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Paper Accepted[1]

ISSN Online 2406-0895

Preliminary and short communication / Претходно и кратко саопштење

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The significance of systemic inflammatory markers in the differentiating benign from malignant parotid gland tumors – a pilot study

Значај системских инфламаторних маркера у разликовању бенигних од малигних тумора паротидних жлезда – пилот студија

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Received: December 19, 2025
Revised: May 17, 2026
Accepted: June 22, 2026
Online First: July 21, 2026
DOI: https://doi.org/10.2298/SARH251219057S

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The significance of systemic inflammatory markers in the differentiating benign from malignant parotid gland tumors – a pilot study

Значај системских инфламаторних маркера у разликовању бенигних од малигних тумора паротидних жлезда – пилот студија

SUMMARY

Introduction/Objective This study aims to assess the diagnostic value aims to explore the potential role of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) in distinguishing benign from malignant parotid gland tumors.

Methods The clinical data of 129 patients who had parotid surgery between 2014 and 2024 were evaluated retrospectively. Demographics, preoperative blood count, and histological results were compared. Patients were categorized as benign and malignant tumors based on histopathological diagnosis.

Results No significant difference was found in sex distribution between the groups ($p > 0.05$). Patients with malignant tumors were significantly older than those with benign tumors ($p = 0.038$). Lymphocyte and platelet counts were significantly higher in the benign tumor group ($p = 0.008$ and $p = 0.029$, respectively). In contrast, mean NLR values were significantly higher in patients with malignant tumors ($p = 0.016$). Although PLR and SII values were also higher in the malignant tumor group, the differences were not statistically significant ($p > 0.05$).

Conclusion NLR may serve as a supportive and adjunctive marker rather than a standalone diagnostic tool to differentiate benign and malignant parotid gland tumors. This study should be considered a pilot study, and larger controlled studies are required.

Keywords: parotid tumors; parotidectomy; neutrophil to lymphocyte ratio; platelet to lymphocyte ratio; systemic inflammation index

САЖЕТАК

Увод/Циљ Циљ ове студије је процена дијагностичке вредности односа неутрофила и лимфоцита (*NLR*), односа тромбоцита и лимфоцита (*PLR*) и индекса системске имуноинфламације (*SII*) у разликовању бенигних од малигних тумора паротидне жлезде.

Методе Ретроспективно су процењени клинички подаци 129 пацијената који су имали паротидну операцију између 2014. и 2024. године. Упоређени су демографски подаци, преоперативна крвна слика и хистолошки резултати. Пацијенти су категорисани као бенигни и малигни тумори на основу хистопатолошке дијагнозе.

Резултати Није пронађена значајна разлика у расподели полова између група ($p > 0,05$). Пацијенти са малигним туморима били су значајно старији од оних са бенигним туморима ($p = 0,038$). Број лимфоцита и тромбоцита био је значајно већи у групи са бенигним туморима ($p = 0,008$ и $p = 0,029$, респективно). Насупрот томе, средње вредности *NLR* биле су значајно веће код пацијената са малигним туморима ($p = 0,016$). Иако су вредности *PLR* и *SII* такође биле веће у групи малигних тумора, разлике нису биле статистички значајне ($p > 0,05$).

Закључак *NLR* може послужити као помоћни и додатни маркер, а не као самостални дијагностички алат за разликовање бенигних и малигних тумора паротидне жлезде. Ову студију треба сматрати пилот студијом и потребне су веће контролисане студије.

Кључне речи: паротидни тумори; паротидектомија; однос неутрофила и лимфоцита; однос тромбоцита и лимфоцита; индекс системске инфламације

INTRODUCTION

Major salivary gland tumors constitute approximately 3–10% of head and neck neoplasms, with nearly 80% originating from the parotid gland [1–3]. Parotid masses may arise from primary neoplasms or reflect inflammatory diseases, metastatic malignancies, or lymphomas [2, 4]. Clinical evaluation relies on physical examination and imaging methods for diagnosis and treatment planning. Features such as pain, rapid growth, fixation to surrounding tissues, or cervical lymphadenopathy suggest malignancy and are commonly assessed with fine-needle aspiration biopsy (FNAB), ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) [1, 5, 6]. Differentiating non-neoplastic from neoplastic lesions, benign from malignant tumors, and low-grade from high-grade malignancies is

essential for appropriate treatment planning and surgical management. Although MRI and CT are valuable for evaluating large or deep-lobe masses with suspected malignancy, FNAB remains the first-line diagnostic method because of its simplicity, low cost, and rapid results [1, 6]. However, intratumoral heterogeneity, morphological overlap, and the histological diversity of salivary gland tumors often hinder definitive preoperative cytological diagnosis, and diagnostic accuracy largely depends on the cytopathologist's experience [1, 2, 6].

The interaction between cancer and the immune system has become an important focus of recent research. While immune surveillance mediated by lymphocytes and natural killer (NK) cells provides protection against transformed cells, chronic inflammation is recognized as a major contributor to carcinogenesis. The tumor microenvironment contains various immune cell populations that influence tumor progression through complex interactions between tumor cells and the host [5–8].

Chronic inflammation contributes to multiple stages of tumor development, including cellular transformation, proliferation, angiogenesis, invasion, and metastasis [3, 5, 9]. Cytokines such as IL-6 and TNF-α released by tumor cells and the tumor microenvironment may promote oxidative stress, genomic instability, and tumor progression [9–11]. In addition, inflammatory mediators may enhance tumor invasiveness through pathways involving vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) [9–11]. Conversely, lymphopenia reflects impaired host immune surveillance, enabling the tumor to achieve immune escape [5].

Peripheral blood inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have emerged as accessible indicators of the balance between tumor-associated inflammation and the host immune response [3, 6]. Cytokines released by tumor cells and the tumor microenvironment may trigger systemic inflammation by altering circulating neutrophil, lymphocyte, platelet, and monocyte levels [10]. This inflammatory response may further promote tumor progression and suppress host immune activity [5, 7, 8, 1]. Therefore, peripheral blood inflammatory cells are considered important mediators of carcinogenesis and tumor progression. Complete blood count (CBC), a routine and cost-effective preoperative test, enables easy calculation of these markers using neutrophil, lymphocyte, and platelet counts [6, 1].

This pilot study aimed to evaluate the potential role of preoperative inflammatory markers (NLR, PLR, and SII) in differentiating benign from malignant parotid gland tumors.

METHODS

Patients

Clinical data of 156 patients who underwent surgery for parotid masses at the Department of Otorhinolaryngology, Medipol Mega University Hospital, between January 2014 and December 2024 were retrospectively reviewed. All consecutive patients meeting the study criteria were screened. Patients aged 10–83 years were included, and no specific age cut-off was applied; therefore, both

pediatric and adult patients were evaluated. To minimize potential inflammatory confounders, patients with acute infection, diabetes, heart failure, autoimmune or hematological diseases, chronic renal failure, corticosteroid use, obesity (BMI > 30), or missing preoperative complete blood count (CBC) data were excluded. Some patients had overlapping exclusion criteria. After exclusions, 129 patients were included in the final analysis. A flow diagram of the patient selection process is presented in Figure 1.

Demographic characteristics, medical history, preoperative hemogram findings, and postoperative histopathological diagnoses were obtained from hospital records. Sex data represented biological sex. Only primary parotid gland neoplasms confirmed by final pathology reports were included. Patients were classified into benign and malignant tumor groups according to postoperative histopathological diagnosis.

Venous blood samples were collected between 09:00 and 11:00 within one week before surgery. Preoperative CBC data were used to determine neutrophil, lymphocyte, and platelet counts. NLR (N/L), PLR (P/L), and SII (N × P/L) were calculated. All measurements were performed using the same automated hematology analyzer.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 27. Descriptive statistics were used to summarize the data: quantitative variables were expressed as mean ± standard deviation, median, minimum, and maximum, while qualitative variables were presented as frequency and percentage. Normality was assessed using the Shapiro–Wilk test. The Student's t-test was applied for normally distributed quantitative variables, and the Chi-square test for categorical comparisons. Risk factors for malignancy were evaluated using binary logistic regression (Enter method). Logistic regression analysis included NLR, PLR, SII, and age as potential predictors. The pseudo-R^2 value (Nagelkerke R^2) was used to assess model fit. Diagnostic performance was assessed with Receiver Operating Characteristic (ROC) curve analysis. A p-value < 0.05 was considered statistically significant at a95% confidence level.

Ethics: For this retrospective study, ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (Registration Number:E-10840098–202.3.02–575, Decision No:09.01.2025/40), and the study was conducted in accordance with the Declaration of Helsinki.

RESULTS

A total of 129 patients were included, comprising 78 males (60.5%) and 51 females (39.5%). The benign tumor group included 103 patients aged 10–83 years (mean age: 44.39 ± 15.36 years, median age: 45 years), whereas the malignant group consisted of 26 patients aged 15–79 years (mean age: 51.88 ± 19.79 years, median age: 50 years). Histopathological evaluation revealed 103 benign (79.8%) and 26

malignant (20.2%) lesions (Table 1). Pleomorphic adenoma (n = 51, 49.5%) and Warthin tumor (n = 30, 29.1%) were the most common benign tumors, whereas squamous cell carcinoma (n = 6, 23.1%), low-grade mucoepidermoid carcinoma (n = 4, 15.4%), and adenoid cystic carcinoma (n = 3, 11.5%) were the most frequent malignant tumors. The benign group included 64 males (62.1%) and 39 females (37.9%), while the malignant group included 14 males (53.8%) and 12 females (46.2%). Sex distribution did not differ significantly between groups ($p > 0.05$). However, mean age was significantly higher in the malignant group than in the benign group (51.88 ± 19.79 *vs.* 44.39 ± 15.36 years, $p = 0.038$) (Table 1).

Mean hematological parameters and inflammatory markers are presented in Table 1 (95% CI). Neutrophil counts did not differ significantly between groups ($p > 0.05$), whereas lymphocyte and platelet counts were significantly higher in the benign group ($p = 0.008$ and $p = 0.029$, respectively). The mean NLR was significantly higher in malignant tumors (2.65 ± 1.74) than in benign tumors (2.05 ± 0.89) ($p = 0.016$). Although PLR and SII values were also higher in the malignant group, these differences were not statistically significant ($p > 0.05$) (Table 1).

Enter logistic regression analysis was performed using NLR, PLR, and SII values. NLR and SII were identified as predictors of malignancy ($p = 0.022$), and the Nagelkerke R^2 value of the model was 0.806. A one-unit increase in NLR was associated with a2.965-fold increase in malignancy risk (95% CI: 1.260–6.976, $p = 0.013$), whereas a one-unit increase in SII corresponded to an odds ratio of 0.996 (95% CI: 0.992–1.000, $p = 0.049$). While NLR showed a statistically significant association with malignancy, the significance of SII was borderline and should be interpreted cautiously (Table 2).

Receiver operating characteristic (ROC) curve analysis demonstrated an optimal cut-off value of 2.199 for NLR (AUC: 0.615, $p = 0.068$) and 716.447 for SII (AUC: 0.522, $p = 0.073$). However, neither marker demonstrated statistically significant diagnostic performance, limiting their clinical applicability (Figure 2, Table 3).

DISCUSSION

The discovery of leukocytes within tumor tissue has strengthened evidence linking chronic inflammation to carcinogenesis. Numerous studies have shown that chronic inflammation in the tumor microenvironment influences tumor initiation, metastasis, prognosis, and treatment response [5, 6, 10, 12, 13]. Systemic inflammatory markers such as NLR, PLR, and SII have similarly been associated with tumor progression and prognosis in various malignancies. Neutrophils and platelets may promote angiogenesis, DNA damage, and tumor proliferation, whereas lymphocytes contribute to antitumor immunity by suppressing tumor growth and metastasis. Consequently, alterations in neutrophil, platelet, and lymphocyte counts have been recognized as independent prognostic indicators in many cancers [1, 2, 6, 1, 12–17]. Lymphopenia reflects impaired cellular immunity and has been associated with poorer prognosis and cancer-related immunosuppression, partly through elevated interleukin-6 (IL-6) and

tumor necrosis factor receptor levels [6, 1, 18]. Reduced lymphocyte counts together with elevated neutrophil and platelet counts may lead to increased NLR, PLR, and SII values [3, 1, 18, 19]. A meta-analysis of 33 studies demonstrated that elevated SII values are associated with increased risks of all-cause, cardiovascular, and cancer-related mortality [20]. Similarly, elevated NLR has been identified as a prognostic marker in various head and neck malignancies [14, 21, 22]. In addition, high SII values have been associated with aggressive pathological features such as perineural invasion, lymphovascular invasion, and extranodal spread [3, 15]. The diagnostic value of inflammatory markers has also been investigated in submandibular and thyroid gland lesions. Bora [23] reported significantly higher preoperative NLR values in malignant submandibular gland tumors compared with benign lesions. Likewise, NLR and PLR have been proposed as supportive markers for differentiating benign from malignant thyroid nodules [5, 23, 24], and Atak et al. [24] demonstrated that elevated PLR values may have moderate diagnostic utility in thyroid malignancies. Parotid gland tumors represent the majority of major salivary gland neoplasms and pose significant diagnostic challenges due to their marked histological heterogeneity and overlapping clinical presentations [10, 15]. Our finding that NLR was independently associated with malignancy risk is consistent with previous studies investigating inflammatory markers in salivary gland tumors [1, 2, 15]. Recent evidence, including the study by Ozcelik Erdem et al. [25], has further supported the potential clinical relevance of inflammatory biomarkers in the preoperative evaluation of salivary gland malignancies. This role may reflect a biological imbalance in which an intensified neutrophil-associated inflammatory response contributes to a tumor-promoting microenvironment, while concomitant lymphopenia reflects impaired host immune surveillance [5, 7, 8, 1]. Our findings are also consistent with previous reports demonstrating higher NLR levels in malignant salivary gland lesions compared with benign lesions [23].

While the SII demonstrated borderline statistical significance in our cohort ($p = 0.049$), this finding reflects the ongoing debate in the literature regarding the diagnostic value of composite inflammatory indices. Sahin et al. reported significantly higher SII values in malignant parotid tumors [3], whereas Ikinciogullari et al. did not observe a statistically significant difference between benign and malignant groups for this parameter [26]. In our ROC analysis, neither NLR nor SII demonstrated statistically significant diagnostic performance, suggesting that these markers should be interpreted cautiously and primarily as supportive rather than standalone diagnostic tools. The variability among studies may partly be explained by the marked histopathological heterogeneity of parotid gland tumors, differences in study design, and the relatively limited number of malignant cases in single-center cohorts, which may reduce the statistical power of subgroup analyses.

Although the PLR is frequently discussed as a negative prognostic factor in several malignancies, our findings suggest that its diagnostic contribution in parotid gland tumors may be more limited and should be interpreted as an adjunctive parameter rather than a primary predictor [16, 19]. The sensitivity and

specificity of PLR may vary substantially depending on tumor subtype, tumor burden, and accompanying inflammatory conditions.

Preoperative assessment of parotid masses continues to rely mainly on imaging methods and FNAB, however, the diagnostic accuracy of FNAB may be limited in cystic, heterogeneous, or low-grade lesions [1, 6, 15]. Recent studies by Abbate et al. [27] and Committeri et al. [28] emphasized that inflammatory biomarkers may serve as useful supportive tools, particularly in indeterminate or suspicious cytological cases. In this context, inflammatory markers such as NLR, PLR, and SII may provide clinicians with easily accessible and cost-effective adjunctive information that can support preoperative risk stratification and surgical planning without disrupting routine clinical workflows. The biological interaction underlying these observations may also be associated with chronic inflammation-related cytokine activity, including IL-6 and TNF-α pathways, which contribute to tumor progression and suppression of antitumor immunity [9–11].

This study has several limitations that should be considered when interpreting the findings. As a retrospective, single-center study, the generalizability of the results may be limited. In addition, some baseline characteristics differed between the benign and malignant groups, particularly age distribution, which may have affected the direct comparability of the groups. Another important limitation is the relatively small number of malignant cases compared with benign tumors, which may have reduced the statistical strength and robustness of the analyses. Moreover, the imbalance between the benign and malignant groups may have further limited the ability to draw definitive conclusions regarding differences between tumor subtypes. Although strict inclusion and exclusion criteria were used to minimize the influence of inflammatory comorbidities, these criteria may also have introduced selection bias and may not fully reflect the broader patient population encountered in daily clinical practice. Therefore, the results should be interpreted with caution. Future larger-scale, prospective, multicenter studies with more balanced study groups are needed to further clarify the diagnostic value and clinical utility of systemic inflammatory markers in parotid gland tumors. In this context, the present study should be considered a pilot study.

CONCLUSION

NLR, PLR, and SII may provide preliminary and supportive information in distinguishing malignant from benign parotid tumors. These findings are exploratory and should not be used alone for diagnostic decision-making. Further large-scale, prospective, multicenter studies are needed to validate these results. This study should be considered a pilot study, and its findings should be interpreted with caution. Future research should prioritize the integration of systemic inflammatory markers with specific molecular profiles – including PD-L1 status, TP53 mutations, and DNA damage response pathways (e.g., ATM/CHK2) – to enhance preoperative risk stratification and better define the immune-inflammatory crosstalk in parotid carcinogenesis.

ACKNOWLEDGEMENTS

This study has been accepted as an oral presentation at the 46th Turkish National Congress of Otorhinolaryngology and Head and Neck Surgery, held in Cyprus from November 5–9, 2025.

Conflict of interest: None declared.

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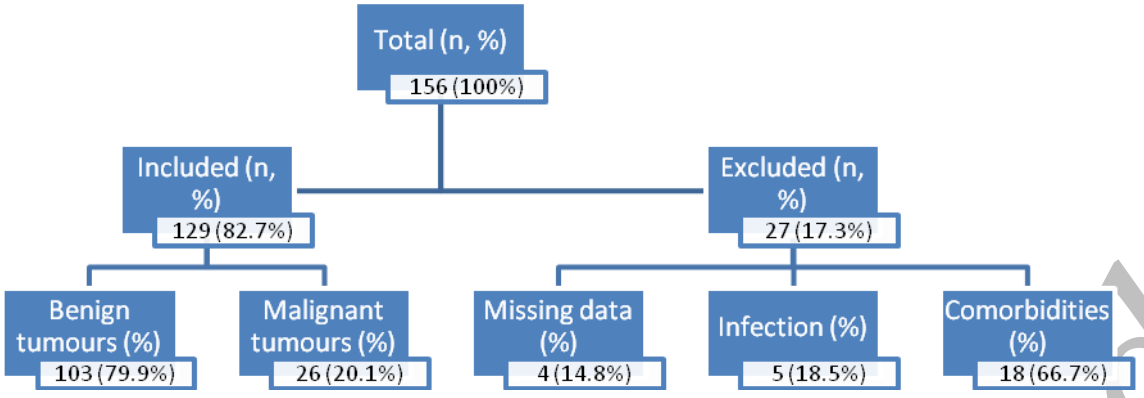

Figure 1. Flow diagram of patient selection and grouping

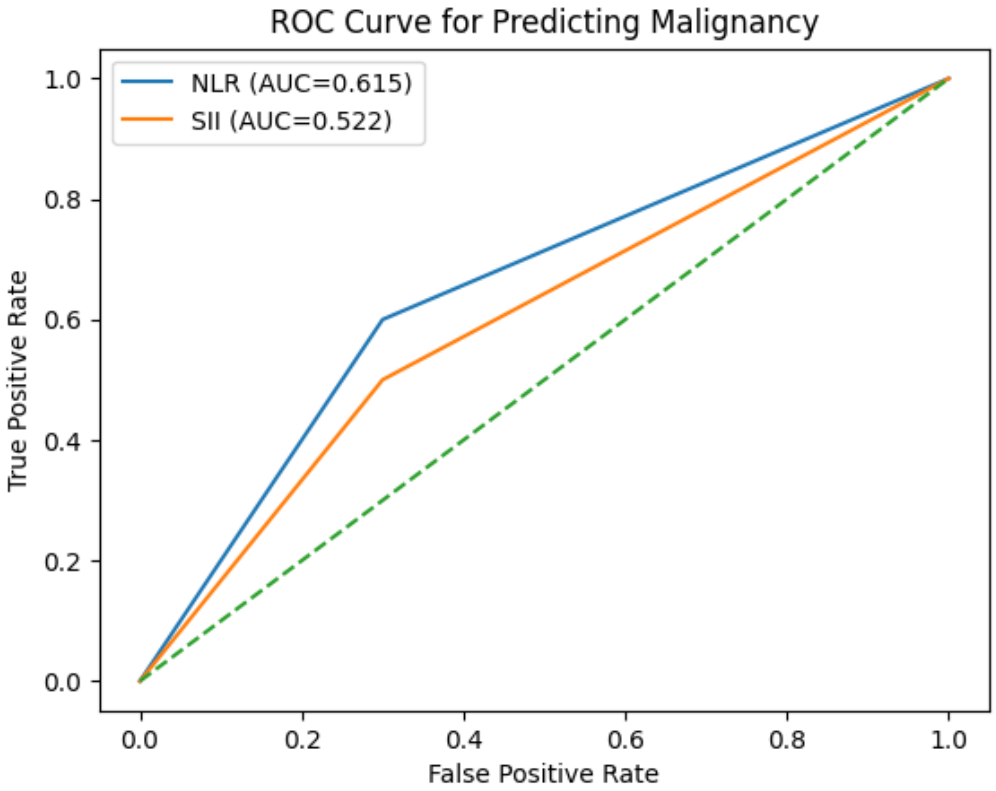

Figure 2. ROC curves demonstrating the diagnostic performance of NLR and SII in distinguishing benign and malignant parotid tumors

Table 1. Comparison of demographic and hematological parameters between benign and malignant parotid tumors

		Benign (n = 103)	Malignant (n = 26)	[a]p
Sex	**Male**	64 (62.1)	14 (53.8)	[a]0.440
	Female	39 (37.9)	12 (46.2)	
Age -Years	Mean ± SD	44.39 ± 15.36	51.88 ± 19.79	[b]0.038*
	Median (Min-Max)	45 (10–83)	50 (15–79)	
Neutrophils	Mean ± SD	4.91 ± 1.99	4.9 ± 2.21	[b]0.999
	Median (Min-Max)	4.6 (2.2–15.2)	4.5 (0.4–10)	
Lymphocytes	Mean ± SD	2.53 ± 0.78	2.08 ± 0.68	[b]0.008**
	Median (Min-Max)	2.4 (0.8–4.6)	2 (0.9–3.8)	
Platelets	Mean ± SD	268.18 ± 66.13	236.65 ± 59.44	[b]0.029*
	Median (Min-Max)	261 (104–443)	223 (167–442)	
NLR	Mean ± SD	2.05 ± 0.89	2.65 ± 1.74	[b]0.016*
	Median (Min-Max)	1.8 (0.9–5.9)	2.4 (0.2–8.2)	
PLR	Mean ± SD	112.83 ± 35.03	126.47 ± 55.95	[b]0.123
	Median (Min-Max)	106 (46.6–246.3)	112.5 (63.6–298.9)	
SII	Mean ± SD	543.37 ± 246.38	617.71 ± 392.09	[b]0.160
	Median (Min-Max)	506.4 (198.6–1374.1)	514.4 (63.6–1750.5)	

NLR – Neutrophil-to-Lymphocyte Ratio; PLR – Platelet-to-Lymphocyte Ratio;

SII – Systemic Immune-Inflammation Index;

[a]Pearson χ^2 test;

[b]Student's t-test;

*$p < 0.05$;

**$p < 0.01$

Table 2. Logistic regression analysis of risk factors affecting malignancy

	p	ODDS	%95 CI	
			Lower	Upper
Constant	0.001**	0.072		
NLR	0.013*	2.965	1.260	6.976
PLR	0.199	1.009	0.995	1.022
SII	0.049*	0.996	0.992	1.000

NLR – Neutrophil-to-Lymphocyte Ratio; PLR – Platelet-to-Lymphocyte Ratio;

SII – Systemic Immune-Inflammation Index;

Method – enter logistic Regression;

*$p < 0.05$;

**$p < 0.01$

Table 3. Diagnostic and ROC analysis for predicting malignancy using NLR and SII

	Diagnostic Scan					ROC Curve		p
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	AUC	95% confidence interval	
NLR	**≥ 2.199**	57.69	69.9	32.6	86.7	0.615	0.481–0.749	**0.068**
SII	**≥ 716.447**	38.46	84.47	38.5	84.5	0.522	0.378–0.665	**0.073**

NLR – neutrophil-to-lymphocyte ratio; SII – Systemic Immune-Inflammation Index; AUC – area under the curve

