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Original Article

Associations Between Systemic Inflammatory Markers Based on Blood Cells and Polysomnographic Factors in Obstructive Sleep Apnea

Minju Kim[1] · Sung-Woo Cho[1] · Tae-Bin Won[1] · Chae-Seo Rhee[1,2] · Jeong-Whun Kim[1,2]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[2]Sensory Organ Research Institute, Seoul National University Medical Research Center, Seoul, Korea

Objectives. Systemic inflammation plays a key role in the pathogenesis of obstructive sleep apnea (OSA); however, easy-to-use methods to evaluate the severity of systemic inflammation have yet to be developed. This study investigated the association between systemic inflammation markers that could be derived from the complete blood count (CBC) profile and sleep parameters in a large number of patients with OSA.

Methods. Patients who visited our hospital's Otorhinolaryngology Sleep Clinic between January 2017 and April 2022 underwent polysomnography and routine laboratory tests, including a CBC. Associations between three systemic inflammatory markers—the systemic immune-inflammation index (SII), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR)—and polysomnographic and demographic factors including age, sex, body mass index, the apnea-hypopnea index (AHI), the hypopnea index (HI), lowest oxygen saturation (%), the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale, and percentages of non-rapid eye movement (REM) sleep stage 3, REM sleep, and snoring time were analyzed. The inflammation markers were compared among OSA subgroups, and associations were also analyzed in subgroups with different OSA severities.

Results. In total, 1,102 patients (968 men and 134 women) were included, and their mean AHI was 33.0±24.3. PSQI was significantly associated with SII (P=0.027). No independent significant factors were identified for the NLR or PLR. Within the simple snoring and mild OSA subgroups, no significant association was found between sleep parameters and the SII. In the severe OSA subgroup, the AHI (P=0.004) and PSQI (P=0.012) were independently associated with the SII.

Conclusion. Our study analyzed systemic inflammatory markers based on the CBC, a simple, relatively cost-effective test, and showed that the AHI and SII were significantly correlated only in the severe OSA subgroup.

Keywords. *Obstructive Sleep Apnea; Systemic Immune-Inflammation Index; Neutrophil-Lymphocyte Ratio; Platelet-Lymphocyte Ratio; Obstructive Sleep Apnea Severity*

INTRODUCTION

Obstructive sleep apnea (OSA) is defined as a collapse of the upper airway, resulting in hypoxemia, sleep disturbance, and systemic inflammation. Systemic inflammation may contribute to a higher risk of cardiovascular disease in patients with OSA [1]. A meta-analysis found higher levels of systemic inflammatory markers, including C-reactive protein (CRP), interleukin (IL)-6, IL-8, vascular endothelial growth factor, and tumor necrosis

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• Corresponding author: **Jeong-Whun Kim**
Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: +82-31-787-7409, Fax: +82-31-787-4057
Email: kimemails7@gmail.com

factor (TNF)-α, in patients with OSA [2]. Treatments for OSA, including positive airway pressure, tonsillectomy, and adenoidectomy in pediatric patients, have been reported to reduce inflammatory serum markers, including CRP [3,4].

Recently, the systemic immune-inflammation index (SII), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), which can be derived from neutrophil, platelet, and lymphocyte counts, have been used as inflammatory markers for several diseases. For example, SII elevation is associated with a worse prognosis in solid tumors, pulmonary embolism, cardiovascular diseases, and even coronavirus disease 2019 (COVID-19) infection [5-7]. A positive correlation was found between the SII and the severity of OSA in a small retrospective study [8]. Similarly, the NLR was reported to be elevated in OSA patients [9], and it decreased after continuous positive airway pressure therapy [10]. The PLR has been reported to be associated with OSA severity and concurrent hypertension [11]. In this study, we assessed the relationship between OSA severity and systemic inflammatory markers that can be derived from simple blood tests.

MATERIALS AND METHODS

Inclusion criteria

Patients who visited the Seoul National University Bundang Hospital Sleep Clinic between January 1, 2017 and April 1, 2022 and underwent polysomnography (PSG) and blood tests, including complete blood count, were included in this study. PSG and blood tests were conducted within 2 weeks interval. Patients diagnosed with central sleep apnea and those with systemic inflammatory diseases, including rheumatologic diseases, chronic infectious diseases, or malignant tumors, were excluded.

This study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (No. B-2210-785-101). Informed consent was waived due to the retrospective and anonymous nature of the study.

HIGHLIGHTS

- The study explored the association between sleep parameters and systemic inflammation markers in 1,102 patients with obstructive sleep apnea (OSA).
- The systemic immune-inflammation index (SII) was significantly correlated with the Pittsburgh Sleep Quality Index (P=0.027).
- In a subgroup analysis, no correlation was found between sleep parameters and SII in non-severe OSA.
- The apnea-hypopnea index was only associated with SII in the severe subgroup (P=0.004).

Polysomnography

All patients underwent a full-night in-laboratory PSG under the supervision of an experienced technician using an Embla N7000 recording system (Embla, Medcare) [12]. Parameters including electroencephalography, electrooculography, chin electromyography, lower leg electromyography, electrocardiography, lower limb, chest, and abdominal movements, nasal and oral airflow (thermistor), pulse oximetry, and body position were recorded. Based on the American Academy of Sleep Medicine (AASM) guidelines, the apnea index was defined as an absence of airflow for more than 10 seconds per hour, and the hypopnea index (HI) was defined as an over 50% decrease in airflow for at least 10 seconds or a moderate reduction in airflow for at least 10 seconds accompanied by arousals or oxygen desaturation >3% per hour [13,14]. Apnea-hypopnea index (AHI) was calculated as the sum of apnea index and HI [15,16].

Systemic immune-inflammation index

The SII was calculated as P×N/L (P, platelet counts per liter of peripheral blood; N, neutrophil counts per liter of peripheral blood; L, lymphocyte counts per liter of peripheral blood). The NLR was defined as the neutrophil count divided by the lymphocyte count, and PLR was defined as the platelet count divided by the lymphocyte count.

Classification of patients for subgroup analysis

Patients were classified into simple snoring (AHI <5), mild (5≤ AHI <15), moderate (15≤ AHI <30), and severe (30≤ AHI) OSA subgroups according to AHI.

Statistical analysis

Multiple linear regression was conducted to analyze the correlation between systemic inflammatory markers and general demographic and polysomnographic variables including age, gender, body mass index (BMI), AHI, HI, lowest oxygen saturation percentage, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale, and percentages of stage 3 non-rapid eye movement (REM) sleep (N_3), REM sleep, and snoring time. A mean value comparison test was performed to compare the values of the inflammatory markers between the different OSA severity groups. Subgroup analysis was performed to assess the correlation between the SII and the demographic and polysomnographic variables mentioned above. Statistical significance was set at P<0.05. IBM SPSS ver. 25 (IBM Corp.) was used in this study.

RESULTS

In total, 1,102 patients (968 men and 134 women) were included in the study. According to the AASM guidelines, 95 patients were simple snorers, 204 had mild OSA, 286 had moderate OSA, and 517 were diagnosed with severe OSA (Table 1). The propor-

tion of men was 73.7%, 85.3%, 85.0%, and 93.0% in the simple snoring, mild, moderate, and severe groups, respectively ($P<0.001$). The mean age was 38.4, 46.9, 48.0, and 47.1 years in the simple snoring, mild, moderate, and severe groups, respectively ($P<0.001$). The mean BMI was 23.8, 25.1, 26.0, and 28.4 kg/m^2 in the simple snoring, mild, moderate, and severe groups, respectively ($P<0.001$).

Polysomnographic characteristics affecting the SII, NLR, and PLR

There were no significant associations of sleep-related parameters with the SII, except for the PSQI ($P=0.027$). No independent significant polysomnographic factors were identified for the NLR or PLR (Table 2).

Differences in inflammatory markers according to OSA severity

We compared the levels of systemic inflammatory markers among the four OSA severity groups (Table 3). A comparison of mean values showed no significant differences in the SII ($P=0.371$) between the different OSA groups. Likewise, no significant difference was observed in the NLR ($P=0.803$) between the OSA subgroups. The PLR values tended to decrease with increasing OSA severity ($P=0.025$); however, a post hoc analysis showed no significant difference between the PLR values and the OSA severity groups.

Subgroup analysis

A subgroup analysis of the SII in different OSA subgroups showed that within the simple snorer and mild OSA subgroups, there was no significant correlation between sleep parameters and SII. The percentage of snoring time was associated with the SII ($P=0.041$) in the moderate-severity group and with the AHI ($P=0.004$) and PSQI ($P=0.012$) in the severe OSA group (Table 4). A subgroup analysis for different age, sex, and BMI groups did not show any significant parameters associated with the SII, PLR, and NLR.

Table 1. Polysomnography characteristics (n=1,102)

Variable	Value
Apnea-hypopnea index (/hr)	33.0±24.3 (6.0–88.0)
Hypopnea index (/hr)	12.1±9.7 (0.0–60.3)
Lowest arterial O_2 saturation (%)	79.8±8.6 (47.0–96.0)
Pittsburgh Sleep Quality Index	7.2±3.2 (0–21)
Epworth Sleepiness Scale	9.6±4.7 (0–27)
Stage 3 non-REM sleep (%)	9.0±7.0 (0.0–45.7)
REM sleep (%)	16.1±6.2 (0.0–14.5)
Snoring time (%)	25.5±19.2 (0.0–90.2)

Values are presented as mean±standard deviation (range).
REM, rapid eye movement.

Table 2. Factors affecting inflammatory markers

Variable	SII		NLR		PLR	
	β	*P*-value	β	*P*-value	β	*P*-value
Apnea-hypopnea index (/hr)	0.015	0.771	–0.008	0.879	–0.079	0.138
Hypopnea index (/hr)	0.028	0.441	0.035	0.342	–0.003	0.938
Lowest arterial O_2 saturation (%)	–0.086	0.067	–0.052	0.278	–0.082	0.085
Pittsburgh Sleep Quality Index	0.071	0.027*	0.059	0.075	0.047	0.151
Epworth Sleepiness Scale	–0.012	0.718	–0.019	0.568	0.008	0.801
Stage 3 non-REM sleep (%)	–0.011	0.747	–0.021	0.564	–0.027	0.446
REM sleep (%)	–0.008	0.810	–0.016	0.616	–0.002	0.959
Snoring time (%)	0.054	0.092	0.055	0.095	0.014	0.673

Adjusted for sex, age, and body mass index.
SII, systemic immune-inflammation index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; REM, rapid eye movement.
*Statistically significant, $P<0.05$.

Table 3. Comparison of SII, NLR, and PLR according to OSA severity

OSA severity	SII	NLR	PLR
Simple snoring (n=95)	415.24±260.39 (95.90–2,019.63)	1.56±0.79 (0.28–5.58)	123.63±41.92 (54.35–245.65)
Mild (n=204)	417.05±274.41 (73.97–2,993.08)	1.62±0.85 (0.54–7.69)	121.49±46.42 (43.77–437.65)
Moderate (n=286)	405.52±202.14 (123.86–1,785.08)	1.60±0.69 (0.38–6.03)	117.54±35.22 (47.63–265.92)
Severe (n=517)	436.80±264.90 (95.86–3,086.66)	1.64±0.82 (0.42–11.14)	113.45±39.03 (43.93–436.77)
P-value	0.371	0.803	0.025*
Total (n=1,102)	423.17±251.63	1.64±0.80	116.88±39.95

Values are presented as mean±standard deviation (range) or mean±standard deviation. Adjusted for sex, age, and body mass index.
SII, systemic immune-inflammation index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; OSA, obstructive sleep apnea.
*Statistically significant, $P<0.05$.

Table 4. Subgroup analysis for factors affecting SII in different OSA severity groups

Variable	Simple snoring (n=95)		Mild (n=204)		Moderate (n=286)		Severe (n=517)	
	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
Apnea-hypopnea index (hr)	–0.280	0.205	–0.020	0.810	–0.070	0.277	0.164	0.004*
Hypopnea index (hr)	0.010	0.963	0.055	0.553	0.049	0.452	0.092	0.050
Lowest arterial O_2 saturation (%)	–0.190	0.129	–0.010	0.953	–0.110	0.079	–0.070	0.201
Pittsburgh Sleep Quality Index	–0.050	0.696	0.006	0.942	0.017	0.794	0.118	0.012*
Epworth Sleepiness Scale	0.039	0.737	0.031	0.686	–0.060	0.357	–0.010	0.876
Stage 3 non-REM sleep (%)	0.207	0.053	0.046	0.530	–0.060	0.339	0.049	0.316
REM sleep (%)	–0.180	0.100	0.000	0.996	0.077	0.217	–0.000	0.975
Snoring time (%)	0.122	0.282	–0.050	0.494	0.125	0.041*	0.087	0.068

Adjusted for sex, age, and body mass index.
SII, systemic immune-inflammation index; OSA, obstructive sleep apnea; REM, rapid eye movement.
*Statistically significant, $P<0.05$.

DISCUSSION

Our study investigated the associations between OSA severity and systemic inflammatory markers that could be simply derived from blood cell counts, and we found that the SII was associated with AHI in severe OSA. Clinically, the impact of chronic systemic inflammation is important for assessing OSA complications, and exploring the value of inflammation markers derived from a simple complete blood count profile would be useful. Complete blood count analysis can be performed more quickly, easily, and cost-effectively than measuring inflammatory markers such as IL-6 or TNF-α in the serum. The SII, which was used in this study to assess systemic inflammation levels in patients with OSA, has been reported to be related to the prognosis of pulmonary embolism, coronary artery disease, solid tumors, and even COVID-19 infection [5-7,17].

A meta-analysis including 15 articles showed that higher SII values were associated with worse outcomes in many solid tumors, including hepatocellular carcinoma, urinary cancers, gastrointestinal tract cancers, and small-cell lung cancers [5]. In a retrospective study of 442 patients, the SII was associated with the severity and prognosis of acute pulmonary embolism [6]. Furthermore, a cohort study of 5,602 coronary artery disease patients after intervention showed that the SII had predictive value for major cardiovascular events, including myocardial infarction, stroke, and death [17]. As the inflammatory status is known to be related to the disease progression and comorbidities of OSA, we attempted to explore the relationship between the SII and the clinical condition of OSA patients. To our knowledge, there has only been one retrospective study regarding SII and OSA in a small group of 194 patients with OSA, and a positive correlation was noted between OSA severity and the SII, a positive correlation with the NLR, and an insignificant correlation with the PLR [8]. However, in the above-mentioned study, a subgroup analysis between the different OSA severity groups was not performed.

Our study, with a larger population including more than 1,000 OSA patients and blood tests that were drawn within a 2-week interval of PSG testing, showed that the PSQI was associated with the SII. The PSQI provides a general assessment of the subjective quality of sleep over a 1-month interval [18], and the association between the subjective sleep quality parameter PSQI and increasing levels of systemic inflammation has been reported before. In a study of 114 patients who underwent hemodialysis, patients with a PSQI >5 tended to have significantly higher serum CRP levels [19]. Higher PSQI scores were also positively correlated with serum CRP levels in a study of 281 postmenopausal women [20]. In our study, the SII was correlated with PSQI in the severe OSA subgroup, as well as the AHI, suggesting a relationship between impaired sleep quality and systemic inflammation in OSA. Among the various sleep variables used in this study, the PSQI was the only parameter that showed a significant correlation with SII. Therefore, assessing sleep quality in clinical settings might be important not only for patients' quality of life, but also for evaluating patients' systemic inflammation levels and the development of comorbidities of OSA.

The severity of OSA, represented by the AHI, is known to be associated with systemic inflammation [1,21]. The prevalence of comorbidities in severe OSA may increase because of the higher level of systemic inflammation. In a retrospective study of 1,119 patients, the NLR and PLR were reported to be significantly higher in OSA patients with chronic obstructive pulmonary disease, asthma, and congestive heart failure [22]. Similarly, a meta-analysis showed that the NLR was higher in patients with OSA than in normal controls [9] and decreased after continuous positive airway pressure [10]. The PLR has been reported to be lower in patients with OSA than in normal controls [23]. Our study showed a similar tendency, but no significant difference was found in the post hoc analysis. The limitations of this study include the fact that an individual's systemic inflammation status is affected by numerous variables that cannot be controlled. For example, the comorbidities and medication status of each individual were not included in the statistical analysis in this study. Furthermore, due to the retrospective nature of this study, other

systematic conditions of individuals that may affect the immune-inflammation system could not be fully considered when blood tests were conducted within a 2-week interval after PSG. In addition, systemic inflammatory markers of healthy subjects without any symptoms of OSA could not be explored since the study only included subjects who had visited a sleep clinic. Furthermore, the study was performed at a single center. Therefore, future studies in a more diverse population might be helpful to validate the results.

In conclusion, our study analyzed systemic inflammatory markers based on a simple, relatively cost-effective test (the complete blood count) and showed that the AHI increased as systemic inflammation reflected by the SII became more severe in the severe OSA subgroup. In the mild and moderate subgroups, increased AHI was not related to increased systemic inflammatory markers. This result might suggest that the role of systemic inflammation could be more important in OSA patients with a higher AHI than those with a lower AHI, and the severity of OSA might need to be over a certain level to provoke meaningful changes in systemic inflammation levels in patients with OSA. Further studies are needed to explore the relationship between increased systemic inflammation and OSA comorbidities, particularly in patients with severe OSA.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Minju Kim https://orcid.org/0000-0003-4612-7624
Sung-Woo Cho https://orcid.org/0000-0003-0827-4471
Tae-Bin Won https://orcid.org/0000-0003-2266-3975
Chae-Seo Rhee https://orcid.org/0000-0002-1361-8585
Jeong-Whun Kim https://orcid.org/0000-0003-4858-3316

AUTHOR CONTRIBUTIONS

Conceptualization: JWK. Methodology: JWK. Formal analysis: MK, SWC. Data curation: MK. Visualization: MK. Project administration: TBW. Writing–original draft: MK. Writing–review & editing: CSR, JWK.

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