The platelet-to-lymphocyte ratio as an inflammation marker in non-dipper hypertensive patients

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Abstract

Background: Non-dipper hypertensive patients have a higher risk of cardiovascular disease (CVD) than dipper hypertensive patients. Inflammation plays an important role in the pathogenesis and progression of CVD. This study aimed to determine the relationship between the platelet-to-lymphocyte ratio (PLR), and dipper and non-dipper hypertension.

Materials and Methods: This prospective study included 199 consecutive patients that were diagnosed with primary hypertension. According to ambulatory blood pressure monitoring measurements, non-dipper and dipper group were determined. PLR was determined based on the platelet count and lymphocyte count in the complete blood count.

Results: The non-dipper group included 103 patients (74 females and 29 males; mean age: 52.37 ± 10.7 years) and the dipper group included 96 patients (65 females and 31 males; mean age: 48.40 ± 11.1 years). Mean systolic blood pressure was significantly higher in the non-dipper group than in the dipper group (124 ± 15.1 mmHg versus 120 ± 11.2 mmHg, p =0.032) and the median PLR was significantly higher in the non-dipper group than in the dipper group [132.15 (range: 69.64-400) versus 117.0 (range: 53.52-192.26), p = 0.001], whereas the mean white blood cell count ($6.86 \pm 1.43 \times 10^3/\mu L$ versus $7.24 \pm 1.26 \times 10^3/\mu L$, p =0.046) and median lymphocyte count [2.09 (range: 0.95-3.92) $\times 10^3/\mu L$ versus 2.24 (range: 0.97-3.98) $\times 10^3/\mu L$, p =0.001) were significantly lower in the non-dipper group.

Conclusion: Median PLR was significantly higher in the non-dipper hypertensive patients than in the dipper hypertensive patients. We think this finding further supports the role of an increase in inflammatory response in non-dipper hypertension. Hippokratia 2015; 19 (2):114-118.

Keywords: Platelet-to-lymphocyte ratio, PLR, non-dipper hypertension, inflammation

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Introduction

Hypertension is a major cause of cardiovascular morbidity and mortality[1]. Although its etiopathogenesis remains unclear, primary hypertension is thought to be closely associated with inflammation[2]. Systolic and diastolic blood pressure are expected to drop >10% during the night, as compared to daytime, varying in accordance with circadian rhythm in normal and hypertensive individuals (dipper); in non-dipper hypertensive individuals systolic and diastolic blood pressure do not decrease[3]. The risk of cardiovascular morbidity and mortality is higher in non-dipper hypertensive individuals, independent of mean blood pressure[4-5]. This increased risk is suggested to be associated with the accelerated atherosclerotic process in non-dipper hypertensive individuals[6].

Inflammation is thought to play an important role in the pathogenesis of atherosclerotic cardiovascular disease (CVD)[7]. Such markers as high-sensitivity C-reactive protein (CRP), cytokines, matrix metalloproteinase-9, myeloperoxidase, intercellular adhesion molecule 1 (ICAM-1), soluble cluster of differentiation 40 (CD40) ligand, etc. have been reported to be indicative of inflammatory status[8]. Indices derived from hemogram parameters have recently been defined as inflammatory markers, including the red cell distribution width (RDW), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)[9-13]. PLR is the newest of these markers and was first studied in patients with malignancy[14]. Subsequent research suggests that higher PLR is related with worse outcome in patients with atherosclerosis-related diseases, such as coronary artery disease (CAD)[12,15] heart valve diseases[16] and pe-

ripheral arterial disease[17]. The present study aimed to determine the relationship between PLR (as a marker of inflammation), and dipper and non-dipper hypertension.

Materials and Methods

This prospective study was conducted in an internal medicine clinic between May and December 2013, and included 199 consecutive patients diagnosed with primary hypertension. Demographic characteristics were recorded. All patients were assessed for cardiovascular risk factors (including smoking status, body mass index, cholesterol levels, duration of hypertension, medications used) and systemic diseases. Diabetes mellitus was defined as a new diagnosis according to 2011 American Diabetes Association (ADA) diagnostic criteria or receiving anti-diabetic therapy. Patients with diabetes mellitus, CAD, acute or chronic renal disease, secondary hypertension, cerebrovascular disease, acute or chronic infection, fever, collagen tissue disease, malignancy, hematological disease, thrombocytopenia (platelet count <150×10^3 μL^{-1}), thrombocytosis (platelet count >450 ×10^3 μL^{-1}), or use of anti-platelet, anti-coagulant, or immunosuppressive agents were excluded from the study.

Renal failure was defined according to the glomerular filtration rate (GFR), which was calculated using the simplified version of the Modification of Diet in Renal Disease study prediction equation formula, GFR=186 x Creatinine$^{-1.154}$ x Age$^{-0.203}$ x 1.212 (if African-American) x 0.742 (if female)[18]. Patients diagnosed with chronic kidney disease were excluded according to the criteria defined by KDIGO (Kidney Disease Improving Global Outcomes) 2012 clinical practice guidelines for the evaluation and management of chronic kidney disease[19].

Infection and acute illness were determined based on the anamnesis and physical examination. Among the few patients with elevated CRP, in those in which clinical findings and symptoms were not consistent with acute illness, CRP was not interpreted in favor of infection or acute inflammation.

The 24-hour ambulatory blood pressure monitoring (ABPM) was performed using a WatchBP 03 device (Microlife WatchBP AG, Switzerland); the cuff was placed on the non-dominant arm. The devices were programmed to perform measurements every 15 min between 07:00 and 23:00 (daytime) and every 20 min between 23:00 and 07:00 (nighttime). The method was considered reliable if >70% of measurements were valid. Patients with a drop in the mean systolic (SBP) and diastolic blood pressure (DBP) >10% during the night were grouped as dipper hypertension and those without such a drop were grouped as non-dipper hypertension. Blood samples were obtained between 08:00 and 10:00 following overnight fasting. Blood biochemistry and complete blood count (CBC) were determined. PLR was determined based on the platelet count and lymphocyte count in the CBC. Twenty-four hour urine was collected to measure 24 hour-urine protein and creatinine excretion. The study protocol was approved by the Ankara Numune Education and Research Hospital Ethics

Committee (decision number: 614/2013, 10-04-2013) and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent in order to participate in the study.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine if data were distributed normally. Numerical variables with normal distribution are shown as mean ± SD and those not normally distributed are shown as median (range). The independent samples t-test was used to analyze normally distributed parameters, whereas the Mann-Whitney U test was used to analyze parameters that were not normally distributed. The relationship between parameters was analyzed via Spearman's correlation analysis. Multivariate logistic regression analysis was used to determine which factors were associated with non-dipper hypertension; variables that were significant based on univariate analysis (p <0.05) were included in multiple regression analysis. Receiver operating characteristic (ROC) curves were plotted to determine the optimal cutoff values for PLR for the prediction of non-dipper in hypertension and to establish optimal cutoff points for use in clinical practice. The true positive rate (sensitivity) and the false-positive rate (100-specificity) were plotted for each measurement, and the area under the curve (AUC) was determined. Cutoff values were determined based on the Youden index.

Results

The study included 199 consecutive patients diagnosed with primary hypertension. Mean age of the patients was 50.93 ± 10.9 years and the median duration of hypertension was 3 years (1-20 years). The dipper group included 96 patients and the non-dipper group included 103 patients. There were not any differences in the demographic and clinical characteristics, or anti-hypertensive therapy between the two groups. In all, 184 of the 199 patients were taking antihypertensive agents; 112 were taking one drug, 61 were taking two drugs, and 11 were taking three drugs. All patients that were taking one pill (one drug or a fixed-dose combination of two drugs) took their pills in the morning; those that were taking two pills took one pill in the morning and the other 12 hours later at night. There were no patients on more than two pills.

Mean 24-hour SBP was significantly higher in the non-dipper group than in the dipper group (124 ± 15.1 mmHg versus 120 ± 11.2 mmHg, p=0.032) Mean asleep SBP was significantly higher in the non-dipper group than in the dipper group (119.25 ± 10.1mmHg versus 113.28 ± 8.2 mmHg, p <0.001). Mean asleep DBP was significantly higher in the non-dipper group than in the dipper group (73.82 ± 6.56 mmHg versus 70.32 ± 7.2 mmHg, p <0.001) (Table 1). Among all patients, the mean creatinine levels were 0.8 ± 0.14 mg/dl; the mean white blood cell (WBC) count was 7.04 ± 1.36 × 10^3/μL,

Table 1: Baseline demographic and clinical characteristics of the study population consisting of 199 hypertensive patients, of whom 103 non-dipper and 96 dipper.

Variables	All patients (n=199)	Non-dipper (n=103)	Dipper (n=96)	p value
Age (years)	50.9 ± 10.9	52.4 ± 10.7	48.4 ± 11.1	0.056
Men, n	60	29	31	0.525
Body mass index (kg/m²)	29.4 ± 4.6	29.6 ± 5.1	29.3 ± 4.2	0.620
Current smokers, n	23	11	12	0.354
Systolic BP, 24 h (mmHg)	122.1 ± 13.5	124.0 ± 15.1	120.0 ± 11.1	**0.032**
Systolic BP, awake (mmHg)	128.1 ± 11.8	128.5 ± 12.6	127.7 ± 11.5	0,649
Systolic BP, asleep (mmHg)	116.4 ± 9.3	119.3 ± 10.1	113.3 ± 8.2	**<0.001**
Diastolic BP, 24 h (mmHg)	76.8 ± 9.1	77.5±9.9	76 ± 8.2	0.228
Diastolic BP, awake (mmHg)	81.4 ± 8.4	81.2 ± 7.2	81.6 ± 9.3	0,748
Diastolic BP, asleep (mmHg)	72.1 ± 6.8	73.8 ± 6.6	70.3 ± 7.2	**<0.001**
Duration of hypertension (years)	3 (1-20)	3 (1-20)	3 (1-20)	0.879
Antihypertensive agents				
ACE inhibitors/ARBs	103 (51.8)	53 (51.5)	50 (52.1)	0.930
β-Blockers	25 (12.6)	13 (12.6)	12 (12.5)	0.979
Calcium antagonists	80 (40.2)	40 (38.8)	40 (41.7)	0.684
Diuretics	62 (31.2)	37 (35.9)	25 (26.0)	0.133

Data are presented as the number of patients or mean value ± standard deviation, p <0.05 is considered statistically significant for all tests, n: number, SBP: blood pressure, DBP: diastolic blood pressure, ACE: angiotensin converting enzyme, ARBs: angiotensin receptor blockers.

the median lymphocyte count was 2.18 (0.95-3.98) ×10³/μL; the mean platelet count was 279.7 ± 57.4 ×10³/μL, and the median PLR was 124 (53.5-400) (Table 2). The median PLR was significantly higher in the non-dipper group than in the dipper group [132.15 (69.64-400) versus 117.0 (53.52-192.26), p =0.001]. The WBC count was significantly lower in the non-dipper group than in the dipper group (6.86 ± 1.43 × 10³/μL versus 7.24 ± 1.26 × 10³/μL, p =0.046). Similarly, the lymphocyte count was significantly lower in the non-dipper group than in the dipper group [2.09 (0.95-3.92) × 10³/μL versus 2.24 (0.97-3.98) × 10³/μL, p =0.001] (Table 2).

Age, gender, body mass index, current smokers, antihypertensive agents, duration of hypertension, SBP, DBP, fasting glucose, creatinine, GFR, albumin, uric acid, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), erythrocyte sedimentation rate (ESR), CRP, proteinuria, WBC, PLR, hemoglobin levels were included in a stepwise regression model. According to the results from multivariable regression analysis, SBP (OR =1.027, p =0.024) and PLR (OR =1.014, p =0.001) were identified to be independent predictors for non-dipper in hypertension patients (Table 3).

A PLR of 101.5 or higher predicted non-dipper status

Table 2: Laboratory findings of the study population consisting of 199 patients, of whom 103 non-dipper and 96 dipper.

Variables	All patients (n =199)	Non-dipper (n =103)	Dipper (n =96)	p value
Fasting glucose (mg/dl)	89.6 ± 6.4	90.1 ± 5.5	89.2 ± 7.1	0.414
Creatinine (mg/dl)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.350
Albumin (mg/dl)	46.4 ± 2.6	46.2 ± 2.4	46.6 ± 2.7	0.314
Triglyceride (mg/dl)	141 (57-735)	144 (57-735)	125 (64-360)	0.123
LDL cholesterol (mg/dl)	125.9 ± 16.3	124.1 ± 16.8	127.8 ± 15.5	0.115
HDL cholesterol (mg/dl)	49.7 ± 13.2	49.1 ± 13.5	50.5 ± 12.9	0.470
ESR (mm/hour)	14.4 ± 3.5	14.5 ± 3.7	13.8 ± 3.3	0.177
CRP (mg/dl)	3.1 (0.3-12)	3.5 (0.4-12)	2.7 (0.3-8)	0.068
Proteinuria (mg/day)	93 (6-1949)	95.4 (13.9-1949)	90.8 (6-1619.5)	0.466
WBC (x10³/μL)	7.0 ± 1.4	6.9 ± 1.4	7.2 ± 1.3	**0.046**
Lymphocyte (x10³/μL)	2.2 (1-4)	2,1 (1-3,9)	2,2 (1-4)	**0,001**
Platelet (x10³/μL)	279.7 ± 57.4	282 ± 60.6	277.2 ± 54	0.559
PLR	124 (53.5-400.0)	132.2 (69.6-400)	117.0 (53.5-192.3)	**0.001**
Hemoglobin (g/dl)	13.9 ± 1.4	13.8 ± 1.4	14.1 ± 1.4	0.109

Data are presented as the number of patients or mean value ± standard deviation, p <0.05 is considered statistically significant for all tests, n: number, LDL: low-density lipoprotein, HDL: high-density lipoprotein, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: White blood cell, PLR: Platelet-to-lymphocyte ratio, SD: standard deviation.

Table 3: Significant predictors of non-dipper pattern in hypertensive patients.

Variables	Odds Ratio	95% CI	
		lower	Upper
24 h- mean SBP	1.027	1.012	1.051
PLR	1.014	1.010	1.022

p <0.05 is considered significant for statistical analyses, SBP: systolic blood pressure, PLR: platelet-to-lymphocyte ratio, CI: confidence intervals.

with 84.5% sensitivity and 39.6% specificity [AUC ± SE (standard error) = 0.636 ± 0.039, 95% CI =0.565-0.703, p <0.001] (Figure 1).

Discussion

Non-dipper hypertension is considered an independent risk factor for all-cause mortality[1,5]. Signs of renal
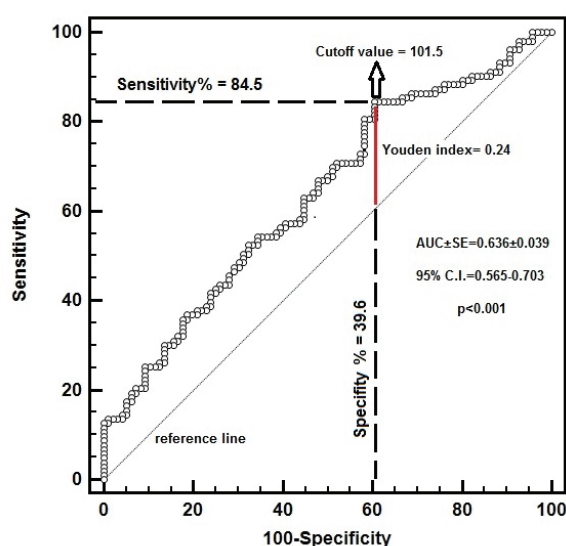

Figure 1: Receiver operating characteristic (ROC) curve for platelet-to-lymphocyte ratio (PLR) to predict non-dipper status.

Cutoff values were determined from the Youden index, AUC: Area under the curve, CI: confidence intervals, SE: Standard error.

damage, including microalbuminuria and rapid GFR loss[20] as well as such cardiovascular signs as left ventricle hypertrophy and heart failure are reported to be more common in non-dipper hypertensive individuals than dippers[21-22]. Its etiology is not clearly known, but non-dipper hypertension is more common in cases with secondary causes of hypertension such as endocrine system diseases[23] sleep apnea syndrome[24] and chronic renal failure[25]. There is evidence indicating that endothelial repair is adversely affected and the inflammatory process is more severe in non-dipper hypertensive individuals than dippers[26].

Inflammation plays a key role in most chronic diseases, particularly CVD, diabetes mellitus, connective tissue diseases, cancer, and chronic kidney disease[7,27-31]. Neutrophils, known as the primary cells that release inflammatory cytokines, closely interact with other blood cells - including platelets - during inflammation[32]. Increased

platelet activity has been reported to correlate with an increase in the severity of inflammation[33]. Increases in the platelet count, MPV, and RDW are indicators of increased platelet activity[34]. Research has shown that a higher PLR in the absence of absolute thrombocytosis is associated with increased thrombosis and inflammation, which might be associated with an increase in platelet activity[13,15,17]. Additionally, it was posited that relative lymphopenia in the presence of a high PLR might be indicative of the effect of an elevated endogenous cortisol level due to inflammatory response[35]. Among a group of patients with obstructive peripheral artery disease, critical vascular stenosis and wounds due to vascular insufficiency were more common in those with a high PLR[17]. A study that examined the relationship between PLR and inflammation in cardiovascular diseases reported that a pre-procedural PLR >150, in patients diagnosed with ST segment elevation myocardial infarction that underwent primary percutaneous coronary stent placement, was predictive of no-reflow, with sensitivity of 75% and specificity of 74%[15]. A similar study that included patients diagnosed with non-ST segment elevation myocardial infarction reported a significantly higher mortality rate in the patients with a PLR >176 and a relative decrease in the mortality rate in response to double antiplatelet therapy[36].

In the present study, the PLR (used as a marker of inflammation) was significantly higher in the non-dipper hypertension group than in the dipper hypertension group. Moreover, PLR was found to be an independent predictive factor. A PLR of 101.5 or higher predicted non-dipper status with 84.5 % sensitivity and 39.6 % specificity. The fact that both of the present study's patient groups were similar in terms of smoking status, body mass index, cholesterol levels, duration of hypertension, medications used, and lack of other known chronic diseases strengthens the validity of the findings. Furthermore, the present findings are similar to those of an earlier relevant study that reported the PLR was significantly higher in non-dipper hypertensive patients, a PLR ≥107 was predictive of non-dipper hypertension (with sensitivity of 66.3 % and specificity of 68.7 %), and that NLR and hs-CRP levels were higher in non-dipper hypertension group[37]. Although specificity of PLR cutoff value was low our study, the values were similar[37]. Limitations of the present study include lack of evaluation of the relationship between markers of inflammation other than the PLR and signs of target organ damage, and the lack of follow-up to identify the effect of a high PLR

level on the prognosis of hypertension. In conclusion, the present findings suggest that the PLR can be used in daily practice as a marker of inflammation because it is easy to calculate using hemogram parameters and is a cost-effective index. The present study also shows that a high PLR might be indicative of high atherosclerotic risk in hypertensive patients and a predictive value can be determined in the future.

Conflict of Interest Statement

The authors report no conflicts of interest, financial or otherwise.

References

1. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA. 1996; 275: 1571-1576.
2. Pauletto P, Rattazzi M. Inflammation and hypertension: the search for a link. Nephrol Dial Transplant. 2006; 21: 850-853.
3. White WB. Ambulatory blood-pressure monitoring in clinical practice. N Engl J Med. 2003; 348: 2377-2378.
4. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. Hypertension. 1994; 24: 793-801.
5. Fan HQ, Li Y, Thijs L, Hansen TW, Boggia J, Kikuya M, et al. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. J Hypertens. 2010; 28: 2036-2045.
6. von Kanel R, Jain S, Mills PJ, Nelesen RA, Adler KA, Hong S, et al. Relation of nocturnal blood pressure dipping to cellular adhesion, inflammation and hemostasis. J Hypertens. 2004; 22: 2087-2093.
7. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999; 340: 115-126.
8. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation. 2006; 113: 2335-2362.
9. Okyay GU, Inal S, Onec K, Er RE, Pasaoglu O, Pasaoglu H, et al. Neutrophil to lymphocyte ratio in evaluation of inflammation in patients with chronic kidney disease. Ren Fail. 2013; 35: 29-36.
10. Ordu S, Ozhan H, Caglar O, Alemdar R, Basar C, Yazici M, et al. Mean platelet volume in patients with dipper and non-dipper hypertension. Blood Press. 2010; 19: 26-30.
11. Ozcan F, Turak O, Durak A, Isleyen A, Ucar F, Ginis Z, et al. Red cell distribution width and inflammation in patients with non-dipper hypertension. Blood Press. 2013; 22: 80-85.
12. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008; 102: 653-657.
13. Acar G, Kalkan ME, Avci A, Alizade E, Tabakci MM, Toprak C, et al. The relation of platelet-lymphocyte ratio and coronary collateral circulation in patients with stable angina pectoris and chronic total occlusion. Clin Appl Thromb Hemost. 2015; 21: 462-468.
14. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg. 2010; 200: 197-203.
15. Yildiz A, Yuksel M, Oylumlu M, Polat N, Akyuz A, Acet H, et al. The Utility of the Platelet-Lymphocyte Ratio for Predicting No Reflow in Patients With ST-Segment Elevation Myocardial Infarction. Clin Appl Thromb Hemost. 2015; 21: 223-228.
16. Gursoy OM, Karakoyun S, Kalcik M, Gokdeniz T, Yesin M, Gunduz S, et al. Usefulness of novel hematologic inflammatory parameters to predict prosthetic mitral valve thrombosis. Am J Cardiol. 2014; 113: 860-864.
17. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One. 2013; 8: e67688.
18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130: 461-470.
19. Summary of Recommendation Statements. Kidney Int Suppl (2011). 2013; 3: 5-14.
20. Mehta R, Drawz PE. Is nocturnal blood pressure reduction the secret to reducing the rate of progression of hypertensive chronic kidney disease? Curr Hypertens Rep. 2011; 13: 378-385.
21. Mancia G, Parati G. The role of blood pressure variability in end-organ damage. J Hypertens Suppl. 2003; 21: S17-S23.
22. Seo HS, Kang TS, Park S, Choi EY, Ko YG, Choi D, et al. Non-dippers are associated with adverse cardiac remodeling and dysfunction (R1). Int J Cardiol. 2006; 112: 171-177.
23. Zelinka T, Strauch B, Pecen L, Widimsky J Jr. Diurnal blood pressure variation in pheochromocytoma, primary aldosteronism and Cushing's syndrome. J Hum Hypertens. 2004; 18: 107-111.
24. Sasaki N, Ozono R, Yamauchi R, Teramen K, Munemori M, Hamada H, et al. Age-related differences in the mechanism of non-dipping among patients with obstructive sleep apnea syndrome. Clin Exp Hypertens. 2012; 34: 270-277.
25. Elung-Jensen T, Strandgaard S, Kamper AL. Longitudinal observations on circadian blood pressure variation in chronic kidney disease stages 3-5. Nephrol Dial Transplant. 2008; 23: 2873-2878.
26. Kim S, Kim NH, Kim YK, Yoo JH, Shin SN, Ko JS, et al. The Number of Endothelial Progenitor Cells is Decreased in Patients With Non-Dipper Hypertension. Korean Circ J. 2012; 42: 329-334.
27. Stenvinkel P, Alvestrand A. Inflammation in end-stage renal disease: sources, consequences, and therapy. Semin Dial. 2002; 15: 329-337.
28. Garcia C, Feve B, Ferre P, Halimi S, Baizri H, Bordier L, et al. Diabetes and inflammation: fundamental aspects and clinical implications. Diabetes Metab. 2010; 36: 327-338.
29. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol. 1996; 14: 397-440.
30. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420: 860-867.
31. Mangge H, Becker K, Fuchs D, Gostner JM. Antioxidants, inflammation and cardiovascular disease. World J Cardiol. 2014; 6: 462-477.
32. Massberg S, Grahl L, von Bruehl ML, Manukyan D, Pfeiler S, Goosmann C, et al. Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases. Nat Med. 2010; 16: 887-896.
33. Projahn D, Koenen RR. Platelets: key players in vascular inflammation. J Leukoc Biol. 2012; 92: 1167-1175.
34. Kaito K, Otsubo H, Usui N, Yoshida M, Tanno J, Kurihara E, et al. Platelet size deviation width, platelet large cell ratio, and mean platelet volume have sufficient sensitivity and specificity in the diagnosis of immune thrombocytopenia. Br J Haematol. 2005; 128: 698-702.
35. Thomson SP, McMahon LJ, Nugent CA. Endogenous cortisol: a regulator of the number of lymphocytes in peripheral blood. Clin Immunol Immunopathol. 1980; 17: 506-514.
36. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis. 2012; 34: 326-334.
37. Sunbul M, Gerin F, Durmus E, Kivrak T, Sari I, Tigen K, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratio in patients with dipper versus non-dipper hypertension. Clin Exp Hypertens. 2014; 36: 217-221.