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Neutropjil to lymphocyte and platelet to lymphocyte ratio in patients with different types of hypertensions and obstructive sleep apnea

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Abstract

Introduction: Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are associated with various diseases. Obstructive Sleep Apnea (OSA) is chara cterized by repetitive episodes of cessation or limitation of airflow which result in intermittent noctur nal hypoxia and sleep fragmentation. The NLR and PLR are established as a reliable marker of systemic in flammation. Low-grade inflammation has a key role in the pathogenesis and progression of hypertension (HTN). Systemic inflammation and oxidative stress are both important in the pathophysiology of OSA.

Aims and Objectives: To analyse Neutrophil to Lymphocyte and platelet to lymphocyte ratio in patients with different types of hypertension and obstructive sleep apnea.

Materials and Methods: A prospective hospital-based study was conducted in Department of Physiology and Medicine, S. P. Medical College, Bikaner. A total no. of 120 patients of dipper hypertension (Group A), non-dipper hypertension (Group B) and OSA (Group C) (40 patients in each group) were selected for the study. In all three groups, general physical examination, Neutrophil to Lymphocyte and Platelet to Lymphocyte ratio were analysed.

Results: Mean NLR for group A was 1.94 while for group B it was 3.07 and for group C it was 4.68. There was significant difference seen between these group as p value was <0.05. Mean PLR for group A was 87.5 while for group B it was 117.38 and for group C it was 214.25. There was significant difference seen between these group as p value was <0.05.

Conclusion: Patients with non-dipper hypertension had significantly higher NLR and PLR compared to dipper hypertension. Inflammation in OSA patients can be predicted by platelet lymphocyte ratio. NLR and PLR, could be used to identify patients at high risk for adverse endpoints. Findings must be confirmed on a study with a larger patient population.

Keywords: NLR, OSA, PLR. PDW.

Introduction

Neutrophil to lymphocyte ratio (NLR) and platelet to lym phocyte ratio (PLR) are associated with worse outcome in various diseases. Systemic inflammation can be measured by using a variety of biochemical and Hema to logical markers. Although novel disease-specific bio markers have been identified, most of which are time consuming and expensive. Blood neutro phil to lym phocyte (N/L) ratio is an easily accessible and reliable marker of subclinical inflammation. that can be easily obtained from the differential white blood cell count. This ratio integrates information on two different immune path ways -the neutrophils that are responsible for ongoing inflammation and the lymphocytes that represent the regulatory pathway [1,2]. Obstructive sleep apnea (OSA) is a chronic inflammatory disorder chara cterized by recurrent episodes of partial or complete upper airway obstruction during sleep [1,2], affecting 3 % –9% of the general population. [3] OSA is a serious health problem associated with cardiovascular diseases, neurological diseases and various types of mortality. [4] Although the precise underlying mechanisms are not fully understood, systemic inflammation has been proposed as a key factor in the pathogenesis of cardio vascular complications in OSA patients. [5] Recently, several markers of systemic inflammation that are obtainable from routine blood tests have attracted attention because of their wide availability and low cost. Among them, the neutrophil-to-lymphocyte ratio (NLR) has been recognized as a reliable measure of systemic inflammation with prognostic value in various chronic diseases likely because chronic systemic inflammation activates white blood cells during disease progression. [6-7]

The NLR is a ratio of two different yet complementary immune pathways, which serves as a marker of poor general health and physiological stress. Indeed, it has been proved to be a good indicator of the prognosis of a variety of diseases, especially in patients with systemic lupus erythematous (SLE) and cancer. [8-9]

Increased platelet activation plays a major role in the initiation and progression of atherosclerosis. [23] Recent studies have also introduced a new inflammatory marker, the platelet-to-lymphocyte ratio (PLR), which can predict adverse outcomes in CVD. [24] Furthermore, interactions between platelets, leukocytes and endothelial cells during the inflammatory cascade may promote atherosclerotic changes. [25] During an inflammatory response, there is an increase in the platelet number and platelet swelling, both of which may affect the platelet distribution width (PDW) [26]

Hypertension is one of the most common cardiovascular diseases in the elderly patients. Inflammation and oxidative stress have been implicated in the pathogenesis of hypertension and are the hotspot of hypertension research lately. Patients over 80 years of age are a special group population, usually coming with coronary heart disease, diabetes mellitus (DM), hyperlipidemia, which means that a variety of risk factors superposition together. It was found out there is a certain difference existed between old patients who are aged above 80 and ordinary senile patients indeed through our clinical experience.

Such very elderly patients showed differences in the clinical manifestations, treatment response and prognosis and needed more attention. For such kind of patients admitted for all kinds of reasons, whether inflammation markers, such as NLR as well as RDW, can be a predictor for all-cause mortality is still not clear. Accordingly, we designed this preliminary study to investigate the role of these inflammation makers in the

evaluation of the prognosis of hypertensive patients. [10-11]

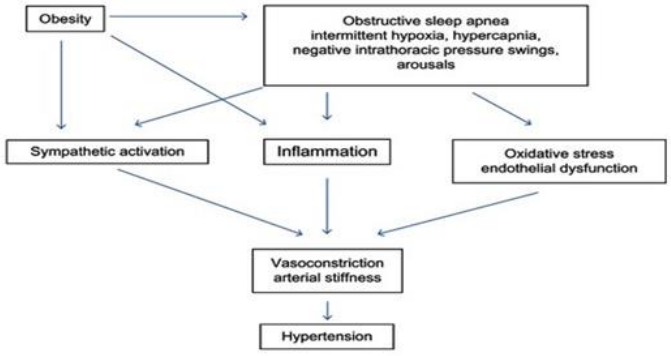

Figure 1: Schematic diagram showing the patho physio logical mechanisms linking obstructive sleep apnea with the development of hypertension.

Hypertension is one of the most common cardiovascular diseases in the elderly patients. Inflammation and oxidative stress have been implicated in the pathogenesis of hypertension and are the hotspot of hypertension research lately. For such kind of patients admitted for all kinds of reasons, whether inflammation markers, such as NLR as well as RDW, can be a predictor for all-cause mortality is still not clear.[12]

Diastolic dysfunction may cause heart failure symptoms even in the patients with preserved left ventricular function.[13] There is no specific therapy to improve left ventricular (LV) diastolic function directly. Thus, investigation of related parameters and if present, possible predictors, has been the focus of interest in order to prevent this process. Neutrophil to lymphocyte ratio (NLR), a novel marker, has been studied in various oncologic, Hema to logic, immunologic and infectious diseases as well as cardiologic disorders. [14] NLR has been evaluated in various cardiac disorders, athero sclerotic heart disease, being in the first place. Predictive value of NLR in peripheral arterial disease, calcific aortic stenosis, prognostication, presence, severity and extent of coronary artery disease and many other cardiovascular disorders. [15] Resistant hypertension (RHT) is an impor tant disease that causes an increase in cardiovascular risk, yet its etiology remains unclear. The authors aimed to investigate neutrophil/lymphocyte ratio (NLR) as an in flammation marker in patients with RHT. NLR and neutrophil count are increased in RHT patients than both controlled hypertension and normotension patients and patients with RHT, may imply the importance of inflammation in blood pressure control.[16]

Obstructive sleep apnea (OSA) is characterized by recurrent periods of complete or partial collapse of the upper airway during sleep (apneas and hypopneas), causing sleep fragmentation and frequent awakenings which often result in excessive daytime sleepiness. In more severe forms of the disease, periods of obstructed breathing result in profound intermittent hypoxia (IH) with underlying bursts in sympathetic nerve activity (SNA) and dramatic increases in heart rate (HR) and blood pressure (BP). The severity of OSA is determined by the apnea hypopnea index (AHI) which is a measure of the number of periods of obstructed breathing per hour of sleep. [27] The prevalence of OSA (AHI > 5 events/ hour) with associated daytime sleepiness has been esti mated at between 2% and 7% in diverse middle aged adult populations, whilst the prevalence of OSA (AHI > 1 event/hour) in children is between 1%–3%. [28-29] Referred to as “BP dipping”, this reduction coincides with the sympathetic withdrawal and subsequent para sympathetic predominance that occurs when going from wake to non-rapid eye movement (NREM) sleep. Indeed all measures of cardiovascular activity show diurnal variations in activity with levels higher during the day and reducing during sleep, due to the interacting effects of the sleep–wake and circadian cycles. Compared with wakefulness, NREM sleep is associated with lower BP, HR, cardiac output and systemic vascular resistance.

Rapid eye movement (REM) sleep on the other hand is punctuated by transient surges in SNA, HR, and BP. However, as REM constitutes only approximately 20% of total sleep, the net effect on cardiovascular measures is still a reduction from wake levels. [20]

Sleep-related BP dipping is considered important for cardiovascular health, whilst absent or diminished nocturnal dipping of BP has been shown to be a strong independent predictor of cardiovascular risk. Nighttime, as well as daytime BP measured by 24-hour ambulatory blood pressure monitoring (ABPM), were linearly related with stroke risk. In addition, in the Anglo-Scandinavian Cardiac Outcomes Trial, increased nighttime systolic BP (SBP) was associated with an increased risk of cardiovascular events. Other population studies have confirmed the cardiovascular benefit of the normal sleep-related decrease in BP. [21-22]

Aims and Objectives

To analyse Neutrophil to Lymphocyte and platelet to lymphocyte ratio in patients with different types of hypertensions and obstructive sleep apnea.

Materials and Methods

- **Study design:** Prospective Hospital based study
- **Study place:** Department of Physiology, S.P. Medical College and Associated Group of PBM Hospitals, Bikaner
- **Study population:** All patients who were diagnosed for obstructive sleep apnea and hypertensive patients OPD at Department of Medicine, Sardar Patel medical college and Prince Bijay Singh Memorial Hospital, (P.B.M.) Associated Group of Hospitals, Bikaner.
- **Sample size:** 120 samples.
- **Sampling method:** Simple Random Sampling.

Inclusion criteria

- Willing to participate.
- Age 18 to 80 Years
- All cases of obstructive sleep apnea and hypertensive patients admitted to the P. B. M. Hospitals.

Exclusion criteria

- Patients with chronic renal failure.
- Chronic Liver Diseases
- Acute myocardial infarction in last 6 months.
- Patients on diuretics
- Neurologic disorders,
- Any Malignancy,
- Critical illness
- Refractory Arrhythmia or any revascularization procedure.
- Patients receiving magnesium supplements or magne sium-containing antacids
- Malabsorption or chronic diarrhea.
- Patients with a history of alcohol abuse
- Pregnant women with hypertension, proteinuria, and Eclampsia.
- Patients with a history of epilepsy.

Data collection & analysis

After obtaining permission from Ethical Committee and informed written consent of study population selected through analyzing inclusion and exclusion criteria and with help of consecutive sampling, the questionnaire were administered to study subjects. All relevant in formation related to study subjects' socio demographic details, clinical profile, biochemical parameters were collected.

The collected data was coded, tabulated and statistically analyzed using primer software version 6.0 and Microsoft excel. Descriptive statistics for numerical data by mean, standard deviation and minimum and maximum of the range. Analysis was done for parametric qualitative data between the three groups using one-way Anova test. Analysis for quantitative data was done by using chi square test.

Observations and Results

Table 1: distribution of patients according to age, gender and Bmi

Parameters	Group A (Dipper Hypertension)		Group B (Non-Dipper Hypertension)		Group C (Obstructive Sleep Apnea)		Chi Square	p value
	n	%	n	%	n	%		
Age groups (In Years)							20.724	0.002
<25	8	20.00	2	5.00	1	2.50		
25-40	19	47.50	26	65.00	13	32.50		
41-55	8	20.00	10	25.00	20	50.00		
>55	5	12.50	2	5.00	6	15.00		
Mean	38.20		37.88		43.40			
SD	15.96		9.63		10.57			
Gender							6.097	0.047
Male	27	67.50	30	75.00	20	50.00		
Female	23	57.50	10	25.00	20	50.00		
BMI							3.944	0.139
<18.5	0	0.00	0	0.00	0	0.00		
18.5-24.9	0	0.00	0	0.00	0	0.00		
25-29.9	36	90.00	40	100.00	37	92.50		
≥30	4	10.00	0	0.00	3	7.50		

In Table-1 we found that majority 47.5% patients in group A while 37.8% patients in group B and 50% patients in group C were of age group 41-55 years. The mean age for group A was 38.2years while for group B it was 37.8 years and for group C it was 43.4 years. There was significant difference found between these group as p value was <0.05. We found in Table-1 that 67.5% male in group A while 75% patients in group B and 50% patients in group C were male. There was significant difference found between these group as p value was <0.05.

In Table-1 we found that 90% patients in group A while 100% patients in group B and 92.5% patients in group C were of BMI 25-29.9 category. There were 10% patients in group A and 7.5% patients in group C with BMI ≥30.

Table 2: Distribution of cases according to blood pressure (mm. Hg), neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR)

	Group A (Dipper Hypertension)		Group B (Non Dipper Hypertension)		Group C (Obstructive Sleep Apnea)		p value
	Mean	SD	Mean	SD	Mean	SD	
BP (mm. Hg)							

SBP	128.85	2.64	128.60	2.98	128.95	2.56	0.840
DBP	83.00	3.42	83.15	3.59	82.75	3.35	0.872
Neutrophil Lymphocyte Ratio	1.94	0.11	3.07	0.22	4.68	0.42	0.0001
Platelet Lymphocyte Ratio	87.57	4.18	117.38	6.41	214.25	20.39	0.0001

In Table-2 we found that mean SBP for group A was 128.8 while for group B it was 128.6 and for group C it was 128.95. The mean DBP for group A was 83 while for group B it was 83.15 and for group C it was 82.75.

In Table-2 we found that mean NLR for group A was 1.94 while for group B it was 3.07 and for group C it was 4.68. There was significant difference seen between these group as p value was <0.05.

In Table-2 we found that mean PLR for group A was 87.5 while for group B it was 117.38 and for group C it was 214.25. There was significant difference seen between these group as p value was <0.05.

Discussion

Obstructive sleep apnea (OSA) is a chronic inflammatory disorder characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, affecting 3%–9% of the general population. OSA is a serious health problem associated with cardiovascular diseases, neurological diseases, and various types of mortality. Chronic systemic inflammation has been proposed in several recent studies as a possible mechanism.

Demographic data

In the present study we found that majority 47.5% patients in group A while 37.8% patients in group B and 50% patients in group C were of age group 41-55 years. The mean age for group A was 38.2years while for group B it was 37.8 years and for group C it was 43.4 years. There were 67.5% male in group A while 75% patients in group B and 50% patients in group C were male. There was significant difference found between these group as p value was <0.05.

Song Y J et al [27] found that out of 290 patients, 193 men (66.6 %) and 97 women (33.4 %) included in the study. The mean age was 48.6 ± 13.4 years (range: 18–78).

Koseoglu S et al found that one hundred ninety-six (69%) patients were male and 88 (31%) were female. The mean age of the patients was 47 (75–23). The mean age of the female patients was 49 and male patients was 46.

A similar study by Sun X et al found that out of 341 cases 328 were male and 13 were female with the average age of 87.43 ± 5.21 (81–102) years.

BMI analysis

In the present study we found that 90% patients in group A while 100% patients in group B and 92.5% patients in group C were of BMI 25-29.9 category. There were 10% patients in group A and 7.5% patients in group C with BMI ≥30.

We found that 90% patients in group A while 100% patients in group B and 92.5% patients in group C were of BMI 25-29.9 category. There were 10% patients in group A and 7.5% patients in group C with BMI ≥30.

Song Y J et al [27] found that the BMI, SBP, heart rate were higher in the OSAS groups than the control group.

Koseoglu S et al found that patients included in this study were generally middle-aged and obese. The BMI of the patients varied from 50.1 to 18.3 kg/m2 (mean 30.67 ± 4.6).

NLR analysis

Inflammation is thought to play a role in the etio patho genesis of sudden idiopathic hearing loss and a significant increase was shown in NLR value in

patients with sudden idiopathic hearing loss. NLR was also described as a potential marker for the diagnosis of cardio vascular diseases. Because neutrophils and lym phocytes play a major role in inflammatory responses through the release of various inflammatory mediators, their absolute counts or relative values may reflect the status of systemic inflammation.

NLR is superior to other individual leukocyte parameters (e.g., neutrophil, lym phocyte, and total leukocyte counts) in terms of stability, because it is a ratio of two different immune pathways.

In above table we found that mean NLR for group A was 1.94 while for group B it was 3.07 and for group C it was 4.68. There was significant difference seen between these group as p value was <0.05.

A study by Sunbul M et al [1] found that patients with non-dipper hypertension had significantly higher NLR compared to dipper hypertension (2.3±0.9 versus 1.8 ± 0.5, p=0.001).

Although some evidence study by Kaya M G et al supported that hypertensive patients with non-dippers had increase platelet activation and a high inflammatory state, the inflammatory biomarkers, which were RDW, MCV, NLR, in the study did not significantly associate with non-dipping status.

A contrary study by Demir M [2] showed that patients with non-dipper hypertension had higher NLR compared with dipper patients. However, the number of sample size was smaller in his study and he did not report whether NLR was an independent predictor of non-dipper status.

Sun X et al found that the median and interquartile range of NLR was 3.01 and 2.05–6.12, respectively.

All patients were grouped in the quartile based on their NLR score as follows: less than2.05, quartile 1, (n = 85); between2.05 and2.99, quartile 2 (n = 88); between 3.00 and 6.12, quartile 3 (n = 83); greater than 6.12, quartile 4 (n = 85).

The NLR is a particularly reliable marker in patients with out conditions that may affect inflammatory response. The mechanism underlying the elevation of the NLR in OSA patients may be related to hypoxia-induced chronic inflammation.

Neutrophils from patients with moderate and severe OSA demonstrate prolonged survival, which is associated with higher NF-κB levels and worse balance of pro-apoptotic and anti-apoptotic proteins.

Unlike many other inflammatory markers and bioassays, the NLR is an inexpensive and readily available marker which is a combination of two independent markers of inflammation, providing us with additional information.

PLR analysis

The PLR combines the predictive risk of platelet and lymphocyte counts into a new prognostic marker of inflammation for many types of cardio vascular disease in cluding hyper tension, coronary artery disease, occlusive peripheral arterial disease], and atherosclerosis. Elevated platelet counts reflect underlying inflammatory states, because platelets are acute phase reactants that are produced in response to various stimuli including systemic infections, inflammatory conditions, bleeding, and tumors.

Low levels of lymphocytes represent an un controlled inflammatory pathway. Therefore, an elevated PLR is a useful inflammatory marker because it reflects the increase in platelet count, and decrease in lymphocyte count in an inflammatory state.

We found that mean PLR for group A was 87.5 while for group B it was 117.38 and for group C it was 214.25. There was significant difference seen between these group as p value was <0.05.

Pack A I et al stated that 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, signifi cant decrease in these markers occur.

Korkmaz M et al also supports this investigation with results that increased systemic inflammation assessed by platelet lymphocyte ratio with severity of obstructive sleep apnea syndrome.

Song Y J et al [27] found that as the OSAS severity increased, there were significant gradual increases in PLR (controls: 99.5 ± 42.1, mild OSAS; 113.8 ± 45.2, moderate OSAS; 121.3 ± 62.9 and severe OSAS; 138.6 ± 59.9, p = 0.001).

Koseoglu S et al found that the mean PLR value of the OSAS group was 109.50 ± 35.72. When evaluated with the Kruskal-Wallis test, the PLR values in patients decreased gradually from to the severe OSAS group (except for moderate OSAS) and were statistically significant (p = 0.019, CC = –0.167).

Conclusion

We found that higher NLR levels and PLR Levels in admitted to the hospital are good predictors. We demonstrated that patients with non-dipper hypertension had significantly higher NLR and PLR compared to dipper hypertension. 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.

This indicated that NLR and PLR, which is easily determinable, broadly available and inexpensive markers, could be used to identify patients at high risk for adverse endpoints. However, these findings must be confirmed on a study with a larger patient population.

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