

# Systemic Immune Inflammatory Index of Patients With Idiopathic Sudden Sensorineural Hearing Loss: Comparison of NLR and PRL Values

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## Introduction

Sudden sensorineural hearing loss (SSNHL) is sensorineural hearing loss of 30 dB or more in 3 consecutive frequencies within 3 days.<sup>1,2</sup> The incidence rate is 5 to 20/100 000. It is commonly seen after 40 years of age. A detailed history taking and physical examination should be done for the differential diagnosis. The etiology is unknown in 85% of cases. The identifiable causes of SSNHL include autoimmune inner ear diseases like Behçet disease, Cogan syndrome, and systemic lupus erythematosus (SLE); infections like meningitis, Lyme disease, and syphilis; some neoplasms like vestibular schwannoma or cerebellopontine angle (CPA) tumors; neurological diseases like migraine, multiple sclerosis, and pontine ischemia; ear diseases like Meniere disease and otosclerosis; some ototoxic drugs like aminoglycosides and chemotherapeutic agents; trauma; and vascular diseases such as sickle cell anemia. Cases with unknown etiology are defined as idiopathic sudden sensorineural hearing loss (ISSNHL), which has vascular, viral, and immune theories. However, its etiopathogenesis has not yet been clearly delineated. In previous studies, inflammation has been found to play a role in SSNHL.<sup>3–6</sup> Response to steroid therapy supports this theory. Clinical *in vitro* animal studies and human temporal bone studies support this etiology. For example, erythrocyte sedimentation rate is a nonspecific marker of inflammation. Erythrocyte sedimentation rate was found to be elevated in patient with ISSNHL in several studies<sup>7</sup>

The blood supply to the cochlea originates from 2 small terminal arteries with no collateral blood supply. Thus, the cochlea is susceptible to injury with even minor vascular changes. Idiopathic SSNHL could result from an acute vascular hemorrhage, occlusion by emboli, vascular diseases, vasospasm, or changes in blood viscosity.<sup>7</sup>

Recent studies have shown that the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) can be used as inflammatory markers. Previous studies reported

that these are useful prognostic factors for various malignant solid tumors, inflammatory conditions, and SSNHL.<sup>8,9–12</sup> A novel inflammatory index, the systemic immune inflammation index (SII), defined as  $SII = \text{platelets} \times \text{neutrophils/lymphocytes}$ , can serve as a prognostic marker for malignancies and inflammatory conditions. Lolli et al reported that the SII was a significant predictor of progression-free survival and overall survival in patients with cancer. Systemic immune inflammation index values significantly predicted clinical outcomes in patients with metastatic renal cell cancer treated with sunitinib and metastatic castration-resistant prostate cancer.<sup>13,14</sup>

In the literature, we did not find any studies delineating the correlation between ISSNHL and the SII. In this study, we therefore aimed to identify the possible diagnostic correlations between NLR, PLR, and a new novel index, SII, in ISSNHL.

## Materials and Methods

The study included patients of a university hospital from 2010 to 2019 diagnosed with and treated for ISSNHL. An age- and sex-matched healthy control group was also assembled. The study thus retrospectively reviewed 47 patients with ISSNHL and 50 control group patients.

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**Table 1.** Neutrophil, Lymphocyte, Platelet, SII, NLR, and PLR Values of Participants.

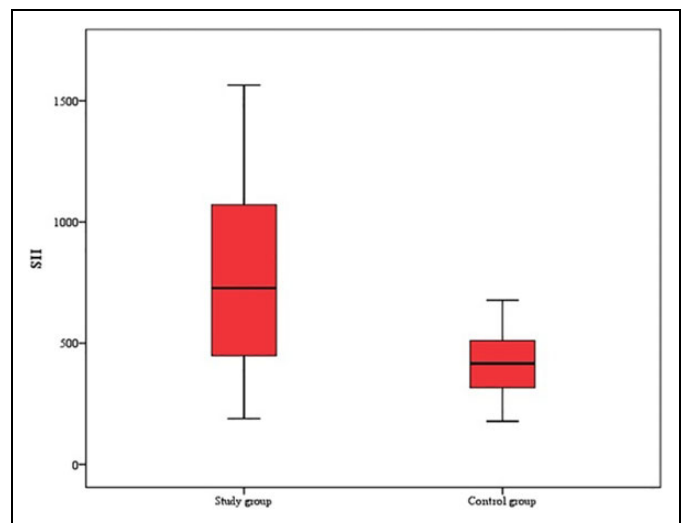
	Patients Median	(Min-Max)	Controls Median	(Min-Max)	P
Neutrophils	5.48	(2.50-13.20)	3.87	(1.80-14.90)	<.001
Platelets	246.00	(89.00-364.00)	253.00	(147.00-559.00)	.254
Lymphocytes	1.90	(0.73-4.51)	2.30	(1.06-5.05)	.002
SII	727.09	(188.46-3609.51)	416.75	(177.95-3187.71)	<.001
NLR	2.86	(1.08-11.46)	1.65	(0.79-5.84)	<.001
PLR	118.57	(39.31-438.36)	106.35	(39.55-232.34)	.097

Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ROC, receiver operator characteristic; SII, systemic immune inflammation index.

In the patient and control groups, the following exclusion criteria were applied: inner ear pathologies that might lead to SSNHL such as Meniere disease, autoimmune inner ear diseases, Cogan syndrome, SLE, otosyphilis, and other infectious agents like meningitis, HIV, Lyme disease, mumps, Mycoplasma, and toxoplasmosis; middle and inner ear pathologies such as acute otitis media, chronic otitis media, otosclerosis, temporal bone fractures, perilymphatic fistula, iatrogenic trauma/surgery, vestibular schwannoma, and CPA tumors; external ear pathologies such as external auditory canal osteoma, exocytosis, and otitis externa; ototoxic drugs like aminoglycosides or chemotherapeutic agents; salicylate usage; and neurological pathologies like migraine, multiple sclerosis, and pontine ischemia.

The control group was age- and sex-matched. In the control group, inflammatory conditions like autoimmune diseases and rheumatoid arthritis, diabetes mellitus, inflammatory bowel diseases, asthma, dermatitis, hepatitis, AIDS, and others were also excluded.

A complete blood count (CBC) was performed for all participants and contrast temporal magnetic resonance imaging was performed for the differential diagnosis of ISSNHL. Pure tone audiometry (PTA) hearing thresholds of the patients at 250, 500, 1000, 2000, 4000, and 8000 Hz were recorded. Pure tone audiometry was done at 3-day intervals. Audiological examinations were performed with an AC 40 instrument (Interacoustics). In the healthy control group, audiometry results were normal and all thresholds were below 20 dB. All patients with ISSNHL had hearing loss of a minimum of 30 dB at 3 consecutive frequencies. Audiometric patterns were assessed initially and after 1 month of treatment. Patients were evaluated according to their recovery after a month in the follow-up period. Patients were evaluated according to response to treatment and were divided into 2 groups as “recovered” and “unrecovered.” The recovered group had PTA values (dB) within 10-dB hearing levels (HLs) of the initial HL or within 10-dB HLs of the HL of the unaffected ear; the unrecovered group had less than 10-dB HL improvement relative to the initial HL after medical treatment.<sup>11</sup> The medical treatment of patients with ISSNHL was mainly based on corticosteroid treatment. All patients were treated with intravenous methylprednisolone tapered over a period of a minimum of 12 days. The initial dose was 1 mg/kg of methylprednisolone daily for 3 days, followed by a taper by 20 mg every 3 days.



**Figure 1.** The mean systemic immune inflammation index values of the patients and the control group. Systemic immune inflammation index values are significantly higher in the patient group ( $P < .001$ ).

Complete blood count parameters were analyzed with a hematology analyzer (Sysmex XE-2100, Sysmex Corporation), and hemoglobin, erythrocytes, leukocytes, neutrophils, lymphocytes, and platelet counts were measured, and PLR, NLR, and SII values were calculated.

The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. The Mann-Whitney  $U$  test was used for continuous variables without normal distribution. Spearman correlation analysis was used to assess the relationships. Receiver operator characteristic (ROC) curve analysis was used to determine the threshold value in disease prediction. A value of  $P < .05$  was accepted as significant. For statistical calculations, SPSS version 20.0 for Windows (IBM Corp) was used. Power analysis was performed to assess the validity of the study. The G\* Power 3.0 program was used for this assessment.

## Results

The study included 47 patients diagnosed with and treated for ISSNHL from 2010 to 2019 and 50 controls. These groups were matched for age and sex.

**Table 2.** ROC Curve Analysis and Sensitivity, Specificity, Positive (+) Predictive Values, and Negative (–) Predictive Values for Neutrophils, Lymphocytes, SII, and NLR.<sup>a</sup>

	Value	AUC	P	95% CI		Sensitivity (%)	Specificity (%)	+PV (%)	–PV (%)
				Lower	Upper				
Neutrophils	4.92	0.716	<.001	0.613	0.819	59.6	78.0	71.8	67.2
Lymphocytes	1.72	0.684	.002	0.577	0.791	46.1	86.0	75.9	63.2
SII	510	0.731	<.001	0.628	0.833	70.2	76.0	73.3	73.1
NLR	1.87	0.786	<.001	0.694	0.877	80.8	70.0	71.7	79.5

Abbreviations: AUC, area under the curve; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; ROC, receiver operator characteristic; SII, systemic immune inflammation index.

<sup>a</sup>Cutoff values were as follows: neutrophil count: 4.92, lymphocyte count: 1.72, SII value: 510, and NLR value: 1.87.

The mean age of the patient group was 48.94 years, while that of the control group was 47. The male to female ratio was 24:23 in the patient group and 25:25 in the control group.

The patient and control groups had similar distributions with regard to age and sex. Characteristic features and CBC results of the patient and control groups are summarized in Table 1. The SII values were significantly higher in the patient group ( $P < .001$ ). The mean NLR value was 2.86 for the patient group and 1.65 for the control group, which was statistically significant ( $P < .001$ ). Neutrophil count was significantly higher in the patient group ( $P < .001$ ). Lymphocyte count was significantly higher in the control group ( $P = .002$ ). The mean PLR values and platelet counts of the groups were not statistically significant (Figure 1).

Results of the ROC analysis of these values are presented in Table 2. In Table 2, the neutrophil counts, SII values, and NLR values of patients are seen to be higher than those of the control group. Lymphocyte counts in patients were found to be lower than those of the control group ( $P < .05$ ).

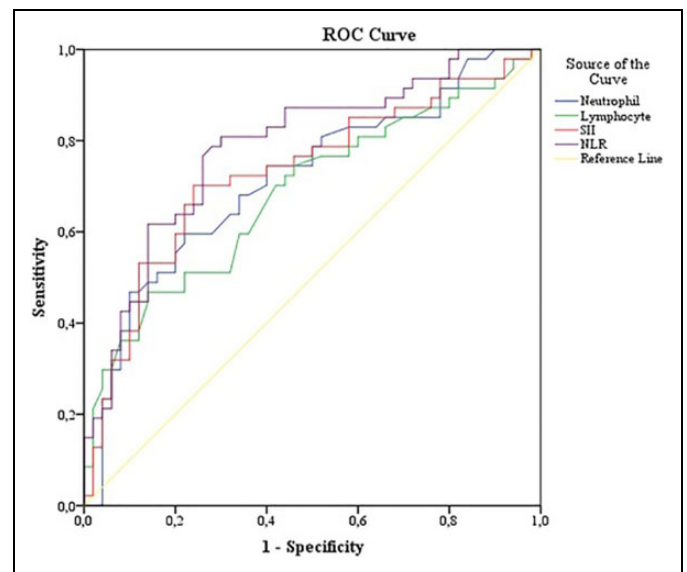
For the ROC curves, the area under the curve was highest for NLR and lowest for lymphocyte count. The cutoff value for SII was 510 and for NLR was 1.87. The SII value was 70% sensitive in patients with ISSNHL and 76% specific, and 73% positively predictive and 73% negatively predictive (Figure 2).

The correlation between neutrophil count and SII was strong and positive ( $\rho: .717, P < .001$ ), while the correlation between platelet count and SII was moderate and positive ( $\rho: .410, P < .001$ ).

The SII levels were higher in unrecovered patients compared with recovered ones, and this was statistically significant ( $P < .001$ ). There is not a threshold that divides SII scores between these groups.

All patients with ISSNHL had sensorineural hearing loss of more than 30 dB compared to the control group. In this study, we did not find any threshold shift above 30 dB between sensorineural hearing loss level and SII.

Post hoc power analysis was performed to assess the study. According to power analysis, our study has a sufficient power level for all values, except platelets (39%) and PLR (60%). The power analysis values of neutrophil count, lymphocyte count, SII, and NLR were  $\geq 80\%$ .

**Figure 2.** Receiver operator characteristic curves of the values.

## Discussion

Idiopathic SSNHL is defined as sensorineural hearing loss of 30 dB or more at 3 continuous frequencies in PTA within 3 days. It is characterized by sudden onset and is unilateral in most cases.

The incidence ranges from 5 to 20/100 000. Idiopathic SSNHL also affects patients in psychosocial ways.<sup>15</sup> Lehnhardt<sup>16</sup> was the first to contradict the “immunoprivileged site” theory about the inner ear. He reported a patient in whom progressive hearing loss in 1 ear became bilateral after a period of time, suggesting that degeneration of inner ear tissues in 1 ear led to the production of anti-cochlear antibodies that eventually damaged the other ear. McCabe<sup>17</sup> later showed that corticosteroids improved SSNHL in a young patient.

More recently, Ciccone et al<sup>18</sup> evaluated cardiovascular risk factors and endothelial function with the flow-mediated dilation (FMD) technique in patients affected by ISSNHL. Twenty-nine patients with ISSNHL and 29 healthy control patients underwent audiovestibular and clinical evaluation, carotid intima-media thickness measurement, and FMD measurement

of the brachial artery, assessed as early markers of atherosclerosis. The results showed that FMD was significantly lower in the patients with ISSNHL than in the controls ( $P < .01$ ). Vestibular involvement was shown to be associated with lower FMD values ( $P < .05$ ).

Cochlear microcirculation has been proposed as an etiology in ISSNHL. The labyrinthine artery has no collateral vessels and cochlear hair cells are very sensitive to ischemic damage. Endothelial dysfunction or vasospasm can cause ISSNHL, and inner ear cochlear microvascular embolism, thrombosis, or blood viscosity may also cause ISSNHL.<sup>7</sup>

White blood cells (WBCs) and a number of their subgroups increase, especially during cardiovascular diseases, and are used as inflammatory markers.<sup>9</sup> As a novel inflammatory index, the SII is an applicable prognostic marker in malignancies and inflammatory conditions.

In our previous study, we showed increased NLR levels in SSNHL.<sup>11</sup> In addition to SSNHL, NLR increases in cases of inflammatory diseases, such as Bell's palsy, and vascular pathologies, such as ischemic cerebrovascular events or acute coronary diseases.<sup>9,10,11</sup> Several single-inflammatory indexes, such as WBC count, neutrophils, lymphocytes, and monocytes, were much higher in patient with ISSNHL groups than in healthy control groups.<sup>19</sup> In our study, we found neutrophil counts, NLR values, and SII values to be statistically significantly higher in the patient group. Masuda et al<sup>6</sup> reported that increases in the neutrophil count have a negative prognostic value in ISSNHL.

Looking at the relation of SSNHL and NLR values, the NLR value was found to be higher in studies of ISSNHL. In our earlier study,<sup>11</sup> we found that the NLR value was correlated with unfavorable prognosis of SSNHL. İkinçioğulları et al<sup>12</sup> also found NLR to be significantly higher in the patient group, and it was a negative prognostic factor for ISSNHL. Durmus et al<sup>20</sup> found that the NLR level was significantly higher in patients with SSNHL who did not recover and was thus a negative prognostic factor. Ozler<sup>21</sup> described possible associations between high NLR levels and SSNHL; higher NLR values were indicative of a poorer prognosis.

The PLR value can also be used as an inflammatory marker and can be correlated with poor prognosis,<sup>12,19</sup> especially in vascular events like myocardial infarction. However, PRL levels were found to be insignificant in all studies about ISSNHL. We also found that PRL was insignificant in our previous study.<sup>11</sup>

In some studies, the SII was reported to be superior to other systemic inflammation indexes, such as PLR and NLR, in malignancies and inflammatory conditions.<sup>13,14,22</sup> This is the first study evaluating SII values in ISSNHL. Since both the sensitivity and the specificity of the SII are above 70%, it can be concluded that the SII can also be an indicator of ISSNHL. We found that SII values higher than 510 can indicate an inflammatory condition such as that in patients with ISSNHL.

In this study, SII levels were higher in unrecovered patients compared with recovered ones. In this severe SII group, additional to the standard corticosteroid therapy,

alternative treatment could be considered. For example, in the beginning, a high dose of pulse methylprednisolone treatment (eg, treatment of 250-mg methylprednisolone for 3 days) could be considered.

## Conclusion

Idiopathic SSNHL has an inflammatory component and therefore we recommend corticosteroid therapy in patients with ISSNHL; however, patients with severe SII scores may not respond to therapy. As steroids have risks, alternative treatments should be considered in those group and risk and benefits of steroids should be considered.

Recent studies have shown new inflammatory markers for predicting inflammatory conditions. As a novel index, the SII can be an indicator of ISSNHL and it can predict prognosis in ISSNHL. Larger studies with more patients with ISSNHL are needed to better understand the importance of the SII.


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