ORIGINAL ARTICLE

Hematological indices in renovascular hypertension: A propensity score matching analysis

Renovasküler hipertansiyonda hematolojik endeksler: Eğilim skoru eşleme analizi

Ahmet Seyfeddin Gürbüz, M.D.,[1] Semi Öztürk, M.D.[2]

[1]Department of Cardiology, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Turkey
[2]Department of Cardiology, Haseki Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: Various hematological blood count parameters, including the neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV), were analyzed to assess differences in patients with renovascular (RVH) and essential hypertension (EH).

Methods: A propensity score analysis was performed to match 51 patients with RVH and 173 patients with EH. After matching, 49 pairs of patients were compared.

Results: Before matching, patients with RVH had significantly higher NLR values [1.35 (range: 1.14–1.76) vs. 1.05 (range: 0.81–1.3); p<0.001] and MPV [8.7 fL (range: 8.3–9.5 fL) vs. 8.4 fL (range: 7.3–9.2 fL; p=0.002]. After propensity score matching was performed (49 vs 49 patients), age, sex, atherosclerosis risk factors, frequency of atherosclerosis, and the medications used were similar between groups. The NLR was significantly greater in patients with RVH [1.00 (range: 0.76–1.40) vs 1.35 (range: 1.15–1.75; p<0.001]. The MPV did not differ significantly between groups. The NLR was the only parameter independently associated with RVH in a multivariate logistic regression [odds ratio: 5.563, 95% confidence interval (CI): 2.089–14.814; p≤0.001]. Receiver operating characteristic curve analysis results indicated that NLR >1.16 predicted RVH with a sensitivity of 72% and a specificity of 60% [area under curve: 0.724, 95% CI: 0.624–0.823; p≤0.001].

Conclusion: The results of the present study demonstrated that NLR, which is a simple, clinical parameter of inflammation, was elevated in patients with RVH.

ÖZET

Amaç: Bu yazıda, renovasküler (RVH) ve esansiyel hipertansiyon (EH) olan hastalarda nötrofil lenfosit oranı (NLO) ve ortalama trombosit hacmini (OTH) içeren çeşitli hematolojik kan sayımı parametrelerinin farklılığını değerlendirdik.

Yöntemler: Renovasküler hipertansiyonlu 51 hasta ve EH'li 173 hastaya eğilim skoru eşleme analizi uygulandı. Eşleştikten sonra 49 çift hasta karşılaştırıldı.

Bulgular: Eşleşmeden önce, RVH hastaları anlamlı olarak daha yüksek NLO değerlerine sahipti [1.35 (aralık, 1.14–1.76) ve 1.05 (aralık, 0.81–1.3), (p <0.001)] ve OTH [8.7 (aralık, 8.3–9.5) ve 8.4 (aralık, 7.3–9.2), (p=0.002)] değerlere sahipti. Eğilim skoru eşleme analizi sonrası (49'a karşı 49 hasta), yaş, cinsiyet, aterosklerotik risk faktörleri, ateroskleroz sıklığı, kullanılan ilaçlar açısından benzer özellikte gruplar elde edildi. Eşleşme sonrası, RVH olan hastalarda NLO anlamlı olarak yüksek kalırken [1.00 (aralık, 0.76–1.40) ve 1.35 (aralık, 1.15–1.75)] p <0.001, OTH gruplar arasında farklılık göstermedi. NLO, çok değişkenli lojistik regresyonda RVH ile bağımsız olarak ilişkilendirilen tek parametre idi (Odds Oranı=5.563, %95 Güven Aralığı=2.089–14.814, p <0.001). ROC eğrisi analizinde NLR >1.16, %72 duyarlılık ve %60 özgüllük ile RVH'yi tahmin ettirmekteydi [(AUC)=0.724, %95 GA=0.624–0.823, p <0.001].

Sonuç: Bu çalışmanın sonuçları, RVH hastalarında basit ve klinik bir inflamasyon parametresi olan NLO'nun arttığını göstermiştir.

Hypertension is the leading cause of chronic kidney disease, stroke, atherosclerosis, and cardiovascular mortality. As many as 95% of patients are diagnosed with EH, while secondary hypertension accounts for only a minority of cases. Renovascular hypertension (RVH) due to atherosclerotic renal artery

Received: April 16, 2018 *Accepted:* September 25, 2018

Correspondence: Dr. Ahmet Seyfeddin Gürbüz. Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Konya, Turkey.
Tel: +90 332 - 223 60 00 e-mail: ahmetseyfeddingurbuz@hotmail.com

stenosis (RAS) is a significant cause of secondary hypertension that increases vascular morbidity and mortality.[1]

Complete blood count (CBC) subsets, such as counts of neutrophils, lymphocytes, and platelets, as well as derived parameters, such as the neutrophil-to-lymphocyte ratio (NLR) are simple and clinically available measures of inflammation. Many recent studies have demonstrated the utility of these parameters to predict outcomes of various atherosclerotic pathologies, including cardiovascular and peripheral vascular disease.[2,3]

The aim of this study was to evaluate the difference between various CBC parameters, such as the NLR, in patients with RVH and EH. A propensity score matched analysis was used to avoid confounding bias.

METHODS

Study population

A group of 244 hypertensive patients was retrospectively analyzed. EH was confirmed with Doppler ultrasound and laboratory tests in 173 patients. Patients with recurrent pulmonary edema without overt left ventricular dysfunction or with resistant, accelerated, malignant hypertension who had evidence of RAS with a positive Doppler ultrasound screening test or computed tomography underwent digital subtraction angiography (DSA). In all, 51 patients who had ≥50% diameter stenosis observed on DSA were diagnosed with atherosclerotic RAS. The exclusion criteria were renal insufficiency (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), disorder of the liver or thyroid, hematological or oncological dysfunction, an inflammatory disorder, or active infection. Three patients with a diagnosis of fibromuscular dysplasia and 2 patients with suspicious vasculitis were excluded. In addition, 15 patients with various clinical conditions, such as systemic lupus erythematosus, rheumatoid arthritis, malignancy, and infectious disease were excluded. CBC and biochemical values from within 4 weeks of Doppler examination were assessed. Demographic characteristics were recorded, including the presence of diabetes mellitus, hyperlipidemia, or a history of coronary artery disease (CAD). The biochemical parameters and risk factors of a total of 51 patients with RVH and 173 patients with EH were reviewed.

Renal Doppler ultrasound

Abbreviations:

CAD	*Coronary artery disease*
CBC	*Complete blood count*
CI	*Confidence interval*
CRP	*C-reactive protein*
DSA	*Digital subtraction angiography*
eGFR	*Estimated glomerular filtration rate*
EH	*Essential hypertension*
MPV	*Mean platelet volume*
NLR	*Neutrophil-to-lymphocyte ratio*
RAS	*Renal artery stenosis*
ROC	*Receiver-operating characteristic*
RVH	*Renovascular hypertension*

Renal Doppler ultrasound was performed as previously described.[4] The examination was performed in the supine position with a 3.0-MHz ultrasound probe on a Voluson 730 ultrasound machine (GE Healthcare, Inc., Chicago, IL, USA). The aorta and its branches were visualized. The left renal vein was imaged in the longitudinal section and used as a reference to identify the aortic origins of the main renal arteries. While maintaining an angle of insonation of 60° or less, Doppler samples were taken from each renal artery from the aortic origin to the renal hilus. The peak systolic velocity within the main renal arteries, intrarenal blood flow measurements, and renal aortic velocity ratio were evaluated. A peak systolic velocity of <100 cm/second was considered normal, those between 100 and 200 cm/second were suggestive of mild stenosis (<50% narrowing), and those >200 cm/second were suggestive of severe stenosis (50–99% narrowing).

Biochemical and hematological parameters

Blood was collected from an antecubital vein. CBC analysis were performed using a Beckman Coulter HMX-AL (Beckman Coulter Inc., Brea, CA, USA). White blood cell, neutrophil, lymphocyte, hemoglobin, platelet, red cell distribution width and mean platelet volume (MPV) values were recorded, and the NLR was derived from these parameters.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The data were presented as mean±SD or median (interquartile range) for quantitative variables, and as percentages for categorical variables. The normality of data distribution was tested with the Kolmogorov-Smirnov test. Numerical variables were tested with an independent samples t-test or the Mann-Whitney U-test, and categorical variables were tested using Fisher's exact test or a chi-square test, whichever was appropriate. Yates continuity correction was used when applicable. Re-

ceiver-operating characteristic (ROC) curve graphics were used to determine the cut-off values of independent predictors. A p value <0.05 was regarded as significant.

Propensity scores for all of the patients were estimated using a logistic regression model, which included all covariates: age, sex, dyslipidemia, diabetes mellitus, current smoking, coronary artery disease, beta-blocker use, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, calcium channel blocker use, diuretic use, statin use, antiplatelet use, and estimated glomerular filtration rate (eGFR). One-to-one nearest-neighbor matching was performed using a caliper width of 0.1. The resulting score-matched pairs were used to re-evaluate the analysis. The baseline variables that were found to be significant (p<0.05) in the univariate analysis were included in the multivariate logistic regression analysis (enter model) to determine the independent components of RVH.

RESULTS

Patient characteristics

Before propensity score matching, the RVH group was composed of 51 patients who were diagnosed with atherosclerotic RAS, and the EH group comprised 173 patients. The baseline characteristics of the EH and RVH groups are presented in Table 1. Age, sex, atherosclerosis risk factors, frequency of atherosclerosis, and medications used were similar between groups. Patients with RVH had significantly higher values of NLR [1.35 (range: 1.14–1.76) vs. 1.05 (range: 0.81–1.3); p<0.001] and MPV [8.7 fL (range: 8.3–9.5 fL) vs. 8.4 fL (range: 7.3–9.2 fL); p=0.002].

Table 1. Characteristics of the essential hypertension and renovascular hypertension groups

	Before matching			After matching		
	EH (n=173)	RVH (n=51)	*p*	EH (n=49)	RVH (n=49)	*p*
Age (years)	51.2±15.5	53.4±14.1	0.386	51.5±15.9	52.3±13.2	0.772
Sex (male), n (%)	99 (57.2)	27 (52.9)	0.703	29 (59.2)	27 (55.1)	0.999
Dyslipidemia, n (%)	54 (31.2)	20 (39.2)	0.369	15 (30.6)	19 (38.8)	0.782
DM, n (%)	58 (33.5)	19 (37.3)	0.745	16 (32.7)	18 (36.7)	0.999
CAD, n (%)	24 (13.9)	9 (17.6)	0.657	7 (14.3)	8 (16.3)	0.999
Smoking, n (%)	55 (31.8)	19 (37.3)	0.576	22 (44.9)	18 (36.7)	0.647
Beta-blocker, n (%)	37 (21.4)	12 (23.5)	0.895	10 (20.4)	11 (22.4)	0.999
ACE inhibitor/ARB, n (%)	112 (64.7)	32 (62.7)	0.924	29 (59.2)	31 (63.3)	0.874
Ca channel blocker, n (%)	71 (41.0)	24 (47.1)	0.546	26 (53.1)	22 (44.9)	0.654
Diuretic, n (%)	84 (48.6)	22 (43.1)	0.602	21 (42.9)	21 (42.9)	
Statin, n (%)	51 (29.5)	19 (37.3)	0.378	13 (26.5)	18 (36.7)	0.581
Antiplatelet, n (%)	30 (17.3)	12 (23.5)	0.428	10(20.4)	11 (22.4)	0.999
eGFR (mL/min/1.73 m^2)	83.9±26.2	77.0±18.0	0.063	78.2±18.5	77.8±17.9	0.914
Hemoglobin (g/dL)	12.4±1.0	12.4±0.9	0.874	12.1±1.1	12.4±0.9	0.756
Platelet ($10^3/mm^3$)	285 (236≠348)	267 (237–345)	0.492	297 (261–369)	267 (236–340)	0.050
MPV (fL)	8.4 (7.3–9.2)	8.7 (8.3–9.5)	0.002	8.5(8–9.0)	8.7 (8.3–9.3)	0.124
RDW (%)	14 (12.8–15.3)	13.5 (13.1–15.1)	0.657	14.3 (12.9–15.4)	13.9 (13.1–15.2)	0.782
Leukocyte ($10^3/mm^3$)	8.26±1.23	8.04±0.94	0.188	8.18±1.27	8.00±0.91	0.408
NLR	1.05 (0.8–11.3)	1.35 (1.14–1.76)	<0.001	1.00 (0.76–1.40)	1.35 (1.15–1.75)	0.001

EH: Essential hypertension; RVH: Renovascular hypertension; CAD: Coronary artery disease; DM: Diabetes mellitus; MPV: Mean platelet volume; RDW: Red cell distribution width; NLR: Neutrophil-to-lymphocyte ratio; ACE: Angiotensin-converting-enzyme; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate.

Table 2. Univariate logistic regression analysis for renovascular hypertension

	OR	95% CI	*p*
Age (years)	1.004	0.977–1032	0.78
Sex (male)	1.181	0.530–2632	0.68
Dyslipidemia	0.697	0.302–1.608	0.39
Diabetes mellitus	1.198	0.521–2.755	0.67
CAD	0.854	0.284–2.571	0.78
Smoking	1.403	0.625–3.151	0.41
eGFR (mL/min/1.73 m^2)	0.999	0.977–1.021	0.91
Hemoglobin (g/dL)	1.458	0.960–2.216	0.07
Platelet (10^3/mm^3)	0.994	0.998–0.999	0.03
MPV (fL)	1.528	0.977–2.392	0.06
RDW (%)	0.899	0.696–1.162	0.41
Leukocyte (10^3/mm^3)	0.856	0.594–1.233	0.40
NLR	5.563	2.089–14.814	0.01

CAD: Coronary artery disease; eGFR: Estimated glomerular filtration rate; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; RDW: Red cell distribution width.

Table 3. Multivariate logistic regression analysis for renovascular hypertension

	OR	%95 CI	*p*
NLR	5.360	1.913–15.022	0.001
Platelet (10^3/mm^3)	0.996	0.991–1.001	0.127

NLR: Neutrophil-to-lymphocyte ratio.

After propensity score matching (49 vs. 49 patients), the age, sex, atherosclerosis risk factors, frequency of atherosclerosis, and medications used were similar between groups. The NLR value remained significantly greater in patients with RVH [1.00 (range: 0.76–1.40) vs. 1.35 (range: 1.15–1.75); p=<0.001] (Fig. 1). The MPV did not differ significantly between groups, and the difference in platelet count did not reach statistical significance [297 103/mm^3 (range: 261–369 103/mm^3) vs. 267 103/mm^3 (range: 236–340103/mm^3; p=0.050] (Table 1). Univariate logistic regression analysis demonstrated that NLR and platelet count were significantly associated with RVH (Table 2). NLR was the only parameter independently associated with RVH in multivariate logistic regression (odds ratio: 5.563, 95% CI: 2.089–14.814; p<0.001) (Table 3).

In the ROC curve analysis, NLR >1.16 predicted RVH with a sensitivity of 72% and a specificity of 60% (area under curve: 0.724, 95% CI: 0.624–0.823; p=<0.001; positive and negative predictive values respectively: 64%, 68%) (Fig. 2).

DISCUSSION

To the best of our knowledge, this is the first study to show an increased NLR in RVH using propensity score-matched analysis. Despite the low sensitivity and specificity of these results, NLR may be useful to predict renovascular hypertension. Increased NLR in RVH demonstrated an increased inflammatory

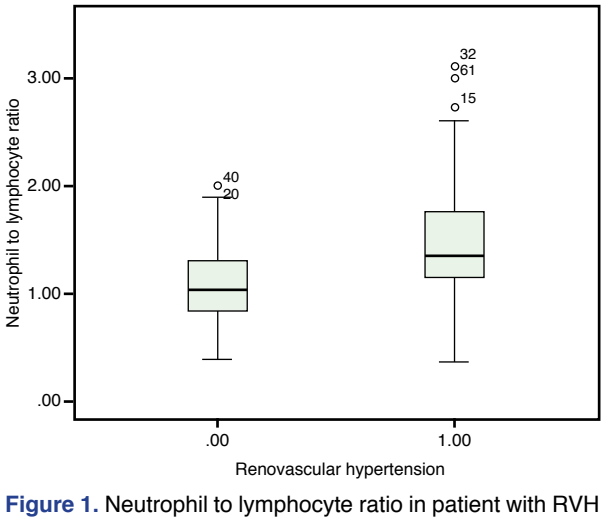

Figure 1. Neutrophil to lymphocyte ratio in patient with RVH and EH after propensity score matching.

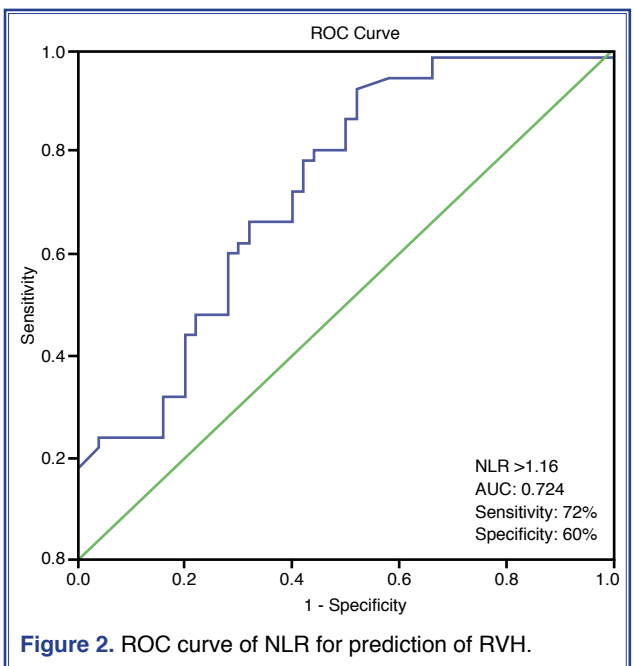

Figure 2. ROC curve of NLR for prediction of RVH.

process. This finding clearly illustrated the contribution of inflammation in RVH.

An increased level of angiotensin II as a result of renin-angiotensin-aldosterone system activation is the hallmark of inflammation in RVH. The induction of proinflammatory, pro-oxidant, and procoagulant cascades has been documented in both animal and human models. The increased production of markers such as interleukin 6, tumor necrosis factor alpha, chemokine monocyte chemoattractant protein 1, interferon gamma, and endothelin 1 in RVH have been reported in several studies.[5–8] Inflammatory mediators cause monocyte infiltration, fibrosis, and subsequent loss of kidney function. Additionally, systemic inflammation induces atherosclerosis, which can lead to coronary and peripheral artery disease.

Studies have confirmed a close relationship between CAD and RVH.[1,9,10] However, in the present study, the frequency of CAD was not significantly different between the patients with EH and RVH. Although increased inflammation was confirmed in our research, consistent with previous studies, coronary atherosclerosis development is a complex process to explain simply with inflammation.

A recent comprehensive study confirmed an increase in several inflammatory markers and cell adhesion molecules in the renal veins of RVH patients.[5] Furthermore, reduced levels of systemic CD34+/KDR+ positive progenitor cells were detected in RVH patients. Progenitor cells exhibited a negative gradient in the kidneys as a result of net removal from systemic circulation during passage. Recruitment of monocytes and lymphocytes to the kidneys may alter NLR in circulation. Saeed et al.[8] demonstrated elevated levels of C-reactive protein (CRP) and peripheral leukocytes in patients with atherosclerotic RAS versus EH. However, Eirin et al.[5] did not find a significant difference in the white blood cell count or CRP level in a comparison of EH and RVH. Since recent studies have proposed NLR as a more reliable marker of inflammation, we preferred to use this ratio rather than the white blood cell count.[11] Consistent with previous work, our study data revealed increased inflammation in RVH.

Several studies have demonstrated an association between platelet volume and the atherosclerotic process.[12,13] Bath et al.[14] first described increased platelet volume and mass in patients with atherosclerotic RAS. Recently, Sayın et al.[15] confirmed increased platelet volume in patients with RAS. Furthermore, they evaluated NLR in patients with RAS for the first time. Their findings reflected a similar NLR in patients with critical, non-critical, or no RAS.[16] The aforementioned 2 studies found an increased platelet volume in patients with RAS; however, we did not find a significant difference in the comparison with matched controls. MPV may be affected by multiple factors; in this instance, adjusting the covariates resulted in a similar MPV in patients with RAS and matched controls.

Limitations

The retrospective nature of this study is the major limitation. The absence of a healthy group and a classical inflammatory marker, such as CRP, are also limitations. NLR is a less sensitive marker of inflammation than CRP.

Conclusion

The results of the present study demonstrated that NLR, which is a simple, clinical parameter of inflammation, was greater in patients with RVH.

Ethics Committee Approval: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: Concept: A.S.G., S.Ö.; Design: A.S.G., S.Ö.; Supervision: S.Ö.; Materials: A.S.G.; Data: A.S.G.; Analysis: A.S.G., S.Ö.; Literature search: A.S.G., S.Ö.; Writing: A.S.G.; Critical revision: A.S.G., S.Ö.

REFERENCES

1. Edwards MS, Craven TE, Burke GL, Dean RH, Hansen KJ. Renovascular disease and the risk of adverse coronary events in the elderly: a prospective, population-based study. Arch Intern Med 2005;165:207–13. [CrossRef]
2. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. Expert Rev Cardiovasc Ther 2016;14:573–7. [CrossRef]
3. Paquissi FC. The role of inflammation in cardiovascular diseases: the predictive value of neutrophil-lymphocyte ratio as a marker in peripheral arterial disease. Ther Clin Risk Manag 2016;12:851–60. [CrossRef]
4. Motew SJ, Cherr GS, Craven TE, Travis JA, Wong JM, Reavis SW, et al. Renal duplex sonography: main renal artery versus

hilar analysis. J Vasc Surg 2000;32:462–9. [CrossRef]
5. Eirin A, Gloviczki ML, Tang H, Gössl M, Jordan KL, Woollard JR, et al. Inflammatory and injury signals released from the post-stenotic human kidney. Eur Heart J 2013;34:540–548a. [CrossRef]
6. Zhu XY, Chade AR, Krier JD, Daghini E, Lavi R, Guglielmotti A, et al. The chemokine monocyte chemoattractant protein-1 contributes to renal dysfunction in swine renovascular hypertension. J Hypertens 2009;27:2063–73. [CrossRef]
7. Eirin A, Zhang X, Zhu XY, Tang H, Jordan KL, Grande JP, et al. Renal vein cytokine release as an index of renal parenchymal inflammation in chronic experimental renal artery stenosis. Nephrol Dial Transplant 2014;29:274–82. [CrossRef]
8. Saeed A, Herlitz H, Nowakowska-Fortuna E, Nilsson U, Alhadad A, Jensen G, et al. Oxidative stress and endothelin-1 in atherosclerotic RAS and effects of renal angioplasty. Kidney Blood Press Res 2011;34:396–403. [CrossRef]
9. Edwards MS, Hansen KJ, Craven TE, Bleyer AJ, Burke GL, Levy PJ, et al. Associations between renovascular disease and prevalent cardiovascular disease in the elderly: a population-based study. Vasc Endovascular Surg 2004;38:25–35.[CrossRef]
10. Tanındı A, Erkan AF, Ekici B, Alhan A, Töre HF. Neutrophil to lymphocyte ratio is associated with more extensive, severe and complex coronary artery disease and impaired myocardial perfusion. Turk Kardiyol Dern Ars 2014;42:125–30. [CrossRef]
11. Sari I, Sunbul M, Mammadov C, Durmus E, Bozbay M, Kivrak T. Relation of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio with coronary artery disease severity in patients undergoing coronary angiography. Kardiol Pol 2015;73:1310–6. [CrossRef]
12. Khode V, Sindhur J, Kanbur D, Ruikar K, Nallulwar S. Mean platelet volume and other platelet volume indices in patients with stable coronary artery disease and acute myocardial infarction: A case control study. J Cardiovasc Dis Res 2012;3:272–5. [CrossRef]
13. Ekici B, Erkan AF, Alhan A, Sayın I, Aylı M, Töre HF. Is mean platelet volume associated with the angiographic severity of coronary artery disease? Kardiol Pol 2013;71:832–8.
14. Bath PM, Missouris CG, Buckenham T, MacGregor GA. Increased platelet volume and platelet mass in patients with atherosclerotic renal artery stenosis. Clin Sci (Lond) 1994;87:253–7. [CrossRef]
15. Sayın MR, Yavuz N, Karabağ T, Çetiner MA, Öz İİ, Güngördük OA, Aydın M. Renal artery stenosis and mean platelet volume. Anatol J Cardiol 2016;16:197–201.

Keywords: Essential hypertension; mean platelet volume; neutrophil-to-lymphocyte ratio; renal artery stenosis.

Anahtar sözcükler: Esansiyel hipertansiyon; ortalama trombosit hacmi; nötrofil lenfosit oranı; renal arter darlığı.