Original Article

The Role of the Lymphocyte-to-C-reactive Protein Ratio in Obstructive Sleep Apnea

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Abstract

Context: This was an investigation of inflammation markers on the prediction and prognosis of patients with sleep apnea. **Aims:** Clinical detection of inflammatory markers is useful to assess systemic inflammation in patients with obstructive sleep apnea syndrome (OSAS). The aim of the study was to evaluate whether the lymphocyte-to-C-reactive protein (CRP) ratio (LCR) was a predictive marker in diagnosing and determining the severity of OSAS. **Settings and Design:** This was a retrospective clinical study. **Subjects and Methods:** One hundred and forty-one patients who had undergone polysomnography were included in the study. The sex, age, Apnea–Hypopnea Index (AHI), body mass index, and complete blood count parameters of the patients were recorded. AHI scores were used to classify the severity of OSAS. **Statistical Analysis Used:** Differences among the groups for each parameter were analyzed using Student's *t*-test and one-way analysis of variance with Tukey correction for normally distributed parameters and the Mann–Whitney U test and Kruskal–Wallis test for nonnormally distributed parameters. The correlation between LCR, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, CRP, and AHI scores was assessed using Pearson's correlation coefficient. **Results:** First, the patients were divided into four groups according to their AHI results, as control group, mild, moderate, and severe OSAS groups. The median LCR levels were 2.57 (1.59, 3.51) in the control group, 1.28 (0.74, 3.27) in Group 2, 1.63 (0.86, 2.6) in Group 3, and 1.05 (0.62, 2.31) in Group 4. In the comparison of all patients with OSAS and the control group, the median LCR level was 1.27 (0.7, 2.74) in patients with OSAS and 2.57 (1.59, 3.51) in the control group ($P = 0.002$). **Conclusions:** This study demonstrated that LCR is an important marker for systemic inflammation in patients with OSAS. LCR may be a new predictive marker in the diagnosis and prognosis of patients with OSAS.

Keywords: *C-reactive protein, obstructive sleep apnea, lymphocytes, inflammation*

Submitted: 20-Nov-2019
Revised: 20-Apr-2020
Accepted: 24-Apr-2020
Published: 16-Sep-2020

Introduction

Obstructive sleep apnea syndrome (OSAS) is a disease characterized by recurrent periods of a complete or partial collapse of the upper airway during sleep. The prevalence of moderate-to-severe OSAS is approximately 6%–13% in the adult population.[1] OSAS is associated with elevated levels of various circulating inflammatory markers. Inflammation is closely correlated with OSAS and the severity of the disease.

The respiratory obstructions in OSAS induce hypoventilation, hypoxia, and hypercapnia. Hypoxia episodes increase inflammation and oxidative stress which contribute to cardiovascular events in patients with OSAS. Several studies demonstrated

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How to cite this article: Koseoglu S, Unal Y, Saruhan E, Bek VS, Kutlu G. The role of the lymphocyte-to-C-reactive protein ratio in obstructive sleep apnea. Neurol Sci Neurophysiol 2020;37:124-8.

Access this article online

Quick Response Code:

Website: www.nsnjournal.org

DOI: 10.4103/NSN.NSN_24_20

that hypoxia affects the vascular endothelium in OSAS by promoting inflammation and oxidative stress.[2-4] Inflammation markers such as white blood cell count, lymphocyte (LCT), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are useful markers in the diagnosis and prediction of the severity of OSAS.[5-7]

The lymphocyte-to-C-reactive protein (CRP) ratio (LCR) is a new marker that was first used to evaluate the medical and surgical treatment outcomes of patients with colorectal cancer. This study aims to analyze the LCR levels in patients with OSAS and to show whether it was associated with disease severity.

Subjects and Methods

Two hundred and forty-five patients who were referred to for polysomnography (PSG) at Mugla Sıtkı Kocman University Sleep Centre between February 2018 and April 2019 were included in the study. One hundred and four applicants with active infection, receiving immunosuppressive therapy, who were aged under 18 years, morbidly obese (body mass index [BMI] >40 kg/m^2), and those with uncontrolled hypertension, diabetes mellitus, and congestive heart failure were excluded from the study. After the exclusions, 141 patients were enrolled in the study. The study protocol was approved by the human research ethics committee at Mugla Sıtkı Kocman University University (1302019). No written consent was required or obtained from the patients due to the study's retrospective design.

After an overnight fast, blood samples were collected into ethylenediaminetetraacetic acid and gel-separated blood tubes through venipuncture from patients admitted to the sleep laboratory for PSG. The gel-separated blood tubes were left at room temperature for 10–20 min for the separation of serum, followed by centrifugation at 1000 g for 10 min. Serum CRP concentrations were determined using a turbidimetric assay performed with a commercial reagent (CRPLX, Lot: 41449501) in an automated clinical chemistry analyzer (Cobas c702, Roche Diagnostics, Mannheim, Germany). Complete blood count parameters including platelets, neutrophils, and lymphocytes (LCT) were analyzed using a Sysmex XN-1000 hematology analyzer (Sysmex, Kobe, Japan). We calculated inflammation factors LCR, NLR, and PLR using the formulas given in Table 1.

All-night sleep PSG was performed in the Neurophysiology Laboratory of Mugla Sıtkı Kocman University Hospital for patients with symptoms such as excessive daytime sleepiness, snoring, and witnessed apnea using an Embla N7000 (Natus, Kanata, Canada) PSG system. PSG was performed under technician guidance and during the patients' spontaneous sleep. Electroencephalogram, electromyogram (submental and right–left tibialis anterior), electrooculogram (left-right), nasal airflow, thoracic and abdominal respiratory movements, blood oxygen saturation (pulse oximetry), and body position were recorded during the night. These data were scored manually by the same certificated neurologist using the Embla N7000 device in accordance with the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events.[8] The Apnea–Hypopnea Index (AHI) was taken as the total number of apneas and hypopneas during sleep in hours.

Table 1: Calculation of inflammation factors

Parameters	Calculation
NLR	Neutrophil (number/μl)/lymphocyte (number/μl)
PLR	Platelet (number/μl)/lymphocyte (number/μl)
LCR	Lymphocyte (number/μl)/CRP (mg/L)

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, LCR: Lymphocyte-to-CRP ratio

The patients were divided into four groups according to AHI values. Patients with AHI values lower than 5 were considered as the control group (Group 1, n = 29), patients with AHI values between 5 and 14.9 were diagnosed as having mild OSAS (Group 2, n = 30), patients with AHI values between 15 and 29.9 were diagnosed as having moderate OSAS (Group 3, n = 33), and patients with AHI values higher than 30 were diagnosed as having severe OSAS (Group 4, n = 49). We also determined the rapid eye movement (REM) AHI, non-REM (NREM) AHI, and Epworth Sleepiness Scale scores of the groups. In addition, two groups were formed as patient (AHI >5, n = 29) and control (AHI <5, n = 112) groups.

Statistical analysis

The study data were assessed using the SPSS Version 22 software (SPSS, Chicago, IL, USA). The Shapiro–Wilk test was used to evaluate the distribution of variances. Variables with normal distribution are presented as mean ± standard deviation, and nonnormally distributed variables are expressed as median and quartiles. The differences between the groups for each parameter were analyzed using Student's t-test and one-way analysis of variance with Tukey correction for normally distributed parameters and the Mann–Whitney U test and Kruskal–Wallis test for nonnormally distributed parameters. All P values were two-sided, and values <0.05 were considered statistically significant. The correlation between LCR, NLR, PLR, CRP, and AHI scores was

assessed using Pearson's correlation coefficient. The area under the curve (AUC) of LCR was calculated by constructing receiver operating characteristics curves to determine the cutoff value.

Results

One hundred and forty-one patients were included in the study. Fifty-one (63.8%) patients were female and 90 (36.2%) were male. The mean age of the patients was 45.7 (range, 26–69) years, and there were no significant differences between the groups. The BMIs of the patients were 27.3, 28.2, 29.9, and 30.7 kg/m^2 in the groups, respectively, and there were no significant differences between the groups (P = 0.084) [Table 2].

The median LCR levels were 2.57 (1.59, 3.51) in the control group, 1.28 (0.74, 3.27) in Group 2, 1.63 (0.86, 2.6) in Group 3, and 1.05 (0.62, 2.31) in Group 4. LCR levels decreased statistically significantly from controls to patients with severe OSAS (P = 0.012).

The median NLR values of the groups were 1.52 (1.09, 1.76), 1.43 (1.15, 1.61), 1.2 (0.9, 1.34), and 1.28 (1.09, 1.75), respectively. There were no significant differences between the groups (P = 0.132).

The median PLR values were 98.11 (77.74, 117.72), 92.75 (80.08, 114.83), 93.75 (79.68, 101.75), and 92.35 (73.61, 113.55) from Group 1 to Group 4, respectively. There were no significant differences between the OSAS groups and the control group (P = 0.889).

When all patients with OSAS were compared with the control group, the median LCR level was 1.27 (0.7, 2.74) in patients with OSAS and 2.57 (1.59, 3.51) in the control group (P = 0.002) [Figure 1]. Even though NLR and PLR values were less in the OSAS group, no statistical significance was found [Table 3].

There was no statistically significance between age and LCR (r = −0.95, P = 0.26), NLR (r = 0.10. P = 0.21), and PLR (r = 0.03, P = 0.64) levels. LCR levels were negatively correlated with AHI (r = −0.268, P < 0.001), REM AHI (r = −0.325, P < 0.001), and non-REM AHI (r = −0.243, P = 0.004) with statistical significance [Figures 2-4]. CRP levels were significantly correlated with AHI (r = 0.353, P < 0.001).

The AUC of LCR used to discriminate patients with OSAS from controls was 0.683 (95% CI: 0.600–0.759), with the cutoff value, sensitivity, and specificity at 1.48, 58.93, 79.31, respectively [Figure 5].

Discussion

The most important result of this study was that the LCR value was lower in patients with OSAS compared with the control group, and the LCR value decreased with increasing disease severity. Low LCR levels have been found to be associated with poor prognosis in gastric cancer and colorectal cancer in recent oncologic studies.[9,10] This is explained by the impaired immune response and increased systemic inflammation. A decrease in lymphocyte numbers leads to a decrease in immune response, and an increase in CRP levels indicates systemic inflammation.[10] In this study, the LCR value was found to be significantly lower when the OSAS and control groups were separated, as well as mild–moderate–severe OSAS and control groups. LCR was negatively correlated with AHI, REM AHI, and NREM AHI. We think that there was a significant decrease in this value due to systemic inflammation in OSAS.

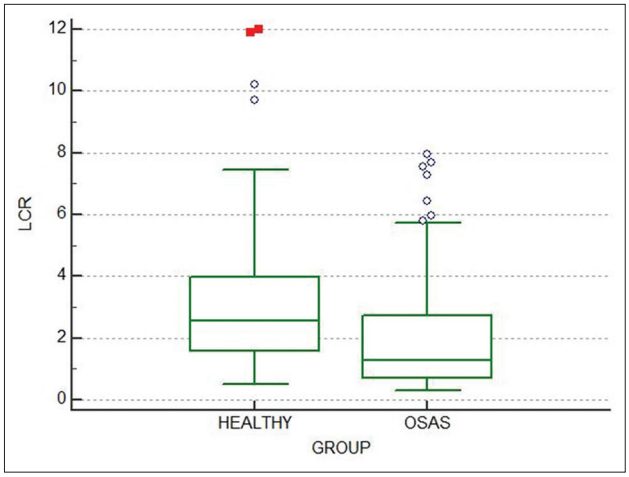

Figure 1: LCR levels in patients with OSAS and controls LCR: Lymphocyte-to-C-reactive protein ratio, OSAS: Obstructive sleep apnea syndrome

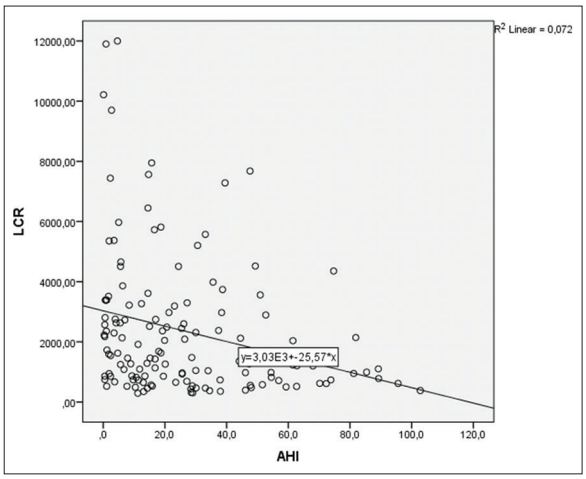

Figure 2: Scatter diagram showing the correlation between LCR and AHI. LCR levels were negatively correlated with AHI (r = −0.268, P < 0.001). LCR: Lymphocyte-to-C-reactive protein ratio, AHI: Apnea–hypopnea index

Table 2: Demographic data and apnea-hypopnea index, rapid eye movement apnea-hypopnea index, nonrapid eye movement apnea-hypopnea index, and Epworth sleepiness scale score of groups

	Group 1 (*n*=29)	Group 2 (*n*=30)	Group 3 (*n*=33)	Group 4 (*n*=49)	Total (*n*=141) (*P*)
Age	41.8±7.8	45.5±10.1	47±9.5	47.2±9.9	0.08
Gender (female/male)	10/19	11/19	13/20	18/31	0.864
BMI	27.3±3.4	28.2±4.6	29.9±3.9	30.7±4.5	0.084
AHI	1.7 (0.7-2.7)	10.1 (6.7-13)	20.6 (17-26.1)	49.3 (38.4-62.8)	<0.001
REM AHI	1.8 (0.7-5.2)	21.3 (10-33.2)	28.9 (21-38)	49.8 (26.8-65.9)	<0.001
NREM AHI	1.1 (0.5-2.7)	7.4 (5.1-9.7)	19.4 (14.2-25.3)	54.3 (37.1-65.1)	<0.001
ESS	4 (2-7)	5 (2-8)	6 (4-11)	8 (5-12)	0.023

Data are presented as mean±SD for normally distributed variables and as median and quartiles (25th-75th percentiles) for nonnormally distributed variables. BMI: Body mass index, AHI: Apnea-hypopnea index, REM AHI: Rapid eye movement AHI, NREM AHI: Non-REM AHI, ESS: Epworth sleepiness scale, SD: Standard deviation

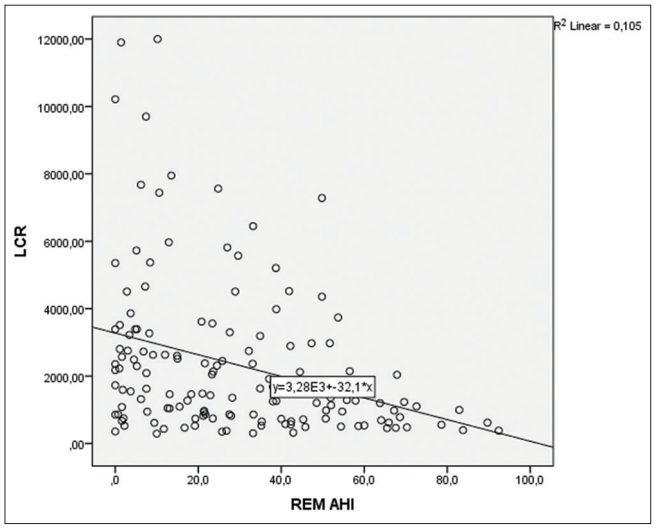

Figure 3: Scatter diagram showing the correlation between LCR and REM AHI. LCR levels were negatively correlated with REM AHI ($r = -0.325$, $P < 0.001$). LCR: Lymphocyte-to-C-reactive protein ratio, NREM AHI: Non-rapid eye movement apnea–hypopnea index

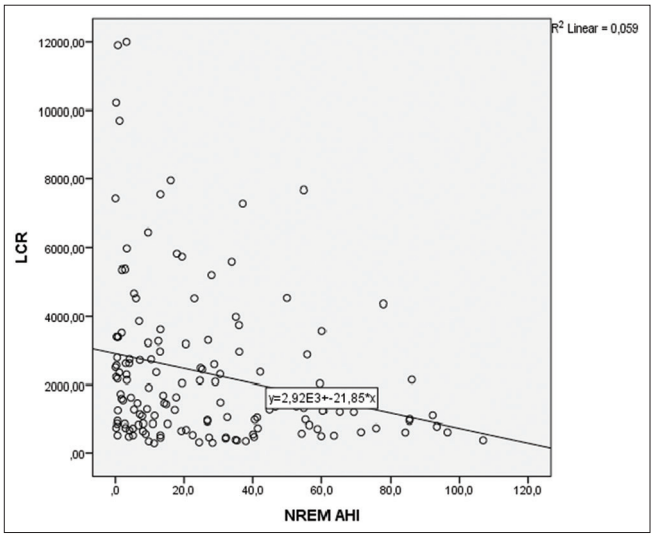

Figure 4: Scatter diagram showing the correlation between LCR and NREM AHI. LCR levels were negatively correlated with NREM AHI ($r = -0.243$, $P = 0.004$). LCR: Lymphocyte-to-C-reactive protein ratio, NREM AHI: Non-rapid eye movement apnea–hypopnea index

Obstructive sleep apnea has been associated with many comorbidities such as cardiovascular diseases, metabolic dysfunctions, and cerebrovascular diseases.[2,11-13] Although the etiology remains unclear, chronic inflammation has been implicated in their pathogeneses.

In a review study based on interleukin-6 and tumor necrosis factor alpha, it was emphasized that OSAS caused persistent chronic low-grade inflammation.[14] Complex changes in the markers of systemic inflammation occur due to chronic hypoxia, sympathetic hyperactivity, and chronic inflammation in patients with OSAS.[15] Recent studies investigated the role of hematologic markers such as NLR, PLR, mean platelet volume, platelet distribution width, and red cell distribution width, which are cheap and easily accessible, in the diagnosis of OSAS and determining the severity of the disease. Some of these markers were found to be increased and some of them decreased. In a recent meta-analysis, CRP was reported to be higher in patients with OSAS when all other causes were excluded and thus could only be due to systemic inflammation in sleep apnea.[16]

A meta-analysis study concluded that NLR increased with increasing severity of OSAS, but there was a significant heterogeneity among the studies.[15] In some studies, there was no relationship between NLR and OSAS, as in this study.[5,17] In some studies, it was reported that NLR was higher in patients with OSAS and correlated with the severity of the disease.[7,18]

PLR is a marker mostly used in the diagnosis and prognosis of cardiovascular diseases. It was determined that PLR values were high in patients with OSAS, and there was a correlation between disease severity and PLR values. A stronger association with PLR was found in patients with OSAS who had cardiovascular disease.[6,19] In this study, no correlation was found between OSAS severity and PLR.

The sample size and retrospective design of our study are the limitations of the manuscript. However,

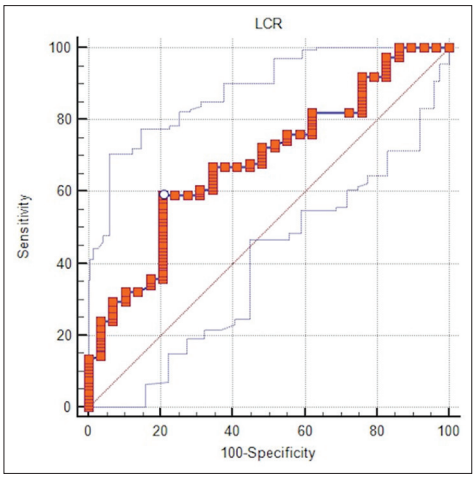

Figure 5: ROC curve of LCR in predicting OSAS (AUC = 0.683). OSAS: Obstructive sleep apnea syndrome, ROC: Receiver operating characteristics, LCR: Lymphocyte-to-C-reactive protein ratio, AUC: Area under curve

Table 3: Lymphocyte-to-C-reactive protein ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio values in obstructive sleep apnea syndrome and control groups

	Control (*n*=29)	OSAS (*n*=112)	*P*
LCR	2.57 (1.59-3.51)	1.27 (0.7-2.74)	0.002
NLR	1.52 (1.09-1.76)	1.25 (1.03-1.6)	0.142
PLR	98.11 (77.74-117.72)	93.05 (78-114.05)	0.592

Data are presented as median and quartiles (25^{th}-75^{th} percentiles). CRP: C-reactive protein, LCR: Lymphocyte-to-CRP ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, OSAS: Obstructive sleep apnea syndrome

this noninvasive and simple biomarker has not been investigated in patients with sleep apnea previously.

Conclusions

This study investigated the role of LCR values in OSAS for the first time. LCR is an easily obtainable and inexpensive marker that can be used as a predictive marker for the diagnosis and severity of OSAS. However, to understand the importance of LCR, studies with larger samples are needed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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