European Review for Medical and Pharmacological Sciences 2015; 19: 3234-3240

Neutrophil-to-lymphocyte ratio in obstructive sleep apnea; a multi center, retrospective study

N. ALTINTAS[1,2], E. ÇETINOĞLU[3], M. YUCEEGE[4], A.N. ACET[3], A. URSAVAS[3], H. FIRAT[4], M. KARADAG[3]

[1]Department of Pulmonary and Sleep Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[2]Department of Pulmonary and Sleep Medicine, Tekirdag University, Tekirdag, Turkey
[3]Department of Pulmonary and Sleep Medicine, Uludag University, Uludag, Turkey
[4]Department of Pulmonary and Sleep Medicine, Diskapi Research and Education Hospital, Ankara, Turkey

Abstract. – OBJECTIVE: Systemic inflammation is important in pathophysiology of obstructive sleep apnea (OSA) and its comorbidity. Neutrophil to lymphocyte ratio (N/L ratio) is a novel inflammation index that has been shown to independently predict poor clinical outcomes. In this study, we aimed to evaluate the role of N/L ratio in OSA patients and comparing with other well-known inflammatory marker, C-reactive protein (CRP).

PATIENTS AND METHODS: We conducted a retrospective analysis of 481 patients with mild, moderate and severe OSA (163,158 and 160 patients, respectively) and leukocyte profiles of 80 sex-, age- and body mass index- matched healthy controls. Patients were excluded if they had underlying cancer, chronic inflammatory disease, any systemic infection, uncontrolled hypertension and diabetes mellitus, a known acute coronary syndrome, valvular heart disease, a known thyroid, renal or hepatic dysfunction.

RESULTS: We found that N/L Ratio in severe OSA patients was significantly higher compared with mild, moderate, OSA patients and healthy controls ($p < 0.001$). However, there was no difference between mild and moderate OSA patients ($p = 0.636$). There was also no significant difference between mild-moderate OSA patients and healthy groups ($p = 0.150$). CRP levels were not different in all OSA stages ($p = 0.595$). By Spearman correlation, there was no correlation between CRP and N/L ratio.

CONCLUSIONS: N/L ratio, which is quick, cheap, easily measurable novel inflammatory marker with routine complete blood count analysis, is a surrogate marker of obstructive sleep apnea severity.

Key Words:
C-reactive protein, Inflammation, Neutrophil/lymphocyte ratio, Obstructive sleep apnea.

Introduction

Obstructive sleep apnea (OSA) is a common disease that affects 3-7% of the middle-aged population (30-70 years) and becomes more prevalent with age[1]. OSA is characterized by repetitive episodes of cessation or limitation of airflow which result in intermittent nocturnal hypoxia and sleep fragmentation[2,3].

Systemic inflammation and oxidative stress are both important in the pathophysiology of OSA and its comorbidity. A potential mechanism involved is intermittent nocturnal hypoxemia produces a decline in oxygen levels followed by reoxygenation when breathing resumes. The cyclical episodes of hypoxia-reoxygenation, analogous to cardiac ischemia/reoxygenation injury causing ATP depletion and xanthine oxidase activation, and increases the generation of oxygen-derived free radicals and, therefore, cause local and systemic inflammation[4,5]. In a recent study[6], OSA patients showed a significant increase in levels of systemic inflammatory mediators such as interleukin-8 (IL-8) and intercellular adhesion molecule-1 (ICAM-1) in both plasma and exhaled condensate. In addition, they showed a higher neutrophil percentage in induced sputum. These findings were significantly and positively correlated to AHI; however, CPAP-therapy did have a significant effect[7].

Systemic inflammation can be measured by using a variety of biochemical and hematological markers. Although novel disease-specific biomarkers have been identified, most of which are time consuming and expensive. Blood neutrophil to lymphocyte (N/L) ratio is an easily accessible and reliable marker of subclinical inflammation

Corresponding Author: Nejat Altintas, MD; e-mail: nejataltintas@gmail.com

that can be easily obtained from the differential white blood cell count. This ratio integrates information on two different immune pathways – the neutrophils that are responsible for ongoing inflammation and the lymphocytes that represent the regulatory pathway[8,9].

In recent years, there have been some studies investigating the potential role of leukocyte subtypes' ratios during the inflammatory process of chronic diseases[10-12]. However, to the best of our knowledge, the N/L ratio in OSA patients has not been investigated so far. It has been demonstrated in an animal model that apnea and hypoxemia trigger systemic inflammation by inducing changes in the leukocyte function in OSA patients and we assumed that a higher N/L ratio may be found in OSA patients with more advanced disease[13,14]. Therefore, the aim of the current study is to clarify the role of the N/L ratio in OSA patients and to evaluate whether this inexpensive, readily- measurable laboratory marker can be used as a surrogate marker of systemic inflammation in this patient population.

Patients and Methods

Patient Population

A retrospective analysis of patients diagnosed as OSA with level-1 polysomnography (PSG) at two tertiary hospitals and a university hospital from January 2013 through April 2014 was performed. Differential blood count of healthy controls- who were community residents presented for their yearly physical examinations, and had no specific complaints or illness requiring treatment- were evaluated. Patients were excluded if they had underlying cancer, chronic inflammatory disease, any systemic infection, uncontrolled hypertension and diabetes mellitus, a known acute coronary syndromes, valvular heart disease, a known thyroid, renal or hepatic dysfunction and ongoing steroid or pegylated interferon, nucleoside analogue therapy[15]. Smoker patients were also excluded from the study[16]. The patients' clinical and demographic data, including age, sex, body mass index (BMI), predisposing factors, and comorbid conditions were noted.

Blood Samples

Data on blood cell counts were extracted in a retrospective fashion from the medical records. All white blood cell and differential counts were taken prior to sleep study. Total leukocyte count and its subtypes, including neutrophil, lymphocyte, and monocyte absolute counts, were analyzed using an automated blood cell counter (cell-dyn 3700; Abbott Laboratories, abbott Park, IL, USA and Sysmex XE-2100; Sysmex Corp., Kobe, Japan). Serum levels of C-reactive protein (CRP) were measured by immunonephelometry (IMMAGE Nephelometer; Beckman Coulter, Fullerton, CA, USA). The N/L ratio was defined as the absolute count of neutrophils divided by the absolute count of lymphocytes determined from the full blood count. Control blood samples taken from healthy individuals at the time of the study were also evaluated.

Sleep Study

All participants underwent full polysomnography (Compumedics P-series sleep system; Compumedics sleep, Melbourne, Victoria, Australia and Somnosecreen plus; Somnomedics, Randersacker, Germany). At least 6-h PSG data were recorded. PSG recordings included 6-channel electroencephalography, 2-channel electrooculography, 2-channel submental electromyography, oxygen saturation by an oximeter finger probe, respiratory movements via chest and abdominal belts, airflow both via nasal pressure sensor and oro-nasal thermistor, electrocardiography, and leg movements via both tibial anterolateral electrodes. Sleep stages were scored in 30-s epochs by a certified registered polysomnographic technologist according to the criteria of the American Academia of Sleep Medicine[17]. Apneas were defined as decrements in airflow ≥ 90% from baseline for ≥ 10 seconds using an oronasal thermal sensor. Hypopneas were defined as a 30% or greater decrease in flow lasting at least 10 seconds using a nasal cannula pressure transducer and associated with a 3% or greater oxyhemoglobin desaturation or associated with an arousal. The number of apneas and hypopneas per hour of sleep was calculated to obtain the apnea-hypopnea index (AHI). The oxygen desaturation index (ODI) was defined as the total numbers of episodes of oxyhemoglobin desaturation ≥ 3% from the immediate baseline, ≥ 10 s but < 3 min, divided by the total sleep time. OSA severity was assessed as mild, moderate, and severe according to the AHI values of 5-14, 15-29, and more than 30, respectively[17].

Ethical Committee

The study complied with the Declaration of Helsinki and was approved by the Ethics Com-

mittee of the Okmeydani Research Hospital Ethical Committee number = 2014 04.11.241 and waived the requirement for informed consent.

Statistical Analysis

Descriptive statistics were computed for all factors. Continuous variables were presented as mean (standard deviation) or median (25^{th}, 75^{th} percentiles) and categorical variables as frequency (percentage). For comparisons among groups, the chi-square test (or Fisher's exact test when any expected cell count was < 5 for a 2 × 2 table) was used for categorical variables and the unpaired Student's *t* test or the Mann-Whitney rank sum test for continuous variables after testing for normality which was performed using histograms and the Shapiro-Wilk test). If tests of normality were met, One way Analysis of Variance (ANOVA) were used to compare more than two groups; the cutoff level of error was reduced to 0.05/(number of tests) (Bonferroni correction), and the Kruskal-Wallis test was used when tests of normality failed. Bivariate relationships between variables were determined by Pearson's or Spearman rank correlation coefficients (rho).

Receiver operating characteristics curve (ROC) analysis was used to evaluate the role of N/L ratio in distinguishing subjects with severe OSA. Cutoff value that maximized both sensitivity and specificity were chosen. Two-sided *p* values <0.05 were considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences for Mac version 20.0 (SPSS Inc., Chicago, IL, USA; serial number = 10229569).

Results

The hospital records of 481 patients with mild, moderate and severe OSA (163,158 and 160 patients, respectively) and leukocyte profiles of 80 sex-, age- and BMI- matched healthy control subjects were evaluated. The characteristics and laboratory findings of involved subjects stratified by OSA severity are given in Table I. There was no statistical difference between the groups with respect to age, sex and BMI. As expected, AHI and desaturation index increased progressively with the severity of disease. The current findings indicated that the N/L Ratio in severe OSA patients was significantly higher than in mild or moderate OSA patients and healthy controls ($p < 0.001$). However, there was no significant difference between mild and moderate OSA patients ($p = 0.636$). We created a new group (mild-moderate group) by combining mild and moderate groups, since there was no significant difference between these two groups. However, N/L ratio in severe OSA patients was also significantly higher than the new mild-moderate group ($p < 0.001$). N/L ratio in the new mild-moderate group was not different from the healthy group ($p = 0.150$) (Figure 1).

By Spearman correlation, there was no correlation between CRP and BMI (r = 0.014, $p = 0.757$) or AHI (r = 0.046, $p = 0.293$). CRP levels were the same in all OSA stages ($p = 0.595$) (Table I).

Using an obstructive AHI ≥30 event/hour on PSG as the cut-off[17], the best N/L ratio to find patients with severe OSA was calculated with

Table I. Characteristics, laboratory findings of study groups.

Number	Healthy control	OSA patients 5 ≤ AHI < 15	OSA patients 15 ≤ AHI < 30	OSA patients 30 ≤ AHI	*p*
Number	80	163	158	160	
Age, year, mean (SD)	47.3 (10.8)	48.9 (12.8)	48.3 (10.8)	48.9 (10.5)	0.709†
Sex, male, n (%)	56 (70)	90 (73)	111 (70)	110 (69)	0.880§
BMI, mean (SD)	32.5 (7.8)	32.4 (7.3)	32.6 (8.4)	34.3 (7.5)	0.130†
Laboratory findings					
Leukocyte, × 10^3 µl	3.34 (3.01-3.62)	3.37 (3.03-3.69)	3.32 (2.96-3.67)	4.29 (4.05-4.48)	< 0.001‡
Neutrophil, ×10^3 µl	2.11 (1.84-2.41)	2.14 (1.87-2.45)	2.02 (1.72-2.31)	1.80 (1.59-1.97)	< 0.001‡
N/L ratio	1.52 (1.16-1.78)	1.54 (1.25-1.84)	1.63 (1.30-2.05)	2.37 (2.01-2.86)	< 0.001‡
CRP, mg/dl	NA	5.62 (3.37-9.45)	5.43 (3.38-9.15)	5.63 (2.48-9.14)	0.595‡
AHI, mean (SD)	NA	9.83 (2.66)	21.44 (4.46)	62.80 (25.01)	< 0.001†
Desaturation index	NA	3.45 (2.30-5.95)	12.60 (9.5-17.4)	47.95 (26.59-84.48)	< 0.001‡

BMI, body mass index; CRP, C-reactive protein; N/L ratio, neutrophil-lymphocyte ratio; AHI, apnea-hypoapnea index; NA, Not applicable. Data are median (25^{th}-75^{th} percentiles) unless otherwise indicated. †One-way analysis of variance (ANOVA). §Chi-square test. ‡Kruskal-Wallis test.

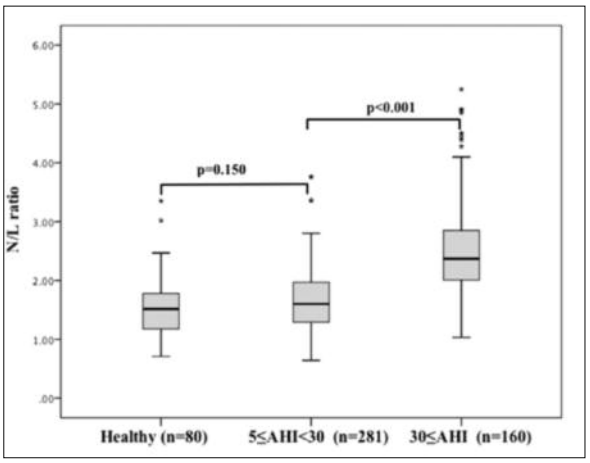

Figure 1. Neutrophil-lymphocyte ratio in the three study groups; severe OSA group, combined mild-moderate OSA group and healthy controls. OSA, obstructive sleep apnea.

the receiver operator curve analysis. The area under curve (AUC) was 0.840 (95% confidence interval 0.790-0.880, $p < 0.001$). The cut-off level for N/L ratio with optimal sensitivity and specificity was calculated as 1.85 with sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 85%, 71%, 62%, 89%, and 76%, respectively (Figure 2).

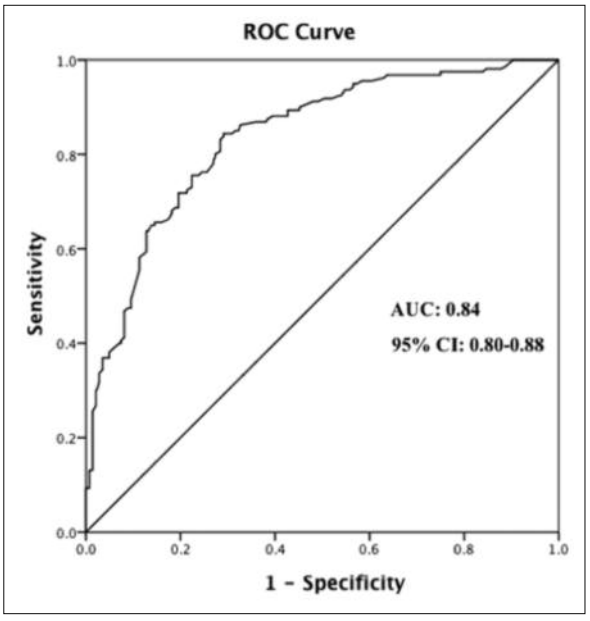

Figure 2. Receiver operating characteristic curves of neutrophil-to-lymphocyte ratio (N/L ratio), for predicting severe obstructive sleep apnea patients. AUC, area under the curve.

Discussion

The main findings of our study were as follows; severe OSA patients had a higher N/L ratio than both mild, moderate OSA patients as well as healthy controls. N/L ratio was not significantly changed in mild or moderate OSA patients, or healthy controls. Finally, CRP levels were the same in all OSA severities.

The N/L ratio is a combination of two independent markers of inflammation; neutrophils as a marker of the ongoing nonspecific inflammation, and lymphocytes as a marker of the regulatory pathway[18]. Recent evidence suggests that the ratio of the neutrophil count-to-lymphocyte count ensures a higher predictive value than the standalone leukocyte differential, because by itself it can reveal, in a synergetic manner, more about disease severity[19].

Obstructive sleep apnea involves sleep fragmentation, tonic elevation of sympathetic neural activity, oxidative stress and inflammation[20]. Elevation of the plasma norepinephrine level reflects activation of the sympathetic nervous system in response to systemic stress. The stress response is also manifested by an elevation of serum cortisol. However, the physiological diurnal variation in plasma cortisol levels, their short half-life, and their pulsatile pattern of secretion, render these levels difficult to use in a clinical setting. Increased cortisol levels result in a decrease in the relative concentration of lymphocytes[9]. Furthermore Horne et al[21] reported that relatively low lymphocyte count was associated with worse clinical outcome.

It has been demonstrated in an animal model that apnea and hypoxemia trigger systemic inflammation by inducing changes in the leukocyte function[14]. Neutrophils are the front-line defensive cells of the immune system. However, uncontrolled release of their formidable array of toxic substances (i.e. reactive oxygen metabolites, inflammatory cytokines, lipid mediators, antibacterial peptides, and tissue-damaging enzymes) may inflict damage to surrounding tissues and propagate inflammatory responses[22]. An increase of neutrophils was shown in OSA patients[23]. But the reason why neutrophils are increased in airways of OSA patients remains unclear. However, even if different mechanisms could be involved, the common hypothesis is that this phenomenon is secondary to intermittent hypoxia[24]. The combination of these two markers (neutrophil count-to-lymphocyte count) has been

proven to be the most powerful simple leukocyte count predictor[21]. Accordingly, in the current study, neutrophil levels were increased; lymphocyte levels were decreased with disease severity so that N/L ratio was significantly increased in severe OSA patients. However N/L ratio remained the same in mild, moderate and healthy controls.

Obstructive sleep apnea is associated with a variety of adverse consequences, including daytime sleepiness, increased cardiovascular morbidity and mortality, impairment of cognitive function, motor vehicle collisions, and reduced quality of life[25,26]. Despite adverse consequences, it is estimated that most individuals with OSA neither receive a diagnosis nor treatment, suggesting that current resources may be inadequate to meet growing demands[27]. Therefore, predicting high-risk patients and giving priority to them in sleep laboratories could decrease morbidity. Neutrophil-to-lymphocyte ratio is an inexpensive, readily available and reproducible test that has prognostic and predictive values in systemic inflammatory diseases such as cardiovascular diseases, kidney diseases, liver disease, inflammatory bowel diseases and chronic obstructive pulmonary disease (COPD)[10,28,29]. To the best of our knowledge, this is the first clinical study to demonstrate the increased levels of N/L ratio in severe OSA patients. In this study, we provided a cut-off value of 1.85 for N/L ratio, derived from receiver-operating characteristic curve analysis. The ROC analysis indicated that the AUC of the N/L ratio was significantly high in predicting severe OSA patients with sensitivity, specificity, PPV, NPV and diagnostic accuracy of 85%, 71%, 62%, 89%, and 76%, respectively. Therefore, our results suggest that the N/L ratio at admission may contribute additional data for early risk stratification of patients with OSA.

In the study, N/L ratio was not significantly different in mild and moderate OSA patients and healthy controls. These findings suggest that a more substantial or a different pattern of hypoxemia might be necessary to activate systemic inflammation, that the system may need to be primed before hypoxic exposure, or that increases in inflammatory markers. OSA patients may be more related to other factors such as nocturnal arousal.

C-reactive protein is believed to be a biomarker of inflammation. The association between OSA and CRP has been inconsistent, perhaps because CRP is also elevated in obese patients independent of OSA[30]. Studies comparing otherwise healthy obese men with and without OSA have found that OSA is associated with increased CRP levels after controlling for BMI in both adults and children[31]. On the other hand, another study comparing groups with different OSA severity matched for age and BMI and a fourth group of obese subjects with OSA matched in AHI to the severe OSA group found no increase in CRP in the three BMI-matched groups, whereas the obese group had higher CRP than the AHI-matched group, suggesting that the elevation in CRP was due to obesity and not OSA[32]. In the current study, we did not find any correlation between CRP levels and OSA severity. We believe that the strong relationship between CRP levels and obesity might have biased the results of various researches investigating CRP levels in adults with OSA. We did not find an association between N/L ratio and CRP. It is likely that there is a complex interaction of pro-inflammatory and anti-inflammatory proteins.

Previous works[33,34] have shown that both obesity and smoking are associated with chronic systemic inflammation and increased white cell count, and can induce migration of neutrophils from the intravascular compartment to peripheral tissue because of an increase in chemotactic and adhesion molecule activities. In the current study, smokers were excluded and patients were matched according to their BMI so that the effects of smoking and BMI were eliminated from the study, this is one of the powerful aspects of this report. Furthermore, low levels of N/L ratio in obese patients should be expected because obesity can lead to an increase in lymphocyte count compared with neutrophil count with the end result being a deceptively low N/L ratio[34].

This was a retrospective study and was subject to bias. However, we included a relatively well-characterized large group of patients from different city centers, all of whom underwent level I polysomnography. Moreover we used a cross-sectional design for this study, which is not the best design to investigate any causal relationships, although we performed adjustment for significant clinical variables, there remains the possibility of residual confounding from unmeasured variables. Our study was not designed to elucidate the mechanistic pathways that lead to higher N/L ratio in patients with OSA. Finally we did not measure cortisol level to confirm its elevation in association with a reduction of the relative lymphocyte count.

Despite these criticisms, we observed that individuals with severe OSA are significantly more likely to have higher level of systemic inflammation and N/L ratio seems a reasonable measure to detect this condition.

Conclusions

Neutrophil-lymphocyte ratio – which is calculated from complete blood count with differential – is an inexpensive, easy to obtain, widely available marker of inflammation that might, in combination with other markers, assist in identifying patients with severe OSA. Future researches are needed to show a significant fall in N/L ratio with effective continuous positive airway pressure (CPAP) therapy.

Ethical Approval

The study was approved by local Ethical Committee of Okmeydani Research Hospital. Ethical committee number = 2014 04.11.241.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Durán J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001; 163: 685-689.
2) Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328: 1230-1235.
3) Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. Ann Rev Med 1976; 27: 465-484.
4) Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, Naseem J, Loomba R. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. J Clin Sleep Med 2013; 9: 1003-1012.
5) Yoshikawa M, Yamauchi M, Fujita Y, Koyama N, Fukuoka A, Tamaki S, Yamamoto Y, Tomoda K, Kimura H. The impact of obstructive sleep apnea and nasal CPAP on circulating adiponectin levels. Lung 2014; 192: 289-295.
6) Carpagnano GE, Spanevello A, Sabato R, Depalo A, Palladino GP, Bergantino L, Foschino Barbaro MP. Systemic and airway inflammation in sleep apnea and obesity: the role of ICAM-1 and IL-8. Transl Res 2010; 155: 35-43.
7) Lacedonia D, Salerno FG, Carpagnano GE, Sabato R, Depalo A, Foschino-Barbaro MP. Effect of CPAP-therapy on bronchial and nasal inflammation in patients affected by obstructive sleep apnea syndrome. Rhinology 2011; 49: 232-237.
8) Avanzas P, Quiles J, López de Sá E, Sánchez A, Rubio R, García E, López-Sendón JL. Neutrophil count and infarct size in patients with acute myocardial infarction. Int J Cardiol 2004; 97: 155-156.
9) Ommen SR, Hodge DO, Rodeheffer RJ, McGregor CG, Thomson SP, Gibbons RJ. Predictive power of the relative lymphocyte concentration in patients with advanced heart failure. Circulation 1998; 97: 19-22.
10) Günay E, Sarinç Ula li S, Akar O, Ahsen A, Günay S, Koyuncu T, Ünlü M. Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. Inflammation 2014; 37: 374-380.
11) Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med 2012; 5: 2.
12) Jankova L, Dent OF, Chan C, Chapuis P, Clarke SJ. Preoperative neutrophil/lymphocyte ratio predicts overall survival but does not predict recurrence or cancer-specific survival after curative resection of node-positive colorectal cancer. BMC Cancer 2013; 13: 442.
13) Nácher M, Serrano-Mollar A, Farré R, Panés J, Seguí J, Montserrat JM. Recurrent obstructive apneas trigger early systemic inflammation in a rat model of sleep apnea. Respir Physiol Neurobiol 2007; 155: 93-96.
14 Levy P, Pepin JL, Arnaud C, Tamisier R, Borel JC, Dematteis M, Godin-Ribuot D, Ribuot C. Intermittent hypoxia and sleep-disordered breathing: current concepts and perspectives. Eur Respir J 2008; 32: 1082-1095.
15) Balta S, Demirkol S, Unlu M, Arslan Z, Celik T. Neutrophil to lymphocyte ratio may be predict of mortality in all conditions. Br J Cancer 2013; 109: 3125-3126.
16) Yasue H, Hirai N, Mizuno Y, Harada E, Itoh T, Yoshimura M, Kugiyama K, Ogawa H. Low-grade inflammation, thrombogenicity, and atherogenic lipid profile in cigarette smokers. Circ J 2006; 70: 8-13.
17) Berry RB, Brooks R, Gamaldo CE, Marcus CL, Vaughn AL. for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.0. www.aasmnet.org, Darien, Illinois: American Academy of Sleep Medicine, 2012.
18) Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, Gobunsuy R, Jadonath S, Baldari D,

McCord D, Lafferty J. Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction. Am J Cardiol 2010; 106: 470-476.

19) Turak O, Özcan F, Ileyen A, Baar FN, Gül M, Yilmaz S, Sökmen E, Yüzgeçer H, Lafçi G, Topaloglu S, Aydogdu S. Usefulness of neutrophil-to-lymphocyte ratio to predict in-hospital outcomes in infective endocarditis. Can J Cardiol 2013; 29: 1672-1678.

20) Fava C, Montagnana M, Favaloro EJ, Guidi GC, Lippi G. Obstructive sleep apnea syndrome and cardiovascular diseases. Semin Thromb Hemost 2011; 37: 280-297.

21) Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, Renlund DG, Muhlestein JB, Intermountain Heart Collaborative Study Group. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005; 45: 1638-1643.

22) Dyugovskaya L, Polyakov A, Lavie P, Lavie L. Delayed neutrophil apoptosis in patients with sleep apnea. Am J Respir Crit Care Med 2008; 177: 544-554.

23) Shen Y, Qin Q, Xu Z, Shen K. Serum leukotrienes, circulating neutrophils, and high sensitivity C-reactive protein in Chinese children with sleep-disordered breathing. Int Immunopharmacol 2014; 22: 120-125.

24) Carpagnano GE, Lacedonia D, Foschino Barbaro MP. Non-invasive study of airways inflammation in sleep apnea patients. Sleep Med Rev 2011; 15: 317-326.

25) Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet 2009; 373: 82-93.

26) Herman J, Kafoa B, Wainiqolo I, Robinson E, McCaig E, Connor J, Jackson R, Ameratunga S. Driver sleepiness and risk of motor vehicle crash injuries: a population-based case control study in Fiji (TRIP 12). Injury 2014; 45: 586-591.

27) Rosen CL, Auckley D, Benca R, Foldvary-Schaefer N, Iber C, Kapur V, Rueschman M, Zee P, Redline S. A multisite randomized trial of portable sleep studies and positive airway pressure autotitration versus laboratory-based polysomnography for the diagnosis and treatment of obstructive sleep apnea: the HomePAP study. Sleep 2012; 35: 757-767.

28) Farah R, Khamisy-Farah R. Association of Neutrophil to Lymphocyte Ratio With Presence and Severity of Gastritis Due to Helicobacter pylori Infection. J Clin Lab Anal 2014; 28: 219-223.

29) Chen L, Lou Y, Chen Y, Yang J. Prognostic value of the neutrophil-to-lymphocyte ratio in patients with acute-on-chronic liver failure. Int J Clin Pract 2014; 68: 1034-1040.

30) Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? Thorax 2009; 64: 631-636.

31) Kosacka M, Korzeniewska A, Jankowska R. The evaluation of body composition, adiponectin, C-reactive protein and cholesterol levels in patients with obstructive sleep apnea syndrome. Adv Clin Exp Med 2013; 22: 817-824.

32) Ryan S, Nolan GM, Hannigan E, Cunningham S, Taylor C, McNicholas WT. Cardiovascular risk markers in obstructive sleep apnoea syndrome and correlation with obesity. Thorax 2007; 62: 509-514.

33) MacNee W, Wiggs B, Belzberg AS, Hogg JC. The effect of cigarette smoking on neutrophil kinetics in human lungs. N Engl J Med 1989; 321: 924-928.

34) Nieman DC, Henson DA, Nehlsen-Cannarella SL, Ekkens M, Utter AC, Butterworth DE, Fagoaga OR. Influence of obesity on immune function. J Am Diet Assoc 1999; 99: 294-299.