ACH Med J
(2023) 3: 152-157
ISSN:2822-5872
Doi : 10.5505/achmedj.2023.58066

RESEARCH ARTICLE

Association of Systemic Immune-Inflammation Index with the Presence and Severity of Obstructive Sleep Apnea Syndrome

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Article Info

Received Date: 15.05.2023
Accepted Date: 13.06.2023

Keywords:

inflammation, OSAS, SII index

Abstract

Introduction: PThe systemic immune-inflammation (SII) index provides information about the inflammatory status. Therefore, in the present study, we aimed to show the role of the SII index in patients with OSAS.

Methods: Patients who were taken to a tertiary center for apnea, excessive daytime sleepiness, or snoring between May 2019 and December 2022 were analyzed. The SII index was calculated as follows: (neutrophil × platelet) / lymphocyte.

Results: The study included 300 OSAS patients with an apnea-hypopnea index (AHI) of over 5 according to PSG.A control group of 106 people with an AHI of less than 5 was also part of the study. OSAS patients were separated into three groups according to their AHI: mild (5 ≥ AHI < 15), moderate (15 ≥ AHI < 30), and severe (AHI ≥ 30). The SII index had a larger area under the ROC curve for the presence and severity of OSAS than other CBC parameters (AUC for AHI 5 = 0.733 and AHI 30 = 0.699). After adjustment, multivariable logistic regression analyses revealed that the SII index, age, and BMI were independent predictors of OSAS [ORs (CI 95%) = 1.053 (1.030-1.076); p<0.001, 1.009 (1.006-1.012); p<0.001 and 1.360 (1.244-1.487); p<0.001], respectively.

Conclusion: In our study, we showed that an increased SII index was associated with the presence and severity of OSAS. We believe that it can be used as a novel and important marker since the higher SII index provided relevant information regarding the presence and severity of OSAS patients.

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Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is defined by recurrent respiratory arrest brought on by repeated obstruction of the upper airway, resulting in a decrease in blood oxygen saturation during sleep.[1] It affects up to 5% of people.[2] The polysomnography (PSG) is the gold standard to determine OSAS patients.[3] OSAS is thought to have a role in the etiology of many systemic disorders, including neurologic and cardiovascular diseases.[4] The etiology of OSAS is yet unknown, but the role of inflammation in the upper airway is well-known.[5]

A simple and relatively cheap laboratory test, the complete blood count (CBC), is often used in routine clinical practice. This test is promising for learning more about a variety of diseases. In a number of studies, it has been observed that CBC parameters are helpful in order to assess inflammation and thrombotic risk. There are many studies investigating whether CBC indicators such as the neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), and white blood cell count/MPV ratio (WMR) alone or in any combination can be used to provide prognostic information for various diseases.[6-10] Furthermore, several CBC parameters, such as NLR, PLR, and WMR, were evaluated in OSAS patients and provided valuable information about the prognosis of the disease.[6, 7, 9, 10]

The systemic immune-inflammation (SII) index is a novel predictor of adverse outcomes in various cancers.[11-14] Recent studies also show that the SII index may be utilized to predict the prognosis of cardiovascular diseases.[15,16] In addition, it has been demonstrated that the SII index outperformed other CBC indicators in predicting the prognosis of cardiovascular diseases since it contains more information about the inflammatory status.[15,16]

The association between the SII index and the presence and severity of OSAS has not been shown. Therefore, in the present study, we aimed to show the role of the SII index in patients with OSAS.

Material and Methods

Study Cohort

In the current retrospective cohort study, we analyzed the data of 710 patients admitted to Ankara City Hospital with complaints of witnessed apnea, snoring, and excessive daytime sleepiness between May 2019 and December 2022. A total of 304 patients were excluded from the study due to the following reasons: diabetes mellitus (n=51), active infection (n=31), history of acute coronary syndrome (n=21), history of chronic obstructive pulmonary disease (n=14), history of autoimmune or rheumatologic diseases (n=13), malignancy (n=8), and missing data (166).

Blood Samples

All patients' age, sex and body mass index (BMI) were recorded. Patients whose complete blood count data were available were included in the study. An automated blood cell counter (Beckman Coulter analyzer, California, USA) was used for measuring CBC parameters. The parameters that were measured were: white blood cells; neutrophils; lymphocytes; monocytes; platelets; and eosinophils. NLR, PLR, LMR, and ELR values were calculated by dividing related values by each other. The SII index was calculated as follows: (neutrophil×platelet) / lymphocyte.

Polysomnography

During spontaneous sleep, a full-night PSG (Alice 6 Model PSG - Philips Respironics, The Netherlands) was performed under the control of a sleep technician in sleep laboratory. Parameters including minimum oxygen saturation, oxygen desaturation index, sleep efficiency, the time in minutes spent in sleep with oxygen saturation below 90%, and the ratio of time in rapid eye movement (REM) to total sleep time were recorded. All data were manually scored by at least two independent Ear, Nose, and Throat (ENT) physicians according to the standard criteria set by the American Academy of Sleep Medicine. Apnea was defined as a cessation of airflow at the nose and mouth lasting at least 10 seconds. Hypopnea was defined as a 30% decrease in airflow for 10 seconds accompanied by a 3% decrease in oxygen saturation or an arousal. AHI was measured as the number of apneas and hypopneas per hour in the sleep test (PSG) performed during nighttime sleep. In total, 300 patients with OSAS [> 5 AHI as assessed by PSG] were included in the study. Additionally, 106 individuals with less than 5 AHI were included in the study as a control group. OSAS patients were separated into three groups: mild ($5 \geq AHI < 15$), moderate ($15 \geq AHI < 30$), and severe ($AHI \geq 30$).

Statistical Analyses

All statistical analyses were performed using Stata (version 17.0 MP; StataCorp). After the appropria-

te tests for the assessment of distribution, continuous variables were presented as mean and standard deviation (SD), and categorical variables were presented as the number of individuals and their percentage. The Student's t-test was used for two different groups. The Pearson correlation test was used to evaluate the association between the SII and AHI indices. Receiver operating characteristics (ROC) curve analysis was used to demonstrate the discriminative value of CBC parameters, including NLR, PLR, LMR, ELR, and SII index, in predicting the presence and severity of OSAS (for AHI ≥ 5 and 30). The area under the curve (AUC) was calculated for each parameter. A univariate logistic regression model was used to show significant predictors of OSAS patients, and then those with $p < 0.05$ were tested using a multivariable logistic regression model. The results of multivariable logistic regression analysis were presented as odds ratios (OR) with lower and upper 95% confidence intervals (95% CIs) of independent predictors of OSAS patients. Finally, a nomogram containing significant predictors was plotted as a graph. A p-value of < 0.05 was considered significant in all the statistical analyses.

Results

As shown in Table 1, in total, the study population consisted of 406 individuals. A total of 300 patients consisted of 114 (38.0%) females and 186 males (62.0%) in the OSAS group. The control group consisted of 106 people, 34 (32.1%) of whom were female and 72 (67.9%) of whom were male. The mean (SD) ages of the patients and control groups were 49.2 (10.4) and 38.4 (12.6) years, respectively. While the mean BMI of the OSAS group was 30.8 (4.6), it was 26.5 (3.4) in the control group (p<0.001). Furthermore, when compared to the control group, neutrophil count, NLR, PLR, SII index, and ELR were significantly higher in the OSAS group (p = 0.002, p = 0.001, p = 0.001, p = 0.046, respectively).

Table 1. Baseline characteristics and laboratory markers of study population according to control and OSAS Patients

	Overall N=406	Control (<5) N=106	OSAS (≥5) N=300	p-value
Age, years	46.4 (12.0)	38.4 (12.6)	49.2 (10.4)	<0.001
Male, (%)	258 (63.5%)	72 (67.9%)	186 (62.0%)	0.28
Body Mass Index, kg/m2	29.7 (4.7)	26.5 (3.4)	30.8 (4.6)	<0.001
White Blood Cell, (mm3)	7814.0 (1856.7)	7530.2 (1627.0)	7914.3 (1923.8)	0.067
Neutrophil, (mm3)	4508.0 (1421.6)	4149.1 (1055.0)	4634.8 (1511.5)	0.002
Lymphocyte, (mm3)	2480.0 (639.3)	2549.1 (624.5)	2455.7 (643.8)	0.20
Monocyte, (mm3)	595.4 (338.0)	550.9 (106.2)	611.1 (387.1)	0.12
Eosinophil, (mm3)	205.3 (198.4)	188.7 (136.2)	211.1 (216.1)	0.32
Systemic Immune Inflammatory Index	486.7 (284.9)	391.2 (111.8)	520.5 (318.1)	<0.001
Neutrophil Lymphocyte Ratio	1.9 (0.8)	1.7 (0.4)	2.0 (0.9)	<0.001
Platelet Lymphocyte Ratio	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	<0.001
Lymphocyte Monocyte Ratio	4.5 (1.4)	4.7 (0.9)	4.5 (1.5)	0.24
Eosinophil Lymphocyte Ratio	0.1 (0.1)	0.1 (0.0)	0.1 (0.1)	0.046

Figure 1 shows a statistically significant and positive correlation was found between the SII index and AHI as well as the SII index and severity of OSAS (p < 0.001; r = 0.370 and p < 0.001; r = 0.298, respectively).

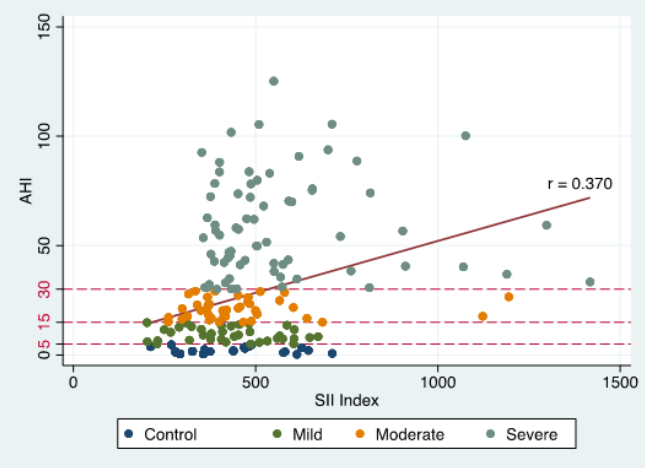


Figure 1. Correlation between the SII index and AHI

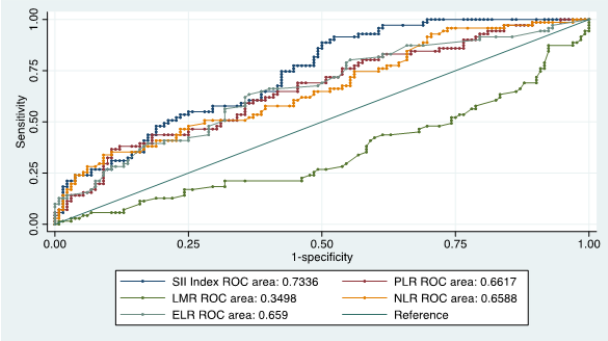
As shown in Table 2, 72 patients had mild OSAS, 86 patients had moderate OSAS, and 142 patients had severe OSAS. According to the severity of OSAS, age (p<001), BMI (p<001), WBC (p=0.008), neutrophil (p<001), monocyte (p<001), eosinophil (p<001), SII index (p<001), PLR (p<001), LMR (p<001), ELR (p<001) were statistically significantly increased with an increasing degree of disease.

Table 2. Baseline characteristics, laboratory and PSG markers of study population according to severity of OSAS Patients

	Mild N=72	Moderate N=86	Severe N=142	p-value
Age, years	45.0 (8.6)	49.3 (9.7)	51.3 (11.0)	<0.001
Male, (%)	38 (52.8%)	60 (69.8%)	88 (62.0%)	0.11
Body Mass Index, kg/m2	29.0 (3.8)	29.7 (4.0)	32.4 (4.9)	<0.001
White Blood Cell, (mm3)	7486.1 (1667.8)	7764.9 (1915.3)	8222.0 (2008.5)	0.008
Neutrophil, (mm3)	4234.7 (1222.1)	4466.3 (1368.6)	4939.7 (1664.5)	<0.001
Lymphocyte, (mm3)	2517.2 (672.8)	2524.9 (618.6)	2382.5 (640.3)	0.16
Monocyte, (mm3)	551.1 (159.9)	554.7 (197.6)	675.8 (522.9)	0.006
Eosinophil, (mm3)	153.3 (109.8)	171.9 (97.3)	264.2 (285.9)	<0.001
Systemic Immune Inflammatory Index	428.4 (132.6)	456.1 (184.9)	606.2 (413.3)	<0.001
Neutrophil Lymphocyte Ratio	1.8 (0.6)	1.8 (0.5)	2.2 (1.1)	<0.001
Platelet Lymphocyte Ratio	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	<0.001
Lymphocyte Monocyte Ratio	4.8 (1.3)	4.9 (1.8)	4.1 (1.4)	<0.001
Eosinophil Lymphocyte Ratio	0.1 (0.0)	0.1 (0.0)	0.1 (0.1)	<0.001
Minimum Oxygen Saturation	85.0 (4.0)	81.8 (5.7)	70.8 (13.4)	<0.001
Oxygen Desaturation Index, (%)	8.1 (7.5)	18.7 (7.9)	56.6 (25.0)	<0.001
Sleep efficiency, (%)	78.5 (18.7)	80.8 (18.1)	81.9 (12.8)	0.34
Sleep with oxygen saturation below 90%, (min)	7.9 (29.4)	10.2 (16.3)	83.6 (100.5)	<0.001
Ratio of REM, (%)	17.6 (6.5)	16.9 (6.8)	16.6 (13.8)	0.81

When compared to other CBC parameters such as PLR, NLR, LMR, and ELR, the SII index had the highest discriminative value for the presence and severity of OSAS (AUC for AHI 5 = 0.733 and AUC for AHI 30 = 0.699). (Figure 2 A and B).

A



B

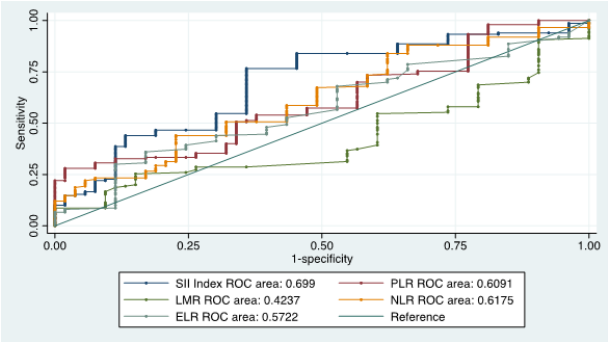


Figure 2. Receiver operating characteristics (ROC) curve analyses
2A Capable of discriminating the presence of OSAS (AHI ≥ 5)
2B Capable of discriminating the severity of OSAS (AHI ≥ 30

After adjustment, multivariable logistic regression analyses revealed that the SII index, age, and BMI were independent predictors of OSAS [ORs (CI 95%) = 1.053 (1.030-1.076), 1.009 (1.006-1.012), and 1.360 (1.244-1.487)], respectively. Using these parameters, we also created a new nomogram scale, as shown in Figure 3.

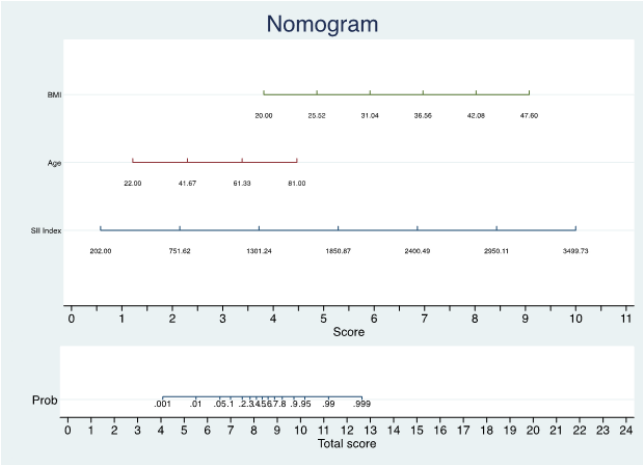


Figure 3. The nomogram of independently significant predictors of OSAS patients

Discussion

In this study, we found that the SII index, a routine marker that is easy to get and not too expensive, gave useful information about the presence and severity of OSAS in patients. Also, the SII index is better at telling people apart than CBC markers like PLR, NLR, LMR, and ELR.

OSAS is characterized by recurrent complete or partial collapse of the upper airway. Obstructions in the upper airway during sleep leading to hypoxemia, hypercapnia, autonomic nervous system changes, and sleep disruption are determinants in the development of OSAS. It can be said that genetic and environmental factors affect processes such as facial structure, collapsibility in the upper airway, body fat distribution, neurological control of the upper airway, central regulation of respiration, and the development of OSAS. The disease has a very complex pathophysiology, and the roles of contributing factors also vary among individuals with OSAS17.

Inflammation is increased in both the mucosal tissue and the muscular compartment in patients with OSAS. The vibration of snoring, intense activation of muscles during airway reopening, and increased oxidative stress associated with hypoxia-reoxygenation

are thought to be responsible for increased inflammation. In patients with OSAS, there is an increase in connective tissue, both in the upper respiratory tract mucosa and muscles. Changes in the connective tissue content in the upper respiratory tract cause changes in airway caliber and compliance18.

It has been suggested that inflammation plays a role in the development of many diseases19. Prior studies show stenosis in the uvulopalatal arch region in half of the patients with OSAS, and in the base of the tongue in the other half20. It has been shown by MRI that narrowing of the upper airway in patients with OSAS is associated with thickening of the lateral pharyngeal wall21. This wall thickening is characterized not only by an increase in pharyngeal fat tissue or an abnormality in the bony roof but also by an increase in soft tissue. Some of this swelling is edema due to inflammation.

In various studies, the increase in many biomarkers such as CRP, leptin, TNF-alpha, IL-6, vascular endothelial growth factor, and reactive oxygen radicals which are indicating that systemic inflammation is increased in OSAS22. In light of the above-mentioned, local and systemic inflammation have an important role in the development and severity of OSAS.

We speculate that several mechanisms may be responsible for the SII index being a stronger predictor of the presence and severity of OSAS than other CBC parameters. The SII index is more sensitive than neutrophils, lymphocytes, the NLR, and the PLR since it is caused by the combination of three different inflammatory parameters in a single combination. Single-component inflammatory markers, such as neutrophils, lymphocytes, or platelets, and two-component inflammatory markers, such as NLR or PLR, are relatively poor prognostic markers. Therefore, the SII index could be a more sensitive predictor of host immunological and inflammatory states.

In the current study, we found that BMI and age are also significant and independent predictors of the presence of OSAS23-24. Our findings were similar to prior studies. According to our multivariable logistic regression results, we created a nomogram using the SII index, age, and BMI. We believe that our nomogram can be used in routine clinical practice to predict the presence of OSAS, which can easily be used to provide prognostic information for ENT physicians.

Limitations

There are several limitations to the study. First, it is a retrospective and relatively single-center study. Second, alterations in parameters based on response were not analyzed. Finally, since the SII index is a novel biomarker in the field of OSAS, prospective, multicenter studies with a larger study population are needed.

Conclusions

In our study, we showed that an increased SII index was associated with the presence and severity of OSAS. There are few studies in the literature on this subject. In addition, we found that the SII index has a better informative value than other CBC parameters in patients with OSAS. We believe that it can be used as a novel and important marker since the higher SII index provided relevant information regarding the presence and severity of OSAS patients.

Ethics Statement:

Ankara City Hospital's local ethics committee approved the study. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki.

Funding: None

Conflict of Interest: None

Ethical Approval: Approved, no: E2-23-128

Informed consent: Yes

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