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Original Article

Diagnostic Role of Neutrophil-Lymphocyte Ratio in Oral Cavity Cancers

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Abstract

Aim: In this study, we aimed to evaluate the diagnostic role of neutrophil–lymphocyte ratio (NLR) and other hemogram parameters in differentiating nonmalignant oral cavity lesions from oral cavity cancers. **Methods:** Ninety-five patients who were performed oral cavity biopsy between the years 2013 and 2015 were retrospectively reviewed. The control group comprised consecutive 70 patients who underwent septoplasty/septorhinoplasty procedures. Inclusion criteria were to be available with common blood count (CBC) just prior to procedure. The hemogram parameters including NLR were compared between the groups. **Results:** Lymphocyte count and mean platelet volume (MPV) were found to be significantly decreased in oral cavity squamous cell carcinoma (SCC) and in other oral cavity cancers (OCCs) compared with benign oral cavity lesions and control group. In contrast, NLR revealed significantly higher in OCCs and in oral SCC compared with nonmalignant oral cavity lesions and control group. The receiver operating characteristics curve analysis suggested cutoff value of 2.88 for NLR in predicting malignancy [area under curve (AUC) 0.756, sensitivity 51%, specificity 88%]. **Conclusions:** NLR was first shown to be significantly elevated in oral cavity cancers and in oral cavity SCC in this study. In our opinion, NLR may be helpful in identifying the oral cavity lesions at high risk for harboring malignancy.

Keywords: *Lymphocyte, neutrophil, neutrophil–lymphocyte ratio, oral cavity cancer, squamous cell carcinoma*

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Introduction

The relation between inflammation and cancer development is one of the most investigated issues in the last decade.[1] Some hematological and biochemical markers of inflammation such as leukocyte count neutrophil-lymphocyte ratio (NLR) and C-reactive protein (CRP) levels were found to be associated with the presence or prognosis of several cancer types.[2-11] NLR is one of the most studied and confirmed prognostic parameter among these. Elevated NLR was shown to be correlated with poor survival in esophageal, lung, breast, gastric, colorectal, and genitourinary system cancers.[5-11] There is also growing evidence about potential diagnostic and prognostic role of NLR in head and neck malignancies. In the study of Kum *et al.*[12] NLR was found to be significantly increased in laryngeal squamous cell carcinoma (SCC) compared with benign and premalignant laryngeal disorders. Likewise, in our previous study, NLR was found to be significantly higher in laryngeal SCC compared with control (patients undergoing septorhinoplasty) group.[13]

Differentiating benign and malign oral cavity lesions is a challenging issue for oral cavity lesions. Visual appearance and tactile sensation on physical examination is very crucial for diagnosis. Depending on visual appearance, leukoplakia and erytroplakia are the most commonly used clinical terms to point out oral cavity lesions; those are at high risk for harboring malignancy.[14] There are also other methods of identifying malignant oral cavity lesions such as fluorescence imaging and salivary protoporphyrin examination.[15]

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In this study, we aimed to show the potential diagnostic role of NLR and other hemogram parameters in differentiating nonmalignant oral cavity lesions from oral cavity cancers and SCC in particular.

Material and Methods

Study design

After taking approval from local ethics committee, the patient charts of our outpatient clinic between the years 2013 and 2015 were retrospectively reviewed. The patients who were performed oral cavity biopsy (incisional, excisional, punch, etc.) under topical or local anesthesia for diagnostic or therapeutic purposes were reviewed. Inclusion criteria were to be available with common blood count (CBC) just prior to procedure. Exclusion criteria were having acute/chronic systemic inflammatory condition (including oral manifestations of pemfigius vulgaris or bullous pemfigoid) and lacking histopathological confirmation. The consecutive 70 subjects who were performed septorhinoplasty or septoplasty procedures constituted the control group. There were totally 95 subjects meeting inclusion criteria in the study group. The study population was grouped according to histopathologic diagnosis. The group I was composed of all malignant cases, including epithelial, salivary gland, lymphoid, or soft tissue originated (Group I). The Group II was including all of the remaining nonmalignant lesions, benign or premalignant tumors and cystic or infectious lesions. The CBC parameters including neutrophil, lymphocyte, white blood cell (WBC) and platelet (Plt) count, hemoglobin value (Hb), mean platelet volume (MPV), and mean corpuscular volume (MCV) were recorded. NLR of the subjects were calculated subsequently. All of these hemogram parameters (including NLR) were compared between the groups. After excluding premalignant, cystic, and infectious diseases and above-mentioned nonepithelial originated malignancies, the comparison was repeated between oral SCC, and benign oral cavity lesions. To examine whether the age difference between the groups (study and control) would affect the value of any CBC parameter, all 165 subjects were classified into two groups according to age: being above or under than 45 years to compare hemogram parameters.

Statistical analysis

SPSS version 20.0 package program (IBM, Chicago, Illinois, USA) was used for statistical analysis. Continuous variables were tested for normality using Kolmogorov-Smirnov or Shapiro-Wilks test depending on number of subjects, histograms and *P-P* plots. $\chi 2$ test used for comparison of gender distributions. Analysis of variance or Kruskal-Wallis tests were used for comparison of parametric and nonparametric variables respectively, between three or more groups. However Standard *t* test or Mann-Whitney *U* tests were used for comparison of parametric and nonparametric variables, respectively, between two groups. Receiver operating characteristics curve (ROC) analysis was performed to suggest cutoff value for NLR in predicting malignancy. In all the tests $P < 0.05$ was considered to be significant statistically.

Results

There were totally 95 subjects suffering from an oral cavity lesion available with preoperative CBC record and histopathological confirmation [Table 1]. Of these 95 subjects, 41 of them were diagnosed with malignancy. In these 41 patients, 30 cases were diagnosed with oral cavity SCC [Table 1]. Within the remaining 54 patients diagnosed with nonmalignant oral cavity mucosal lesion, there were several histopathologic subgroups including premalignant lesions as shown in [Table 1]. The control group was including 34 males and 36 females with the mean age 36.43 ± 14.20 years. No significant difference in M/F ratio revealed between groups ($P = 0.321$). However, group II (malignant group) was found to be older compared with Group I and control group ($P < 0.001$). The neutrophil and lymphocyte count, NLR, Hb level, and MPV were all found to be significantly different between groups [Table 2]. Comparison of hemogram parameters between Groups I and II are shown in [Table 3]. NLR was found to be significantly

Table 1: Histopathological distribution of oral cavity lesions included in the study

Nonmalignant	*N*	Malignant	*N*
Melanosis	2	SCC	30
Capillary hemangioma	2	Mucoepidermoid carcinoma	4
Cavernous hemangioma	1	Adenoid cystic carcinoma	6
Fibroepithelial polyp	1	Sarcomatoid carcinoma	1
Squamous papilloma	11		
Mucocele	1		
Lymphoid hyperplasia	1		
Ossifiying fibroma	1		
Irritation fibroma	1		
Fibroma	1		
Chronic inflammation	3		
Spongiotic mucositis	2		
Actinic cheilitis	1		
Nodular fasciitis	1		
Dysplasia	1		
Squamous epithelial hyperplasia and/or hyperkeratosis	10		
Pyogenic granuloma	1		
Lichen planus	10		
Pseudoepitheliomatous hyperplasia	3		
Total			95

SCC = squamous cell carcinoma.

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Table 2: Comparison of demographic data and hemogram parameters between groups

	Group I (nonmalignant)	Group II (malignant)	Control group	Total	*P*
N	54	41	70	165	–
Gender (M/F)	25/29	25/16	34/36	84/81	0.321*
Age	48.09 ± 13.48	58.90 ± 12.47	36.43 ± 14.20	45.83 ± 16.24	<0.001***
WBC	7.78 ± 2.24	7.59 ± 1.66	7.34 ± 1.63	7.55 ± 1.88	0.641**
Neutrophil	4.63 ± 1.72	5.03 ± 1.48	4.24 ± 1.35	4.58 ± 1.55	0.020**
Lymphocyte	2.33 ± 0.70	1.81 ± 0.56	2.32 ± 0.68	2.19 ± 0.70	<0.001**
NLR	2.09 ± 0.83	3.07 ± 1.30	1.95 ± 0.83	2.29 ± 1.07	<0.001**
Hemoglobin	14.17 ± 1.37	13.30 ± 2.07	14.42 ± 1.61	14.08 ± 1.72	0.003***
Platelet	248.72 ± 52.18	250.04 ± 65.98	251.66 ± 55.97	250.00 ± 57.13	0.934***
MPV	8.62 ± 0.97	8.08 ± 1.15	8.60 ± 1.05	8.47 ± 1.07	0.019**
MCV	88.31 ± 5.00	87.38 ± 7.03	87.44 ± 4.62	87.67 ± 5.35	0.694***

MCV = mean corpuscular volume; MPV = mean platelet volume; *N* = sample size; NLR = neutrophil–lymphocyte ratio; *P* = significance level; WBC = white blood cell. *Pearson χ^2 **Kruskal-Wallis ***One-way analysis of variance

Table 3: Comparison of demographic data and hemogram parameters between malign and nonmalignant oral cavity lesions

	Group I (Non-malignant)	Group II (malignant)	Total	*P*
N	54	41	95	–
Gender (M/F)	25/29	25/16	50/45	0.156*
Age	48.09 ± 13.48	58.90 ± 12.47	52.76 ± 14.06	<0.001**
WBC	7.78 ± 2.24	7.59 ± 1.66	7.71 ± 2.04	0.631**
Neutrophil	4.63 ± 1.72	5.03 ± 1.48	4.82 ± 1.64	0.068***
Lymphocyte	2.33 ± 0.70	1.81 ± 0.56	2.10 ± 0.70	<0.001**
NLR	2.09 ± 0.83	3.07 ± 1.30	2.54 ± 1.16	<0.001***
Hemoglobin	14.17 ± 1.37	13.30 ± 2.07	13.84 ± 1.77	0.051***
Platelet	248.72 ± 52.18	250.04 ± 65.98	248.77 ± 58.24	0.854**
MPV	8.62 ± 0.97	8.08 ± 1.15	8.38 ± 1.08	<0.019**
MCV	88.31 ± 5.00	87.38 ± 7.03	87.84 ± 5.85	0.693***

MCV = mean corpuscular volume; MPV = mean platelet volume; *N* = sample size; NLR = neutrophil–lymphocyte ratio; *P* = significance level; WBC = white blood cell. *Pearson χ^2 **Standard *t* test ***Mann-Whitney *U* test

Table 4: Comparison of demographic data and hemogram parameters between benign oral cavity lesions and SCC

	Benign	SCC	*P*
N	34	30	–
Gender (M/F)	18/16	20/10	0.265*
Age	46.80 ± 10.20	60.20 ± 12.38	<0.001**
WBC	7.90 ± 2.31	7.43 ± 1.36	0.340**
Neutrophil	4.78 ± 1.61	4.92 ± 1.21	0.152***
Lymphocyte	2.32 ± 0.79	1.76 ± 0.52	0.002**
NLR	2.19 ± 0.72	3.07 ± 1.21	<0.001***
Hemoglobin	14.55 ± 1.29	13.35 ± 1.98	0.023***
Platelet	247.73 ± 59.01	248.75 ± 71.53	0.950**
MPV	8.67 ± 0.86	7.81 ± 0.89	<0.001**
MCV	88.20 ± 4.18	89.02 ± 5.47	0.502**

MCV = mean corpuscular volume; MPV = mean platelet volume; *N* = sample size; NLR = neuthphil–lymphocyte ratio; *P* = significance level; SCC = squamous cell carcinoma; WBC = white blood cell. *Pearson χ^2 **Independent Samples *t* test ***Mann–Whitney *U* test

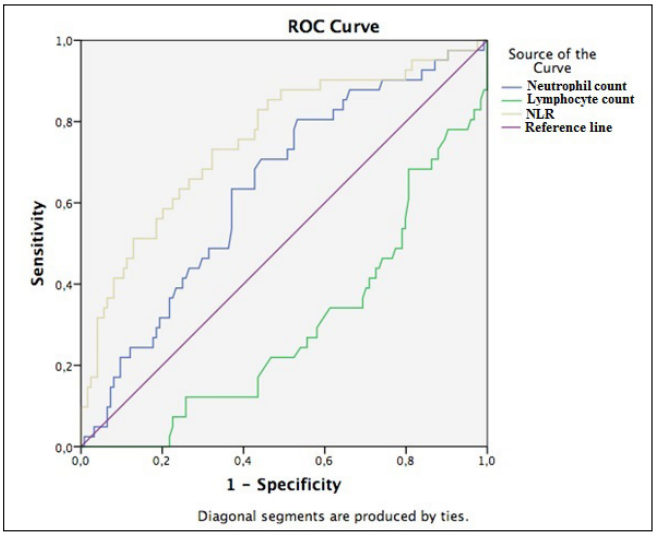


Figure 1: Receiver-operating characteristics curve (ROC) analysis for neutrophil, lymphocyte count and NLR. The ROC analysis suggested cutoff value of 2.88 for NLR in predicting malignancy (AUC: 0.756, sensitivity 51%, specificity 88%).

higher in malignant group compared with nonmalignant group, 3.07 ± 1.30 and 2.09 ± 0.83, respectively ($P < 0.001$). Lymphocyte count and MPV were significantly decreased in malignant group [Table 3]. Similar findings revealed in comparison of benign oral

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lesions and oral cavity SCC [Table 4]. ROC analysis suggested cutoff value of 2.88 for NLR in predicting malignancy [area under curve (AUC): 0.756, sensitivity 51% specificity 88%] [Figure 1]. Finally, no significant difference revealed between hemogram parameters of the subjects older or younger than 45 years old ($P > 0.05$).

Discussion

In this study, lymphocyte count and MPV were shown to be significantly decreased in oral cavity SCC and in other oral cavity malignancies compared with benign oral cavity lesions and control group. In contrast, NLR revealed significantly higher in OCCs as well as in oral cavity SCC compared with non-malignant oral cavity lesions and control group. The ROC analysis suggested cutoff value of 2.88 for NLR in predicting malignancy (AUC: 0.756, sensitivity 51%, specificity 88%). Therefore, an NLR value greater than 2.88 may be helpful in clinical use in predicting malignancy for oral cavity lesions. Elevated NLR may be due to a relative neutrophilia or lymphopenia. In our study a nonsignificant elevation of neutrophil count and a significant decrease in lymphocyte count were found in malignant oral cavity lesions and SCC in particular. In addition, Hb level revealed significantly decreased in oral SCC compared with benign oral cavity lesions.

Leucocytes also called white blood cells (WBC) are responsible for protecting the body against infectious diseases and foreign invaders.[3] Neutrophils are the most common cell type seen in the early stages of acute inflammation whereas lymphocytes are enrolled in chronic infections. Systemic inflammation activated by cancer cells is known to be involved in tumor growth by promoting angiogenesis.[3,16] Lymphocytes and neutrophils seem to have reverse effects on cancer cell growth and progression.[16,17] Lymphocytes, in particular T-lymphocytes inhibit proliferation and metastatic spread of tumor cells via cytotoxic cell death and production of cytokines, respectively.[18,19] Neutrophils also take place in anti-tumoral immune response.[20,21] In the meantime, neutrophils increase angiogenesis mainly via vascular endothelial growth factor (VEGF), which in turn promote development and spread of cancer cells.[16,17,22] As a result, an elevated NLR owing to a relative neutrophilia and lymphopenia is commonly observed in case of malignancy.

In head and neck malignancies, NLR was first studied in nasopharyngeal carcinoma. Elevated NLR was shown be associated with poor survival in nasopharyngeal carcinoma.[23,24] Later on other reports were published regarding the association of elevated NLR for laryngeal SCC diagnosis and survival.[12,13,25] In the study of Perisanidis *et al.*[26] elevated NLR was shown to be associated with poor survival in patients with oral cavity cancer who were given preoperative chemoradiotheraphy. Likewise Fang *et al.*[3] studied the prognostic role of inflammatory markers: CRP and NLR in oral cavity SCC. Elevated NLR and CRP were found to be significantly associated with tumor stage and survival. In the present study a nonsignificant increase in neutrophil count was observed in OCCs compared with nonmalignant oral cavity pathologies. However, lymphocyte count was found to be significantly decreased and NLR was significantly increased in oral cavity SCC compared with benign oral cavity pathologies and control group.

In addition, Hb level and MPV were significantly different in oral SCC compared with benign pathologies. Plt count and MPV were shown to be increased in lung, colorectal, and ovarian cancer previously.[27-29] Two mechanisms are postulated for Plt and MPV increase in cancer. It may be due to thrombocytosis of cancer cells or due to activation of bone marrow megacaryocytes by cytokines such as interleukin-6 (IL-6) and VEGF.[27,30,31] However, in our study MPV was found to be significantly decreased in cancer cases contrary to above-mentioned reports and mechanisms.

Hb levels were found to be significantly decreased in oral cavity SCC compared with benign oral cavity diseases in our study. This is an expected finding as anemia is a common condition occurring up to 50% of cancer patients.[32] In addition, anemia is associated with poor prognosis in head and neck cancers.[33]

The main limitation of the study is the diversity of the oral cavity lesions included in the study. Therefore, the comparison was repeated for oral cavity SCC and benign lesions. In addition, comparison of benign-premalignant-malignant disorders would be valuable. However, the number of premalignant conditions was not adequate for such a comparison in our study group. Another limitation is the significant mean age difference between groups. Head and neck cancer is more common in elderly, as a result the malignant group revealed with advanced age compared with benign and control group. However, we did not observe any difference in hemogram parameters of the subjects younger or older than 45 years. Nevertheless, this issue may be targeted in another study with age-matching groups.

Conclusions

In conclusion, NLR was first shown to be significantly elevated in OCCs as well as in oral cavity SCC compared with benign oral cavity pathologies and healthy control group in this study. In contrast, lymphocyte count and MPV were found to be significantly decreased in cancer cases. In our opinion, NLR may be helpful in identifying

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the oral cavity lesions at high risk for harboring malignancy. However, future studies with larger sample size are needed to specify cutoff points for its efficiency in clinical use.

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Conflicts of interest

There are no conflicts of interest

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