Correlation of Histopathological Findings in Laryngeal Squamous Cell Carcinoma with Inflammatory Biomarkers

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Abstract

Objective: The goal of this research was to investigate how biomarkers, i.e. SII (an index calculated from blood counts of various leucocytes), NLR and MLR correlate with features used in the staging of laryngeal squamous cell carcinoma (LSCC), i.e. perineural infiltration, lymphatic involvement and histological grade.

Methods: A retrospective review of clinical records from 146 cases (143 men and 3 women) of LSCC occurring between January 2008 and January 2018 was undertaken. The sample included every stage of LSCC and all biomarker results were found from the full blood count (FBC) results obtained prior to surgery and documented for each case. SII is a newly introduced index of inflammation calculated according to the formula: $SII = NxP/L$, where N represents neutrophil, P platelet and L lymphocyte counts. Histopathological parameters (presence of perineural or lymphatic involvement, grade of tumour) were evaluated alongside results for NLR, MLR and SII.

Results: All three biomarkers were different at the level of statistical significance between individuals with LSCC and the controls. For NLR, p=0.003; for MLR, p=0.008; for SII, p<0.001.
Both NLR and SII were different at a statistically significant level when compared at early and advanced stages of LSCC (p values were 0.011 and <0.001, respectively. MLR did not differ at the level of statistical significance (p=0.944). (See Table 3).
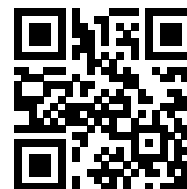
Conclusion: SII is straightforward to calculate, economical and reproducible from FBC results. It can provide important clues to the likelihood of perineural or lymphatic involvement in cases of LSCC.

Keywords: Laryngeal squamous cell carcinoma, inflammatory biomarkers, systemic immune-inflammation index

Compliance with Ethical Standards:

Financial disclosure: There is no funding or financial disclosure.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the research ethical committee of the Health Science University Umraniye Education and Research Hospital in Istanbul, Turkey as a review (protocol number: 6919).

Informed consent: Routine informed consent was obtained from all patients before the hospitalization and also inform consent from the individuals of the control group was obtained in the study.

Introduction:

Squamous cell carcinoma of the larynx (hereafter, LSCC) is amongst the most frequent neoplasms to occur in the respiratory system. The incidence of new cases in 2016 reached 13,430, resulting in 3,620 mortalities [1]. Around 60% of LSCC cases were already advanced (i.e. TNM staging III or IV) by the time they were diagnosed. Despite a fall in incidence of LSCC, survival at the five year mark has continued to worsen in the last four decades, from 66% to 63% [1]. Smoking and alcohol use are the principal aetiological risk factors for LSCC, alongside pollutants found in the environment, namely asbestos, dust produced by textiles and the polycyclic aromatic hydrocarbons [2].

The American Joint Committee on Cancer is responsible for the TNM staging methods in use for this condition, and this staging influences prognosis in important ways. Additionally, histopathological grading including degree of differentiation and presence of perineural infiltration or lymphatic involvement influence the prognosis [4].

Links between inflammatory processes and progression of neoplasms were first found many years ago. The area immediately surrounding a neoplasm features cells of inflammatory system lineage, the activities of which influence how neoplastic cells divide, invade and metastasize [5]. Previous studies have been published establishing a link between tumour behaviour and biomarkers of inflammation, especially the neutrophil to lymphocyte ratio (NLR) and the monocyte to lymphocyte ratio (MLR) [6-9]. In re-

search that is newly published, elevated levels of SII have been linked to worsened outlook in several neoplams of solid tissue type, e.g. hepatocellular carcinoma [10], esophageal squamous cell cancer [11], small cell lung cancer [12], renal cell carcinoma [13], colorectal cancer [14], nasopharyngeal cancer [15], and oral cavity cancer [16]. As far as the authors are aware, there has been no attempt to date to report on the usefulness of SII in LSCC.

The goal of this research was to investigate how biomarkers, i.e. SII (an index calculated from blood counts of various leucocytes), NLR and MLR correlate with features used in the staging of laryngeal squamous cell carcinoma (LSCC), i.e. perineural infiltration, lymphatic involvement and histological grade.

Materials and Methods:

Patient Selection:

Ethical approval (protocol number: 6919) was granted by the Research Ethics Committee of the Umraniye Educational and Research Hospital (protocol number: 6919), and the actual research was performed in the ENT Department of the Health Science University attached to the same hospital.

A retrospective review of clinical records from 146 cases (143 men and 3 women) of LSCC occurring between January 2008 and January 2018 was undertaken. The sample included every stage of LSCC and all biomarker results were found from the full blood count (FBC) results obtained prior to surgery and documented for each case. The values of the neutrophil, monocyte, lymphocyte and platelet counts were noted. SII is a newly introduced index of inflammation calculated according to the formula: SII = NxP/L, where N represents neutrophil, P platelet and L lymphocyte counts. SII, NLR and MLR were ascertained for each case and each control. The demographic profile of each individual was established and, for the LSCC cases, TNM staging was undertaken according to the criteria of the American Joint Committee on Cancer (AJCC), 8th edition [3], according to which cases were divided into early stage (correponding to TNM staging I and II) or advanced (TNM III or IV). Histopathological parameters (presence of perineural or lymphatic involvement, grade of tumour) were evaluated alongside results for NLR, MLR and SII.

The control group comprised 95 individuals (93 men and 2 women) chosen at random from those who had an

FBC performed in the course of a routine check-up and were considered healthy.

Exclusion criteria:

The following cases were excluded from the study:
- Cardiac disorders, including heart attack, valve disease, congestive cardiac failure
- Autoimmune disorders, e.g. Behçet's syndrome or Autoimmune thyroiditis
- Acute infective episode resulting in a leucocytosis ($>12,000mL^{-1}$, neutrophilia >70%, haemoglobinopathy with raised or low haemoglobin
- Other disorder. Sickle cell disorder, coagulation disorders (e.g. Factor V Leiden)
- Distant metastases present.

Analysis of biochemical and haematological parameters

Circulating FBC was obtained from all participants prior to surgery. The machine responsible for the FBC was the CELL-DYN 3700 automatic analyser produced by Abbott in the US. Leucocyte count, haemoglobin levels, haematocrit, thrombocytes and white cell differential (neutrophils, lymphocytes and monocytes) were all noted to enable calculation of the biomarkers – i.e. NLR, MLR and SII.

Statistical Analysis

The SPSS 20.0 (IBM Corporation, New York, NY) statistical application was used for all statistical analyses. The usual descriptive statistics were obtained (mean, median, standard deviations) and normal distribution was assessed by means of the independent sample t-test. Parameters whose distribution was not normal were assessed by means of the Mann-Whitney U test. The sex composition was compared with Fisher's Exact Test. To what extent the variance was homogenous was ascertained by Kolmogorov-Smirnov testing. Qualitative data were analysed with the Pearson chi-square or Fisher's Exact Test. A p value of less than 0.05 was taken to indicate statistical significance. To ascertain the ideal cutoff points for the SII, NLR and MLR, ROC curves (Receiver operating characteristics) were plotted.

Results:

Table 1 indicates the demographic spread of the participants from both control and cases groups. The cases had a mean age of 59.78±9.7 years, whilst controls were 57.48 ±8.4 years old on average. Men outnumbered women in both groups. For the cases, by 143:3, and for controls, by 93:2. The LSCC cases were followed-up on average for 40.86 ± 25.26 months. Table 2 lists the mean value and accompanying standard deviation for NLR, MLR and SII in both groups. As can be seen from Table 2, the biomarkers were each (NLR, MLR and SII) different at the level of statistical significance (P values, 0.003, 0.008 and <0.001) between the two groups.

Within the cases group, NLR and SII were different at the level of statistical significance when compared in early or advanced cases (p=0.011 and p<0.001, respectively), but the result for MLR failed to reach the level of statistical significance (p=0.944). See Table 3.

Receiver operating characteristic (ROC) curve was calculated to determine the optimal SII, NLR and MLR cut-off values. The LSCC cases were apportioned to two groups, on the basis of values above or equal to and below a particular set cutoff point. If perineural infiltration was present, this point was set as 1.925, 0.249 and 534.105 for NLR, MLR and SII, respectively (Table 4). Whilst for NLR (p=0.026)

Table 1: Demographic paramaters of groups.

		Larynx Ca.	Control	*p-values*
	Number of subjects	146	95	
	Sex (M/F); *n*	143/3	93/2	[a]0.65
Age (*year*)	*Mean±SD*	59.78±9.7	57.48±8.4	[b]0.06
	Median (Range)	59 (40-81)	57 (43-82)	
Follow-up (*month*)	*Mean±SD*	40.86±25.26		
	Median (Range)	38 (1-108)		

aFisher Exact Test   bIndependent Sample t Test   *p<0,05

Table 2: The comparison of the mean ± standard deviation and median of NLR, MLR and SII parameters of the LSCC and control groups

Paramaters		Larynx Ca. n:146		Control n:95		p-values
NLR	Mean ± Std. Dev		2,39 ± 1,37		1.94 ± 0.88	a0.003*
	Median (Min-Max)	2.09	(0.56-9.46)	1.81	(0.27-5.56)	
MLR	Mean ± Std. Dev		0,28 ± 0,12		0,25 ± 0,14	a0.008*
	Median (Min-Max)	0,25	(0,07-0,80)	0,23	(0,03-1,10)	
SII	Mean ± Std. Dev		747,01 ± 603,61		514,50 ± 295,14	a<0.001*
	Median (Min-Max)	580,63	(131,82-5.024,65)	472,70	(75,92-2.053,80)	

aMann-Whitney U Test   *p<0.05

Table 3: The comparison of NLR, MLR, and SII of early and advanced stage LSCC patients

Parameters		Early Stage n:72		Advanced Stage n:74		p-values
NLR	Mean ± Std. Dev		2,02 ± 0,37		2.75 ± 1.72	a0.011*
	Median (Min-Max)	1.88	(0.56-4.42)	2.33	(0.84-9.46)	
MLR	Mean ± Std. Dev		0,27 ± 0,09		0.29 ± 0.14	a0.944
	Median (Min-Max)	0,25	(0,07-0,63)	0,25	(0.08-0,80)	
SII	Mean ± Std. Dev		553,34 ± 572,10		935.44 ± 576.52	a<0.001*
	Median (Min-Max)	460.25	(131,82-5.024,65)	755.62	(284.27-3170.36)	

aMann-Whitney U Test   *p<0.05

Table 4: The correlation of NLR, MLR and SII with the presence of perineural and lymphovascular invasion in patients with LSCC

Cut-off values	Perineural Invasion n:146		p-values	Cut-off values	Lymphovascular Invasion n:146		p-values
	positive	negative			positive	negative	
NLR≤1,925	24	39	a0,026*	NLR≤2,245	9	73	a0,073
NLR>1,925	47	36		NLR>2,245	14	50	
MLR≤0,249	29	42	a0,067	MLR≤0,238	9	46	a0,875
MLR>0,249	42	33		MLR>0,238	14	77	
SII≤534,105	17	45	a<0,001*	SII≤613,025	7	72	a0,013*
SII>534,105	54	30		SII>613,025	16	51	

aPearson Chi-Square test   *p<0,05

Table 5: The correlation of NLR, MLR and SII with pathological differentiation degree of LSCC

Cut-off values	Differantiation Degree n:146		p-values
	Well&Moderate	Poor	
NLR ≤ 2,06	55	16	0,692
NLR > 2,06	56	19	
MLR ≤ 0,2445	49	18	0,287
MLR > 0,2445	62	17	
SII ≤ 603,71	62	16	0,294
SII > 603,71	49	19	

aPearson Chi-Square test   *p<0,05

and SII (p<0.001) there was a correlation between an elevated value and the presence of perineıral infiltration, this did not hold for MLR (p>0.05). The corresponding values for NLR, MLR and SII in cases of lymphatic involvement were set as 2.245, 0.238 and 613.025, respectively (Table 4). Correlation with lymphatic involvement was statistically significant only where SII was markedly raised (p=0.013). To investigate correspondence with histological grade, the cutoff values were set as 2.06 for NLR, 0.2445 for MLR and 603.71 for SII (Table 5). Correlation did not hold between the biomarkers and histological grade (p>0.05). The ROC characteristics of the three biomarkers are illustrated for perineural infiltration in figure 1, lymphatic involvement in figure 2 and histological grade in figure 3.
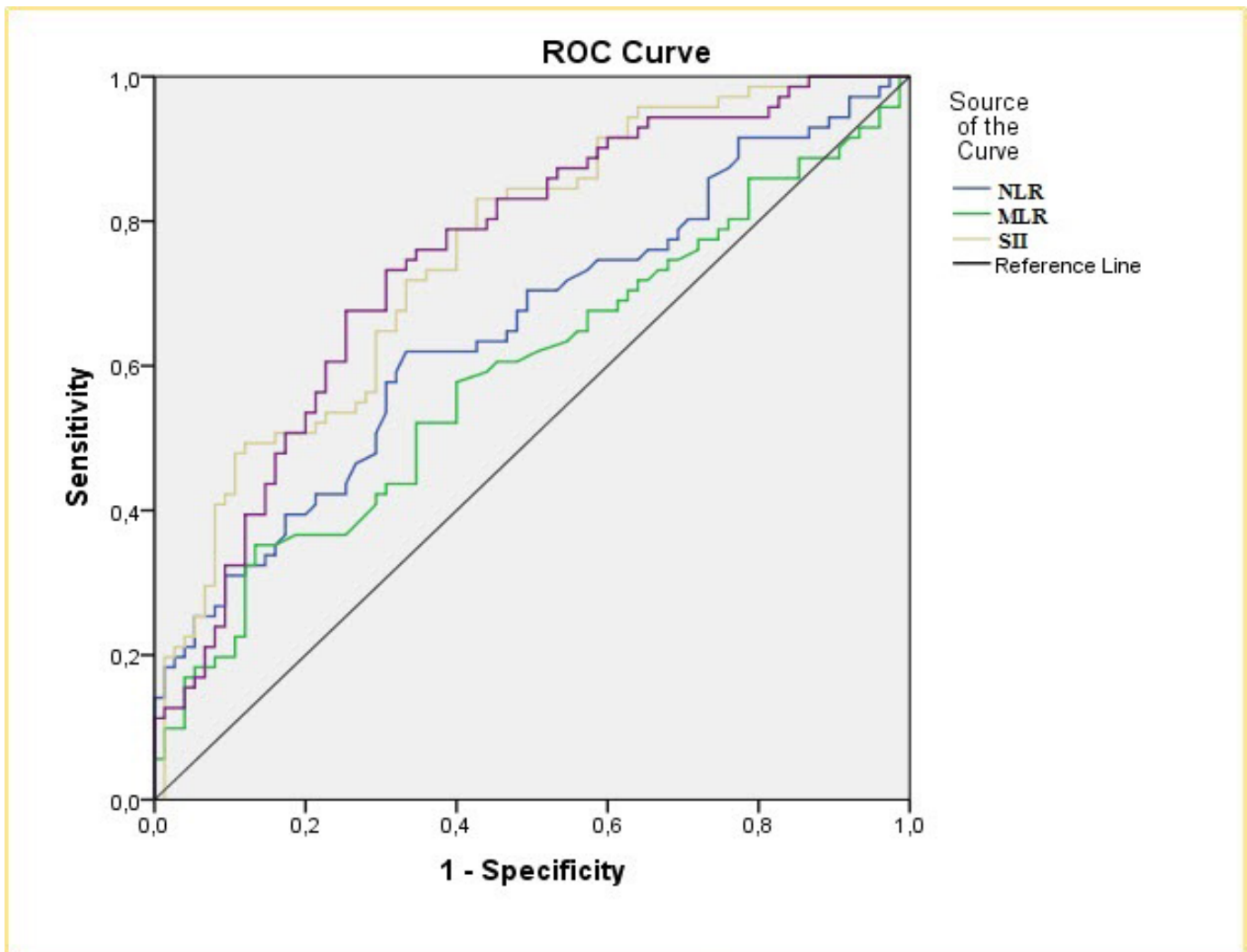

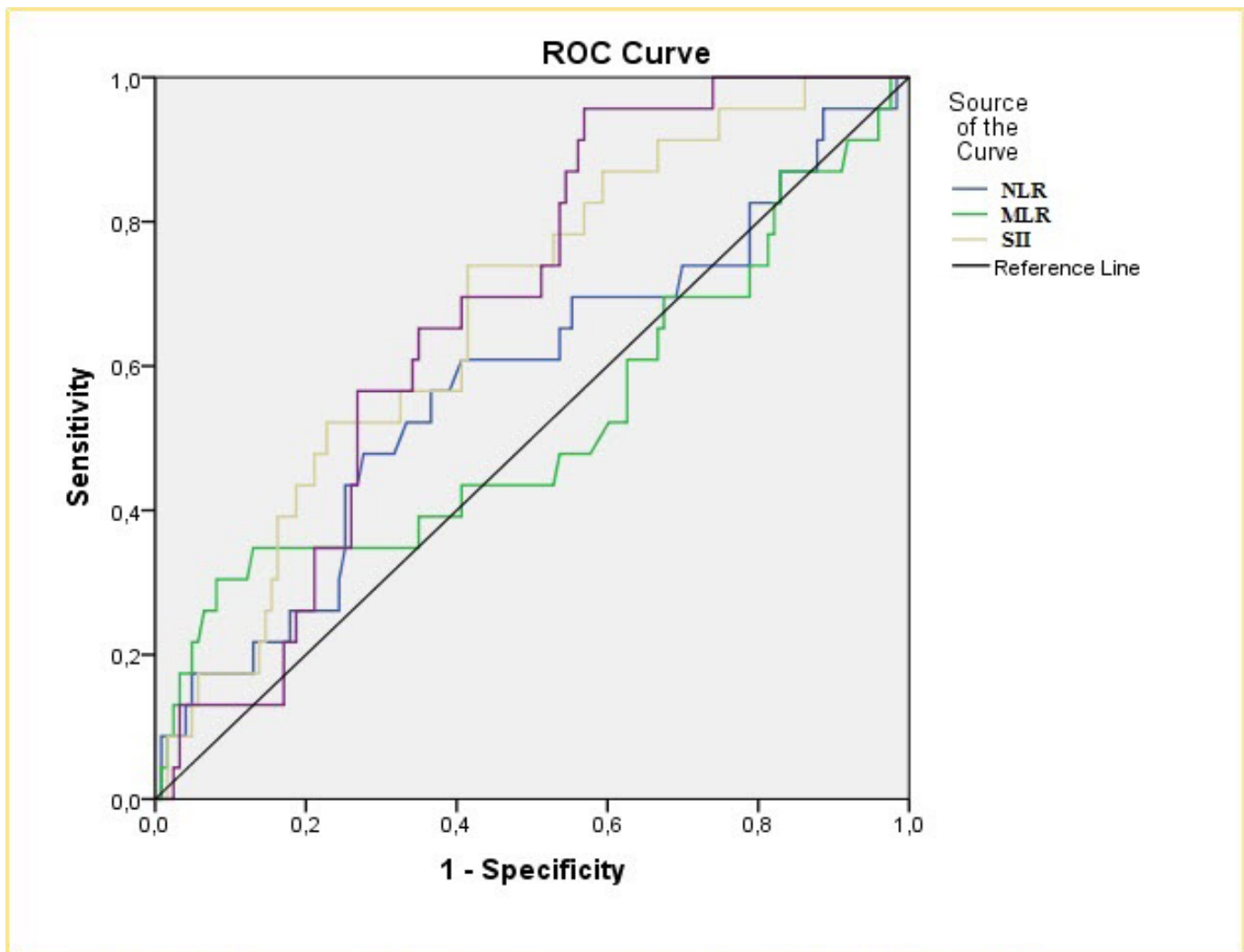**Figure 1.** The ROC curve analysis of perineural invasion for NLR, MLR and SII.

Figure 2. The ROC curve analysis of lymphovascular invasion for NLR, MLR and SII

Discussion

Laryngeal carcinoma has a male predilection [6], a fact reflected in the composition of the cases that made up this research sample.

The intimate connections between neoplasia and immune responses have been extensively researched, as has the role of inflammation in neoplastic transformation. The surrounding area around a tumour, with its accompanying inflammatory processes, forms the substrate for neo-angiogenesis, invasion and metastasis [5]. A number of previous studies have looked at the value of the same biomarkers in prognosis. Neutrophilic activity stimulates cancers to grow via release of vascular endothelial growth factor (which enables new vessel formation), chemokines and proteases. Moreover, neutrophils help metastatic satellites to adhere to distant body locations [17, 18]. Malignant cells secrete factors, e.g. interleukins 8 and 6 and TNF-α, which exert a chemoattractive effect on neutrophils [19]. These factors induce a neutrophilia, promote damage to DNA within the cells, hinder programmed cell death and cause new vessels to form [18]. Thrombocytes and the coagulatory cascade also play a part in how malignancy takes hold. Thrombocytes, for example, ensure metastatic adhesion to the endothelial lining and hinder apoptosis [20]. Notably, an association has been found between prescription of aspirin for its antico-
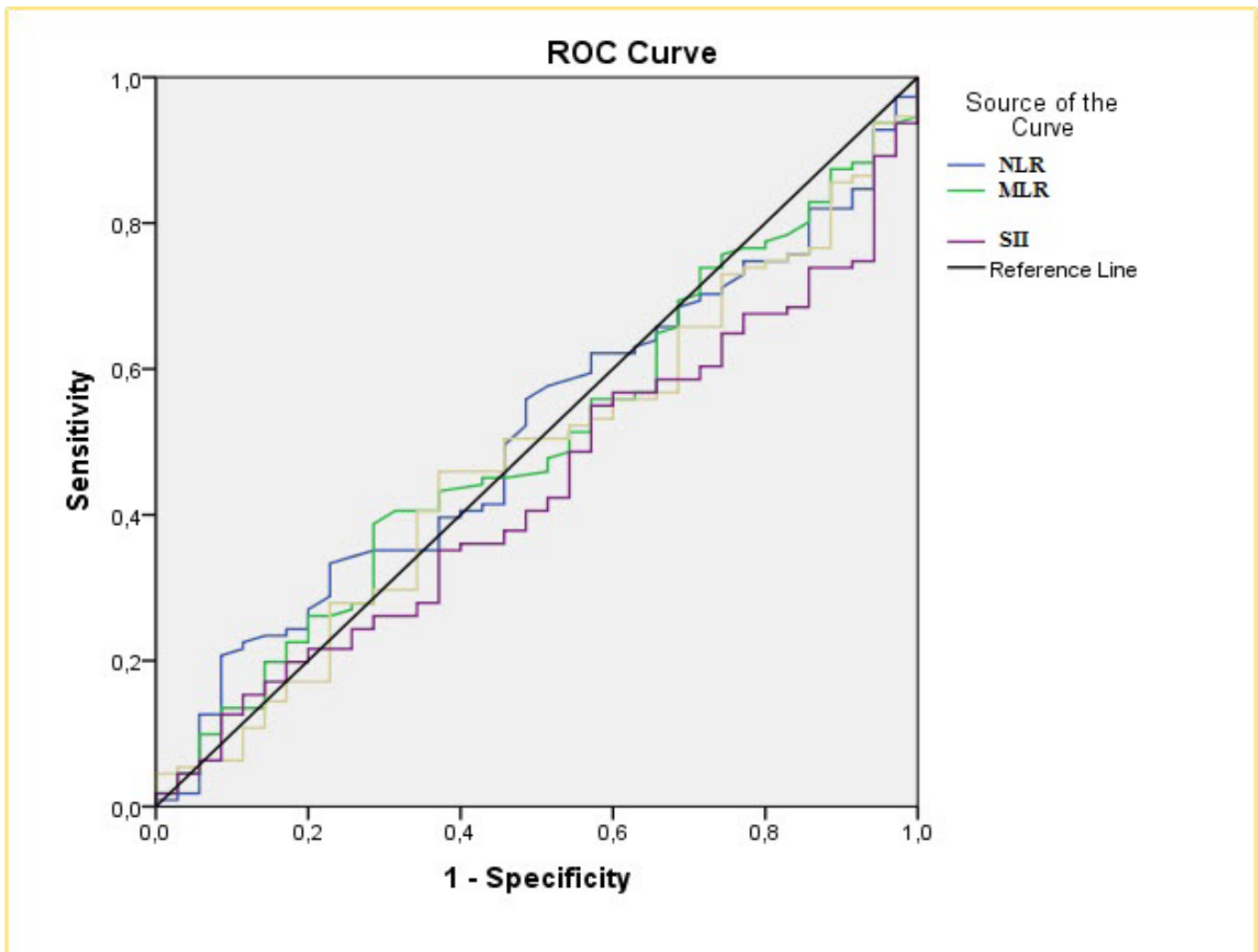
Figure 3. The ROC curve analysis of histological grade with NLR, MLR, and SII

agulant effect and a reduction of around 25% in immediate risk for certain neoplastic types [21].

Monocytosis has similarly received attention as an indicator of worsened prognosis in both haematological and non-haematological solid-type malignancies [9]. Circulating monocytes develop into histiocytes in the region of the malignancy and act to favour malignant progression through dampening down localised immune responses and promoting the growth of new vessels [22, 23]. Lymphocytes of both adaptive and innate lineages, by contrast, act to suppress malignant progression [24]. Their actions via cytokines prevent malignant cell division and inhibit metastasis, as well as promote cytotoxic killing of malignant cells [25]. Thus, if numbers of lymphocytes in the circulation fall, the

restraining influence of the immune system on malignant lesions may decrease, with resulting increases in malignant infiltration and metastasis [24]. Indeed, earlier research has demonstrated that the level of circulating lymphocytes independently predicts both survival time and progression-free survival in a wide variety of malignant lesions at their advanced stage [26].

Within the last ten years, multiple biomarkers based on inflammatory activity (e.g. NLR and MLR) have been in use clinically to predict likely prognosis. According to our results, NLR is the only biomarker that is elevated in LSCC cases compared to healthy individuals at the level of statistical significance.

The NLR gives a measure of the balance of the im-

mune system in either fostering or hindering neoplastic progression. A rise in neutrophil or a fall in lymphocyte numbers correlates with a raised NLR, indicative of an immune response that favours tumour progression [27]. Kum and colleagues were the first to specifically evaluate NLR in laryngeal malignancy, based on a retrospective analysis [6]. Their findings indicated that the raise in NLR in LSCC cases may form an effective basis to distinguish between LSCC and pre-malignant or benign laryngeal neoplasms. Elevated NLR reveals a reduced survival rate in cases of squamous cell malignancies of the head and neck, according to Mascarella *et al.* [7]. Kara and colleagues [8] attempted to correlate NLR, PLR and RDW (red cell distribution width) with prognosis in cases of LSCC, concluding that NLR was indeed elevated at the level of statistical significance in individuals with recurrent lesions, but did not predict death accurately. Both elevated RDW and PLR correlated with higher mortality. Chandrasekara *et al.* [28] assessed NLR in head and neck malignant squamous lesions as a biomarker following definitive chemotherapy and radiotherapy. The present study confirms that NLR is elevated significantly in individuals whose malignancy is advanced. Whilst perineural infiltration did appear to be reflected in a raised NLR, this was not the case for lymphatic involvement.

Park *et al.* looked at how biomarkers correlate with TMN staging [29]. LMR correlated with T stage, N stage and histological grade, NLR correlated with T stage and histological grade and PLR correlated with N stage and histological grade in cases of mouth cancer. They proposed a scoring system for prognosis on the basis of the three biomarkers which was shown to correlate with survival in mouth cancer cases treated by operation. Similarly, Nishijima *et al.* suggest that if the PMR prior to therapy is low, the outcome is worse for individuals with neoplasms of non-haematological origin [9]. According to our findings, whilst MLR is elevated in LSCC cases compared to normal, the early and advanced stages of the disease are not reflected in a statistically significant difference in the MLR, nor does a statistically significant difference exist reflecting change in status of perineural infiltration, lymphatic involvement or histological grade.

Newly published research has looked at the role of SII as a new biomarker for use in calculating the prognosis for various malignant neoplasms and has indicated that NLR, LMR and SII have a correlation for multiple tumour types [10-15, 30]. In situations where neutrophil and thrombocyte numbers are raised alongside depleted lymphocytes, a high SII may reflect a pro-inflammatory bias and lesser immune protection in cases of malignancy. Many solid neoplasms have poorer survival rates when the SII is high [30]. For both nasopharyngeal and oesophageal squamous malignant neoplasms, SII has been shown to have a greater prognostic capability than either NLR or MLR [11,15]. Whilst SII has been evaluated in a variety of malignancies, ours is the first research to look specifically at LSCC. The present study has revealed that SII is indeed elevated in cases of LSCC in comparison with healthy controls, and is also further raised in advanced compared to early stage disease.

Both survival free from disease and recurrence of the lesion are significantly related to whether perineural infiltration or lymphatic involvement have yet occurred [4]. There is a correlation between N and T staging and perineural infiltration, as well as survival free from disease. In the present study, how the SII relates to the key factors influencing the outlook in malignancy, i.e. perineural infiltration, lymphatic involvement and high histological grade, has also been examined. There was frequent co-occurrence of perineural infiltration and lymphatic involvement in cases with a high SII, and an association with higher histological grade has been confirmed.

Conclusion:

SII is a straightforward, inexpensive and reproducible value that is obtainable from the FBC. Its value in LSCC is in providing information on the likelihood of perineural infiltration and lymphatic involvement. Assays for cytokines, namely interleukins 8 and 6 and TNF-α are not found in usual clinical settings. Thus, the authors recommend that where the SII is raised in LSCC, careful follow-up is indicated.

Conflict of Interest: The authors confirm that they have no conflict of interest to declare.

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