

Relationship of Platelet-Lymphocyte Ratio with Severity of Obstructive Sleep Apnea Syndrome

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ABSTRACT

Objective: To assess the inflammation in obstructive sleep apnea syndrome patients by using platelet lymphocyte ratio and relationship between platelet lymphocyte ratio and severity of obstructive sleep apnea.

Study Design: Retrospective cohort study

Place and Duration of Study: This study was conducted at the Medicine department of Nishtar Hospital Multan from June 2016 to March 2017.

Materials and Methods: Total 280 patients were selected by non-probability consecutive sampling. All patients underwent whole night polysomnography. Patients were divided into control group (AHI <5), mild OSAS group (AHI 5-15), moderate OSAS group (AHI 15-30) and severe OSAS group (AHI >30) according to their AHI score. Numerical variables like age, body mass index, white cell count, platelets, hemoglobin (Hb) and platelet lymphocyte ratio were statistically analyzed by mean and standard deviation and t-test applied to assess their significance. Qualitative variables like gender and smoking status were statistically analyzed by frequency and percentage. Chi square test was applied to check the significance. P value <0.05 was regarded as significant.

Results: Platelet lymphocyte ratio was significantly raised in patients with obstructive sleep apnea syndrome. There was significant correlation between platelet lymphocyte ratio and AHI ($p<0.05$). So study showed that there was significant association between obstructive sleep apnea syndrome severity (represented by AHI) and systemic inflammation (represented by PLR). Significant differences were found between age ($p=0.000$), ESR ($p=0.000$), CRP ($p=0.003$), Cholesterol ($p=0.000$), Platelets ($p=0.048$), Hb ($p=0.000$), PLR ($p=0.000$) and white blood cells ($p=0.000$), in groups. Association was found between gender ($p=0.000$) and smoking status ($p=0.030$) in groups. So, gender and smoking were the effect modifiers.

Conclusion: New inflammatory markers are required to investigate the level of systemic inflammation in obstructive sleep apnea syndrome patients. Platelet lymphocyte ratio, an easy, quick and cheap measurable marker on routine CBC analysis, could be considered for assessing the inflammation in patients of obstructive sleep apnea syndrome.

Key Words: Obstructive sleep apnea syndrome, Platelet lymphocyte ratio, polysomnography

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is very common sleep disorder¹. Snoring is most common symptom of obstructive sleep apnea syndrome. It affects 7% of women and 20% of men in whole population¹. It is one of the bigger health problem of adults. Upper airway collapse during sleep results in recurring apnea, disturbed sleep, excessive daytime sleepiness and intermittent hypoxia².

Most occurring nocturnal symptoms of obstructive sleep apnea syndrome are snoring and observed apneas.

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Disruption of normal sleep pattern and ventilation results in many complications through various pathophysiology. Obstructive sleep apnea syndrome patients suffer impaired quality of life and decrease performance status¹. Several factors have been considered for development of obstructive sleep apnea syndrome. Obesity is one of major risk factor for developing obstructive sleep apnea syndrome³. It is reported that 70% patients of obstructive sleep apnea syndrome are obese³. Other risk factors are alcohol consumption, smoking, chronic pain and chronic opioid therapy⁴. This disorder develops due to reduction of the expansion forces of the pharyngeal dilator muscles, as it occurs in engorged muscle dysfunction and coordination between the respiratory effort and inspiratory activity of the muscle. It is also reported that obstructive sleep apnea syndrome is associated with vitamin D deficiency⁵. Obstructive sleep apnea syndrome is contributing factor for many diseases. It is associated with cardiovascular diseases, neurological

diseases and metabolic diseases⁶. So physicians should properly investigate and address this issue.

Many studies have shown that systemic inflammation, endothelial damage, oxidative stress, and increased coagulation factors in patients of obstructive sleep apnea syndrome are caused by many factors⁷. White blood cells and its subtypes are recognized inflammatory markers⁸. One of this is neutrophil-lymphocyte ratio (NLR). The rationale of this is because in inflammation there is decrease in lymphocytes count and increase in neutrophils count, so the ratio of these two can be used as marker of inflammation. Recent studies have shown platelet-lymphocyte ratio another inflammatory marker that can predict adverse outcome in cardio vascular diseases⁹. Because platelet count is indicator of severity of inflammation. Pro-inflammatory cytokines stimulate the megakaryocytes that result in thrombocytosis¹⁰.

Like NLR, platelet lymphocyte ratio (PLR) is also associated with mortality of acute myocardial infarction¹¹. But data is lacking about the association of inflammation in obstructive sleep apnea syndrome patients and platelet lymphocyte ratio. We want to investigate the issue in our region. So that it can help to establish the relationship between platelet lymphocyte ratio and severity of obstructive sleep apnea syndrome. It will also provide base for further research on this topic in coming days. Study done by Yeo-Jeong Song Et al. was taken as reference study²⁰.

MATERIALS AND METHODS

This retrospective cohort study was conducted in department of Medicine, Nishtar Hospital Multan, from June 2016 to march 2017 after approval of the study was taken from institutional ethical committee. Written permission was taken from all patients enrolled in study. Total 280 patients were selected by non-probability consecutive sampling. Patients with following disorders were excluded: 1) patients with history of any systemic disease like liver disease 2) history of secondary hypertension 3) complaint of respiratory infection and failure 4) central nervous system disorders 5) any history of malignancy 6) having critical illness with poor functional status 7) history of heart failure and acute coronary syndrome or having myocardial infarction or any revascularization procedure. Sample size of the study calculated by a reference study done by Yeo-Jeong Song Et al. For which confidence interval was taken as 95 %, power of study 80, odd ratio of platelet lymphocyte ratio was 3.37 (www.openepi.com).

All patients participated in study were enrolled from outpatient department. Patients who presented with history of fatigue, day time sleepiness, snoring and disturbed sleep were selected. Patients who had high malampati score and short neck and also having history of disturbed sleep and snoring were also selected. A

detailed physical examination was conducted in each patient to investigate the features of obstructive sleep apnea syndrome, its complications and also any clues of other systemic disease. All patients with normal renal status and age between 18 to 80 were include. During first visit demographic variables like age, gender, weight, height, income, medication history and other diseases were recorded. All patients underwent polysomnography.

The system of polysomnography contains four channels of electroencephalogram and two channels of electrooculography, submental electromyography (EMG), pulse oximeter for recording oxygen saturation, thoracic and abdominal movements, electrocardiogram, tracheal sound and orinasal air flow. A complete cessation in airflow for more than 10s was taken as apnea. Air flow reduction >30% for greater than 10s with 4 % decrease in oxygen saturation of patient was defined as hypopnea.¹² Severity of obstructive sleep apnea was calculated by apnea hypopnea index. Apnea hypopnea index is number of events of apnea and hypopnea per hour during sleep. All patients were divided into four groups according to their apnea hypopnea index scores: 1) the control group with AHI <5, 2) mild OSAS group with AHI 5–15, 3) moderate OSAS group with AHI 16–30, and 4) severe OSAS group with AHI score >30.

Complete blood count was analyzed along with serum glucose, cholesterol, erythrocyte sediment rate and c reactive protein. Platelet lymphocyte ratio was calculated by dividing lymphocytes from platelets.

Data was analyzed by SPSS volume 23. Numerical variables like age, body mass index, white cell count, platelets, hemoglobin (Hb) and platelet lymphocyte ratio were statistically analyzed by mean and standard deviation and t-test applied to assess their significance. Qualitative variables like gender and smoking status were statistically analyzed by frequency and percentage. Chi square test was applied to check the significance. P value <0.05 was regarded as significant.

RESULTS

Overall, 100% (n=280) patients were enrolled in this study; divided according to OSAS status i.e. control group (n=63), mild OSAS group (n=60), moderate group (n=67) and severe OSAS group (n=90). The mean age and BMI of the control group patients was 45.22 ± 2.57 years and 23.90 ± 2.66 kg/m² respectively. There were 57.1% (n=36) males and 42.9% (n=27) females. Smoking status showed that there were 87.3% (n=55) non-smokers and 12.7% (n=8) were smokers. The mean age and BMI of the Mild OSAS group patients was 49.85 ± 2.11 years and 24.03 ± 2.74 kg/m² respectively. There were 76.7% (n=46) males and 23.3% (n=14) females. Smoking status showed that there were 90% (n=54) non-smokers and 10% (n=6) were smokers. The mean age and BMI

of the moderate OSAS group patients was 50.37 ± 2.28 years and 27.00 ± 3.03 kg/m² respectively. There were 89.6% (n=60) males and 10.4% (n=7) females. Smoking status showed that there were 74.6% (n=50) non-smokers and 25.4% (n=17) were smokers. The mean age and BMI of the severe OSAS group patients

was 52.34 ± 2.60 years and 26.54 ± 2.66 kg/m² respectively. There were 82.2% (n=74) males and 17.8% (n=16) females. Smoking status showed that there were 74.4% (n=67) non-smokers and 25.6% (n=23) were smokers. (Table. 1).

Table No. 1: Demographic Variables

Variable	Control group n=(63)	Mild OSAS group n=(60)	Moderate OSAS group n=(67)	Severe OSAS group n=(90)	Test of Sig.
Age	45.22 ± 2.57 years	49.85 ± 2.11 years	50.37 ± 2.28 years	52.34 ± 2.60 years	F=3.95 p=0.000
BMI	23.90 ± 2.66 kg/m ²	24.03 ± 2.74 kg/m ²	27.00 ± 3.03 kg/m ²	26.54 ± 2.66 kg/m ²	F=1.25 p=0.175
Gender	M=57.1%, F=42.9%	M=76.7%, F=23.3%	M=89.6%, F=10.4%	M=82.2%, F=17.8%	$\chi^2=21.47$, p=0.000
Smoking Status	Non-smoker=87.3%, Smoker=12.7%	Non-smoker=90%, Smoker=10%	Non-smoker=74.6%, Smoker=25.4%	Non-smoker=74.4%, Smoker=25.6%	$\chi^2=8.95$, p=0.030

Table No. 2: Characteristics of OSAS patients

Variable	Control group n=(63)	Mild OSAS group n=(60)	Moderate OSAS group n=(67)	Severe OSAS group n=(90)	Test of Sig.
ESR, mm/hour	8.01 ± 2.27	18.25 ± 2.29	17.71 ± 9.27	14.38 ± 3.80	F=5.21, p=0.000
CRP, mg/L	0.63 ± 0.35	1.31 ± 0.85	0.78 ± 0.33	1.72 ± 1.47	F=1.92, p=0.003
Cholesterol, mg/dl	170.21 ± 11.88	185.72 ± 5.58	190.42 ± 11.21	175.34 ± 5.90	F=3.49 p=0.000
Platelets, $10^9/L$	221.35 ± 12.11	225.23 ± 5.88	230.96 ± 4.69	254.01 ± 10.78	F=1.49 p=0.048
Lymphocytes, %	36.25 ± 5.00	35.20 ± 2.66	31.88 ± 4.37	28.24 ± 4.96	F=1.39, p=0.085
Hb, g/dl	12.95 ± 1.30	15.26 ± 2.14	13.01 ± 2.08	14.06 ± 1.14	F=2.71, p=0.000
PLR	98.80 ± 7.69	114.90 ± 2.13	121.63 ± 5.53	141.60 ± 19.83	F=2.59, p=0.000
WBC, $10^6/L$	6760.23 ± 14.10	7287.03 ± 24.08	7314.83 ± 23.36	7720.83 ± 27.44	F=4.81, p=0.000

The mean ESR, CRP, cholesterol, platelets, lymphocytes, Hb, PLR and WBC of the control patients was 8.01 ± 2.27 mm/hr, 0.63 ± 0.35 mg/L, 170.21 ± 11.88 mg/dl, $221.35 \pm 12.11 \times 10^9/L$, 36.25 ± 5.00 %, 12.95 ± 1.30 g/dl, 98.80 ± 7.69 and $6760.23 \pm 14.10 \times 10^6/L$ respectively. The mean ESR, CRP, cholesterol, platelets, lymphocytes, Hb, PLR and WBC of the mild OSAS patients was 18.25 ± 2.29 mm/hr, 1.31 ± 0.85 mg/L, 185.72 ± 5.58 mg/dl, $225.23 \pm 5.88 \times 10^9/L$, 35.20 ± 2.66 %, 15.26 ± 2.14 g/dl, 114.90 ± 2.13 and $7287.03 \pm 24.08 \times 10^6/L$ respectively. The mean ESR, CRP, cholesterol, platelets, lymphocytes, Hb, PLR and WBC of the moderate OSAS patients was 17.71 ± 9.27 mm/hr, 0.78 ± 0.33 mg/L, 190.42 ± 11.21 mg/dl, $230.96 \pm 4.69 \times 10^9/L$, 31.88 ± 4.37 %, 13.01 ± 2.08 g/dl,

121.63 ± 5.53 and $7314.83 \pm 23.36 \times 10^6/L$ respectively. The mean ESR, CRP, cholesterol, platelets, lymphocytes, Hb, PLR and WBC of the severe OSAS patients was 14.38 ± 3.80 mm/hr, 1.72 ± 1.47 mg/L, 175.34 ± 5.90 mg/dl, $254.01 \pm 10.78 \times 10^9/L$, 28.24 ± 4.96 %, 14.06 ± 1.14 g/dl, 141.60 ± 19.83 and $7720.83 \pm 27.44 \times 10^6/L$ respectively. (Table. 2).

Significant differences were found between age (p=0.000), ESR (p=0.000), CRP (p=0.003), Cholesterol (p=0.000), Platelets (p=0.048), Hb (p=0.000), PLR (p=0.000) and white blood cells (p=0.000), in groups. Association was found between gender (p=0.000) and smoking status (p=0.030) in groups. So, gender and smoking were the effect modifiers. (Table. 1-2).

DISCUSSION

Study was concluded with two main findings. One, that platelet lymphocyte ratio, an inflammatory marker, was significantly raised in obstructive sleep apnea syndrome patients. Second, there was significant correlation between platelet lymphocyte ratio and AHI ($p<0.05$). So study showed a significant association between obstructive sleep apnea syndrome severity (represented by AHI) and systemic inflammation (represented by PLR).

Previous studies had shown that there is association of elevated platelet counts with poor outcome of cardiovascular (CV) diseases¹³⁻¹⁴, and also there is association of lower lymphocytes count with higher mortality and morbidity of cardiovascular diseases¹⁴. So combination of these two markers have emerged as potential inflammatory marker and outcome predictor in many malignant diseases and cardiovascular diseases¹⁵⁻¹⁶. It has been also reported that platelet lymphocyte ratio is predictor of long term and in hospital mortality in patients with STEMI and non-STEMI¹⁷⁻¹⁸.

Platelets can interact with many inflammatory cells like dendritic cell, neutrophils, T-lymphocytes, mono-nuclear phagocytes and can also interact with endothelial cells. The relation between these cells and platelets might initiate the inflammation. Previous studies reported that activated platelets could initiate inflammation by recruitment of white blood cells.

Obstructive sleep apnea syndrome is not simple disorder that occurs during sleep. Multiple studies had shown that obstructive sleep apnea syndrome patients have increased levels of inflammatory markers compared to matched controls and after using continuous positive airway pressure as treatment, significant decrease in these markers occur¹⁹.

Previous study also reported results that are equivocal to our study and these results show that there is significant association between platelet lymphocyte ratio and severity of obstructive sleep apnea syndrome²⁰. In this study there was also significant correlation between higher age and body mass index with higher AHI index.

Another study also supports this investigation with results that increased systemic inflammation assessed by platelet lymphocyte ratio with severity of obstructive sleep apnea syndrome²¹.

In past there were conflicting reports about association of upper airway obstruction and inflammatory markers²²⁻²³. Korkmaz M. et al²² reported that severity of systemic inflammation cannot be predicted by other traditional markers like C-reactive protein and ESR.

Explanation to the relationship between inflammation and severity of obstructive sleep apnea syndrome is sleep deprivation and intermittent hypoxia. Many reports had shown that obstructive sleep apnea

syndrome develop inflammatory response and high level of inflammatory mediators like coagulation factor, inter cellular adhesion molecules (ICAM) and CRP²⁴. Calculation of platelet lymphocyte ratio is very cheap and easy method as compared to other mediators like interleukins (IL-6, IL-1b) and TNF-alpha. Study results showed that inflammation in obstructive sleep apnea syndrome patients can be predicted by platelet lymphocyte ratio. So this inexpensive and easy procedure should be adopted by pulmonologists to assess the inflammation in patients of obstructive sleep apnea syndrome on first stage.

Limitation of the study was that sample size was very small relatively and other inflammatory markers like ESR and CRP were not compared with platelet lymphocyte ratio.

CONCLUSION

New inflammatory markers are required to investigate the level of systemic inflammation in obstructive sleep apnea syndrome patients. Platelet lymphocyte ratio, an easy, quick and cheap measurable marker on routine CBC analysis, could be considered for assessing the inflammation in obstructive sleep apnea syndrome patients.

Author's Contribution:

Concept & Design of Study: Rafia Komal Masood
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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