Ann Med Res 2020;27(4):1088-94

Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.12.876

Original Article

Routine hematological parameters do not reflect disease severity and cardiovascular risk in obstructive sleep apnea syndrome

Asli Akyol Gurses[1], Kadri Murat Gurses[2], Utku Ogan Akyildiz[3]

[1]Gazi University, Faculty of Medicine, Department of Neurology, Division of Neurophysiology, Ankara, Turkey
[2]Adnan Menderes University, Faculty of Medicine, Department of Basic Health Sciences, Aydin, Turkey
[3]Adnan Menderes University, Faculty of Medicine, Department of Neurology, Aydin, Turkey

Abstract

Aim: Obstructive sleep apnea syndrome (OSAS) is characterized by transient obstruction of the upper airway and intermittent hypoxia during sleep and known to co-exist with a background low-grade systemic inflammation. In this study, we aimed to evaluate the routine hematological parameters which have recently been suggested as alternatives to specific inflammatory biomarkers and their association with disease severity and concurrent cardiovascular risk factors in OSAS.

Material and Methods: 210 patients, who were examined for sleep disordered breathing complaints and diagnosed OSAS after overnight polysomnography, were included in the study. Patients who suffer from at least one of the following disorders; diabetes mellitus, hypertension and hyperlipidemia were classified as "patients with cardiovascular risk". Results of routine hemogram studies and polysomnographic analyses were recorded.

Results: 71% of the patients were male and 29% were female. 12% of the patients had mild, whereas 29% had moderate and 59% had severe obstructive sleep apnea syndrome. Platelet counts, mean platelet volume, platelet distribution width, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio revealed no difference among three groups of disease severity. Comparison of patients with and without cardiovascular risk either showed no difference in terms of the aforementioned parameters.

Conclusion: Our findings indicate that routine hematological parameters such as mean platelet volume, platelet distribution width, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio are not appropriate indices for predicting disease severity and cardiovascular risk in OSAS patients. As severe disease corresponds to a worse inflammatory state, these markers might not be appropriate for predicting systemic inflammation either.

Keywords: Blood count; cardiovascular risk; hematological parameters; obstructive sleep apnea syndrome

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent obstruction of the upper airway and intermittent hypoxia during sleep that results in sleep fragmentation, excessive daytime sleepiness and various undesirable consequences. According to International Classification of Sleep Disorders-3 (ICSD-3); the diagnosis depends on polysomnographic evidence, which demonstrate ≥5 obstructive respiratory events per hour during sleep, in the presence of at least one of the typical symptoms like snoring, daytime somnolence, snoring and vascular risk factors; or ≥15 obstructive respiratory events even in the absence of symptoms (1).

OSAS is a growing public health problem which affects approximately 5-7% of males and 2-5% of females in adult population and frequently accompanied by certain cardiovascular (CV) risk factors such as hypertension, diabetes mellitus, obesity and dyslipidemia (2,3). The pathogenesis is thought to be multifactorial comprising of both mechanical factors that pave the upper respiratory system for collapse easily, and the inflammatory etiology proven by many histopathological studies (4-6).

Growing evidence from translational models, as well as clinical studies indicate that inflammatory response to intermittent hypoxia plays a central role during development of CV morbidity in OSAS (7,8). Activation of inflammatory pathways in response to hypoxia-sensitive transcription factors throughout the vascular endothelium and carotid body, and pro-inflammatory cytokines released from adipose tissue in the co-existence of obesity are putative

Received: 23.12.2019 **Accepted:** 04.02.2020 **Available online:** 16.04.2020
Corresponding Author: Asli Akyol Gurses, Gazi University, Faculty of Medicine, Department of Neurology, Division of Neurophysiology, Ankara, Turkey **E-mail:** akyol1984@yahoo.com

mechanisms which facilitate this pathological process (9). Other potential contributors include sympathetic excitation, vascular endothelial dysfunction, oxidative stress and metabolic dysregulation (10).

As expected, the inflammatory state in OSAS patients has been the subject of many investigations in recent years. In addition to well-known inflammatory biomarkers like C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), intercellular adhesion molecule (ICAM), interleukin-6 (IL-6), interleukin-8 (IL-8), vascular cell adhesion molecule (VCAM) and selectins, which are demonstrated to be higher in OSAS patients when compared to controls (11); routine hematological indices have been the focus of evaluation in other studies, because of their easy and practical availability (12).

Neutrophil/Lymphocyte ratio (NLR), Platelet/Lymphocyte Ratio (PLR) and platelet indices like platelet count, mean platelet volume (MPV) and platelet distribution width (PDW) are some of these markers which are assumed to reflect the inflammatory state in OSAS patients. Higher NLR is shown to predict mortality and adverse outcomes in stable coronary artery disease, and there are a number of studies indicating higher values in severe OSAS patients, in comparison to normal controls or mild-moderate disease (13-15). Platelet system is also known to be activated during an inflammatory process and increased MPV, PDW and PLR values have recently been demonstrated in severe OSAS patients either in reference to healthy controls or mild to moderate disease (16,17). Beyond that, some of these reports emphasize significant increase of aforementioned hematological indices particularly in OSAS patients with concurrent hypertension and cardiovascular disease (CVD), which is interpreted as a determinant of worse inflammatory state in this subgroup. (15,17,18). However various reports of negative results also exist and the association between hematological parameters and disease severity in OSAS is still ambiguous (19-21) and needs further elucidation.

In order to clarify this ambiguity, we aimed to evaluate the relationship between routine hematological parameters and disease severity in OSAS. We also assessed the association of regarded parameters with well-known CV risk factors (hypertension, diabetes mellitus and dyslipidemia) in OSAS patients who do not have a diagnosis of overt CV disease.

MATERIAL and METHODS

Study Design and Patients

A retrospective analysis of patients, who had been examined for sleep disordered breathing complaints (at least one of the following; snoring, excessive daytime sleepiness / insufficient sleep quality, witnessed apneas) in Aydin State Hospital Clinical Neurophysiology and Sleep Disorders Department between June 2017 and February 2019, was performed. All of the patients underwent overnight polisomnography. Laboratory findings and polysomnographic data were recorded.

Patients with systemic diseases which could affect blood count, known hematological, cardiovascular (coronary artery disease, myocardial infarction, heart failure) and cerebrovascular disorders and active infections were excluded. Patients who suffer from at least one of the following disorders; diabetes mellitus, hypertension and hyperlipidemia were classified as “patients with CV risk” and the remaining were classified as “patients without CV risk”. Diabetes mellitus was defined as fasting plasma glucose >126mg/dL or HbA1c ≥6.5% and/or use of antidiabetic medications. Patients with an arterial blood pressure >140/90 mmHg and/or the ones who are already receiving antihypertensive medications were considered as hypertensive. Patients taking lipid-lowering agents and in whom lipid lowering medications are recommended by the current dyslipidemia guidelines were considered to be hyperlipidemic (22). The study protocol was approved by local ethics committee (2019/50).

Routine hemogram studies had been performed on admission to outpatient clinic, prior to the polysomnographic analysis. Blood samples were collected in tubes containing ethylene diamine tetra acetic acid and the samples were analyzed using SYSMEX XE-2100 automated hematology analyzer (Sysmex Corporation, Kobe, Kansai, Japan).

Polysomnography

All-night polisomnography was performed by using Nox Medical programme which recorded six channel electroencephalogram (EEG), Electrooculogram (EOG), Chin and Leg electromyogram (EMG), electrocardiogram (ECG), oronasal thermal and nasal airflow, thoracic and abdominal respiratory effort, pulse oximetry, and body position. The data was scored manually by the same certified clinical neurophysiologist according to AASM 2014 v2.4 guidelines (23).

Patients with apnea-hypopnea index (AHI) between 5-15 events/hour were classified as mild OSAS, whereas 15-30 events/hour were classified as moderate and >30 events/hour as severe OSAS (23,24).

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, Illinois). Shapiro-Wilk test was used to test the data for normality. Normally distributed continuous parameters are presented as mean±SD and skewed continuous parameters as median (minimum-maximum). Categorical data are presented as frequencies and percentages and were compared using chi-square test. Continuous variables from different disease levels of OSAS patients were compared by using one way analysis of variance (ANOVA), and Kruskal-Wallis test was used if the distribution was not normal. Spearman test was used to assess correlation between polysomnographic and hematological parameters. Comparisons of the OSAS patients with and without CV risk were performed via Mann-Whitney U test or independent samples' t test according to the normality. A 2-tailed p value <0.05 is considered statistically significant.

RESULTS

210 patients who were diagnosed OSAS according to ICSD-3 criteria were included in the study. 149 (71%) of the patients were male and 61 (29%) were female. Mean age was 51.1±12.24 years and mean body mass index (BMI) was 32.5±6.24 kg/m2. 12% of the patients had mild (n=25), 29% had moderate (n=61) and 59% had severe (n=124) OSAS.

Baseline demographic and laboratory characteristics of the whole study population are demonstrated in Table1. Age and gender distribution were similar among disease severity categories, however BMI was significantly higher in the severe OSAS group (p<0.001). Median AHI was 9.4 (5.3-14.4) in mild, 21.1 (15.5-29.8) in moderate and 58.4 (30.1-116.4) in severe OSAS patients (p<0.001). As expected; AHI and oxygen desaturation index (ODI) were

Table 1. Baseline demographic and clinical characteristics of the study population

	mild OSAS	moderate OSAS	severe OSAS	p value
Age (years)	49.3±13.2	50.05±12.9	51.98±1.71	0.454
Gender (female % vs male %)	12(48%) vs 13 (52%)	15 (24.6%) vs 46 (75.4%)	34 (27.4%) vs 90 (72.6%)	0.078
BMI (kg/m2)	28.7±4.98	30.57±5.46	34.2±6.24	<0.001*
Polysomnographic Data				
TST (min)	364.5 (267.5-446)	363.25 (177.5-477.1)	341.25 (97.5-448)	0.025*
Sleep Efficiency (%)	83.3 (51-93.2)	80.3 (41.3-94.5)	74.55 (26.8-95)	0.001*
N3 Ratio (%)	18.5 (1.4-48.5)	18.35 (1.1-41.5)	9.8 (0-38.3)	<0.001*
AHI	9.4 (5.3-14.4)	21.1 (15.5-29.8)	58.45 (30.1-116.4)	<0.001*
ODI	9 (0.8-32)	23.2 (5.6-47.3)	64.05 (17.6-123.3)	<0.001*
spO2<90% duration	1.3 (0-14.4)	1.6 (0-83.5)	13.95 (0-100)	<0.001*
Average spO2 (%)	93.1 (90.5-96.6)	93 (87.9-96.7)	91.55 (71.7-96.1)	<0.001*
Nocturnal HR (/min)	61.5 (50.3-79.2)	65.3 (47-94.9)	66.05 (43.1-97.8)	0.100
Laboratory Data				
WBC (10^3/µl)	8.0±1.3	7.41±1.55	7.83±1.5	0.184
Neu (10^3/µl)	4.68±1.29	4.26±1.27	4.4±1.23	0.381
Lymph (10^3/µl)	2.51 (1.19-3.67)	2.46 (1.11-4.28)	2.50 (1.38-4.83)	0.217
NLR	1.89 (0.6-4.46)	1.83 (0.81-4.73)	1.73 (0.63-4.78)	0.701
PLT (10^3/µl)	259 (154-357)	263 (152-451)	263 (154-482)	0.939
MPV (fL)	10.6±0.87	10.52±0.92	10.82±0.98	0.116
PDW (%)	13.3 (10-15.5)	12.6 (8.9-20.3)	13.2 (9.3-20)	0.116
PLR	103.03 (50.83-172.27)	111.59 (50-220.25)	104.47 (42.79-273.91)	0.174

BMI: body mass index; TST: total sleep time; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; Nocturnal HR: nocturnal heart rate; WBC: white blood cell; Neu: neutrophil; Lymph: Lymphocyte; NLR: Neutrophil / Lymphocyte ratio; PLT: Platelet; MPV: mean platelet volume; PDW: platelet distribution width; PLR: Platelet / Lymphocyte ratio

* p<0.05 denotes statistical significance

Table 2. Spearman Correlation of AHI and hematological parameters		
WBC	r	0.115
	p	0.097
Neu	r	0.010
	p	0.882
Lymph	r	0.121
	p	0.094
NLR	r	-0.090
	p	0.193
PLT	r	0.060
	p	0.388
MPV	r	0.077
	p	0.267
PDW	r	0.091
	p	0.189
PLR	r	-0.104
	p	0.134
Spearman correlation analysis did not demonstrate significant correlation between apnea-hypopnea index (AHI) and hematological parameters		

significantly different among three groups (p<0.001). Median total sleep time [TST] (p=0.025), sleep efficiency (p=0.001), N3 ratio (p<0.001) and average oxygen saturation (p<0.001) were significantly lower; but time spent <90% spO2 (p<0.001) was higher in severe OSAS patients in comparison to mild and moderate disease. On the other hand, nocturnal heart rate was similar among groups (p=0.100). Neither WBC, Neutrophil, Lymphocyte, Platelet counts nor MPV, PDW, NLR, PLR values were different regarding disease severity. Spearman correlation analysis also did not demonstrate significant correlation between AHI and the aforementioned parameters (Table 2).

The patients were also stratified according to the presence of CV risk factors (hypertension, diabetes mellitus and hyperlipidemia). 110 out of 210 patients had at least one of the risk factors and those were referred as "patients with CV risk". 81 of them had hypertension, whereas 58 had diabetes mellitus and 34 had hyperlipidemia. The remaining 100 patients were classified as "patients without CV risk". Mean age (54.75±10.39 vs. 47.09±12.89, p<0.001) and median BMI (33.3[21.3-45.3] vs. 30.65[19-58.8], p=0.005) were higher in the patients with CV risk. Gender distribution (p= 0.53) and smoking history (p=0.94) were similar in both groups. Among the patients with CV risk; 10% (n=11) had mild, 23% had moderate (n=25) and 67% had severe (n=74) OSAS. On the other hand, among patients without CV risk; 14% (n=14) had mild, 36% (n=36)

Table 3. Blood count values of patients with and without cardiovascular risk

	mild OSAS			moderate OSAS			severe OSAS		
	CV risk (-) (n=14)	CV risk (+) (n=11)	p value	CV risk (-) (n=36)	CV risk (+) (n=25)	p value	CV risk (-) (n=50)	CV risk (+) (n=74)	p value
WBC (10^3/µl)	7.9±0.91	8.12±1.72	0.68	7.01±1.5	7.99±1.45	0.01*	7.78±1.54	7.87±1.47	0.72
Neu (10^3/µl)	4.78±0.9	4.54±1.7	0.65	3.99±1.17	4.65±1.33	0.04*	4.3±1.29	4.47±1.2	0.44
Lymph (10^3/µl)	2.46 (1.19-3.3)	2.62 (2.01-3.67)	0.27	2.21 (1.11-3.31)	2.61 (1.28-4.28)	0.11	2.54 (1.69-4.71)	2.42 (1.38-4.83)	0.1
NLR	1.92 (0.87-4.46)	1.47 (0.6-3.16)	0.32	1.81 (0.87-4.44)	1.85 (0.81-4.73)	0.6	1.54 (0.66-3.45)	1.76 (0.63-4.78)	0.15
PLT (10^3/µl)	237.5 (154-340)	280 (218-357)	0.06	262.5 (155-451)	269 (152-413)	0.73	262 (165-482)	268.5 (154-407)	0.53
MPV (fL)	10.48±0.99	10.79±0.71	0.4	10.43±0.99	10.66±0.82	0.35	10.88±1.01	10.79±0.97	0.62
PDW (%)	12 (10-15.5)	13.5 (11.2-15.2)	0.28	12.3 (9-20.3)	13.2 (8.9-17)	0.73	13.5 (9.8-18.7)	13.1 (9.3-20)	0.37
PLR	109.28 (50.83-172.27)	93.12 (67.9-157.21)	0.87	111.7 (50-210.8)	111.5 (58.9-220.2)	0.22	99.4 (42.7-163.1)	105.6 (48.4-273.9)	0.22

WBC: white blood cell; Neu: neutrophil; Lymph: Lymphocyte; NLR: Neutrophil / Lymphocyte ratio; PLT: Platelet; MPV: mean platelet volume; PDW: platelet distribution width; PLR: Platelet / Lymphocyte ratio

* p<0.05 denotes statistical significance

had moderate and 50% (n=50) had severe OSAS. For mild and severe OSAS groups; pair-wise comparisons of WBC, neutrophil, lymphocyte, platelet counts and MPV, PDW, NLR, PLR values did not show significant difference between the patients with and without CV risk. Moderate OSAS patients with CV risk had higher WBC and neutrophil counts when compared to patients without (p=0.01, p=0.04 respectively); however lymphocyte, platelet counts and MPV, PDW, NLR, PLR values did not have a significant difference regarding presence of CV risk (Table 3).

DISCUSSION

To our knowledge, this is the first study evaluating NLR, PLR values and platelet indices in OSAS patients with respect to the presence of traditional CV risk factors and disease severity. Our results revealed that NLR, PLR values or platelet indices did not have an association with disease severity and concomitant cardiovascular risk factors in OSAS patients. The only positive finding was that, moderate OSAS patients with CV risk had higher WBC and neutrophil counts in comparison to the ones without CV risk.

OSAS is known to co-exist with a low-grade systemic inflammation, but the direction of cause-effect relationship is still debatable. Recurrent desaturation episodes and intermittent hypoxia in turn, do not cause only sleep fragmentation and restriction but also activates several biochemical cascades in different tissues; both of which contribute to the maintenance of this inflammatory state (8,25). In addition to well defined inflammatory markers such as CRP, TNF-α, ICAM, IL-6, IL-8, VCAM and selectins; NLR, PLR and platelet indices such as platelet count, MPV and PDW have recently been introduced as simple indicators of systemic inflammation and reported to reflect adverse outcomes or disease severity in cardiovascular diseases and OSAS (12,26). However, results from OSAS patients are inconsistent in the literature.

Activation of platelet system during an inflammatory process leads to quantitative and morphological changes in platelets (increase in number, platelet swelling etc.) which finally give rise to an increase in MPV and PDW (27,28). Regarding OSAS; one of the suggested mechanisms underlying this platelet activation is excess sympathetic activity due to recurrent hypoxemia and arousals during sleep and elevated levels of serum catecholamines as a result (concentration-dependent platelet activation) (29,30). The other probable mechanisms include direct activation owing to chronic hypoxia (31).

Nena et al. demonstrated that MPV and PDW were significantly higher in severe OSAS patients when compared to mild-moderate disease and controls; both of which were found to correlate with oxygen saturation parameters (32). While Kurt et al. found no difference in terms of MPV and instead reported higher PDW; Koseoglu et al. stated that MPV and PLR values were higher in severe OSAS patients but PDW did not differ significantly among disease levels (18,33). Sokucu et al. observed no difference among disease severity groups regarding platelet count, MPV and PDW values in a population of 200 patients without any cardiovascular disease (19). Similar to these findings, our results also demonstrated that there were no significant relationship between platelet indices and disease severity in OSAS patients. In addition, platelet indices did not have a significant association with the presence of CV risk factors in these patients.

There are also conflicting data in the literature regarding the association between white blood cell parameters, NLR values and OSAS disease severity. Data from a study including 178 OSAS patients and 118 control subjects revealed that severe OSAS patients had higher WBC, Neutrophil counts and NLR than controls. NLR was stated to be different between disease severity groups and additionally found to be independently associated with presence of cardiovascular disease in OSAS patients (15). On the other hand, another data from a study enrolling 147 OSAS patients demonstrated no difference in terms of NLR values regarding disease severity (21). A study from Koseoglu et al. also reported no difference among disease severity groups regarding NLR (20). Our findings also did not reveal an association between NLR and disease severity in OSAS patients.

To our knowledge, this is the first study evaluating NLR, PLR and platelet indices in OSAS patients with respect to the presence of traditional cardiovascular risk factors. According to our results; routine hematological parameters like NLR, PLR, MPV and PDW are not appropriate indices for predicting disease severity and cardiovascular risk in OSAS patients. As severe disease corresponds to a worse inflammatory state, it is also plausible to argue that these are not appropriate markers for predicting systemic inflammation either.

The current study has some limitations because of its retrospective design. However, we included a large number of patients, who were clearly classified according to disease severity and presence of cardiovascular risks, and that enabled us to make a reliable analysis for each group. Nevertheless, further prospective studies are needed to clarify the value of these parameters as biomarkers of disease severity and CV risk in OSAS patients.

CONCLUSION

Routine hematological parameters like NLR, PLR and platelet indices are highly non-specific markers and can be affected from various conditions. While determining systemic inflammation or its grade; one should be careful for interpretation of these results and confirm via proven inflammatory markers such as TNF-α, interleukins or adhesion molecules, if possible.

*The study was presented as an oral abstract -in part-, in the 20th National Congress of Sleep Medicine, in Istanbul, Turkey (2th-6th October, 2019).

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.
Ethical approval: Ethical approve was gathered from Adnan Menderes University School of Medicine to use retrospective data of the patients in this research.

Asli Akyol Gurses ORCID: 0000-0002-3106-7190
Kadri Murat Gurses ORCID: 0000-0003-3904-0985
Utku Ogan Akyildiz ORCID: 0000-0001-6452-0492

REFERENCES

1. Berry RB, Lee-Chiong T, Marcus C, et al. Sleep Related Breathing Disorders. In: Sateia M, ed. International Classification of Sleep Disorders. 3rd edition. Darien, IL: American Academy of Sleep Med 2014;53-62.
2. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3:310-8.
3. Baguet JP, Nadra M, Barone-Rochette G, et al. Early cardiovascular abnormalities in newly diagnosed obstructive sleep apnea. Vasc Health Risk Manag 2009;5:1063-73.
4. Sekosan M, Zakkar M, Wenig BL, et al. Inflammatio in the uvula mucosa of patients with obstructive sleep apnea. Laryngoscope 1996;106:1018-20.
5. Bergeron C, Kimoff J, Hamid Q. Images in allergy and immunology: obstructive sleep apnea syndrome and inflammation. J Allergy Clin Immunol 2005;116:1393-6.
6. Puig F, Rico F, Almendros I, et al. Vibration enhances interleukin-8 release in a cell model of snoring induced airway inflammation. Sleep 2005;28:1312-6.
7. McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnea; Overlaps in patophysiology, systemic inflammation and cardiovascular disease. Am J Respir Crit Care Med 2009;180:692-700.
8. Kent BD, Ryan S, McNicholas WT. Obstructive sleep apnea and inflammation: Relationship to cardiovascular co-morbidity. Respiratory Physiology & Neurobiology 2011;178:475-81.
9. Williams A, Scharf SM. Obstructive sleep apnea, cardiovascular disease and inflammation – is NF-kB the key? Sleep Breath 2007;11:69-76.
10. Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. Eur Respir J 2009;33:1195-205.
11. Nadeem R, Molnar J, Madbouly EM, et al. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. J Clin Sleep Med 2013;9:1003-12.
12. Wu M, Zhou L, Zhu D, et al. Hematological indices as simple, inexpensive and practical severity markers of obstructive sleep apnea syndrome: a meta-analysis. J Thorac Dis 2018;10:6509-21.
13. Bressi E, Mangiacapra F, Ricottini E, et al. Impact of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio on 5-Year Clinical Outcomes of Patients with Stable Coronary Artery Disease Undergoing Elective Percutaneous Coronary Intervention. J Cardiovasc Transl Res 2018;11:517-23.
14. Altintas N, Çetinoğlu E, Yuceege M, et al. Neutrophil-to-lymphocyte ratio in obstructive sleep apnea; a multi center, retrospective study. Eur Rev Med Pharmacol Sci 2015;19:3234-40.
15. Uygur F, Tanriverdi H, Aktop Z, et al. The neutrophil-to-lymphocyte ratio in patients with obstructive sleep apnoea syndrome and its relationship with cardiovascular disease. Heart Lung 2016;45:121-5.
16. Varol E, Ozturk O, Gonca T, et al. Mean platelet volume is increased in patients with severe obstructive sleep apnea. Scand J Clin Lab Invest 2010;70:497-502.
17. Song YJ, Kwon JH, Kim JY, et al. The platelet-to-lymphocyte ratio reflects the severity of obstructive sleep apnea syndrome and concurrent hypertension. Clin Hypertens 2016;22:1.
18. Koseoglu HI, Altunkas F, Kanbay A, et al. Platelet-lymphocyte ratio is an independent predictor for cardiovascular disease in obstructive sleep apnea syndrome. J Thromb Thrombolysis 2015;39:179-85.
19. Sökücü SN, Ozdemir C, Dalar L, et al. Is mean platelet volume really a severity marker for obstructive sleep apnea syndrome without comorbidities? Pulm Med 2014; 2014:754839.
20. Koseoglu S, Ozcan KM, Ikinciogullari A, et al. Relationship Between Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio and Obstructive Sleep Apnea Syndrome. Adv Clin Exp Med 2015;24:623-7.
21. Korkmaz M, Korkmaz H, Kucuker F, et al. Evaluation of the association of sleep apnea-related systemic inflammation with CRP, ESR, and neutrophil-to-lymphocyte ratio. Med Sci Monit 2015;21:477-81.
22. Catapano AL, Graham I, De Backer G. et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 2016;253:281-344.
23. Berry RB, Marcus CL, Parthasarathy S, et al. Respiratory Rules. In: Berry RB, Brooks R, Gamaldo CE, et al. eds. The AASM Manual for the Scoring of Sleep and Associated Events. Rules, Terminology and Technical Specifications, Darien, IL: American Academy of Sleep Med 2017;56-61.
24. American Academy of Sleep Medicine Task Force. Sleep related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999:22:667-89.
25. Faraut B, Boudjeltia KZ, Vanhamme L, et al. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. Sleep Med Rev 2012;16:137-49.
26. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther 2013;11:55-9.

27. Jagroop IA, Clatworthy I, Lewin J, et al. Shape change in human platelets: measurement with a channelyzer and visualisation by electron microscopy. Platelets 2000;11:28-32.
28. Vagdatli E, Gounari E, Lazaridou E, et al. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia 2010;14:28-32.
29. Larsson PT, Wallen NH, Hjemdahl P. Norepinephrine induced human platelet activation in vivo is only partly counteracted by aspirin. Circulation 1994;89:1951-7.
30. Von Kanel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo .Eur J Haematol 2000;65:357-69.
31. Dunleavy M, Dooley M, Cox D, et al. Chronic intermittent asphyxia increases platelet reactivity in rats. ExpPhysiol 2005;90:411-6.
32. Nena E, Papanas N, Steiropoulos P, et al. Mean Platelet Volume and Platelet Distribution Width in non-diabetic subjects with obstructive sleep apnoea syndrome: new indices of severity? Platelets 2012;23:447-54.
33. Kurt OK, Yildiz N. The importance of laboratory parameters in patients with obstructive sleep apnea syndrome. Blood Coagul Fibrinolysis 2013;24:371-4.