days in patients with septic shock have been reported as a good marker for mortality. APACHE II score was also able to foresee outcomes in patients with sepsis, but stressed that the MCV was a stronger predictor[17]. However, in our study, no correlation was determined between mortality and PLT, MPV 1, and MPV 2, but 2 days after admission there was a statistically significant association between mortality and an increase in MPV.Similarly, we found an association between mortality and scores of pediatric mortality PIM, PRISM, PELOD and PMODS ($p<0.001$).

Gao et al.[18] assessed 124 patients with septic shock and determined significantly higher MPV in the non-surviving group compared with the survivors. In 2014, Zampieri et al. [19]observed higher mortality in patients with rising MPV values and decreasing platelet numbers and reported that every 1% increase in MPV values raised mortality 1.28-fold but identified no correlation between inflammatory cytokine levels and changes in MPV. We also determined that every 1% increase in MPV increased mortality 4.3-fold. Mortality in patients with $\Delta MPV < 0$ was 21.4%, compared with 65.1% in those with $\Delta MPV > 0$. In the logistic regression analysis, $\Delta MPV > 0$, the decrease of albumin and PRISM score were identified as independent risk factors for mortality.

In 2016, a meta-analysis of 15 trials found no correlation between initial MPV values and

hospital mortality, and no significant difference was determined between ethnicity, sepsis and mortality rates in a subgroup analysis.However, in our study, the increase in the MPV a few days after admission was associated with increased hospital mortality rate [20].

One study involving preterm infants with sepsis reported higher MPV and PDW values in the non-survivor group and identified a positive correlation between MPV, IL-6, and CRP. The authors reported that a cut-off value of MPV >10.35 fL had 97.8% sensitivity and 84.9% specificity in determining mortality in this patient group[21]. In our study, the mean MPV1 value was 9.5 fL and the mean MPV2 was 9.6 fL. No relation was determined between mean MPV1 and MPV2 values and mortality (p= 0.480 and p= 0.213).

We determined that an increase in MPV following hospitalization in the pediatric intensive care unit was correlated with higher hospital mortality. This finding suggests that increased MPV may be a marker of hospital mortality in critically ill children. MPV, a simple, economical and easily accessible parameter may be useful in estimating prognosis, in addition to clinical and laboratory scoring systems.

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