

## ORIGINAL RESEARCH

# New validation of a well-known marker in cochlear implant infections: A retrospective, case-controlled, observational study

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**Abstract**

**Objectives:** Cochlear implant (CI) infection is the most common complication after CI surgery. We investigated whether the preoperative neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) values could predict the CI infection and the NLR and PLR values obtained at the first admission to the hospital with an CI infection could help the clinician in the diagnosis.

**Methods:** This retrospective case-controlled study included 26 patients with postsurgical CI infection. To prevent age-related incompatibility in the blood analysis of the infected group, the patients were divided into three age groups: 0–4 years, 5–18 years, and over 18 years old. To compare the infected group, 29 patients who did not have implant infection after CI surgery and whose age ranges were compatible with the infected group were randomly selected from the hospital records as the control group. The infected group preimplantation (PREs) and postinfection (POSTi) NLR and PLR values were compared with each other and the control group values. The area under the curve, sensitivity, specificity, and cutoff values were calculated by ROC analysis.

**Results:** The POSTi NLR values of the infected group patients aged 0–4 years and over 18 years were significantly greater than the PREs NLR values ( $p = .038$  and  $p = .008$ , respectively). Significant differences were found between the POSTi NLR values of the infected group patients aged 0–4 years and over 18 years and those of PREs in the control group ( $p = .011$  and  $p = .015$ , respectively).

**Conclusions:** Preoperative NLR and PLR values cannot predict postoperative CI infection. However, NLR and PLR values increased significantly after CI infection, even if systemic symptoms did not occur. At the first admission to the hospital, NLR values can guide the clinician in diagnosing the CI infection in patients between 0 and 4 years and over 18 years.

Trial Registration ClinicalTrials.gov Identifier: NCT04120181.

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## KEYWORDS

artificial implant, cochlear implant, diagnosis, infection, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

## 1 | INTRODUCTION

Cochlear implant (CI) surgery is one of the most common artificial organ operations worldwide. It is often the only way to help patients with severe hearing loss not improved with hearing aids.<sup>1</sup> Although cochlear implantation is a safe procedure, local and systemic infections occur in 1.08%–8.2% of cases.<sup>2,3</sup>

Regional wound infection or systemic infections such as meningitis are up to 16 times more common in CI patients than in the normal population.<sup>2</sup> In CI infection, removing the implant is the last resort because the process of implant removal, wound healing, and reimplantation is surgically difficult, expensive, and the patient loses the sensation of hearing for a while.<sup>4</sup>

Moyes et al. showed that postoperative infectious complications might occur when patients have a preoperative inflammatory response.<sup>5</sup> Therefore, it is important to identify susceptible patients before surgery to prevent infection. In addition, the early diagnosis of CI infection and initiation of appropriate treatment are also crucial in controlling it without removing the implant. Because patients who develop CI infection apply to the hospital at different stages of the infection. Some patients apply to the hospital in the early stage of the infection with mild swelling at the implant site, while others apply when fever occurs in the late stage. This variation among patients extends the time it takes for the clinician to diagnose the CI infection and initiate appropriate treatment. Therefore, clinicians need more information than currently available markers provided, to distinguish between bacterial, viral, and other causes of fever and provide cost-effective, fast, and easy results.<sup>6</sup>

White blood cell (WBC) count, neutrophil count, neutrophilic granulocyte percentage, CRP level, and procalcitonin (PCT) levels are traditional inflammatory markers used to diagnose infections. They are costly options with limited evaluation potential.<sup>7</sup> Because the normal levels of WBCs ( $4\text{--}11 \times 10^3/\mu\text{l}$ ) and platelets ( $300,000 \pm 50,000 \times 10^3/\mu\text{l}$ ), which are the most used laboratory markers, vary widely, it is difficult to determine an appropriate threshold level. In addition, cytokines released by the resultant inflammation affect all WBCs. Therefore, it is thought that using the ratio of different WBCs to each other may be more representative of the infection and inflammation status.<sup>8</sup> In this context, the relationship between NLR and PLR values has been investigated. They can be easily calculated from peripheral blood analysis and are now accepted inflammatory markers. They have been shown to have better performance than traditional laboratory parameters in determining the presence and severity of inflammation.<sup>9</sup> It has been used to assess inflammation in chronic obstructive pulmonary disease patients and has been associated with poorer clinical prognosis in advanced age in patients with COVID-19.<sup>10,11</sup> In addition to being an indicator of inflammation, it has been suggested that pretreatment NLR can be used as an important

prognostic biomarker in metastatic gastric cancer patients.<sup>12</sup> However, increased NLR has been shown to be a predictive marker for poor overall survival and progression-free survival in patients with melanoma.<sup>13</sup> However, the relationship between CI infections and NLR and PLR values has not been investigated until now.

Our primary hypothesis was that implant infection in patients undergoing CI could be predicted by preoperative NLR and PLR values.

Our secondary hypothesis was that the NLR and PLR values at the time of the first admission to the hospital in patients who developed implant infection might increase with local infection at the cochlear implant site, without systemic signs of infection.

## 2 | SUBJECTS AND METHODS

### 2.1 | Trial design

Ethics approval was obtained from the Selcuk University Faculty of Medicine Ethics Committee for this cross-sectional, retrospective, case-controlled, and observational study (Ref No. 2019/03). This study was conducted in accordance with the Declaration of Helsinki and all its amendments. The trial was registered with the NIH Clinical Trials Registry [ClinicalTrials.gov NCT04120181](https://clinicaltrials.gov/ct2/show/study/NCT04120181).

### 2.2 | Participants

We examined the files of patients who underwent CI surgery between 2014 and 2018 in the Department of Otolaryngology, Faculty of Medicine, Selcuk University. Patients who had regular follow-up visits for at least 3 years after surgery were included in the study. Patients who underwent implant surgery were checked every 6 months in the first year (excluding the adjustment sessions for the implant) and yearly after that. Although the inflammatory and immune response to surgery may be protective for the body in the early postoperative period, the magnitude of the postoperative systemic inflammatory response is also an independent risk factor for postoperative complications.<sup>14</sup> Therefore, patients who developed implant infections within the first month after surgery were excluded from the study. However, to examine the long-term prognosis for the implants, we examined the 3-year postoperative period. According to Olsen et al., it has been shown that most CI infections occur within the first 3 years.<sup>15</sup> Therefore, the control group patients were selected from those who were followed up for 3 years after the implant surgery and remained free of infection. The patients were divided into two main groups. The infection group comprised patients who developed CI infection within 1 month to 3 years of CI surgery. The control group

comprised patients who were followed up for 3 years after CI surgery, did not develop CI infection, and had similar age and demographic data as the infection group patients.

### 2.3 | Inclusion criteria for the infection group

Patients who developed redness, warmth, tenderness, rash, erosion, abscess formation, purulent drainage, skin necrosis, and wound dehiscence at the implant site and required any partial explantation (removal of the implant, cleaning, and replacement with antibiotic solutions and reinsertion) or complete explantation surgery were included in the infected group. During the explantation procedure, the electrode was left in the cochlea to facilitate the insertion of the new electrode array. Data on the causative organism(s) were also collected where possible.

All patients suspected of having implant infections were evaluated by the operating clinician. After the severity of the infection was evaluated, if pus could be obtained, it was sent for microscopic evaluation, culture, and antibiotic sensitivity. The clinician evaluated whether the infection could be treated with oral and intravenous antibiotics or required surgical intervention. In general, a  $\beta$ -lactam antibiotic therapy was first initiated for postoperative infections. Antibiotic therapy was then adjusted according to microscopic evaluation, culture, and sensitivity results. Surgical revision to preserve the implant and clear the infection was sometimes performed, depending on the clinician's judgment.

Hansen et al. categorized CI infection as major and minor infections.<sup>16</sup> Major infection was used for patients requiring hospitalization, intravenous antibiotics, or surgical treatment. Minor infection was used for patients treated with local wound care or oral antibiotics without hospitalization or patients who did not meet the classification criteria for a major infection. All patients in our study who developed CI infection were hospitalized, treated, and categorized as major infections.

### 2.4 | Exclusion criteria for infection and control groups

Signs and symptoms of systemic infection such as high fever or hypothermia, irritability, sleepiness or tiredness, confusion, tachycardia, tachipnea, hypotension, leucocytosis, or leucopenia were recorded, but patients with systemic findings that would support the definitive diagnosis at the time of first admission to the hospital were excluded from the study because systemic involvement could greatly affect blood values.<sup>17</sup> Patients were excluded if they had systemic diseases that impair the tissue healing process, such as systemic inflammatory disease, systemic infection, malnutrition, anemia, hematological disorder, hypertension, diabetes mellitus, metabolic syndrome, acute coronary syndrome, chronic lung, kidney, liver dysfunction, abnormal thyroid function tests, and malignancy. Patients with mental or physical retardation due to various diseases such as craniofacial anomalies,

cerebral palsy, Down syndrome, and neuromuscular diseases were excluded, as were smokers and patients using drugs that could affect hematological parameters. Pediatric and adult patients with otitis media in the implanted ear were excluded from the study.

### 2.5 | Surgical intervention

After a standard multidisciplinary evaluation, all surgical procedures were performed by two experienced surgeons under general anesthesia. CI surgery was performed through a 4–5-cm skin incision in the postauricular sulcus. All patients who underwent CI surgery were discharged the next day, with 7–10 days of prophylactic antibiotic therapy, unless there were complications that required hospitalization.

### 2.6 | Age ranges for the statistical analysis

Patients in both study groups were divided into three subgroups according to their age at the time of surgery to eliminate the effect of age-related physiological changes in the blood test results. The age ranges were determined based on the periods in which neutrophil, lymphocyte counts, NLR, and PLR values changed physiologically in pediatric and adult patients, as defined in the literature: 0–4 years, 5–18, and >18 years. Comparisons were made separately for each age range according to the literature.<sup>18</sup>

### 2.7 | Time frames for analysis of medical records

The data of enrolled patients were extracted from hospital records. The results of blood analysis obtained 1 day before CI surgery of the patients in the infection group (PREs), those obtained when the patients in the infection group presented to the hospital with a preliminary diagnosis of CI infection (POSTi), and those obtained 1 day before CI implantation surgery in the control group patients (PREs) were compared with each other.

### 2.8 | Measurements

Laboratory machines for standard CBC parameters mechanically counted the neutrophils, leukocytes, lymphocytes, and platelets. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. The PLR value was calculated by dividing the platelet count by the lymphocyte count.<sup>19</sup> Patients' blood samples were collected by venipuncture into tubes containing ethylenediaminetetraacetic acid (EDTA) within 1 h of hospital admission. The samples were analyzed in the biochemistry laboratory within 2 h with an automated blood cell counter (Coulter<sup>®</sup> LH 780 Hematologic Analyzer, Beckman Coulter Inc.). The laboratory reference interval was  $4.4\text{--}11.3 \times 10^3/\mu\text{l}$  for leukocytes,  $1.7\text{--}7 \times 10^3/\mu\text{l}$  for neutrophils,  $0.9\text{--}3.2 \times 10^3/\mu\text{l}$  for lymphocytes, and  $150\text{--}450 \times 10^3/\mu\text{l}$  for platelets. The PREs NLR and

PLR values of patients in the infected group were compared with those in the control group. This was to investigate whether the NLR and PLR values in the preoperative period could predict CI infection before surgery. In addition, the POSTi NLR and PLR values of the infected group patients were compared with the PREs NLR and PLR values of the patients in the control group. This was to determine whether these values could be used as markers for early diagnosis of CI infection.

## 2.9 | Statistical analysis

IBM Statistical Package for the Social Sciences (SPSS) version 22 (IBM Corp.) was used for statistical analysis. The Kolmogorov–Smirnov test was used to measure the suitability of the normal distribution of the variables in the study. The mean  $\pm$  standard deviation (SD) was used as descriptive statistics, and categorical data were presented proportionally. A *t* test was used to compare variables. Those that did not fit the normal distribution were compared using the Mann–Whitney *U* test. The efficacy of mean NLR and PLR values in predicting CI infection and diagnosing CI was evaluated by the area under the curve (AUC), calculated using receiver operating characteristic curve (ROC) analysis. The maximum possible sum of sensitivity and specificity levels were accepted as the best cutoff values for NLR and PLR. Values above the specified cutoff values were considered positive. Sensitivity, specificity, predictive, and diagnostic values were calculated for these cutoff values. A *p*-value  $<.05$  was considered statistically significant.

## 3 | RESULTS

Of the 341 patients who underwent cochlear implant surgery between 2014 and 2018, 26 developed local wound infection at the implant site and met the inclusion criteria. The infection group comprised 26 patients (5 females [19%] and 21 males [81%]), while the control group consisted of 29 healthy subjects (7 males [24%] and 22 females [76%]). In our study, wound infection was detected at the incision line in five of the patients who developed CI infection, detachment of the skin covering the implant was detected in 10 patients, and redness and edema were detected only in the implant area in 11 patients. All patients with CI infection were hospitalized immediately after the diagnosis of infection, and IV antibiotic treatment was started. While the CI infection of eight of these patients regressed with antibiotic treatment and wound care, excision of the infected area skin and revision of the local flap were performed in four of them, and partial explantation was performed in six patients. The implants of eight patients had to be removed because the infection could not be brought under control despite all the interventions. *Staphylococcus aureus* growth was observed in 11 patients, *Corynebacterium* in 1 patient, while no growth was observed in the cultures of 14 patients.

The mean age of the nine infection group patients aged 0–4 years was  $2.22 \pm 0.22$ , while it was  $2.36 \pm 0.24$  years in the nine control

group patients. The PREs and POSTi NLR values of the infection group patients aged 0–4 were significantly different ( $p = .038$ ), but no significant difference was observed between their PLR values ( $p = .110$ ) (Table 1A). The PREs NLR and PLR values for the infection group 0–4-year-old patients were not significantly different from those of the control group patients ( $p = .268$ ,  $p = .603$ , respectively) (Table 1B). The NLR cutoff value of the patients in this group was 0.85 (sensitivity 35%, specificity 34%), the AUC was 0.26, the PLR cutoff value was 91.69 (sensitivity 45%, specificity 44%), and the AUC was 0.34 (Figure 1A). Therefore, the NLR and PLR values do not have a predictive value for estimating the onset of CI infection in the preoperative period. However, the statistical difference between preoperative and post-infection NLR values is valuable when we consider that CI infection was limited to a local area in our patients. Because, in similar studies conducted to date, the change of NLR in the presence of the systemic infection has been investigated. We excluded patients with systemic infection signs at the time of admission to the hospital, unlike studies conducted to date.<sup>20</sup> The POSTi NLR values of the infection group patients aged between 0 and 4 years showed a statistically significant difference compared with the PREs NLR values of the control group ( $p = .011$ ). No significant difference was observed between the PLR values ( $p = .214$ ) (Table 1C). In this comparison, the cutoff value for the NLR was 0.89 (sensitivity 89%, specificity 65%), and the AUC was 0.75, while the cutoff value for the PLR was 95.72 (sensitivity 79%, specificity 70%), and the AUC was 0.66 (Figure 1B). This result showed us that the NLR values obtained at the first admission to hospital with a CI infection of the patients aged 0–4 years could be a guide to clinician for diagnosing CI infection with 89% sensitivity and 65% specificity for a cutoff value of 0.89.

The mean age of the eight patients in the infection group, in the 5–18-year age range, was  $13.50 \pm 6.21$ , while the mean age for the nine patients in the control group was  $9.80 \pm 3.71$ . The PREs and POSTi NLR and PLR values of the patients in the infection group in the 5–18 age range showed no statistically significant differences ( $p = .287$ ,  $p = .661$ , respectively) (Table 2A). In the same age range, no statistical difference was detected between the PREs NLR and PLR values of the infection group patients and those in the control group ( $p = .376$  and  $.768$ , respectively) (Table 2B). In the ROC analysis, the cutoff value for the NLR was 1.72 (sensitivity 20%, specificity 37.5%), and the AUC was 0.35, while the cutoff value for the PLR was 155.48 (sensitivity 44%, specificity 37.5%), and the AUC was 0.55 (Figure 2A). The POSTi NLR and PLR values of the infection group patients in this age range were compared with those of PREs of the control group patients; however, no significant difference was detected ( $p = .500$  and  $.345$ , respectively) (Table 2C). In this comparison, the cutoff value for the NLR was calculated as 1.92 (sensitivity 63%, specificity 77%), the AUC was 0.65, while the cutoff value for the PLR was calculated as 164.48 (sensitivity 66%, specificity 77%), and the AUC was 0.59 (Figure 2B). These results showed that for this age range, NLR and PLR values do not have a predictive value for estimating the onset of CI infection in the preoperative period and for diagnosis at the first admission to the hospital with a CI infection.

The mean age of the nine patients in the infection group over 18 was  $49.44 \pm 13.02$ , and the mean age in the control group was

Variable	Group	Median	Q1–Q3	Test statistic	<i>p</i>
(A) NLR and PLR values of infection group in PREs and POSTi					
NLR	Infection PREs	0.38	0.31–1.18	2.038	.038 <sup>aa</sup>
	Infection POSTi	1.04	0.81–1.46		
PLR	Infection PREs	71.27	64.34–120.25	1.599	.110 <sup>a</sup>
	Infection POSTi	101.05	76.42–118.65		
(B) NLR and PLR values of infection group and control group in PREs					
NLR	Infection PREs	0.38	0.31–1.18	–1.107	0.268 <sup>b</sup>
	Control PREs	0.76	0.74–0.92		
PLR	Infection PREs	71.27	64.34–120.25	–0.572	0.603 <sup>b</sup>
	Control PREs	96.27	78.81–99.46		
(C) NLR and PLR values of control group in PREs and of infection group in POSTi					
NLR	Control PREs	0.76	0.74–0.92	–2.547	0.011 <sup>ab</sup>
	Infection POSTi	1.04	0.81–1.46		
PLR	Control PREs	96.27	78.81–99.46	–1.244	0.214 <sup>b</sup>
	Infection POSTi	Final test	101.05		

**TABLE 1** Comparison of NLR and PLR values in PREs and POSTi of infection and control group patients aged 0–4 years

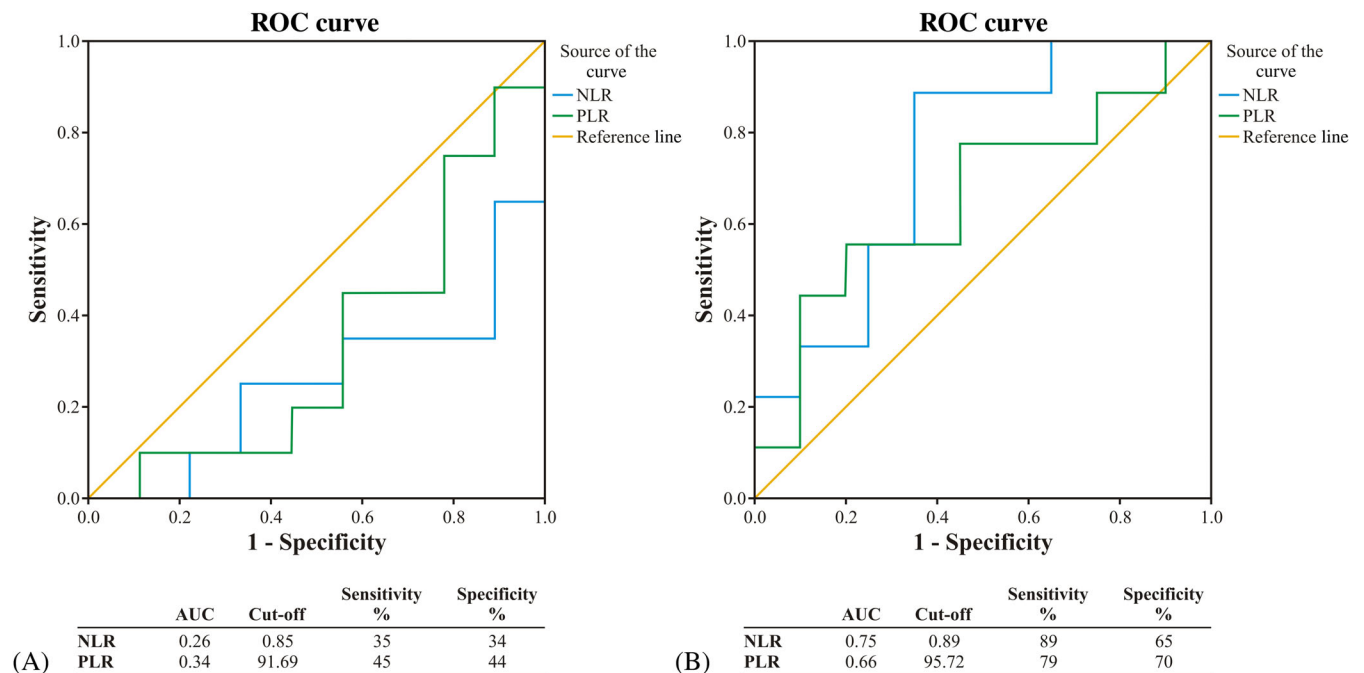
Note: Q1–Q3: interquartile range.

Abbreviations: NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; PREs, pre-implantation; POSTi, post-infection.

<sup>a</sup>Comparing the two groups by exact Wilcoxon signed-rank test.

<sup>b</sup>Comparing the two groups by exact Mann–Whitney test.

\**p* < .05.



**FIGURE 1** ROC curves for (A) predicting the onset of CI infection in the perioperative period aged 0–4 years; areas under the curves were 0.26 for the NLR and 0.34 for the PLR, respectively. (B) Diagnosing CI infection at the first admission to hospital in patients aged 0–4 years; areas under the curves were 0.75 for the NLR and 0.66 for the PLR, respectively. CI, confidence interval; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; ROC, receiver operating characteristic

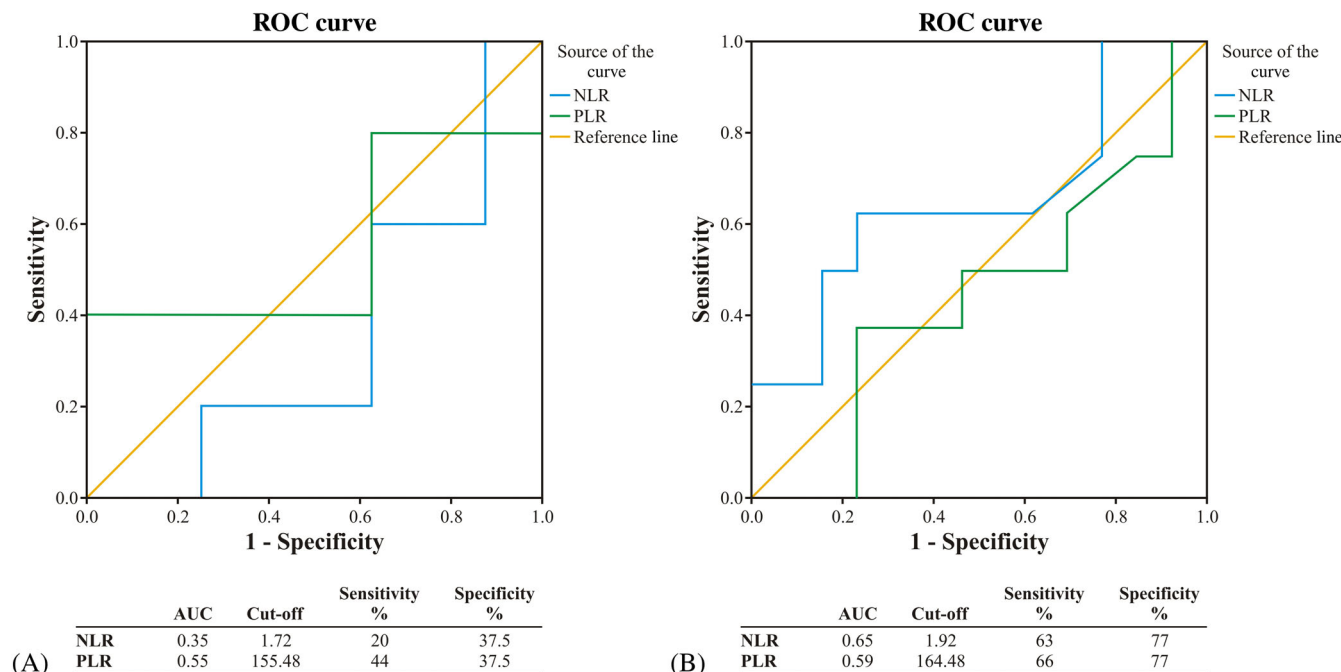
46.08 ± 21.19. The PREs and POSTi NLR and PLR values of the patients in the infection group showed a statistically significant difference (*p* = .008 and .008, respectively) (Table 3A). However,

no significant difference was detected between the PREs NLR and PLR values of the infection group patients in the same age group and the PREs NLR and PLR values of the control group patients

**TABLE 2** Comparison of NLR and PLR values in PREs and POSTi of infection and control group patients aged 5–18 years

Variable	Group	Median	Q1–Q3	Test statistic	p
(A) NLR and PLR values of infection group in PREs and POSTi					
NLR	Infection PREs	1.94	1.48–2.81	–1.152	.287 <sup>a</sup>
	Infection POSTi	2.41	0.81–4.37		
PLR	Infection PREs	163.05	128.00–169.61	0.458	.661 <sup>a</sup>
	Infection POSTi	150.96	100.53–177.86		
(B) NLR and PLR values of infection group and control group in PREs					
NLR	Infection PREs	1.94	1.48–2.81	0.886	.376 <sup>b</sup>
	Control PREs	1.48	0.61–1.93		
PLR	Infection PREs	163.05	128.00–169.61	–0.295	.768 <sup>b</sup>
	Control PREs	154.47	97.48–202.96		
(C) NLR and PLR values of control group in PREs and of infection group in POSTi					
NLR	Control PREs	1.48	0.61–1.93	–0.674	.500 <sup>b</sup>
	Infection POSTi	2.41	0.81–4.37		
PLR	Control PREs	154.47	97.48–202.96	–0.944	.345 <sup>b</sup>
	Infection POSTi	150.96	100.53–177.86		

Note: Q1–Q3: interquartile range.  
 Abbreviations: NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; PREs, pre-implantation; POSTi, post-infection.  
<sup>a</sup>Comparing the two groups by exact Wilcoxon signed-rank test.  
<sup>b</sup>Comparing the two groups by exact Mann–Whitney test.



**FIGURE 2** ROC curves for (A) predicting the onset of CI infection in the perioperative period aged 5–18 years; areas under the curves were 0.35 for the NLR and 0.55 for the PLR, respectively; (B) diagnosing CI infection at the first admission to hospital in patients aged 5–18 years; areas under the curves were 0.65 for the NLR and 0.59 for the PLR, respectively. CI, confidence interval; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; ROC, receiver operating characteristic

( $p = .240$  and  $.051$ , respectively) (Table 3B). In this analysis, the cutoff value for the NLR was 2.06 (sensitivity 46%, specificity 33.5), and the AUC was 0.35, while the cutoff value for the PLR was 119.05 (sensitivity 77%, specificity 88%), and the AUC was

0.75 (Figure 3A). These results showed that, NLR and PLR values could not predict the emergence of CI infection before CI implantation surgery in the adult age group patients. However, just as in patients aged 0–4 years, the statistical difference between NLR

Variable	Group	Median	Q1-Q3	Test statistic	p
<b>(A) NLR and PLR values in PREs and POSTi of infection group patients</b>					
NLR	Infection PREs	1.99	1.46-3.13	2.666	0.008 <sup>*a</sup>
	Infection POSTi	2.77	2.06-3.77		
PLR	Infection PREs	98.84	90.91-177.62	2.666	0.008 <sup>*a</sup>
	Infection POSTi	124.98	96.75-196.23		
<b>(B) NLR and PLR values in PREs of infection group and control group patients</b>					
NLR	Infection PREs	1.99	1.46-3.13	1.176	0.240 <sup>b</sup>
	Control PREs	1.77	1.21-2.04		
PLR	Infection PREs	98.84	90.91-177.62	-1.982	0.051 <sup>b</sup>
	Control PREs	128.71	117.41-182.34		
<b>(C) NLR and PLR values in PREs of control group and POSTi of infection group patients</b>					
NLR	Control PREs	1.77	1.21-2.04	-2.429	0.015 <sup>*b</sup>
	Infection POSTi	2.77	2.06-3.77		
PLR	Control PREs	128.71	117.41-182.34	-0.178	0.859 <sup>b</sup>
	Infection POSTi	124.98	96.75-196.23		

**TABLE 3** Comparison of NLR and PLR values in PREs and POSTi of infection and control group patients aged >18 years

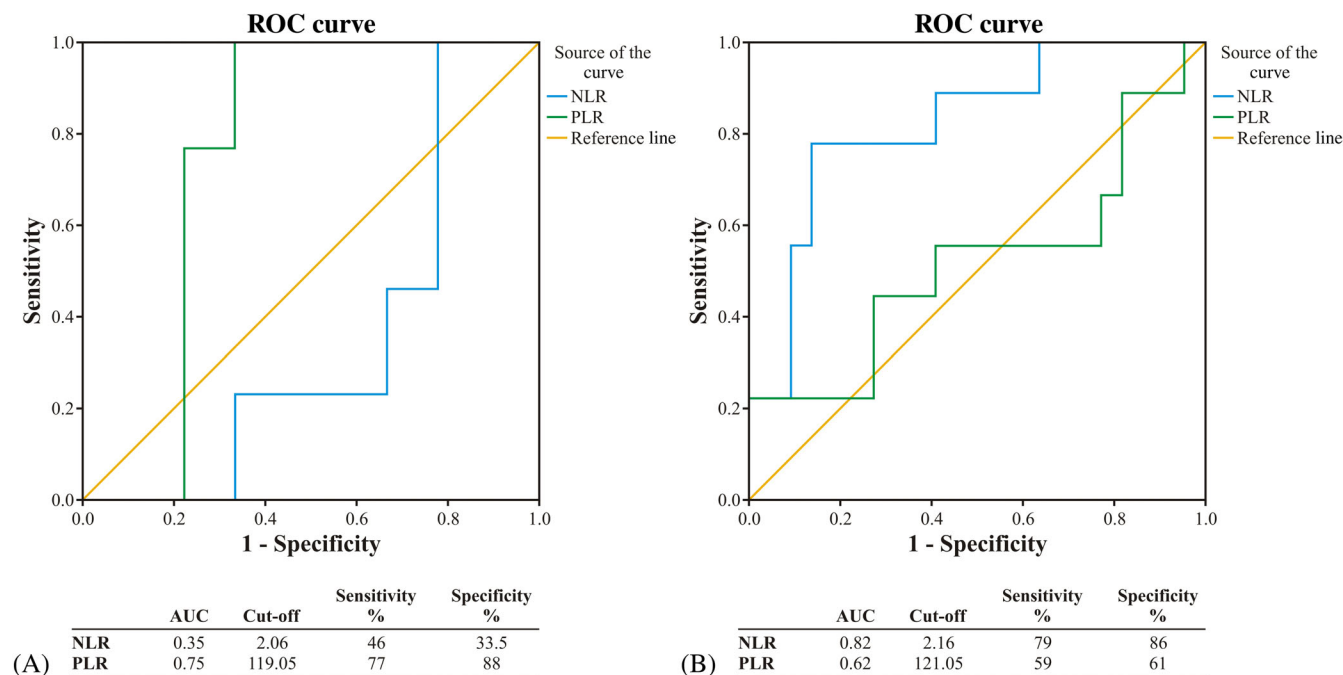
Note: Q1-Q3: interquartile range.

Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PREs, pre-implantation; POSTi, post-infection.

<sup>a</sup>Comparing the two groups by exact Wilcoxon signed-rank test.

<sup>b</sup>Comparing the two groups by exact Mann-Whitney test.

\*p < .05.



**FIGURE 3** ROC curves for (A) predicting the onset of CI infection in the perioperative period aged >18 years; areas under the curves were 0.35 for the NLR and 0.75 for the PLR, respectively; (B) diagnosing CI infection at the first admission to hospital in patients aged >18 years; areas under the curves were 0.82 for the NLR and 0.62 for the PLR, respectively. CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; ROC, receiver operating characteristic

and PLR values calculated preoperatively and after infection is valuable by showing that NLR and PLR values are affected even in a local infection focus.

The POSTi NLR values of the patients over 18 years in the infection group were significantly different from the PREs NLR values of the control group patients ( $p = .015$ ), but no difference was found in

the PLR values ( $p = .859$ ) (Table 3C). The cutoff value for the NLR was 2.16 (sensitivity 79%, specificity 86%), and the AUC was 0.82, while the cutoff value for the PLR was 121.05 (sensitivity 59%, specificity 61%), and the AUC was 0.62 (Figure 3B). These results showed that the NLR value of patients at the time of the first admission to the hospital after the infection developed might have predictive use in terms of guiding the diagnosis of CI infection, while the PLR value does not.

## 4 | DISCUSSION

The NLR and PLR are new markers that can indicate the severity and prognosis of systemic inflammation. Our study is the first to investigate the use of preoperative NLR and PLR values to predict implant infection in patients with post-CI infection. It is also the first study to investigate the diagnostic value of NLR and PLR values at the first admission to hospital for CI infection. Up-to-date, age-related physiological changes in blood cell counts have not been considered in NLR and PLR studies. We examined the predictive accuracy and reliability of NLR and PLR values in three different age ranges in which physiological differences in the number of blood cells are expected.

Our study shows that preoperative NLR and PLR values could not predict postoperative CI infection in patients who underwent CI surgery. However, a significant difference was found between the preoperative and post-infection NLR values of patients aged 0–4 years and the preoperative and post-infection values of patients older than 18 years. Since we excluded patients with systemic symptoms at the time of admission to the hospital, this result is valuable in showing that NLR and PLR values are affected after CI infections, even if it does not turn into a systemic infection. In addition, it has been shown that the NLR results obtained at the first admission to the hospital after the infection develops can help the clinician diagnose CI infection in patients aged 0–4 years and older than 18 years. The results of our study show that NLR and PLR values can help the clinician in diagnosing the CI infection at the first admission to the hospital with an CI infection, even in patients who developed CI infection but do not have systemic symptoms. There was no predictive effect of the NLR and PLR values for patients aged 5–18 years.

Preoperative NLR and PLR values can indicate postoperative prognosis after lung and liver transplantation surgery.<sup>21,22</sup> They can also determine long-term prognosis in noninfectious chronic disease states, such as certain cancer types.<sup>23,24</sup> In addition, it has been shown that in infectious conditions such as septicemia and spinal epidural abscess, it helps early diagnosis of infection with higher specificity and sensitivity than traditional laboratory parameters.<sup>25,26</sup> There are also studies evaluating the predictive role of NLR for surgical site infection and prosthetic device infection. Shen et al. showed the predictive value of NLR for surgical site infection after posterior lumbar spinal surgery.<sup>27</sup> Bolat et al. showed the validity of NLR in predicting early penile prosthesis implant infection.<sup>28</sup> Kilickaya et al. investigated the systemic inflammatory effect of cholesteatoma via NLR and found that cholesteatoma is a localized infection and does not cause

systemic effects.<sup>29</sup> In our study, we also showed that cochlear implant wound infection is not local but has a systemic effect.

Neutrophils are the WBC subset that increases the most in acute infection. An increase in the number of neutrophils and a decrease in the number of lymphocytes are a physiological response of the innate immune system in any inflammatory condition. Further, platelets are also involved in infection pathogenesis, as they are involved in the hemostatic process of inflammation along with neutrophils and lymphocytes.<sup>30</sup> Therefore, NLR and PLR values represent the severity of inflammation, the capacity of immunity, and the balance between the two. High NLR and PLR values indicate a relative lymphopenia, and an increase in neutrophil and platelet counts representing inflammation.<sup>31,32</sup>

The lymphopenia detected in the preoperative period is important in representing the strength of the immune system, showing the risk of postoperative infection and the malnutrition status, which is a prognostic factor after surgery.<sup>31</sup> In the case of systemic inflammation, relative lymphopenia is seen with neutrophilia. This is because endogenous glucocorticoids released in the physiological response to local and systemic inflammation affect WBCs and lymphocytes.<sup>32</sup> Therefore, the ratio (i.e., NLR and PLR) of cells affected by this complex process can be more understandable for the clinician. In a study conducted on infants who underwent liver transplantation due to congenital biliary atresia, it was reported that infants with a preoperative NLR value greater than the mean cutoff value had worse survival after transplantation. At the same time, the nutritional intervention required for these infants could guide NLR rates.<sup>22</sup>

In addition to the complex changes caused by inflammation, WBC counts follow a physiologically fluctuating course during life. The neutrophil count rises in the first 12 h after birth, decreases between 1 month and 1 year after birth, and then rises gradually, stabilizing at  $4.4 \times 10^3 \mu\text{l}$  at about 4 years of age.<sup>18</sup> Lymphocytes make up about 30% of WBCs immediately after birth and, by 4–6 months, constitute 60% of WBCs, unlike neutrophils. The proportion of lymphocytes in WBCs decreases to 50% at 4 years of age, 40% at 6, and 30% at 8 and gradually decreases until 18 years of age.<sup>33</sup> Therefore, to minimize the effect of physiological changes in the number of blood cells on the results of our study, we divided the participants into three age groups, namely, 0–4 years, 5–18 years, and over 18 years old, based on the ages at which physiological changes occur. In this context, our study is the first to consider the effect of age-related changes in the number of blood cells.

According to the results of our study, the lack of predictive value of NLR and PLR values in patients aged 5–18 years with CI infection can be explained by the physiological changes occurring in this age group. It is known that the neutrophil count remains stable after the age of 4, and the lymphocyte count gradually decreases until the age of 18.<sup>33</sup> In addition, the lowest NLR value occurs in the 0–1 age group. The NLR value increases after the age of 1 until the 20s, remains constant between 20 and 60 years old, and tends to increase again after that. NLR values tend to increase in the 5–18 age group and follow an unstable course regardless of inflammation. Therefore, the increase in the physiological NLR value seen in the 5–18 age



group may mask the expected increase in NLR value in inflammation, as in our study.

Platelets are powerful pro-inflammatory cells that can act as mediators between innate and adaptive immune systems and their role in hemostasis. They secrete high amounts of pro-inflammatory substances when activated in inflammatory regions. There is a common but imprecise relationship between bacterial infection and neutrophilia and viral infection and lymphocytosis. In general, higher NLR values indicate a greater likelihood of bacterial infection and lower likelihood of viral infection.<sup>34</sup> Therefore, the NLR values may also be affected by whether the infection is bacterial or viral.

## 5 | LIMITATIONS

Our study has some limitations. The evaluation did not include traditional inflammation markers such as CRP, ESR, and PCT since nature of a retrospective single-center study. In addition, for laboratory results to be considered clinically significant, a comparison between healthy individuals and patients is required. Although we made this comparison considering parameters such as age, time, and measurement method, hematological values may also be affected by variables that were not taken into account in our study, such as gender, race, nutrition, environment, and mean sea level. In addition, inflammatory markers may provide limited clinical benefits in the postoperative period, as an inflammatory response is inevitable during the surgical procedure.

## 6 | CONCLUSION

Identifying patients who are more likely to develop CI infection may affect the timing of CI surgery and the care needed after surgery. In addition, early diagnosis and treatment of patients with CI infection may prevent implant explantation. Our study showed that preoperative NLR and PLR values, inflammatory markers which are easily calculated, reproducible, and cheap, were not predictive for both pediatric and adult age groups for postoperative CI infection. However, it was shown that they could help to clinician in diagnosing CI infection during the first admission to the hospital with a CI infection. These markers may provide significant diagnostic benefits to the clinician as part of overall patient assessment, especially with pediatric patients who cannot accurately describe their complaints or other patients who cannot hear and speak which are the populations where CI surgery is most frequently performed. This effect may be beneficial in managing the CI infection process, including the severity of the infection, its onset, which treatment it responds to, and the decision for implant explantation. However, the NLR-expressed marker showing the preoperative balance between systemic inflammation and immunity is a time-sensitive variable, and multicenter prospective studies in large patient populations are needed to determine the effect of CI on long-term function without infection.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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