Original Article

HAEMATOLOGICAL PARAMETERS AND THEIR SIGNIFICANCE IN PREDICTING SEVERITY IN TERMS OF TUMOR GRADE IN PATIENTS WITH ORAL SQUAMOUS CELL CARCINOMA

Sundas Ali[1], Manal Rauf[1], Syeda Kiran Riaz[1], Ahmareen Khalid Sheikh[1], Ahson Ahmad[3], Javera Tariq[1]

[1]Pakistan Institute of Medical Sciences, Islamabad Pakistan
[2]Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad Pakistan
[3]Shifa International Hospital, Islamabad Pakistan

ABSTRACT

Objectives: The objective of our study was to determine the most reliable haematological parameters for assessing the tumor severity with respect to histological grade in patients with Oral Squamous Cell Carcinoma.

Material and Methods: This retrospective cross-sectional study was conducted at Pathology Department, Pakistan Institute of Medical Sciences, Islamabad from January to December 2019. Fifty-eight patients of Oral Squamous Cell Carcinoma were selected by consecutive non-probability sampling. Preoperative hemogram values including total leukocyte count, red cell count, hematocrit, hemoglobin, red cell indices, platelet count, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio were recorded and was studied how these parameters differed among the histological grades of tumor. Stratification of patients was done based on gender and histological grade of tumor. Independent-sample t-test for gender and ANOVA-test for histological grade was applied to assess differences in haematological parameter measurements between the groups. $P< 0.05$ was considered significant.

Results: Anemia was observed as a common finding in our patients seen in 24% cases. Mean platelet count was within normal range. We observed that the haematological parameters i.e. total leukocyte count, absolute neutrophil count, absolute lymphocyte count, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio varied significantly with the advancing grades of the tumor from well-differentiated to poorly-differentiated keratinizing oral squamous cell carcinoma.

Conclusion: The pre-surgical haematological profile holds many prognostic indicators, useful in predicting tumor severity in terms of histological differentiation of tumor.

Key Words: Oral squamous cell carcinoma, Prognosis, Histology.

This article can be cited as: Ali S, Rauf M, Riaz SK, Sheikh AK, Ahmad A, Tariq J. Haematological parameters and their significance in predicting severity in terms of tumor grade in patients with oral squamous cell carcinoma. Pak J Pathol. 2022; 33(3): 88-93.

DOI: 10.55629/pakjpathol.v32i3.710.

INTRODUCTION

Oral cancer, a malignant neoplasm arising from the oral cavity, is among the ten most common tumors of body. Ninety percent of these tumors are Oral Squamous Cell Carcinoma (OSCC), originating from the squamous cells of the overlying epithelium [1]. It has different grades based on degree of differentiation [1,2].

It accounts for 275,000 cases and 128,000 deaths per annum which is variable geographically and comprises more than 50% of all cases occurring in developing countries [3]. In Pakistan, oral squamous cell carcinoma is the second most common malignancies of the country and comprises 15% of new cancer cases, as compared to 3% worldwide [4].

Risk factors include differences in ethnicity, geographic origin, lifestyle and genetic predisposition. Common causative agents are tobacco smoking, chewable tobacco (naswar), poor oral hygiene, alcohol, and Human Papilloma Virus, especially leading to an upward trend in younger population [5,6]. Additionally, the deficiencies of minerals like selenium and vitamins A, C, E and folate are linked with an increased risk of malignant transformation [7,8].

In order to predict prognosis and treatment preferences, Anneroth's classification is used, which employs six histological features in determining the grade of tumor, three associated with tumor cell population i.e. differentiation, proliferation and mitosis; and other three linked with tumor-host connection namely pattern, stage of invasion and cellular response [9]. The determination of prognosis of OSCC patients must take into consideration different factors such as demography (age, gender and ethnicity), general physical factors, clinico-histological profile, and molecular factors [10].

Haematological profile, including many calculated and derived parameters in hemogram may

Correspondence: Dr. Sundas Ali, Department of Pathology, Pakistan Institute of Medical Sciences, Islamabad. Pakistan

Email: **sundasali243@gmail.com**

Received: ***28 Mar 2022****; Revised:* ***23 Aug 2022****; Accepted:* ***05 Sep 2022***

play a potential role in predicting prognosis of tumor in OSCC patients and this subject has been studied extensively by many researchers. As many quantitative changes in blood occur during development of tumor, our objectives were to study the pre-operative changes in the haematological profile in patients diagnosed as OSCC and to find significance of studied parameters in predicting severity with respect to histological grade of the tumor. This may potentially provide a valuable insight into the disease biology, its course and behavior; and may identify key features that may aid in prognosis, prediction of tumor grade and severity and finally to assist in disease progression indications and treatment monitoring.

MATERIAL AND METHODS

It was a retrospective study and was conducted at the Department of Pathology, Pakistan Institute of Medical Sciences (PIMS), Islamabad. After approval from the Hospital Ethics Committee (No. F. 1-1/2015/ERB/SZABMU/637; dated 14.09.2020), fifty-eight diagnosed patients with keratinizing lesions of OSCC on histopathological examination of resected specimens in the year 2019, belonging to various sites, were selected by consecutive non-probability sampling. World Health Organization (WHO) sample size calculator was used in the current study and the sample size calculations were based on the representative disease-affected population and patients visiting Department of Pathology, PIMS Hospital annually (Confidence level = 95%, population proportion = 15% [4]. Patients were divided into three grades as under:

1. Keratinizing well differentiated squamous cell carcinoma: It shows greater than 75% keratinization. The individual neoplastic cells have abundant cytoplasm with mild to moderate nuclear atypia.

2. Keratinizing moderately differentiated squamous cell carcinoma: It shows 25 to 75% keratinization and moderate nuclear atypia.

3. Poorly differentiated keratinizing squamous cell carcinoma: Squamous cell carcinoma showing less than 25% keratinization. The individual neoplastic cells have high nucleo-cytoplasmic ratio and marked nuclear atypia.

Confidentiality of personal information was maintained. Tumors other than squamous cell carcinoma of oral cavity and metastatic tumors to oral cavity were excluded. Patients' demographic data, registration number, site of tumor, histological category and Complete Blood Count (CBC) findings (performed on fully-automated Haematology analyzer by Mindray BC-6200 (Shenzhen Mindray Biomedical Electronics Co., Ltd. China) from the electronic laboratory records (Laboratory Management Information System) preceding the surgical biopsy procedure were noted down on a Proforma. The data was retrieved and analyzed using SPSS version 20. Qualitative and quantitative variables were measured using descriptive statistics. Qualitative variables such as gender, site of tumor and histological grade were expressed in terms of frequency and percentage. Quantitative variables such as age of patient and findings of CBC were measured as Mean ± Standard Deviation. Stratification was done based on gender of cases and histological grade of tumor. Post stratification, independent-sample t-test for gender and ANOVA-test for histological grade was applied to assess differences in haematological parameter measurements between the groups. P value of less than < 0.05 (two-tailed) was taken as significant.

RESULTS

Fifty-eight patients diagnosed as OSCC on histopathological evaluation were studied. The mean age was 56.74 ± 12.68 years (ranging from 27 to 84 years), with 40/58 (69%) patients aged≥50 years. Female to male gender ratio was 1: 1.4. The mean age in male and female groups was 56.2 ± 12.1 years and 57.4 ± 13.5 years respectively (p=0.8). Most patients presented at Otorhinolaryngology and Oromaxillofacial Departments (13/58, 22.4% each), followed by Dental Outpatient Department (OPD) (11/58, 19%). Rest of patients presented at Medicine OPD (7/58, 12.0%), General Surgery OPD (5/58, 8.6%), Oncology OPD (4/58, 6.9%), Emergency Department (4/58, 6.9%) and Plastic Surgery OPD (1/58, 1.7%). The statistics of tumor site showed that the tongue is the most common site (20/58, 34.5%), then is the buccal mucosa (14/58, 24.1%) followed by upper lip (10/58, 17.2%). The other sites included alveolar ridge, lower lip, cheek and submandibular region. On histopathological examination of tumor biopsies, majority of cases were histologically graded as keratinizing well-differentiated (29/58, 50%), followed by moderately differentiated (22/58, 37.9%) and poorly differentiated (7/58, 12.1%)

The pre-operative haematological profile was evaluated which showed that 14/58(24%) patients were anemic, out of them 09/14(64.3%) were males and 5/14(35.7%) were females. Among the anemic cases, 09/14 (64.3%) patients had normocytic, normochromic anemia, while 5/14(35.7%) patients had hypochromic, microcytic anemia. No patient had macrocytic anemia. The mean White Blood Cell Count (WBC) was 8.7±2.6 x10^9/L (range: 4.0 – 16.6 x

10^9/L). Only 4/58 (6.9%) patients had mild thrombocytopenia (platelet count 100-149 x10^9/L) and 2/58 (3.4%) had mild thrombocytosis (platelet count >450 x10^9/L). Rest had normal platelet count. Table-I shows the summary of haematological profile of patients (n=58).

The comparison of haematological parameters according to gender was done using independent sample t test which showed that all parameters were comparable in both gender groups, except for Neutrophil-Lymphocyte Ratio (NLR) which has a significantly higher value in males as compared to females (p=009), as shown in Table-II. Correlation of haematological parameters with different histological subtypes employing ANOVA test is depicted in Table-III**,** which expresses that there is significant statistical difference in terms of WBC, Absolute Neutrophil Count, Absolute Lymphocyte Count, NLR and Platelet to Lymphocyte Ratio (PLR) between the four categories.

Table-I: Haematological parameters in patients.

Haematological Parameters	Reference ranges [11]	Patients (n=58)	
		Range	Mean ± SD
WBC (x 10^9/L)	4.0 – 11.0	4.0-16.6	8.74 ± 2.68
NEUTROPHIL%	45-70	37.8-83.1	64.81 ± 10.48
LYMPHOCYTE%	25-40	11.3-44.7	24.95 ± 8.34
ANC (x 10^9/L)	2.0-7.0	2.0-13.3	5.83 ± 2.38
ALC(x 10^9/L)	1.0-3.0	0.9-3.7	2.06 ± 0.67
RBC (x 10^{12}/L)	4.5-5.5 (M)	2.31-5.56 (M)	4.50 ± 0.62 (M)
	3.8-4.8 (F)	3.70-5.44 (F)	4.51 ± 0.49 (F)
Hb (g/dl)	13-17 (M)	3.8-16.1 (M)	12.77 ± 2.29 (M)
	12-15(F)	11.0-14.6 (F)	12.83 ± 0.97 (F)
HCT (%)	40-50% (M)	15.5-48.3 (M)	38.48 ± 6.04 (M)
	36-46% (F)	31.0-43.7 (F)	38.32 ± 3.57 (F)
MCV (fl)	80-100	67.1-99.0	85.40 ± 7.38
MCH (pg)	27-32	16.5-34.0	28.43 ± 3.08
PLATELET (x 10^9/L)	150 – 450	105-537	302.38 ± 88.52
RDW (CV %)	11-14	11.6-17.0	13.42 ± 1.12
NLR	0.78-3.5	0.8-7.5	3.11 ± 1.66
PLR	36.6-149.1 (M)	9.5-413.0 (M)	173.48 ± 90.9 (M)
	43.4-172.6 (F)	77.5-205.0 (F)	144.03 ± 37.4 (F)

(WBC: White Blood Cell, ANC: Absolute Neutrophil Count, ALC: Absolute Lymphocyte Count, AMC: Absolute Monocyte Count, AEC: Absolute Eosinophil Count, RBC: Red Blood Cell, Hb: Hemoglobin, HCT: Hematocrit, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, CV: Coefficient of Variation, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio)

Table-II: Comparison of haematological parameters with respect to gender.

Parameters	Gender	Mean	Std. Deviation	P value
WBC	Male	9.24	3.09	0.06
	Female	8.02	1.79	
Neutrophil%	Male	66.74	11.36	0.08
	Female	62.08	8.59	
Lymphocyte%	Male	23.32	9.39	0.07
	Female	27.25	6.03	
RBC	Male	4.50	.62	0.91
	Female	4.51	.49	
Hemoglobin	Male	12.77	2.29	0.91
	Female	12.83	.97	
Hematocrit	Male	38.48	6.04	0.89
	Female	38.32	3.57	
MCV	Male	85.57	8.58	0.82
	Female	85.17	5.40	
MCH	Male	28.33	3.66	0.74
	Female	28.58	2.05	
Platelet count	Male	305.47	103.94	0.75
	Female	298.00	62.32	
RDW (Red cell Distribution width)	Male	13.31	1.22	0.36
	Female	13.59	.96	
NLR (Neutrophil-lymphocyte ratio)	Male	3.59	1.97	**0.009**
	Female	2.45	.71	
PLR (Platelet to lymphocyte ratio)	Male	173.48	90.90	0.09
	Female	144.03	37.45	

WBC: White Blood Cell, RBC: Red Blood Cell, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin)

Table-III: Comparison of haematological parameters with respect to histological subtypes.

Histological category	WBC	RBC	Hb	Platelet count	RDW CV%	ANC	ALC	NLR	PLR
Keratinizing well Differentiated	8.6±2.2	4.4±0.6	12.7±2.3	276.7±103.2	13.3±1.2	5.4±1.8	2.2±0.8	2.7±1.6	130.5±78.9
Keratinizing moderately differentiated	8.0±2.4	4.5±.50	12.8±1.3	336.2±55.4	13.3±1.0	5.4±2.2	1.8±0.4	3.1±1.4	193.6±53.2
keratinizing poorly differentiated	11.3±3.7	4.6±.38	12.9±1.1	302.0±80.8	13.9±0.6	8.4±3.4	1.9±0.5	4.7±2.0	187.2±68.1
P value	0.01	0.58	0.96	0.06	0.45	0.006	0.04	0.01	0.005

(WBC: White Blood Cell, RBC: Red Blood Cell, Hb: Hemoglobin, RDW CV: CV: Red Cell Distribution Width -Coefficient of Variation, ANC: Absolute Neutrophil Count, ALC: Absolute Lymphocyte Count, NLR: Neutrophil -Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio)

DISCUSSION

Oral cancer is one of the most common cancers worldwide. Oral Squamous Cell Carcinoma is the leading oral cavity tumor with various clinical manifestations, and according to site specificity, tongue is the commonest site of involvement [12]. In our study, tongue was the most frequently involved location (34.5%) followed by mucosa of buccal cavity (24.1%). In a study, comparable to ours, tongue was the commonest site (37.1%) then is the buccal mucosa (30.3%) [13]. It is mostly a disease of the adult age group, as depicted in our study that mean age was 56.74 ± 12.68 years; comparable to another study conducted in our region which showed that 45.6 ± 12.3 years was the mean age of presentation. [14] Males were affected more (58.6%) as compared to females in our study, similar to another study from Pakistan which showed a gender distribution of 58.4% males and 41.6% females [13]. The reason is possibly the higher use of smoking and chewable tobacco, areca nuts, pan and gutka among males as compared to females in our society. The histopathology of cases indicated that majority cases in our study were histologically graded as keratinizing well-differentiated. Various prognostic markers and indices have been described in association with OSCC. We found that 14(24%) patients were anemic among whom 09 (64.3%) patients had normocytic, normochromic anemia, while 5(35.7%) patients had hypochromic, microcytic anemia. No patient had macrocytic anemia. Mean MCV of patients was 85.40 ± 7.38 fl and mean MCH was 28.4 ± 3.08 pg. In a study done by Cordella *et al* [15], 71.4% patients with oral SCC had normal hemoglobin, 18.5% were mildly anemic and 10.1% were severely anemic. It was also demonstrated in their study that anemic patients were more prone to developing lymph node metastasis (p = 0.005) and also for tumour recurrence (p = 0.001). In another study by Anees *et al*, [16] it was seen that a much higher percentage i.e., 56.4% of males and 76.0% of female patients were anemic with respect to hemoglobin measurement; also, the RBC count, hemoglobin and packed cell volume decreased when tumor size and histopathological grades are increased (p> 0.05). Nutritional anemia was found to be the most striking finding in OSCC patients. It was suggested that the variability in these parameters may be useful in monitoring treatment progress [17]. In another study, 29% of OSCC patients had preoperative anemia. Anemic patients with OSCC had a significantly decreased five-year overall survival (44%) when they were compared to non-anemic patients (69%) [18]. CBC profile showing anemia in our study may be contributed by multifactorial etiology including nutritional anemias, anemia of chronic disorders secondary to malignancy or influence by infections, irrespective of size and site of tumor. In our study, no significant association between hemoglobin and RBC indices was found among various histological grades of tumor.

The mean platelet count of patients in our study was 302.38 ± 88.52 x 10^9/L. Only two (3.4%) had mild thrombocytosis (platelet count >450 x10^9/L). In a meta-analysis, published in 2018 by Takenaka *et al*., an overall conclusion was made that a higher pre-operative platelet count was associated with a worse overall survival in Head and Neck SCC [19]. Activation of platelets is considered to be an important etiological factor for tumorigenesis and its metastasis and platelet count and Mean Platelet Volume (MPV) are considered the chief parameters for identifying the activation of platelets [20]. In one study, the mean platelet count was 243.93±61.382×10^9/L, PLR was 127±39.51 (37.73–252.46) and NLR was 1.92±0.76 (0.53–3.89) [20]. Our study showed no significance in terms of platelet count in various grades.

Recently, it has been studied that immunosuppression is one of the leading causes for the development of tumours in various parts of the body. NLR is the ratio calculated between the absolute numbers of neutrophils to lymphocytes in

the circulating blood. Neutrophilia is considered a pathological marker for observing the tumor-induced systemic inflammatory change in contrast to lymphocytopenia, which indicates immunosuppression. Hence, NLR maintains the balance between protumoral inflammatory status and antitumor immune response. Higher value of this ratio indicates a protumoral status. [21] In our study mean NLR was 3.11 ± 1.66 and showed significant association between histological types. (2.72 ± 1.57 in well differentiated, 3.13 ± 1.40 in moderately differentiated and 4.71 ± 2.01 in poorly differentiated cases. (P=0.01)). In a study by Phulari *et al*, [22] the mean value of absolute neutrophil count was higher in tumour cases than in control group (P < 0.01). The mean value of NLR among cases of squamous cell carcinoma was 2.84, compared to 1.95 in control group and the difference was statistically significant (P < 0.001). NLR along with the other haematological parameters can be labeled as a surrogate marker for determining the aggressiveness of OSCC. This can help in predicting the prognosis of the disease [22]. A study showed that NLR was found to be increased in poorer grades of tumor with poorly differentiated cases having a median of 2.9 [23]. Fang *et al* [24] also analyzed the data taken from OSCC patients and reported a significant correlation of elevated NLR with pathological stage and tumor depth along with disease-free and overall survival.

We found in our study that mean TLC was 8.74 ± 2.68 x 10^9/L. TLC increased significantly between different grades of tumor. In contrast another study concluded that WBC count is not a prognostic factor for determining the aggressive potential of tumour. White blood cell count is highly variable as it is dependent on various factors. It is elevated in stress and infectious state and in presence of chronic irritative compounds like smoking [25]. Similar to this, another researcher found that the patients did not show any significant change in the white blood cell count as shown by leukogram values [26]. OSCC may have compromised the dental hygiene of patients leading to repeated infections as predicted well by raised WBC count. As no follow up of patients was done so no association between raised leucocyte count and lymph node metastases was established in our study.

Limitations of study were that we only studied the lab-based one-time CBC profile in OSCC patients, further clinical work-up and follow-up after treatment was not observed to determine the influence of these parameters on clinical stage and overall survival of patients.

CONCLUSION

Our study showed that TLC, ANC, ALC, NLR and PLR vary significantly as we go from well to poorly differentiated keratinizing OSCC. Thus, the pre-surgical haematological profile holds many prognostic indicators, which may help in predicting the histological differentiation of tumor, the course of illness, treatment response and overall survival.

AUTHOR CONTRIBUTION

Sundas Ali: Study design and concept, data collection, drafting
Manal Rauf: Data collection, data interpretation
Syeda Kiran Riaz: Data analysis
Ahmareen Khalid Sheikh: Data interpretation
Ahson Ahmad: Data analysis
Javera Tariq: Drafting

REFERENCES

1. Rivera C. Essentials of oral cancer. Int J Clin Exp Pathol. 2015;8(9):11884-94.
2. Padma R, Kalaivani A, Sundaresan S, Sathish P. The relationship between histological differentiation and disease recurrence of primary oral squamous cell carcinoma. J Oral Maxillofac Pathol. 2017;21(3):461. DOI: 10.4103/jomfp.JOMFP_241_16.
3. Tandon P, Dadhich A, Saluja H, Bawane S, Sachdeva S. The prevalence of squamous cell carcinoma in different sites of oral cavity at our Rural Health Care Centre in Loni, Maharashtra - a retrospective 10-year study. Contemp Oncol (Pozn). 2017;21(2):178-83. DOI: 10.5114/wo.2017.68628.
4. Sahaf R, Naseem N, Rehman A, Anjum R, Nagi AH. A study of 89 cases of oral squamous cell carcinoma presenting at teaching hospitals of lahore, Pakistan. J Pak Dent Assoc. 2017; 26(1): 26-31.
5. Mirza D, Raza G, Basit A, Naqvi K, Ahmed S, Abassi ZA. Oral squamous cell carcinoma (OSCC) in Karachi city - A retrospective study. Pak Oral Dental J. 2016; 36(3): 391-94.
6. Saira, Ahmed R, Malik S, Khan MF, Khattak MR. Epidemiological and clinical correlates of oral squamous cell carcinoma in patients from north-west Pakistan. J Pak Med Assoc.2019;69(8):1074-78.
7. Lucenteforte E, Garavello W, Bosetti C, La Vecchia C. Dietary factors and oral and pharyngeal cancer risk. Oral Oncol. 2009;45(6):461-67. DOI: 10.1016/j.oraloncology.2008.09.002.
8. Akram S, Mirza T, Mirza MA, Qureshi M. Emerging Patterns in Clinico-pathological spectrum of Oral Cancers. Pak J Med Sci. 2013; 29(3): 783-87.
9. Akhter M, Hossain S, Rahman QB, Molla MR. A study on histological grading of oral squamous cell carcinoma and its co-relationship with regional metastasis. J Oral Maxillofac Pathol. 2011;15(2):168-76.
10. Jadhav KB, Gupta N. Clinicopathological prognostic implicators of oral squamous cell carcinoma: need to understand and revise. N Am J Med Sci. 2013; 5(12): 671-79. DOI: 10.4103/1947-2714.123239.
11. Bates I. Reference Ranges and Normal Values. In: Bain BJ, Bates I, Laffen MA, editors. Dacie and Lewis Practical Haematology. 12th ed. London: Churchill Livingstone; 2017. p.11
12. Abraham S, Mallika B, Reshma A, Kassim RM. An atypical case of oral squamous cell carcinoma of mandibular alveolus. Case Rep Dent. 2019:2521685. DOI: 10.1155/2019/2521685.
13. Sahaf R, Naseem N, Rehman A, Anjum R, Nagi AH. A study of 89 cases of oral squamous cell carcinoma

presenting at teaching hospitals of Lahore, Pakistan. J Pak Dent Assoc. 2017; 26(1):26-31.
14. Mahmood N, Muhammad H, Ahmed A, Jamal Q, Saqib M, Khan A. Impact of age at diagnosis on clinicopathological outcomes of oral squamous cell carcinoma patients. Pak J Med Sci. 2018; 34(3): 595-99. DOI: 10.12669/pjms.343.14086.
15. Cordella C, Luebbers HT, Rivelli V, Grätz KW, Kruse AL. An evaluation of the preoperative hemoglobin level as a prognostic factor for oral squamous cell carcinoma. Head Neck Oncol. 2011;3:35. DOI: 10.1186/1758-3284-3-35
16. Ahmed RAA, Ganvir SM, Hazarey VK. Relation of erythrocyte indices and serum iron level with clinical and histological progression of oral squamous cell carcinoma in Central India. J Investig Clin Dent. 2014;5(1) :65-71. DOI: 10.1111/jicd.12021.
17. Zulfiqar R, Haider SA. Haematological presentation of oral squamous cell carcinoma patients. EC Dent Sci. 2019;18(2):321-5.
18. Spanier G, Böttcher J, Gerken M, Fischer R, Roth G, Lehn P, *et al*. Prognostic value of perioperative red blood cell transfusion and anemia on survival and recurrence in oral squamous cell carcinoma. Oral Oncol. 2020;107:104773. DOI: 10.1016/j.oraloncology.2020.104773.
19. Takenaka Y, Oya R, Kitamiura T, Ashida N, Shimizu K, Takemura K, *et al*. Platelet count and platelet-lymphocyte ratio as prognostic markers for head and neck squamous cell carcinoma: Meta-analysis. Head Neck. 2018; 40(12): 2714-23. DOI: 10.1002/hed.25366.
20. Park JW, Kim CH, Ha YC, Kim MY, Park SM. Count of platelet and mean platelet volume score: serologic prognostic factor in patients with oral squamous cell carcinoma. J Korean Assoc Oral Maxillofac Surg. 2017;43(5): 305-11. DOI: 10.5125/jkaoms.2017.43.5.305.
21. Mattavelli D, Lombardi D, Missale F, Calza S, Battocchio S, Paderno A, *et al*. Prognostic nomograms in oral squamous cell carcinoma: The negative impact of low neutrophil to lymphocyte ratio. Front Oncol. 2019; 30 (9): 339. DO: 10.3389/fonc.2019.00339.
22. Phulari RGS, Rathore RS, Shah AK, Agnani SS. Neutrophil: Lymphocyte ratio and oral squamous cell carcinoma: A preliminary study. J Oral Maxillofac Pathol. 2019; 23(1): 78-81. DOI: 10.4103/jomfp.JOMFP_160_17.
23. Mahalakshmi R, Boaz K, Srikant N, Baliga M, Shetty P, Prasad M, *et al*. Neutrophil-to-lymphocyte ratio: A surrogate marker for prognosis of oral squamous cell carcinoma. Indian J Med Paediatr Oncol. 2018;39(1):8-12.
24. Fang JF, Huang Y, Chen QX. Preoperative platelet lymphocyte ratio is superior to neutrophil lymphocyte ratio as a predictive factor in patients with esophageal squamous cell carcinoma. World J Surg Oncol. 2014; 12: 58. DOI: 10.1186/1477-7819-12-58.
25. Kruse AL, Luebbers HT, Grätz KW. Evaluation of white blood cell count as a possible prognostic marker for oral cancer. Head Neck Oncol. 2011; 3: 13. DOI: 10.1186/1758-3284-3-13.
26. Brunischaki KA, Brew MC, Bavaresco CS, Miguens SAQ. White blood cell count of patients with oral squamous cell carcinoma at the time of diagnosis: A cross-sectional retrospective study of a population from southern Brazil. Rev Odonto Cienc. 2018; 33(1): 1-4. DOI: https://doi.org/10.15448/1980-6523.2018.1.29190.