Platelet Activation and Inflammation in Hypertensive Children with Non-dipper and Dipper Status

Nuran Cetin,[1] Aslı Kavaz Tufan[2]

[1]Department of Pediatric Nephrology, Faculty of Medicine, Eskisehir Osmangazi University, Turkey.
[2]Department of Pediatric Nephrology, Faculty of Medicine, Eskisehir Osmangazi University, Turkey.

Keywords. inflammation, platelet activation, non-dipper hypertension, children

Introduction. The patients with non-dipper hypertension have an increased risk for target organ damage because of inflammation and platelet activation. In this study, we aimed to investigate the association between ambulatory blood pressure monitoring (ABPM) values and inflammation with platelet indices in children with dipper and non-dipper hypertension.
Materials and Methods. A total of 153 patients who underwent ABPM were included in this retrospective study. The participants were divided into three groups (61 non-dipper hypertensive, 28 dipper hypertensive, 64 normotensive). Neutrophil and platelet count, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW) were matched data among groups.
Results. The neutrophil counts were higher in the non-dipper and dipper groups compared with the normotensive group ($P < .05$, $P < .05$, respectively). Also, MPV levels were significantly higher in the non-dipper and dipper groups than in normotensive group ($P < .05$, $P < .05$, respectively). Logistic regression analysis showed significant association between non-dipper status and MPV with platelet count ($P < .05$, $P < .05$, respectively). The abilities of MPV and platelet count to predict the non-dipper status were determined by receiver operating characteristic curve analysis (areas under the curve were 0.709 and 0.604, respectively).
Conclusions. The higher MPV and neutrophil count may be potential indicators of increased risk for the development of hypertension in children. In addition, MPV and platelet count may help to determine the presence of non-dipper status in children with hypertension.

IJKD 2019;13:105-12
www.ijkd.org

Original Paper

INTRODUCTION

Hypertension is one of the important causes of chronic diseases such as coronary heart disease and stroke.[1] The prevalence of hypertension has increased significantly in children in recent years.[2] Children with hypertension have an increased risk of left ventricular hypertrophy and atherosclerosis in their later life.[3-5] The diagnosis of hypertension is usually made by repeated clinical measurements. However, clinical measurements of blood pressure (BP) do not provide enough information about the detailed features of BP.[6] Ambulatory blood pressure monitoring (ABPM) is a diagnostic method which shows the features of BP during 24-hour. Published reports have shown that ABPM gives more accurate information about mean BP level, the diurnal rhythm of BP, and BP variability.[7] It has been shown that ABPM has an ability to estimate target organ damage and cardiovascular risk in children and adults.[8]

The non-dipper hypertension causes an increased risk for the development of cardiovascular events

than in patients with dipper hypertension. It has been reported that increased inflammation and platelet activation have a significant role in the development of target organ damage and cardiovascular events in patients with nondipper hypertension.[9] Platelet indices comprise platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT), and blood platelet count (PLT). PDW and MPV reflect the size and variability of platelets, respectively.[10,11] Several studies have reported that higher MPW is associated with obesity, acute myocardial infarction, diabetes mellitus, hypertension and acute ischemic stroke.[12,13] In addition, it has been reported that PDW is associated with inflammation and atherosclerosis.[14] PCT shows the number of platelets circulating in one unit of blood volume.[15] It is suggested that there is a correlation between PCT and increased risk of cardiovascular diseases.[16]

In the literature, it has been reported that the higher white blood cell (WBC) counts, neutrophil counts and relative lymphocytopenia are associated with atherosclerosis in the general population.[17,18] It has been reported that neutrophil lymphocyte ratio (NLR) could be a biomarker of cardiovascular diseases such as myocardial infarction.[19] In recent years, platelet lymphocyte ratio (PLR) has been suggested as a potential biomarker for cardiovascular events.[20]

In this study, we aimed to investigate the association between ABPM values and WBC, neutrophil count, platelet indices, NLR, and PLR in children with dipper and non-dipper hypertension.

MATERIALS AND METHODS

Study Group

In this retrospective study we evaluated the data from children between 5 and 18 years old who underwent ABPM between December 1, 2014 until December 1, 2017 in the pediatric nephrology outpatient clinic. The indications of ABPM were primary or secondary solitary functioning kidney, cystic kidney diseases, renal scarring due to reflux nephropathy in our outpatient clinic. The diagnosis of ambulatory hypertension was made when the mean systolic or diastolic ambulatory BP were ≥ the 95th percentiles for age, gender, and height during either the sleep or awake period.[21] We excluded patients using antihypertensive treatment, with chronic kidney disease stages 2-5, expressing signs and symptoms of active infection, diabetes mellitus, and obesity. Also, patients diagnosed with thromboembolic disorders, and hematological abnormalities were not included. The study population did not have a history of using drugs that may have affected platelet number and function.

According to the results of ABPM, the patients were divided into three groups (non-dipper, dipper, and control groups). The children in the control group had normal ABPM values and three resting BP measurements.

The clinical and laboratory information were obtained by electronic medical records. Therefore, data for patients with platelet counts of less than 150.000 /mm^3 were not included in this study.

Ambulatory Blood Pressure Monitoring

ABPM was performed over a 24-hour time period using the Scanlight II/III long-term blood pressure monitoring system. BP was measured every 20 minutes during daytime and every 30 minutes during nighttime (only recordings with a minimum of 40 readings and without breaks longer than 2 hours). Mean systolic and diastolic BP at daytime, nighttime, and 24 h were calculated. BP readings were expressed as the BP load (percentage of systolic and diastolic BP readings at daytime and nighttime above the 95th percentile). Non-dipping status was defined as a less than 10% reduction in average nocturnal systolic and/or diastolic BP.

Ethics Committee Approval

This study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis were performed using SPSS 11 (SPSS Inc, Chicago, IL). Values were expressed as mean and SD for continuous variables and interquartile range (IQR) for qualitative variables. The Shapiro–Wilk test was used to determine the normality of data. Means were compared using independent sample *t* test in normally distributed data. Comparisons of the non-normally distributed data were done via the Mann-Whitney U test. Correlations between variables were evaluated using Pearson's or Spearman's tests as appropriate. A *P* value < .05 was considered significant. Qualitative

variables were compared using the chi-square test. Linear regression analysis was performed to explore the relationship of office BP and ABPM values with platelet indices, NLR, and PLR as the dependent variables. A logistic regression analysis was performed to determine the influence of these biomarkers on the presence of non-dipper status in patients with ambulatory hypertension. Receiver-operating characteristic (ROC) analysis was used to determine the cutoff values and the sensitivity/specificity of MPV and platelet count.

RESULTS

The records of 255 patients who underwent ABPM were retrospectively evaluated in our study. The data of 102 patients were excluded from the study because they did not meet the study criteria. The remaining 153 patients were

Table 1. Demographic and Laboratory Data of the Study Population.

	Non-dipper (n = 61)	Dipper (n = 28)	Control (n = 64)	*P*
Age (Years)	11.3 ± 3.70	12.3 ± 3.76	11.7 ± 3.48	P1 = 0.126 P2 = 0.586 P3 = 0.436
Gender (Female, %)	50.8	50	57.8	P1 = 0.379 P2 = 0.448 P3 = 0.397
BMI (kg/m^2)	23 ± 6.16	24.9 ± 7.31	22.5 ± 5.32	P1 = 0.188 P2 = 0.076 P3 = 0.639
Hemoglobin (g/dL)	13.4 ± 1.25	13.8 ± 1.05	13.2 ± 0.99	P1 = 0.261 P2 = 0.402 P3 = 0.191
White Blood Cells (mm^{-3})	7841.7 ± 2195.81	7644.8 ± 2518.24	6941.3 ± 1613.1	P1 = 0.161 P2 = 0.010 P3 = 0.116
Neutrophils (mm^{-3})	4363.3 ± 2140.92	4722 ± 2005.82	3646.2 ± 1314.84	P1 = 0.472 P2 = 0.026 P3 = 0.003
Lymphocytes (mm^{-3})	2608.3 ± 833.06	2562.9 ± 580.54	2538.1 ± 697.7	P1 = 0.582 P2 = 0.612 P3 = 0.871
NLR	1.55 (1.13 - 2.08)	1.79 (1.2 - 2.6)	1.3 (1.06 - 1.78)	P1 > .05 P2 > .05 P3 > .05
Platelet Count (10^3 mm^{-3})	308.2 ± 70.29	267.5 ± 70.9	298.8 ± 65.88	P1 < .05 P2 > .05 P3 < .05
PLR	129.6 ± 54.01	107.7 ± 27.57	127.7 ± 49.93	P1 < .05 P2 > .05 P3 < .05
MPV (fL)	8.69 ± 0.84	9.01 ± 1.14	8.1 ± 0.92	P1 > .05 P2 < .05 P3 < .05
PDW (%)	16.7 ± 0.64	16.4 ± 0.47	16.85 ± 4.03	P1 < .05 P2 > .05 P3 > .05
PCT (%)	0.27 ± 0.06	0.23 ± 0.04	0.24 ± 0.05	P1 < .05 P2 < .05 P3 > .05
CRP (mg/dL)	0.34 (0.32 - 0.93)	0.34 (0.31 - 0.61)	0.34 (0.32 - 0.41)	P1 > .05 P2 > .05 P3 > .05

Values were expressed as mean ± SD or median (interquartile range). BMI; Body mass index, NLR; neutrophil/lymphocyte ratio, PLR; platelet//lymphocyte ratio, MPV; mean platelet volume, PDW; platelet distribution width, PCT; plateletcrit, RDW; red cell distribution width, CRP; C-reactive protein. P1; between non-dipper and dipper group, P2; between non-dipper and normotensive group, P3; between dipper and normotensive group. A *P* value < .05 was considered significant.

divided into three groups on the basis of ABPM findings (dipping status = 28 patients, non-dipping status = 61 patients, control group = 64 patients). The demographic and laboratory characteristics of the study groups are shown in Table 1. Average age, median BMI, and gender distribution were similar between groups.

The WBC count was significantly higher in patients with non-dipper status than in the control group (7841.7 ± 2195.8 / 6941.3 ± 1613.1/mm^3, $P < .05$). There was no statistically significant difference between the dipper and non-dipper groups and control group. The patients with non-dipper and dipper status had significantly higher neutrophil counts when compared to the control group (4363.3 ± 2140.9 /mm^3 in non-dippers, 4722 ± 2005.82 /mm^3 in dippers and 3646.2 ± 1314.8 /mm^3 in control group, $P < .05$, $P < .05$, respectively). Lymphocyte counts and NLR were similar between groups. In addition, there were no significant differences in the CRP levels between groups (Table 1). Moreover, logistic regression analysis did not determine a significant correlation between CRP and the presence of non-dipper status in patients with ambulatory hypertension (Table 2).

The platelet counts and PLRs were higher in non-dipper group than in dipper group (308.2 ± 70.29 /mm^3, 267.5 ± 70.9 /mm^3; $P < .05$, 129.6 ± 54.01 /mm^3, 107.7 ± 7.57 /mm^3; $P < .05$). Therefore, no statistically significant difference was found between the non-dipper and control groups (Table 1). Patients in the non-dipper and dipper groups had the higher MPV levels than in the control group (8.69 ± 0.84, 9.01 ± 1.14, 8.1 ± 0.92 fL, $P < .05$, $P < .05$, respectively). The PCT was higher in patients with non-dipper hypertension than those in the dipper and control groups (0.27 ± 0.06, 0.23 ± 0.04, 0.24 ± 0.05%; $P < .05$, $P < .05$; respectively) (see Table 1). PDW was higher in non-dipper group when compared with dipper group (16.7 ± 0.64, 16.4 ± 0.47%; respectively, $P < .05$). ABPM values were shown in Table 3. Office SBP and DBP values were similar between the dipper and non-dipper groups. Patients with non-dipper status had significantly higher nighttime SBP, nighttime SBP load, and daytime DBP load compared with the dipper group [107.9 ± 9.13, 103.8 ± 7.81 mmHg; $P < .05$; 37.5 (22.5 - 57.8), 17 (6.3 - 36); $P < 0.05$; 48.5 (32.5 - 68), 20.5 (9.3 - 28.3); $P < 0.05$]. The other ABPM values were similar between the non-dipper and dipper groups (Table 3).

Univariate correlation analysis were determined significant positive correlations between MPV and office SBP with DBP (r = 0.346, $P < 0.05$; and r = 0.308, $P < 0.05$; respectively). In addition, a significant positive correlation was found between MPV and WBC with neutrophil count (r = 0.389, $P < .001$; and r = 0.346, $P < .05$; respectively). There was a positive correlation between neutrophil count and 24-hour SBP (r = 0.252, $P < .05$). MPV was not correlated with 24-h, daytime or nighttime BP values ($P > .05$, data not shown). Using linear regression, a significant positive correlation was observed between MPV and office SBP or office DBP ($P < 0.05$, $P < 0.05$; respectively) (see Table 4). The results of a logistic regression analysis evaluating factors associated with the presence of non-dipper status are shown in Table 2. The higher values of MPV and platelet count were associated with non-dipper status in patients with ambulatory hypertension ($P < .05$, $P < 0.05$; respectively). The other platelet indices, hemoglobin, WBC, neutrophil count, PLR, NLR, and CRP were not associated with non-dipper status.

ROC curve analysis showed that the cut-off value of MPV for the prediction of nondipper status was 10.85 fL (sensitivity 98.4% and specificity 96.8%). The area under the curve (AUC ± SE) was 0.709 ± 0.059 [95% confidence interval (CI):

Table 2. Logistic Regression Analysis Evaluating Factors Associated With Presence of Non-dipper Status in Patients With Ambulatory Hypertension

	Beta	95% CI	*P*
BMI	0.046	0.978 - 1.121	> .05
Hemoglobin	0.217	0.851 - 1.814	> .05
WBC	0.00	1 - 1	> .05
Neutrophil Count	0.00	1 - 1	> .05
Lymphocyte Count	0.00	0.99 - 1	> .05
NLR	0.009	0.786 - 1.294	> .05
Platelet Count	0.010	0.983 - 0.997	< .05
MPV	0.567	1.081 - 2.876	< .05
PDW	1.578	0.792 - 29.660	> .05
PCT	-8.304	0.000 - 60.949	> .05
PLR	0.986	0.973 - 1	< .05
CRP	-0.215	0.369 - 1.762	> .05

Beta; regression coefficient, CI; confidential interval, BMI; body mass index, RDW; red cell distribution width, WBC; white blood cell, NLR; neutrophil/lymphocyte ratio, MPV; mean platelet volume, PDW; platelet distribution width, PCT; plateletcrit, PLR; platelet/lymphocyte ratio, CRP; C-reactive protein. A *P* value < .05 was considered significant.

Table 3. Ambulatory Blood Pressure Monitoring Values of the Children With Dipping and Non-dipping Status and Control Group

Parameters	Non-dipper (n = 61)	Dipper (n = 28)	Control (n = 64)	*P*
24-h SBP Values (mmHg)	112.2 ± 10.49	112.2 ± 9.72	104.1 ± 6.88	P1 > .05 P2 < .001 P3 < .05
Daytime SBP (mmHg)	115.3 ± 11.57	117.7 ± 11.74	107.1 ± 6.63	P1 > .05 P2 < .001 P3 < .001
Nighttime SBP (mmHg)	107.9 ± 9.13	103.5 ± 7.87	99.4 ± 6.51	P1 < .05 P2 < .001 P3 < .05
24-h DBP Values (mmHg)	66.1 ± 7.85	66.1 ± 7.85	61.8 ± 6.38	P1 > .05 P2 < .001 P3 < .05
Daytime DBP (mmHg)	67 (63 - 74.5)	72 (66 - 77)	65.2 ± 6.01	P1 > .05 P2 > .05 P3 < .001
Nighttime DBP (mmHg)	62.4 ± 8.31	60.5 ± 6.61	56.7 ± 6.59	P1 > .05 P2 < .001 P3 < .05
24-h MAP (mmHg)	86.2 ± 8.89	86.2 ± 8.89	79.5 ± 4.97	P1 > .05 P2 < .001 P3 < .001
Day-time MAP (mmHg)	88.6 ± 9.19	91.7 ± 9.83	84.6 ± 5.68	P1 > .05 P2 < .05 P3 < .001
Night-time MAP (mmHg)	81.7 ± 9.62	79.1 ± 6.61	76.1 ± 5.61	P1 > .05 P2 < .05 P3 < .05
Daytime SBP Load (%)	20 (8 - 40)	32 (26.8 - 37.5)	0 (0 - 0)	P1 > .05 P2 < .001 P3 < .001
Nighttime SBP Load (%)	37.5 (22.5 - 57.8)	17 (6.3 - 36)	0 (0 - 0)	P1 < .05 P2 < .001 P3 < .001
Daytime DBP Load (%)	17 (5 - 32)	20.5 (9.3 - 28.3)	0 (0 - 3.2)	P1 < .05 P2 < .001 P3 < .001
Nighttime DBP Load (%)	24 (5 - 37)	9 (3 - 18.8)	0 (0 - 6)	P1 > .05 P2 < .001 P3 < .001
Office SBP (mmHg)	120.7 ± 20.78	126.9 ± 17.28	103.6 ± 10.67	P1 > .05 P2 < .001 P3 < .001
Office DBP (mmHg)	69.4 ± 12.28	72.8 ± 13.66	61.6 ± 9.76	P1 > .05 P2 < .001 P3 < .05

Data were shown as mean ± SD or median (interquartile range). SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. P1; between non-dipper and dipper group, P2; between non-dipper and normotensive group, P3; between dipper and normotensive group. A *P* value < .05 was considered significant.

Table 4. Linear Regression Analysis Between MPV and Office Systolic and Diastolic Blood Pressure

	Beta	95% CI	*P*
Office SBP (mmHg)	0.016	0.005 - 0.27	< .05
Office DBP (mmHg)	0.023	0.005 - 0.04	< .05

Beta; regression coefficient, CI; confidential interval, MPV; mean platelet volume, SBP; systolic blood pressure; DBP, diastolic blood pressure. A *P* value < .05 was considered significant.

0.593 - 0.825, $P < .05$]. A platelet count showed a sensitivity of 73.5% and specificity of 70.1% with a cut-off of 351.400 /mm^3 (AUC ± SE: 0.604 ± 0.046, 95% CI: 0. 514 - 0.694; $P < .05$).

DISCUSSION

The results of this study showed that higher

MPV, PCT and platelet count were associated with the presence of non-dipper status in children with ambulatory hypertension. In addition, the results might suggest that higher neutrophil count could be associated with the development of hypertension in children. Platelet activation plays an important role in the development of atherosclerotic complications.[22] Reactive platelets lead to increased platelet volume. The renin-angiotensin system, endothelial dysfunction, and increased sympathetic activity may lead to activation of platelets in hypertension.[23] MPV is closely related to platelet size and activity. Previous studies have shown the higher MPV in patients with hypertension than in normotensive subjects.[24] Tavil et al, reported that MPV was associated with coronary artery disease in patients with hypertension in metabolic syndrome.[25] Coban et al, showed a positive correlation between MPV and ambulatory DBP in essential hypertension.[26] To our knowledge, this is the first study evaluating MPV levels in children with ambulatory hypertension. According to the results of our study, we thought that higher MPV might show increased platelet activation in children with ambulatory hypertension.

Non-dipper status is one of the most important risk factors for cardiovascular disease in hypertension. It was suggested that higher risk for cardiovascular disease in non-dipper group might be due to increased platelet activation.[27] Ordu et al, reported that MPV was significantly higher in non-dipper patients than in dipper patients with hypertension.[28] Plateletcrit is the product of the platelet count and the MPV.[29] In the literature, it has been reported that PCT levels are higher in patients with coronary artery diseases.[30] To the best of our knowledge, there are no studies evaluating the association between PCT and ABPM values in children. Our findings showed that MPV and PCT might be potential biomarkers for non-dipper status in children with ambulatory hypertension.

Systemic inflammation plays an important role in the development of hypertension. It has been reported that increased levels of systemic inflammatory markers are associated with hypertension and cardiovascular diseases.[31] The total WBC, neutrophil, lymphocyte counts, and NLR show systemic inflammation.[32] The increased adhesion ability to vascular endothelium of activated neutrophils may lead to increased vascular resistance.[33] Furthermore, reactive oxygen species release by neutrophil activation results in impairment of endothelium-dependent vasodilatation.[34,35] We have shown that patients with ambulatory hypertension had higher neutrophil counts than those in the control group. Thus, the higher neutrophil counts might be an indicator for increased risk of the development of hypertension in children.

Previous studies have demonstrated that NLR is associated with non-dipper hypertension.[36,37] Demir et al, showed that NLR levels were significantly correlated with BP variability.[38] On the other hand, Tatsukawa et al. reported that neutrophil count was an important risk factor in the development of hypertension.[39] In another study, it has been reported a significant relationship between the development of hypertension and high neutrophil/low lymphocyte counts.[40] In addition, Kawada et al. showed that neutrophil count was associated with hypertension independent of other factors.[41] However, we did not find a significant correlation between NLR and ABPM values in this study.

It has been suggested that inflammation may lead to impaired vasodilatory mechanisms. Hence, inflammation may be an independent risk factor for the development of hypertension. C-reactive protein (CRP) is a systemic inflammatory marker, which is secreted from inflamed tissues.[42] It has been reported that CRP levels are positively associated with blood pressure values.[43] On the other hand, there are controversial reports on the association between CRP and BP values in children. Ford et al. reported that CRP was independently associated with SBP among girls between 12–17 years old.[44] However, several studies have not shown an independent association between elevated BP and CRP in children. Lambert et al, found an association between increased CRP and high SBP in children. However, no statistically significant relationship was found after adjusting for BMI.[45] Similarly; Lopez et al, determined a direct relationship between CRP levels and SBP among boys. But, this association lost statistical significance after a multivariate regression analysis.[46] In our study population, we could not observe a significant correlation between CRP and BP values. We thought that the influence of environmental and genetic factors might affect CRP levels. Furthermore, obese patients were not included in this study. There are several limitations

in this study. Firstly, this is a retrospective analysis. Secondly, the numbers of patients is small. Nevertheless, we tested for the first time whether there is a significant correlation between ABPM values and hematological parameters in children with ambulatory hypertension.

In conclusion, our findings suggest that the higher MPV and neutrophil count may be potential indicators of increased risk for the development of hypertension in children. Higher platelet count, MPV and PCT may help to determine the presence of non-dipper status in children with hypertension. Further studies with larger sample size are needed to confirm the association between platelet activity and inflammation with hypertension and non-dipper status in children.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. World Health Organization. A global brief on hypertension, 2013. Geneva: World Health Organization; 2013.
2. Verdecchia P, Carini G, Circo A, et al. Left ventricular mass and cardiovascular morbidity in essential hypertension: the MAVI study. J Am Coll Cardiol. 2001; 38:1829-35.
3. Burke GL, Arcilla RA, Culpepper WS, Webber LS, Chiang YK, Berenson GS. Blood pressure and echocardiographic measures in children: the Bogalusa Heart Study. Circulation. 1987; 75:106-14.
4. Hanevold C, Waller J, Daniels S, Portman R, Sorof J. The effects of obesity, gender, and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association. Pediatrics. 2004; 113:328-33.
5. Cha SD, Patel HP, Hains DS, Mahan JD. The effects of hypertension on cognitive function in children and adolescents. Int J Pediatr. 2012; 2012:891094.
6. Li AQ, Zhao ZY, Zhang LL, et al. Overweight influence on circadian variations of ambulatory blood pressure in Chinese adolescents. Clin Exp Hypertens. 2005; 27:195-201.
7. Seo HS, Kang TS, Park S, et al. Non-dippers are associated with adverse cardiac remodeling and dysfunction. In J Cardiol. 2006; 112:171–77.
8. McNiece KL, Gupta-Malhotra M, Samuels J, et al. National High Blood Pressure Education Program Working Group. Left ventricular hypertrophy in hypertensive adolescents: analysis of risk by 2004 National High Blood Pressure Education Program Working Group Staging Criteria. Hypertension. 2007; 50:392–95.
9. Kaya MG, Yarlioglues M, Gunebakmaz O, et al. Platelet activation and inflammatory response in patients with nondipper hypertension. Atherosclerosis. 2010; 209:278–82.
10. Akpinar I, Sayin MR, Gursoy YC, et al. Plateletcrit. A platelet marker associated with saphenous vein graft disease. Herz. 2014; 39:142–48.
11. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: Methodological issues. Platelets. 2002; 13:301–03.
12. Coban E, Ozdogan M, Yazicioglu G, Akcit F. The mean platelet volume in patients with obesity. Int J Clin Pract. 2005; 59:981-82.
13. Wiwanitkit V. Plateletcrit, mean platelet volume, platelet distribution width: its expected values and correlation with parallel red blood cell parameters. Clin Appl Thromb Hemost. 2004; 10:175–78.
14. Akpinar I, Sayin MR, Gursoy YC, et al. Plateletcrit and red cell distribution width are independent predictors of the slow coronary flow phenomenon. J Cardiol. 2014; 63:112–18.
15. Ugur M, Ayhan E, Bozbay M, et al. The independent association of plateletcrit with long-term outcomes in patients undergoing primary percutaneous coronary intervention. J Crit Care. 2014; 29:978-81.
16. Akkaya E, Gul M, Ugur M. Platelet to lymphocyte ratio: A simple and valuable prognostic marker for acute coronary syndrome. Int J Cardiol. 2014; 177:597–98.
17. Rudiger A, Burckhardt OA, Harpes P, Muller SA, Follath F. The relative lymphocyte count on hospital admission is a risk factor for long-term mortality in patients with acute heart failure. Am J Emerg Med. 2006; 24:451–55.
18. Ross R, Glomset J, Harker L. Response to injury and atherogenesis. Am J Pathol. 1977; 86:675–84.
19. Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP. Platelets as predictor of vascular risk: is there a practical index of platelet activity? Clin Appl Thromb Hemost. 2003; 9:177–90.
20. Wühl E, Witte K, Soergel M, Mehls O, Schaefer F, German Working Group on Pediatric Hypertension. Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. J Hypertens. 2002; 20:1995–2007.
21. Yazici M, Kaya A, Kaya Y, Albayrak S, Cinemre H, Ozhan H. Lifestyle modifi cation decreases the mean platelet volume in prehypertensive patients. Platelets. 2009; 20:58–63.
22. Celik T, Yuksel UC, Iyisoy A, et al. Effects of nebivolol on platelet activation in hypertensive patients: A comparative study with metoprolol. Int J Cardiol. 2007; 116:206-11.
23. Siebers R, Maling T. Mean platelet volume in human essential hypertension. J Hum Hypertens. 1995; 9:207.
24. Nadar SK, Blann AD, Kamath S, Beevers DG, Lip GY. Platelet indexes in relation to target organ damage in high-risk hypertensive patients: A substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). J Am Coll Cardiol. 2004; 44:415-22.
25. Tavil Y, Sen N, Yazici HU, Hizal F, Abaci A, Cengel A. Mean platelet volume in patients with metabolic syndrome and its relationship with coronary artery disease. Thromb Res. 2007; 120:245–45.
26. Coban E, Yazıcıoglu G, Avcı AB, Akcıt F. The mean

platelet volume in patients with essential and white coat hypertension. Platelets. 2005; 16:435–38.

27. Ordu S, Ozhan H, Caglar O, et al. Mean platelet volume in patients with dipper and non-dipper hypertension. Blood Press. 2010; 19:26–30.
28. Inanc T, Kaya MG, Yarlioglues M, et al. The mean platelet volume in patients with non-dipper hypertension compared to dipper hypertension and normotensives. Blood Press. 2010; 19:81–5.
29. Erhart S, Beer JH, Reinhart WH. Influence of aspirin on platelet countand volume in humans. Acta Haematol. 1999; 101:140–44.
30. Ugur M, Ayhan E, Bozbay M, et al. The independent association of plateletcrit with long-term outcomes in patients undergoing primary percutaneous coronary intervention. J Crit Care. 2014; 29:978-81.
31. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med. 2012; 5:2.
32. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. Hypertension. 2001; 38:399-403.
33. Mügge A, Lopez JA. Do leukocytes have a role in hypertension? Hypertension. 1991; 17:331-33.
34. Lassègue B, Clempus RE. Vascular NAD (P) H oxidase:specific features, expression and regulation. Am J Physiol Regul Integr Comp Physiol. 2003; 285:R277–R297.
35. Yasunari K, Maeda K, Nakamura M, Watanabe T, Yoshikawa J. Benidipine, a long-acting calcium channel blocker, inhibits oxidative stress in polymorphonuclear cells in patients with essential hypertension. Hypertens Res. 2005; 28:107–12.
36. Kılıçaslan B. The relationship between neutrophil to lymphocyte ratio and blood pressure variability in hypertensive and normotensive subjecs. Arch Turk Soc Cardiol. 2015; 43:18-24.
37. Sunbul M, Gerin F, Durmus E, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratio in patients with dipper versus nondipper hypertension. Clin Exp Hypertens. 2014; 36:217-21.
38. Demir M. The Relationship Between Neutrophil Lymphocyte Ratio and Non-dipper Hypertension. Clin Exp Hypertens. 2013; 35:570–73.
39. Tatsukawa Y, Hsu WL, Yamada M, et al. White blood cell count, especially neutrophil count, as a predictor of hypertension in a Japanese population. Hypertens Res. 2008; 31:1391–97.
40. Tian N, Penman AD, Mawson AR, Manning RD Jr, Flessner MF. Association between circulating specific leukocyte types and blood pressure: the atherosclerosis risk in communities (ARIC) study. J Am Soc Hypertens. 2010; 4:272–83.
41. Kawada T, Morihashi M, Ueda H, Sirato T. Neutrophil cell count is related to hypertension in workers: a cross-sectional study. Vasc Dis Prev. 2007; 4:225–28.
42. Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clin Invest 1993; 91:135.
43. Bautista LE, López-Jaramillo P, Vera LM, Casas JP, Otero AP, Guaracao AI. Is C-reactive protein an independent risk factor for essential hypertension? J Hypertens. 2001; 19:857–61.
44. Ford ES, Ajani UA, Mokdad AH. The metabolic syndrome and concentrations of C-reactive protein among US youth. Diabetes Care. 2005; 28:878–81.
45. Lambert M, Delvin EE, Paradis G, O'Loughlin J, Hanley JA, Levy E: C-reactive protein and features of the metabolic syndrome in a population-based sample of children and adolescents. Clin Chem. 2004; 50:1762–68.
46. López-Jaramillo P, Herrera E, Garcia RG, Camacho PA, Castillo VR. Inter-relationships between body mass index, C-reactive protein and blood pressure in a Hispanic pediatric population. Am J Hypertens. 2008; 21:527-32.

Correspondence to:
Nuran Cetin
Department of Pediatric Nephrology, Faculty of Medicine,
Eskisehir Osmangazi University, Turkey
Tel: +90 533 622 7536
Fax: +90 222 229 0064
E-mail: nurancetin17@hotmail.com

Received June 2018
Revised September 2018
Accepted October 2018