ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

Med J SDU / SDÜ Tıp Fak Derg ▶ 2020:27(4):455-461 doi: 10.17343/sdutfd.742573

PROGNOSTIC EVALUATION OF SYSTEMIC IMMUNE INFLAMMATION INDEX IN SUDDEN IDIOPATHIC SENSORINEURAL HEARING LOSS

ANİ İDİYOPATİK SENSORİNÖRAL İŞİTME KAYBINDA SİSTEMİK İMMÜN İNFLAMASYON İNDEKSİNİN PROGNOSTİK AÇIDAN DEĞERLENDİRİLMESİ

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Cite this article as: Kumbul YÇ, Yasan H, Tüz M, Okur E, Sivrice ME, Büyükçelik B. Prognostic Evaluation of Systemic Immune Inflammation Index in Sudden Idiopathic Sensorineural Hearing Loss. Med J SDU 2020; 27(4): 455-461.

Öz

Amaç
Bu çalışma, ani idiyopatik sensorinöral işitme kaybında (AİSNİK) sistemik immün inflamasyon indeksinin (SII) prognostik değerini araştırmayı hedeflemiştir.

Gereç ve Yöntem
AİSNİK tanısı almış 86 hasta çalışmaya dahil edildi. Hastalar hastaneye yatırıldığında tam kan sayımından SII hesaplandı. Hastalar rutin AİSNİK protokolümüze göre tedavi edildi. İşitmenin iyileşmesi Siegel kriterlerine göre değerlendirildi ve iki ana grup oluşturuldu (tam ve tam olmayan iyileşme grupları). Kontrol grubu işitme muayenesi için kliniğimize başvuran hastalardan oluşmaktaydı. Üç grup arasında SII'lar istatistiksel olarak analiz edildi (kontrol, tam iyileşme ve tam olmayan iyileşme grupları).

Bulgular
Üç grubun SII ortalamaları anlamlı olarak farklıydı (p = 0.002). Kontrol grubu diğer iki gruptan anlamlı olarak farklıydı (tam iyileşme grubu: p = 0.023, tam olmayan iyileşme grubu: p = 0.048). Tam iyileşme grubu ile tam olmayan iyileşme grubu arasında anlamlı fark yoktu (p = 0.950).

Sonuç
AİSNİK tanısı alan hastalarda SII'ın prognostik değeri yoktu. Bununla birlikte, SII'lar AİSNİK tanısı alan hasta gruplarında kontrol grubuna göre anlamlı olarak daha yüksekti. Bu bulgu AİSNİK'de SII'ın prediktif değerini desteklemektedir. AİSNİK'de SII'ın prediktif değerini göstermek için daha fazla katılımcının olduğu çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ani İşitme Kaybı; Biyomarkerlar; Prognoz; Etyoloji; İnflamasyon

Abstract

Objective
This study aimed to investigate the prognostic value of systemic immune inflammation index (SII) in sudden idiopathic sensorineural hearing loss (SISNHL).

Materials and Methods
Eighty-nine patients diagnosed with SISNHL were included in this study. SII was calculated from the complete blood count when the patients were hospitalised. The patients were treated in accordance with our routine SISNHL protocol. Hearing recovery was evaluated in accordance with Siegel's criteria, and

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Müracaat tarihi/Application Date: 27.05.2020 • Kabul tarihi/Accepted Date: 02.06.2020
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two main groups were created (complete and incomplete recovery groups). The control group consisted of patients who were admitted to our clinic for hearing examination. SIIs were statistically analysed amongst these three groups (control, complete recovery and incomplete recovery groups).

Results
The mean SII of the three groups significantly differed (p= 0.002). The control group significantly differed from the two other groups (complete recovery group: p= 0.023, incomplete recovery group: p= 0.048). The complete recovery group did not significantly differ from the incomplete recovery group (p= 0.950).

Conclusion
SII had no prognostic value in patients diagnosed with SISNHL. However, SIIs were significantly higher in the patient groups diagnosed with SISNHL than those in the control group. This finding supports the predictive value of SII in SISNHL. Studies with more participants are needed to demonstrate the predictive value of SII in SISNHL.

Keywords: Sudden Hearing Loss; Biomarkers; Prognosis; Aetiology; Inflammation

Introductıon

Sudden idiopathic sensorineural hearing loss (SISNHL) refers to the sensorineural hearing loss of at least 30 dB at three consecutive frequencies within 3 days without a clearly identified cause (1). The incidence of SISNHL is about 5–20 per 100,000 individuals (2). Although this disease is idiopathic, some aetiological factors are identified in clinical studies. These factors are viral infections, vascular insufficiency, vascular obstructions, inflammation and autoimmune and immunological diseases (3).

Some studies have demonstrated the association of SISNHL with chronic inflammation (4). Chronic inflammation has been shown to be an important risk factor in the development of microvascular damage and atherogenesis (5). Cochlear hair cells are highly sensitive to circulatory changes because of their high oxygen consumption and low tolerance to hypoxia. Vascular wall damage due to chronic inflammation is important in organs supplied from a single artery, such as the cochlea (6). Some rates of neutrophil, lymphocyte, monocyte and platelet counts (neutrophil lymphocyte ratio [NLR], platelet lymphocyte ratio [PLR], monocyte lymphocyte ratio [MLR] and lymphocyte monocyte ratio [LMR]) are widely used to predict the prognosis of diseases caused by chronic inflammation. Systemic immune inflammation index (SII) is an inflammatory marker (SII = N×P/L) calculated using neutrophil, lymphocyte and platelet counts. In 2014, Hu et al. developed SII to estimate the prognosis of patients after the curative resection of hepatocellular carcinoma (7). High SIIs are associated with poor prognosis in some cancer types. For example, hepatocellular carcinoma (7) , oesophageal squamous cell cancer (8), nasopharyngeal cancer (9) and oral cavity cancer (10). Our study aimed to investigate the prognostic value of SII in SISNHL.

Materıals and Methods

Patient Selection: The ethical committee of the institution approved the study protocol (date:25/06/2019, number:198) and the study was adhered to the Declaration of Helsinki. Informed consent was obtained from all participants. This retrospective study included patients aged between 18 and 65 years. The patients diagnosed with SISNHL and hospitalised in our clinic from June 2015 to June 2019 were analysed. SISNHL was diagnosed in accordance with the following criteria: sensorineural hearing loss of at least 30 dB at three consecutive frequencies within 3 days. Patients with any otological disease (chronic otitis media, Meniere's disease, barotrauma, etc.), patients with comorbidities (HT, DM, etc.), patients who used continuous medication for any disease, patients who did not come for a follow-up after treatment, patients with abnormal magnetic resonance findings were excluded from the study. The control group was created from patients who were admitted to the ENT outpatient clinic for hearing examination, whose hearing was within normal limits (pure tone average: 0–25 dB), who did not have any systemic diseases, who had no active infection and who did not use medications.

Evaluation, Treatment and Assessment
After otoscopic examination, pure tone audiometry (AC 40; Interacoustics, Middelfart, Denmark) was performed. Hearing thresholds were measured at 0.25, 0.5, 1, 2, 4 and 8 kHz frequencies in pure tone audiometry. Patients with normal otoscopic examination and diagnosed with SISNHL in accordance with pure tone audiometry were hospitalised and treated with standard treatment protocol. Intravenous methyl prednisolone sodium succinate was administered at 1

mg/kg for 3 days, and treatment was discontinued by reducing 10 mg of methyl prednisolone sodium succinate daily. The final pure tone audiometry was performed at least 4 weeks after diagnosis.

Pure tone averages at four frequencies (0.5, 1, 2 and 4 kHz) were used to determine treatment outcomes, which were assessed in accordance with Siegel's criteria (Table 1) (11). The following definitions were used: 'complete recovery' as the final hearing level of <25 dB, 'partial recovery' as the final hearing level of 25–45 dB with a hearing gain of ≥15 dB, 'slight recovery' as the final hearing of >45 dB with a hearing gain of ≥15 dB and 'no recovery' as the final hearing level of >75 dB with a hearing gain of <15 dB. For the statistical analysis 'partial recovery', 'slight recovery' and 'no recovery' groups were combined into an 'incomplete recovery' group. Two patients and one control group were obtained.

On day 1, the venous blood samples of patients with SISNHL were performed before the treatment started. The venous blood samples of the control group were performed when the patients were admitted to the outpatient clinic. Subsequently, neutrophil, platelet and lymphocyte counts were noted and SII was calculated on the basis of the complete blood count (CBC) of the groups with the following formula: N×P/L, where N, P and L represent the number of neutrophils, platelets and lymphocytes (The machine responsible for the CBC was the Beckman Coulter UniCel DxH 800 hematology analyser (Beckman Coulter, Brea, ABD)). Age, gender, side of hearing loss, pure tone averages before and after treatment, accompanying vestibular symptoms (tinnitus, fullness of the ear and dizziness), responses to treatment and SII means of the groups were analysed in this study.

Statistical Analysis

In descriptive findings, categorical variables were presented with percentage, and continuous variables were presented as mean ± standard deviation. Chi-square test was conducted on the basis of gender to determine the relationship between SISNHL and control groups. Parametric tests were performed to evaluate the mean of continuous variables between the groups because the number of people in each group was 30 and above. Therefore, the mean age of the patients in the SISNHL and control groups was evaluated with an independent sample t-test.

One-way ANOVA test was carried out to evaluate the difference between the means of the SII of complete recovery, incomplete recovery and control groups. Post hoc tests were performed to determine the group that caused the difference. Dunnett T3 test was chosen as the post hoc test because the variances were not homogeneous between groups. $p < 0.05$ was accepted as significant. Data analysis was performed using SPSS 24.0.

Results

In our study, 89 patients (50.9%) were in the SISNHL group, and 86 patients (49.1%) were in the control group. The SISNHL group comprised 35 female (39.3%) and 54 male (60.7%). The control group had 29 female (33.7%) and 57 male (66.3%). When the groups were compared in terms of age, the mean age of those diagnosed with SISNHL was 43.66 ± 14.14 years, and the mean age of the control group was 42.43 ± 13.59 years. The groups did not significantly differ in terms of gender and age (p= 0.442 and 0.558, respectively).

In the complete recovery group, the mean pure tone was found to be 33.82 ± 11.83 dB before treatment and 11.51 ± 6.52 dB after treatment. In the incomplete recovery group, the mean pure tones were 64.43 ± 23.30 dB before treatment and 53.06 ± 24.35 dB after treatment. In the SISNHL group, the right ear of 42 (47.2%) patients and the left ear of 47 (52.8%)

Table 1 Defining Siegel's criteria and dividing the SISNHL group into two main groups

Evaluation	Explanation	Group
Complete recovery	Final hearing level* is 25 dB or better regardless of the amount of gain	Complete recovery
Partial recovery	More than 15 dB hearing gain, and the final hearing is between 25 and 45 dB	Incomplete recovery
Slight recovery	More than 15 dB hearing gain, and the final hearing is 45 dB or worse	
No recovery	<15 dB hearing gain, and the final hearing is poorer than 75 dB	

*: Final hearing level: 0.5, 1, 2 and 4 kHz arithmetic mean

patients were affected. When the patients with SISNHL (89 patients) were evaluated in terms of vestibular symptoms, ear fullness was present in 10 patients, dizziness was observed in 9 patients, and tinnitus was detected in 45 patients (Table 2).

The means (10^3/μL) of neutrophils, platelets and lymphocytes in the control group were 4.41 ± 1.41, 247.96 ± 61.72, 2.26 ± 0.72, respectively. According to these values, the mean SII of the control group was 529.81 ± 307.22. Of the 89 patients in the SISNHL group, 48 (53.9%) and 41 (46.1%) were in the complete and incomplete recovery groups, respectively. The means (10^3/μL) of neutrophils, platelets and lymphocytes in the complete recovery group were 6.08 ± 3.49, 258.43 ± 65.79 and 2.09 ± 0.75, respectively. According to these values, the mean SII of the complete recovery group was 905.23 ± 908.71. The means (10^3/μL) of neutrophils, platelets and lymphocytes in the incomplete recovery group were 5.45 ± 2.62, 246.73 ± 63.52 and 1.91 ± 0.60, respectively. These values indicated that the mean SII of the incomplete recovery

Table 2 Descriptive characteristics of SISNHL and control groups

Variable	SISNHL (n:89)	Control (n:86)	p value
Gender Female Male	 35 (39.3%) 54 (60.7%)	 29 (33.7%) 57 (66.3%)	0.442
Age Mean±SD Min. Max.	 43.66±14.14 18 65	 42.43±13.59 18 65	0.558
Affected ear Right Left	 42 (47.2%) 47 (52.8%)		
Vestibular symptoms Tinnitus Fullness in the ear Dizziness	 45 (50.6%) 10 (11.2%) 9 (10.1%)		
Pure tone average Before treatment (dB±SD) After treatment (dB±SD)	**Complete recovery** (n: 48)* 33.82±11.83 11.51±6.52	**Incomplete recovery** (n: 41)* 64.43±23.30 53.06±24.35	

* The SISNHL group was divided into two main groups in accordance with Siegel's criteria.
p <0.05 was accepted as significant.

Table 3 Neutrophil, platelet, lymphocyte and SII means of the groups

CBC parameters (Mean±SD)	SISNHL (n: 89)		Control (n:86)	p value
	Complete recovery (n: 48)	Incomplete recovery (n: 41)		
Neutrophil (10^3/μL)	6.08±3.49	5.45±2.62	4.41±1.41	
Platelet (10^3/μL)	258.43±65.79	246.73±63.52	247.96±61.72	
Lymphocyte (10^3/μL)	2.09±0.75	1.91±0.60	2.26±0.72	
SII	905.23±908.71 *, †	822.45±722.15 *,‡	529.81±307.22 †, ‡	0.002

*, †, ‡ : Specifies comparison of each group pairs *: statistically insignificant †, ‡ : statistically significant
p < 0.05 was accepted as significant.

group was 822.45 ± 722.15. When the mean SIIs of the control group, the complete and incomplete recovery groups were compared, the results revealed statistically significant differences (p= 0.002). The control group was compared separately with the complete and incomplete recovery groups to find the difference between the groups, and the recovery groups differed from the control group (p= 0.023, 0.048, respectively). No statistically significant difference was found between the complete and incomplete recovery groups (p= 0.950; Table 3).

Discussion

SISNHL is one of the mysterious issues in ENT practice, so it has been widely explored. The most interesting issue is that whether a patient will benefit from treatments. Various studies have been conducted to determine the prognostic indicators and biomarkers of SISNHL. The use of clinics and findings of patients in these studies are common features. For example, parameters such as vertigo, hypertension, hyperlipidemia, DM, metabolic syndrome, advanced age, delayed treatment, vasculopathy, alcohol consumption and high-frequency hearing loss negatively affect prognosis (12-16). Young age and the presence of tinnitus positively influence the prognosis (17).

Studies on indices calculated using haematological parameters have been widely performed. These indices are used to predict prognosis of several diseases. They are important because they are calculated on the basis of the CBC of almost every patient. These indices are calculated with a simple, inexpensive and easy methods without any other intervention. SII was first used by Hu et al. to determine the prognosis of patients undergoing curative resection for hepatocellular cancer. Hu et al. set the cutoff value as 330 to distinguish between patients with good and poor prognosis. They found that values greater than 330 are associated with poor prognosis, and they showed that this new index can be used reliably and independently (7). In subsequent studies, Fest et al. claimed that SII is a strong and independent marker of a solid tumour that may occur in patients (18). Meng et al. compared the indices calculated from the CBC (NLR, PLR, MLR, LMR and SII) in healthy people. They showed that SII and PLR are not related with age and gender however NLR, LMR, MLR can be affected by age and gender. This study showed that SII is more reliable than other indices (19).

SII has been used in ENT studies, but almost all of these studies have been performed in malignancies. Deveci et al. studied NLR, MLR and SII biomarkers in patients diagnosed with laryngeal carcinoma. They found that all three biomarkers are higher in the laryngeal cancer group than in the control group. They also compared the same biomarker levels in laryngeal cancers at early and advanced stages; as a result, they observed a strong difference in SII (p<0.001). They reported that SII is a sensitive biomarker of perineural invasion and lymphatic involvement (20). Jiang et al. showed that SII is a more potent biomarker in nasopharyngeal cancer than NLR and MLR (9). Geng et al. showed that SII is an effective prognostic biomarker in oesophageal cancer (8). On the contrary, studies on SII associated with benign pathologies are limited. Fang et al. demonstrated that SII is effective in identifying the risk of developing osteoporotic fractures in postmenopausal patients (21). SII has been shown to be an effective indicator of the acute exacerbation of chronic obstructive pulmonary disease in patients with pulmonary hypertension (22).

Qiao et al. focused on the relationship between chronic inflammation and SISNHL. Chronic inflammation induced by bacteria or viruses causes microvascular damage and atherosclerosis. Hence, the risk of cochlear ischaemia increases. Chronic inflammation causes cochlear damage by inducing endocochlear immune responses, and this process ends with hearing loss. Therefore, increased NLR levels in patients with SISNHL suggest the chronic inflammation of the labyrinth artery (23). In recent studies, PLR is strongly correlated with peripheral arterial occlusion diseases, such as atherosclerosis and arterial thrombosis (24,25). High NLR and PLR are attributed to the low number of lymphocytes because of lymphocyte apoptosis in the early stage of inflammation (26). A high NLR indicates a high inflammation degree, whereas a high PLR indicates atherosclerosis (24). Conversely, NLR is affected by many factors, such as exercise, dehydration, age and gender (27). A SII biomarker covers NLR and PLR. Therefore, SII strongly demonstrates the presence of chronic inflammation and atherosclerosis. It is also not affected by some factors, such as NLR.

NLR, PLR and MLR are indices that have been widely studied in SISNHL. Özler found that NLR level is higher in patients with SISNHL than in control patients (28). Seo et al. showed that both NLR and PLR are higher in patients with SISNHL than in the control group (24). Qiao et al. demonstrated that NLR and PLR are appropriate, reliable and inexpensive prognostic indicators in SISNHL (23). Koçak et al. and Ulu et al. recommended the use of NLR and PLR indices in assessing the prognosis of SISNHL. They further reported that the use of these indices give more

meaningful results than their individual use. NLR and PLR represent two different immune pathways (29,30). SII can be reasonably used to simultaneously evaluate these two different immune pathways. In our study, when evaluating the prognosis of SISNHL, we decided to use SII, which simultaneously represents two different immune pathways. We believed that SII is a comprehensive and reliable parameter. We compared that SII biomarker values that were not previously studied in SISNHL in patient and control groups. We evaluated the prognostic feature of SII at different levels of hearing loss. In our study, the mean SIIs were 905.23 in patients with the complete recovery of SISNHL and 822.45 in patients with the incomplete recovery of SISNHL. The mean SII of our control group was 529.81. The mean SII of patients with SISNHL is higher than that of healthy individuals. However, when the SII means were compared in terms of the level of hearing improvement, SII had no prognostic significance.

Conclusion

We could not find any prognostic significance of SII, but SII was higher in patients with SISNHL than in the healthy group. This finding confirms the particular role of inflammation in the pathogenesis of SISNHL and supports the predictive value of SII in SISNHL. Studies with more participants are needed to demonstrate the predictive value of SII in SISNHL.

Acknowledgment: The authors wishes to thank Dr. Hanım Kumbul for her help with the statistical analysis.

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