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Relationship of Potential Inflammatory Markers Namely Neutrophile Lymphocyte Ratio and Platelet Lymphocyte Ratio With the Severity of Obstructive Sleep Apnea

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ABSTRACT

Aim: The aim of the present study is to evaluate hematological parameters in patients with obstructive sleep apnea syndrome (OSAS).

Material and Methods: Patients underwent a polysomnographic (PSG) test at our sleep laboratory was retrospectively reviewed. Patients with cancer, cardiovascular disease, hematologic disorders, infectious diseases and rheumatologically disorders, renal or hepatic insufficiency were excluded from the study. Two hundred and ten OSAS patients with an apnea-hypopnea index (AHI) of more than five events and 57 controls with an AHI of less than four events were included. Study population was divided into four groups depending on the AHI as: mild OSAS (AHI= 5-15), moderate OSAS (AHI=15-30), severe OSAS (AHI>30), and the control (AHI<5). Hematologic parameters were measured and compared.

Results: Platelet lymphocyte ratio was significantly lower in patients with OSAS compared to the control (p = 0.050). Neutrophil lymphocyte ratio between OSAS and the control was not different (p = 0.947). Serum triglyceride level and mean platelet volume were significantly higher in patients with OSAS (p < 0.0001; p = 0.043). Platelet distribution width was significantly higher in severe OSAS group compared to control, mild and moderate OSAS subgroups (0.014).

Conclusion: No relationship was found between OSAS and NLR. There is a debate over putative relationship between NLR, PLR, and OSAS.

Key Words: *Obstructive sleep apnea syndrome, OSAS, Neutrophil lymphocyte ratio, Platelet lymphocyte ratio*

Enflamatuar Belirteç Olarak Nötrofil Lenfosit Oranı, Platelet Lenfosit Oranı gibi Hematolojik Parametrelerin Tıkayıcı Uyku Apne Sendromunun Şiddeti ile İlişkisinin Değerlendirilmesi

ÖZET

Amaç: Bu çalışmanın amacı tıkayıcı uyku apnesi (OSAS) olan hastalarda hematolojik parametrelerin değerlendirilmesidir.

Gereç ve Yöntemler: Bu araştırmada uyku laboratuvarında Polisomnografi testi yapılan hastalar geriye dönük olarak değerlendirilmiştir. Kanser, kardiyovasküler hastalık, hematolojik bozukluk, enfeksiyon hastalıkları, romatolojik hastalıklar, renal ve hepatik yetmezlik olan hastalar çalışmaya alınmamıştır. Çalışmaya apne-hipopne endeksi 5 olaydan fazla olan 210 hasta ve 57 AHI 5 den az olan kontrol olarak alınmıştır. Araştırma grubu polisomnografideki AHI skorlarına göre 4 gruba ayrılmıştır: hafif OSAS (AHI= 5-15), orta OSAS (AHI=15-30), ciddi OSAS (AHI> 30), ve kontrol (AHI<5). Hematolojik parametreler değerlendirilmiş ve karşılaştırılmıştır.

Bulgular: Trombosit lenfosit oranı OSAS hastalarında kontrol grubuna göre anlamlı düşük saptanmıştır. (p = 0.050). OSAS ve kontrol grupları arasında nötrofil lenfosit oranı yönünden istatistiksel olarak anlamlı farklılık izlenmemiştir (p = 0.947). Serum trigliserid ve ortalama trombosit hacmi OSAS hastalarında anlamlı yüksek izlenmiştir (p < 0.0001; p = 0.043). Trombosit dağılım hacmi ciddi OSAS grubunda kontrol grubuna ve diğer OSAS alt gruplarına göre anlamlı yüksek saptanmıştır. (p = 0.014).

Sonuç: OSAS ve NLR arasında herhangi bir ilişki izlenmemiştir. NLR, PLR, ve OSAS arasındaki olası ilişki üzerine hâlâ araştırmaların sonuçları tartışmalıdır.

Anahtar Sözcükler: *Tıkayıcı uyku apne sendromu, OSAS, Nötrofil lenfosit oranı, Platelet lenfosit oranı*

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS), characterized by recurrent obstruction of the airway during sleep has negative impact on the health of millions of people around the world. This syndrome is characterized by episodic hypoxemia, oxidative stress, and sleep disorders at night. The prevalence is 4% in males and around 2% in females, respectively (1). OSAS is the most prevalent sleep disorder and ranks as the second most prevalent respiratory disorder following asthma (1-3). There is a 2- to 3-fold increase in the incidence and severity of OSAS with age (4, 5). OSAS is known to cause neurologic, metabolic, and cardiovascular disturbances (6-11). This syndrome has an important place in the practice of preventive medicine due to high risk of morbidity and mortality and the treatable nature of it (12, 13).

Complete blood count is a cheap, practical, and easy-to-perform test. Parameters such as red cell distribution width (RDW), mean platelet volume (MPV), neutrophil lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR) can be easily obtained with routine blood count. MPV is a laboratory parameter providing information about platelet functions in the state of thrombosis, and this parameter has therefore been suggested as a marker of hemostasis (14, 15) NLR is currently considered as a parameter indicating both elevation of neutrophils reflecting acute inflammation and decreased lymphocytes reflecting physiological stress. Thus, this parameter has been suggested as a new prognostic marker (16-18). Azab et al. studied changes in PLR in long term follow up as the marker of mortality in patients with sustained non-ST segment elevation myocardial infarction (NSTEMI). It was indicated that elevated PLR was an independent predictor of mortality in the long-term follow up of NSTEMI (19).

The objective of the present study was to examine the changes in PLR and other hematologic parameters in patients with OSAS. The other aim of this study is to evaluate the relationship between severity of OSAS and PLR.

MATERIAL and METHODS

Subjects

Subjects who have been admitted to our hospital for polysomnography test (PSG) between November 2012 and December 2014 were evaluated retrospectively. Patients who have been diagnosed cardiovascular disease according to clinical history, physical examination and EKG were excluded from the study. Subjects who have been taking antibiotics and anti-inflammatory drugs (NSAIDs ets.), with known cardiovascular disease, hematologic disorders, cancer, renal and hepatic failure, infectious disease, and rheumatologic disorders were excluded. This study was approved by local ethic committee.

Biochemical Analysis

Venous blood samples were taken into Becton Dickinson Vacutainer tube following 12 hours fast. Glucose, total cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL) measurements were made with calorimetric methods (Abott Laboratories; Illinois (USA). Whole blood count were evaluated with automatic measurement device (Abbott Cell-Dyne Ruby; IL 60064 USA).

PSG test was performed with Compumedics E series 44 channel PSG device. The PSG recordings included electrocardiography, chest excursions, electroencephalography, pulse oximetry and leg electromyography. The apnea-hypopnea index (AHI) was defined as the average number of apnea and hypopnoea per hour of sleep. Data's were scored manually. Patients were separated into the four groups in according to polisomnographic AHI scores. Groups were determined as; Apnoea Hypopnoea index (AHI) score between, 5-15, 15-30, more than 30 (AHI > 30) and 0-5 (AHI < 5). Patients with AHI < 5 were accepted as control. AHI scores 5-15, 15-30, more than 30 were accepted as mild, moderate and severe OSAS respectively.

Statistical Analysis

Student t test and Mann Whitney U test were used for comparison of numeric parameters between groups either normally or not normally distributed. Comparison of OSAS subgroups according to severity were made with Analysis of Variance (ANOVA) for normally distributed parameters or Kruskal Wallis test for not normally distributed parameters accordingly and multiple comparison test of Bonferroni were used for evaluation of the difference. Chi square test were used for evaluation of categorical variables. Pearson correlation analysis for normally distributed variables or Spearman's correlation analyses for not normally distributed variables were used to evaluate the relation between numeric variables. A model with multiple regression analysis was used for determining parameters affecting the severity of OSAS. All the data analyses were performed using the Statistical Package for Social Sciences SPSS (PASW ver.18). $P<0.05$ probability value was considered as significant.

RESULTS

Mean age and BMI of OSAS group were found to be higher than control (Table 1). There were statistically significant difference between groups in terms of TG, and PLR ($p<0.0001$, $p=0.050$, respectively) (Table 1). AHI, body mass index, glucose, WBC, and MPV values were also statistically different between groups ($p<0.0001$, $p<0.0001$, $p=0.013$, $p=0.029$, and $p=0.043$, respectively) (Table 1; Table 2). Patients were grouped according to the OSAS severity as

mild, moderate and severe: Statistically significant difference were found between groups in terms of age, AHI, BMI, TG, WBC, and MPV (p =0.003, p<0.0001, p<0.0001, p=0.005, p=0.050, and p<0.0001, respectively) (Table 3). The mean TG serum level was lower in control compared to moderate and severe OSAS group (p=0.028 and 0.003, respectively). The mean WBC count was higher in patients with severe OSAS compared to control (p=0.041). The mean MPV was lower in patients with severe OSAS compared to mild and moderate OSAS (p = 0.001), and the mean MPV was higher in patients with moderate and mild OSAS compared to control (p = 0.024). There were significant differences between OSAS and control groups in terms of glucose and PDW (p=0.003 and p=0.014) (Table 3). The mean PDW was higher in patients with severe OSAS compared to patients with mild OSAS (p=0.003). No significant difference was observed between OSAS and control in terms of DM, HT, and smoking status (p > 0.05).

There was a weak positive correlation between HDL and RDW (r = 0.173, p=0.012), AHI and PLT (r = 0.137, p=0.047), AHI and PDW (r = 0.249, p<0.0001), BMI and WBC (r = 0.143, p=0.038), BMI and RDW (r = 0.229, p=0.001), total cholesterol and PLR (r = 0.159, p=0.022), total cholesterol and PLT (r = 0.230, p=0.001), LDL and PLR (r = 0.150, p=0.031), and LDL and PLT (r = 0.216, p=0.002), serum glucose and RDW (r = 0.136, p=0.049). There was a weak negative correlation between LDL and MPV (r = -0.159, p=0.022), HDL and WBC (r = -0.209, p=0.002), AHI and MPV (r = –0.224, p=0.001) (Table 4).

Table 1: Demographic Features

Characteristics	Subjects with OSAS	Control	p Value
Age (Year±SD)	51.06 ± 10.38	47.77 ± 12.74	**0.045**
Gender (Male/Female)	110/100	25/32	0.254
Smoking (Present/Absent)	22/188	9/47	0.246
Hypertension (Present/Absent)	94/116	18/39	0.740
Diabetes mellitus (Present/Absent)	59/151	9/48	0.060
BMI (kg/m2 minimum-maximum)	33.00 (29.00-36.00)	29.00 (26.00-32.00)	**<0.0001**

Parameters with normal distribution were presented as mean ± SD. Parameters without normal distribution was presented as median (25 percentile - 75 percentile)

Table 2: Laboratory parameters and clinical features.

Parameters	Subjects with OSAS	Control	p Value
	165.51 ± 80.69	127.26 ± 67.75	**<0.0001**
Total cholesterol(mg/dl± SD)	199.04 ± 35.81	200.64 ± 38.74	0.768
LDL(mg/dl± SD)	122.49 ± 31.79	127.98 ± 31.57	0.252
HDL(mg/dl± SD)	44.82 ± 10.35	46.38 ± 12.85	0.339
PLR(ratio, minimum-maximum)	109.95 ± 35.03	121.21 ± 51.49	**0.050**
Platelet (PLT/mm3 ± SD)	251.53 ± 65.12	251.22 ± 52.59	0.974
AHI (minimum-maximum)	20.90 (11.90-44.90)	3.20 (1.80-4.00)	**<0.0001**
Glucose(mg/dl± SD)	98.00 (90.00-112.00)	92.00 (88.00-100.00)	**0.013**
WBC/mm3 (minimum-maximum)	7.12 (6.22-8.52)	6.73 (5.66-7.59)	**0.029**
NLR (ratio, minimum-maximum)	1.72 (1.33-2.21)	1.67 (1.40-2.13)	0.947
PDW (minimum-maximum)	13.80 (11.60-19.30)	14.40 (11.90-19.70)	0.345
MPV (minimum-maximum)	10.10 (9.10-10.90)	9.80 (8.10-10.50)	**0.043**
RDW (minimum-maximum)	13.20 (12.40-13.90)	13.10 (12.20-13.50)	0.332

Parameters with normal distribution were presented as mean ± SD. Parameters without normal distribution was presented as median (25 percentile - 75 percentile)

PLR: Platelet lymphocyte ratio, **AHI:** Apnea hyperpnoea index, **WBC:** White blood cell, **NLR:** Neutrophile lymphocyte ratio, **PDW:** Platelet distribution width, **MPV:** Mean platelet volume, **RDW:** Red cell distribution width.

Table 3: The comparison of clinical and laboratory parameters according to the severity of OSAS.

Parameters	Mild OSAS (AHI 5-15)	Moderate OSAS (AHI 15-30)	Severe OSAS (AHI > 30)	Control (AHI < 5)	P value
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	
Age (year)	48.15 ± 9.76	51.04 ± 9.15	53.98 ± 11.40	47.77 ± 12.74	**0.003**
AHI	9.57 ± 2.67	21.51 ± 3.98	64.09 ± 24.23	2.86 ± 1.40	**<0.0001**
BMI (kg/m2)	31.84 ± 5.37	33.22 ± 5.67	35.62 ± 6.70	29.10 ± 4.78	**<0.0001**
Triglycerides (mg/dl)	154.58 ± 74.36	166.29 ± 84.88	175.65 ± 82.23	127.26 ± 67.75	**0.005**
Total Cholesterol (mg/dl)	199.97 ± 35.57	193.30 ± 31.88	203.85 ± 39.31	200.64 ± 38.74	0.378
LDL (mg/dl)	121.80 ± 30.01	117.29 ± 31.20	128.40 ± 33.57	127.98 ± 31.57	0.137
HDL(mg/dl)	46.92 ± 10.90	45.18 ± 10.66	42.35 ± 9.03	46.38 ± 12.85	0.067
Glucose (mg/dl)	94.50 (89.0-106.00)	96.00 (92.00-108.00)	103.00 (92.00-125.00)	92.00 (88.00-100.00)	**0.003**
WBC	7.39 ± 2.08	7.24 ± 1.59	7.89 ± 2.05	6.96 ± 2.05	**0.050**
NLR	1.64 (1.17-2.21)	1.66 (1.25-2.16)	1.81 (1.46-2.26)	1.67 (1.40-2.13)	0.390
RDW	13.15 (12.5-13.90)	13.35 (12.60-13.90)	13.10 (12.10-13.90)	13.10 (12.20-13.50)	0.554
Platelet	243.14 ± 62.06	249.07 ± 59.42	262.38 ± 72.56	251.22 ± 52.59	0.325
MPV	10.16 ± 1.21	10.16 ± 1.39	9.07 ± 2.04	9.33 ± 1.81	**<0.0001**
PDW	13.50 (11.4-15.30)	13.70 (11.50-19.00)	16.70 (12.20-19.80)	14.40 (11.90-19.70)	**0.014**
PLR	106.56 ± 38.26	110.95 ± 35.40	112.33 ± 31.33	121.21 ± 51.49	0.212

Parameters with normal distribution were presented as mean ± SD. Parameters without normal distribution was presented as median (25 percentile - 75 percentile)

BMI: Body mass index, **PLR:** Platelet lymphocyte ratio, **AHI:** Apnea hyperpnoea index, **WBC:** White blood cell, **NLR:** Neutrophile lymphocyte ratio, **PDW:** Platelet distribution width, **MPV:** Mean platelet volume, **RDW:** Red cell distribution width.

Table 4: Correlation analysis between parameters.

Parameters		Subjects with OSAS						
		WBC	**NLR**	**PLR**	**Platelet**	**PDW**	**MPV**	**RDW**
AHI	**r value**	0.117	0.066	0.111	0.137	0.249	-0.224	-0.056
	p value	0.092	0.345	0.110	**0.047**	**<0.0001**	**0.001**	0.421
BMI (kg/m2)	**r value**	0.143	0.040	0.030	0.080	0.079	0.033	0.229
	p value	**0.038**	0.568	0.669	0.246	0.254	0.634	**0.001**
Triglicerides (mg/dl)	**r value**	0.025	-0.128	-0.045	0.092	-0.083	-0.048	0.014
	p value	0.718	0.066	0.519	0.185	0.230	0.493	0.843
Total Cholesterol (mg/dl)	**r value**	-0.063	-0.132	0.159	0.230	0.008	-0.116	0.095
	p value	0.367	0.057	**0.022**	**0.001**	0.906	0.094	0.171
LDL(mg/dl)	**r value**	0.022	-0.029	0.150	0.216	0.097	-0.159	0.050
	p value	0.752	0.679	**0.031**	**0.002**	0.167	**0.022**	0.475
HDL(mg/dl)	**r value**	-0.209	-0.127	0.054	0.000	-0.050	0.084	0.173
	p value	**0.002**	0.067	0.436	0.996	0.470	0.223	**0.012**
Glucose(mg/dl)	**r value**	0.049	-0.069	-0.084	-0.009	0.127	0.033	0.136
	p value	0.479	0.317	0.228	0.895	0.066	0.636	**0.049**

Pearson correlation analysis was performed.

BMI: Body mass index, **PLR:** Platelet lymphocyte ratio, **WBC:** White blood cell, **NLR:** Neutrophile lymphocyte ratio, **PDW:** Platelet distribution width, **MPV:** Mean platelet volume, **RDW:** Red cell distribution width.

DISCUSSION

The present study investigated hematologic parameters in patients with OSAS and their relationship with disease severity and metabolic markers. Accordingly, there was a negative correlation between AHI and MPV and a linear relationship between AHI and PDW. There was also a significant difference in terms of MPV between OSAS and the control groups. NLR, PDW, and RDW parameters were not significantly different in the two groups.

Platelets play an important role in progression of atherosclerosis. An elevated platelet number compared to lymphocyte may result in vascular events (20). In a study performed by Gary T et al. showed that increase in inflammatory markers like CRP correlated with PLR (20). That is why PLR cheap and easy way to be a potential marker for prediction atherosclerotic lesions like coronary artery disease. Koseoglu et al., found that, PLR was significantly higher in patients with OSAS compared to the control group (21). There was also a strong correlation between PLR and OSAS (21). The authors suggested that PLR could be a strong biomarker in patients with OSAS (21). However, in the present study, PLR was significantly lower in patients with OSAS compared to the control group.

Yenigun A et al evaluated the relationship between OSAS and NLR and found a positive correlation between NLR and AHI in patients with OSAS (22). In another study done in patients with metabolic syndrome showed increased NLR (23). In the present study, NLR did not significantly different between patients with OSAS and the control group. Also we have not found any correlation between NLR and OSAS severity. However, based on the findings of the current study and other studies in the literature, it is too early to suggest that NLR could be used as a marker in evaluating severity of OSAS. Further studies are required in this regard.

Another interesting finding of our study is elevation in WBC count in OSAS. WBC count is also different in between OSAS subgroups. Christoffersson G et al revealed increased neutrophile count in acutely sleep deprived healthy young men (24). Boudjeltia KZ et al. demonstrated that: Sleep restriction resulted in increase in WBC (25). The increased WBC in OSAS patients may be related with higher adrenalin and cortisol levels in sleep deprived patients (25). Also, leukocytes have an oxidative damage on the vascular bed (25). These all may be the potential link between cardiovascular disease and OSAS.

There are controversial data regarding the changes in lipid profile of patients with OSAS (26, 27). One study reported significantly higher TG values in patients with OSAS (28). Chou et al. reported that hypertriglyceridemia was more frequently observed in patients with OSAS (29). In a study conducted at the Mayo clinic, the frequency of hyperlipidemia was similar (30). Li et al. showed that chronic intermittent hypoxia stimulated synthesis of triglycerides (31). The present study was consistent with the literature; found significantly higher TG values in patients with OSAS.

OSAS is known to pose a risk for cardiovascular and cerebrovascular disorders (7, 9-11). The pathophysiological basis of this relationship still remains unclear. Increased MPV values indicate platelet activation. Large platelets possess high thrombotic potential. MPV is higher in OSAS and remarkable increase with increasing severity of OSAS (32, 33). Contrary to this opinion, some suggest that platelet markers do not directly indicate platelet activation (34). In the present study, subgroup analysis according to the severity of OSAS showed statistically significant differences in terms of MPV. The interesting finding of our data is decrease in MPV values of the patients with severe OSAS compared to mild and moderate OSAS groups. Gunbatar et al. also reported similar findings in their study (32). It is early for the use of MPV in determining the severity of OSAS and further studies are required in this regard. A negative correlation was also observed between MPV and AHI. Hypoxia, sympathetic over-activation, and chronic inflammation are among the possible mechanisms underlying platelet activation in OSAS.

Another finding of the current study was a linear relationship between AHI and PDW. The study by Kurt et al. reported a positive correlation between PDW and AHI (35). Vagdatli et al. suggested that PDW was a superior marker in determining the severity of OSAS compared to MPV (36). Similar to our findings, PDW could be a useful and easy-to-measure parameter in determining the severity of OSAS.

The limitations of the present study are age difference between groups andabsence of inflammatory markers such as CRP, interleukin and tumor necrosis factor alpha. The lack of testing for endothelial dysfunction is another limitation.

In conclusion, MPV was significantly higher in patients with OSAS; however, the significance of this relationship did not correlate with the severity of OSAS. This finding is consistent with the literature and further studies are required. The correlation between PDW and AHI is another finding of the present study, and PDW might be a promising marker in determining the severity of OSAS. On the other hand, no relationship was found between OSAS and LNR. There is a debate over putative relationship between NLR, PLR and OSAS. Further studies are required on a larger number of patients for this issue.

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