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Care of Patients With Coronary Heart Disease

The neutrophil-to-lymphocyte ratio in patients with obstructive sleep apnoea syndrome and its relationship with cardiovascular disease

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ABSTRACT

Objective: To investigate the association between the neutrophil-to-lymphocyte ratio (NLR) and obstructive sleep apnoea syndrome (OSAS) severity and whether the NLR predicts cardiovascular disease (CVD) in patients with OSAS.
Background: OSAS is known as a risk factor for CVD. An increased NLR was strongly correlated with cardiovascular outcomes in several studies.
Methods: We retrospectively examined the laboratory data for 289 patients with suspected OSAS evaluated using polysomnography.
Results: The study included 171 OSAS patients and 118 controls. The NLR was higher in OSAS group than control group. The NLR was significantly higher in patients with CVD than in those without (3.31 ± 1.1 vs. 1.93 ± 0.8, $p = 0.002$). There were also significant correlations between the NLR and apnoea-hypopnoea index, mean SaO2, and oxygen desaturation index.
Conclusions: There was a significant correlation between the NLR and OSAS severity and the NLR was independently associated with CVD in patients with OSAS.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common disease that develops secondary to recurrent obstruction of the upper respiratory tract during sleep. OSAS is characterized by episodic hypoxia and arousal.[1] Approximately 4% of males and 2% of females have OSAS, which is an important risk factor for cardiovascular diseases (CVD) such as ischemic heart disease, arrhythmia, and hypertension.[2–5] The precise aetiologies of cardiovascular events in OSAS patients are not fully understood but are likely multifactorial, including elevated sympathetic activity developing secondary to recurrent hypoxia and sleep arousal, endothelial dysfunction, and increased oxidative stress secondary to recurring oxygen desaturation and resaturation.[6,7]

OSAS is a multisystem disease in terms of both clinical presentation and underlying aetiological mechanisms; chronic inflammation is a component of the pathology. Although the details of inflammation in OSAS patients are not entirely clear, repeated short periods of hypoxia during the night activate various inflammatory pathways. Recent studies have shown that both the white blood cell (WBC) count and the neutrophil-to-lymphocyte ratio (NLR) are good markers of inflammation. However, the NLR is superior to the WBC as a predictor of inflammation.[8,9] This superiority is explained by the fact that the NLR evaluates two important mediators of inflammation: neutrophils and lymphocytes. Neutrophils act in most inflammatory processes by secreting mediators, while lymphocytes play more specific roles in inflammation, such as chemokine secretion and inflammation regulation.[9] Consequently, the NLR not only gives information about the cell counts but also gives more precise information about their ratio. The NLR is a simple

Abbreviations: AHI, apnoea-hypopnoea index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnoea; BMI, body mass index; PSG, polysomnography; OR, odds ratio; CI, confidence interval; CVD, cardiovascular diseases; NLR, Neutrophil-to-lymphocyte ratio; WBC, White blood cell; LDL, Low-density lipoprotein; ESS, Epworth Sleepiness Scale; EDTA, Ethylenediaminetetraacetic acid; RDW, Red cell distribution width; PDW, Platelet distribution width; MPV, Mean platelet volume.

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parameter that is easy to measure, and indicates the presence of systemic inflammation.[10,11] An elevated NLR is associated with chronic diseases including CVD, diabetes mellitus, chronic obstructive lung disease, and ulcerative colitis.[12–15]

The intermittent hypoxia and reoxygenation experienced nightly by OSAS patients increases the production of reactive oxygen species and activates circulating inflammatory cells, particularly neutrophils and lymphocytes, that contribute to the pathogenesis of CVD in OSAS patients.[7,16] Increased neutrophils are related to worse cardiovascular outcomes.[17] Neutrophils also act in acute myocardial injury by secreting chemicals and increasing oxidative stress-related substances. It has been have shown that patients with OSAS had higher circulating neutrophil and lymphocyte levels than controls.[7] Serum cortisol levels are increased in OSAS due to increased sympathetic activity. Elevated circulating cortisol levels cause a decrease in the relative concentration of lymphocytes. Koseoglu et al reported that the lymphocyte levels decreased with increasing OSAS severity.[18] The decrease in lymphocytes reflects a dysregulated inflammatory response and is related to adverse cardiovascular events.[19]

An elevated NLR was strongly associated with cardiac outcomes in several studies.[20–22] To the our best knowledge, there is no study that evaluated the possible relationship between NLR and CVD in OSAS. Therefore, our objective was to explore whether the serum NLR was associated with OSAS severity and whether the NLR predicts CVD in patients with OSAS.

Methods

Study design and subjects

This retrospective study was performed in a university-based sleep center between September 2012 and March 2014. Subjects were recruited from the hospital digital database. We included non-apnoeic controls and patients with OSAS who underwent sleep studies. We excluded patients for whom WBC counts were lacking, or who had WBC counts of $>12 \times 10^3$/L or $<4 \times 10^3$/L; and those diagnosed with a sleep disorder other than OSAS (e.g. central sleep apnoea syndrome, movement disorder, or narcolepsy). Subjects with liver or kidney disease, thyroid dysfunction, cerebrovascular, hematological, oncological, or inflammatory disease, a lung disease featuring hypoxemia (asthma, chronic obstructive pulmonary disease, or interstitial lung disease), or infections were excluded. Additional exclusion criteria were age <18 years, a blood transfusion within 2 weeks, and the use of drugs such as nonsteroidal anti-inflammatory drugs, steroids, antibiotics, immunosuppressive medications, or alcohol.

Measurements and data collection

Data on demographic features (age, sex, and body mass index [BMI]), smoking habits, the history of chronic disease and drug prescription, sleep habits, sleep patterns, and medical history were recorded before the PSG. Cardiovascular disease was considered present when a patient had coronary artery disease, arrhythmia, or heart failure. Cardiac disease was diagnosed by a cardiologist, and the subjects were taking one or more of an angiotensin-receptor blocker, anti-ischemic agent, angiotensin-converting enzyme inhibitor, anti-aggregant (including acetylsalicylic acid and clopidogrel), beta-blocker, or calcium antagonist.

Patients with an arterial blood pressure >140/90 mm Hg, measured in triplicate in the brachial region after a 5-min rest, and those on antihypertensive therapy, were considered hypertensive. Patients with total cholesterol levels >200 mg/dL, low-density lipoprotein (LDL)-cholesterol levels >130 mg/dL, or triglyceride levels >150 mg/dL; and those using lipid-lowering drugs, were considered to be hyperlipidaemic. Excessive daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS).[23]

This study was approved by the Local Ethics Committee of Zonguldak Bulent Ecevit University School of Medicine, and written informed consent was obtained from each patient.

Sleep study

Each patient underwent full PSG monitoring at our sleep center by a technician. At least 6 h of PSG data were recorded. PSG monitoring included electroencephalography, electro-oculography, submental and bilateral leg electromyography, and electrocardiography. Airflow and snoring levels were measured using an oral thermistor and a nasal transducer, respectively, and by assessing thoracic and abdominal wall movements. Body position was evaluated via inductive plethysmography. Blood oxygen saturation was measured by pulse oximetry. PSG scoring was performed in accordance with the AASM Manual for Scoring Sleep published by the American Academy of Sleep Medicine in 2012.[24] After PSG recording, the sleep stage; changes in heart rate and rhythm; changes in breathing patterns (apnoea, hypopnoea, and arousal); and periodic leg movements during sleep; were manually scored. Apnoea was defined as airflow cessation for at least 10 s, and hypopnoea was defined as an airflow reduction of ≥30% for at least 10 s plus attainment of an oxygen desaturation >3% or an arousal that lasted ≥10 s. The sum of the times spent in apnoea and hypopnoea was divided by the total sleep time to determine the apnoea-hypopnoea index (AHI). Patients with an AHI <5 were considered to exhibit simple snoring. OSAS was defined as either an AHI ≥5 with associated symptoms such as sleep attacks, excessive daytime sleepiness, unsatisfying sleep, insomnia or fatigue, snoring, and/or breathing pauses witnessed by the patient's partner; or an AHI ≥15 regardless of associated symptoms. The severity of OSAS was classified according to the AHI as mild ($5 \leq$ AHI < 15), moderate ($15 \leq$ AHI < 30), and severe ($30 \leq$ AHI).[24]

Laboratory analysis

Blood samples were taken from the antecubital vein in the morning between 08:00 and 10:00 after a 12-h fast, and placed into ethylenediaminetetraacetic acid (EDTA)-containing tubes. Within 1 h, the WBC, neutrophil, and lymphocyte counts, red cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), and other hematological parameters were determined on a Beckman Coulter LH 780 Hematology Analyzer (Beckman Coulter, Brea, CA, USA). The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 software (SPSS, Chicago, IL, USA). Data distributions were examined using the Shapiro–Wilk test. Variables are expressed as means ± standard deviations or as medians (with minima and maxima). Data from the OSAS and control groups were compared using the independent-samples *t* test, the chi-squared test, or the Mann–Whitney *U*-test, as appropriate. When comparing more than two groups, normally distributed data were analyzed using one-way analysis of variance (ANOVA) whereas non-normally distributed data were analyzed using the Kruskal–Wallis test. Spearman's correlation analysis was performed to explore relationships between continuous variables. Receiver operating characteristic (ROC) curve analysis was used to identify optimal NLR cut-off values, thus those affording the maximal sensitivity and