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Association Of Platelet Parameters With Depth Of Invasion In Oral Squamous Cell Carcinoma

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Abstract

Introduction

Oral squamous cell carcinoma (OSCC) is the commonest cancers associated with oral cavity and is most prevalent in Indian population. Platelets are important regulatory factors of immune system and also maintain proper homeostasis. Studies in past few decades have revealed important role of platelet activation in cancer occurrence and metastasis. Depth of invasion (DOI) is the predictor of lymph node metastasis. Hence not only Platelet count (PC) but Mean Platelet Volume (MPV), platelet distribution width (PDW) may be prognostic factors in OSCC. Thus this study aimed to assess the mean platelet volume, platelet distribution width and platelet count and their association with depth of invasion in patients with oral squamous cell carcinoma

Materials and Method

The study included 34 clinically and histologically diagnosed cases of OSCC and 30 healthy controls. Platelet parameters were assessed using conventional blood cell analyzer.

Observational parameters

MPV (fL), PDW, PC (x 10^9 /L), DOI

Results

Results were statistically significant for the platelet parameters in between cases and controls. Significant correlation was observed between platelet parameters and depth of invasion.

Conclusion

Platelet parameters are easy to assess in OSCC patients and their association with DOI can determine the severity of the disease.

Keywords: Depth of invasion (DOI), Oral Squamous Cell Carcinoma (OSCC),Platelet count (PC), Mean Platelet Count (MPV), Platelet Distribution Width (PDW)

Introduction

OSCC is ranked as 8th most prevalent cancers worldwide. Multiple factors like patient demographics, tumor characteristics and treatment modalities affect its prognosis.[1] After being 6th most common cancer globally their annual incidence is over 300000 cases out of which 62% are observed in developing countries. Their prevalence is 5.6% (According to GLOBOCAN 2018) in Indian population contributing over 30% of the total reported cancer cases. OSCC being considered among the top three cancers in India and is also the most common cause of death following oral diseases.[2] Several

staging systems have been proposed out of which AJCC/UICC (American Joint Committee on Cancer

/International Union Against Cancer) TNM classification system being the most commonly employed. The 8th edition of AJCC system has made few modifications by including depth of invasion (DOI) in the T category for oral cavity cancer as well as the inclusion of extranodal extension in the N category with exception of p16+ oropharyngeal and nasopharyngeal cancers. These modifications were based on the clinical and biological behaviour of these neoplasms.[6,7,14]

Cancer associated rise in platelets has been recognized as the leading cause of death following cancer progression.[8] In accordance with the literature several blood parameters have been observed to be elevated in OSCC patients. Among which platelets have been recognized for their important role in proliferation and metastasis of cancer cells. Mean Platelet Volume (MPV), Platelet count (PC), Platelet Distribution Width (PDW) are the most commonly assessed parameters. They can be easily determined using peripheral blood samples in patients with increased risk of development of cancer. Literature demonstrates these parameters to be associated with prognosis of several other cancers like gastric, lung, laryngeal and breast carcinoma.[1] Their prognostic implication in OSCC have been acknowledged by many authors recently including the present study.

Materials and method

The present study included the 34 patients with primary OSCC and 30 healthy controls. The blood analysis using conventional blood cell analyzer helped to assess values of platelet parameters of interest primarily Mean Platelet Volume (MPV in fL), Platelet Distribution Width (PDW), Platelet Count (PC). The values obtained from cases and controls were compared. The association of these parameters with depth of invasion was determined (DOI) which was principally based on tumor staging as well as lymph node metastasis. The patients without definitive histopathological diagnosis of OSCC, with any autoimmune disease, hematologic disease or with cancer other than OSCC were excluded from the study. The study was performed with the approval of institutional ethical committee.

Data Collection

Clinicopathologic data was obtained including medical history of individual patient like age, gender, habits like tobacco or gutkha chewing, smoking, site of the tumor along with its TNM staging and lymph node metastasis, any history of chronic irritation or trauma were also noted down. The TNM staging was assigned based on the current American Joint Commission on Cancer Staging 8th edition. Whereas the platelet values i.e PC, MPV & PDW were obtained by blood test prior to surgery, chemotherapy or a radiotherapy.

Statistical Analysis

The data obtained was subjected to statistical analysis using Statistical package for social sciences (SPSS v 26.0, IBM). Demographic comparisons have been done using parametric tests have been used for comparisons. Inter group comparison (2 groups) was done using t test. Comparison categories of variables with groups was done using chi square test.

Results

A total study sample consisted of 64 individuals with 34 OSCC cases **(Group 1)** and 30 healthy controls **(Group 2)**. Regarding distribution as per sex for OSCC group it was observed that there were 3 females (8.8%) and 31 males (91.2%) **[Table 4]**. Mean age for OSCC group was 48±16.07 years while for control group 43.2±9.2 years. The most common tumor subsite in the present study was tongue (n= 18, 52.9%) followed by buccal mucosa (n= 11,32.4) , hard palate (n=2, 5.4%), lip with floor of the mouth, tongue with buccal mucosa and retromolar trigone (n=1, 2.9% each).Based on TNM staging ,subjects were classified as follows : T1 (n= 7,20.6%), T2 (n= 18,52.9%), T3 (n=7, 20.6%), T4 (n=2, 5.9%) **[Table 7,Fig.7];** N0 (n=1,2.9%) ,N1 (n=15,44.1%), N2 (n=6, 17.6%), N2a (n=1,2.9%), N2b (n=1, 2.9 %), N2c(n=2, 5.9%), N3 (n=5, 14.7%), Nx (n=3,8.8%) **[Table 8, Fig 8]**; M0 (n=25, 73.5%) and M1 (n=9, 26.5%) **[Table 9, Fig.9].** Clinical staging based on TNM classification included 3 patients with stage I (8.82%), only 1 case with Stage II (2.9%), 15 patients were in Stage III and stage IV (44.11%) each. Based on histopathological diagnosis the cases were graded as moderately differentiated squamous cell carcinoma (n= 29, 85.3%) and well differentiated squamous cell carcinoma (n=5, 14.7%) **[Table 6, Fig .6].**

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Comparing test values between each group showed statistically high significant difference for MPV with high values in group 1 ($p < 0.01$). Whereas there was a statistically significant difference seen for the values between the groups for PC and PDW with higher values in group 1 ($p<0.05$) when compared with control **[Table 11, Fig.10].** Depth of invasion (DOI) being predictor of lymph node metastasis, a statistically significant correlation was obtained between platelet parameters particularly MPV and PC and DOI. A linear relationship was obtained between these two test values **[Fig 11 & 12].** Whereas correlation between PDW and DOI was found to be statistically insignificant.

Table 1. Distribution as per Sex for the OSCC and the control group

	Frequency	Percent
F	5	7.8
M	59	92.2
Total	64	100.0

Figure 1. Pie diagram showing age distribution of the study sample

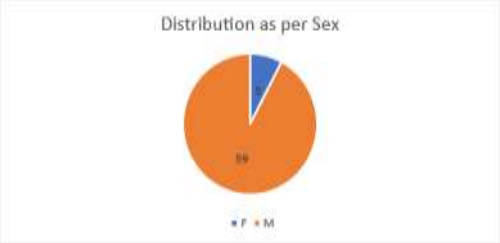

Table 2. Mean & SD of age for the OSCC and the control group

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	64	30	75	45.75	11.595

Table 3. Inter group comparison of distribution as per sex in the OSCC and the control group

		OSCC Group 1	Control Group 2	Total	Chi-Square value	P value of Chi-Square test
Sex	F	3	2	5		
	M	31	28	59	0.103	0.748#
	Total	34	30	64		

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Figure 2: Bar graph intergroup distribution as per sex

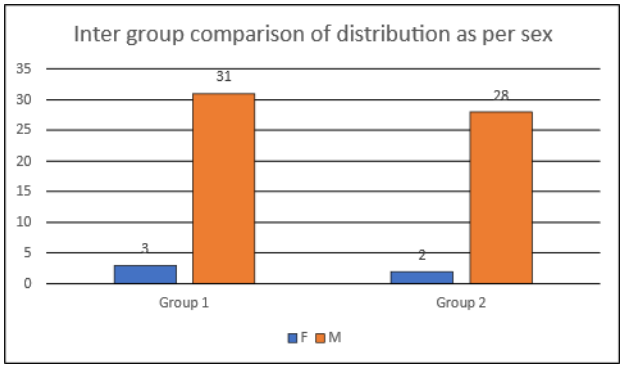

Table 3: Inter group comparison of mean age between the OSCC and the control group

	Group	N	Mean	Std. Deviation	Std. Error Mean	T value	p value of t test
AGE	1	34	48.00	13.076	2.242	1.676	.099#
	2	30	43.20	9.212	1.682		

Figure 3: Pie diagram comparing age between two groups

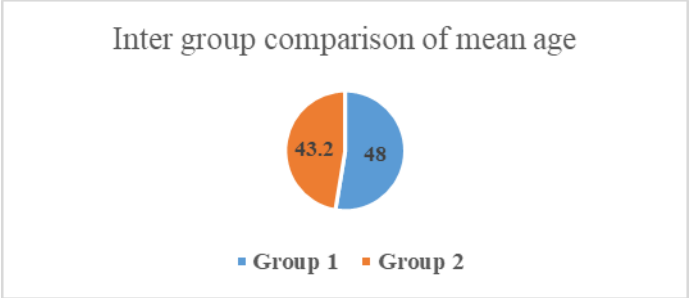

Table 4. Distribution as per Sex for OSCC group

	Frequency	Percent
F	3	8.8
M	31	91.2
Total	34	100.0

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Figure 4: Pie diagram determining distribution of OSCC cases as per sex

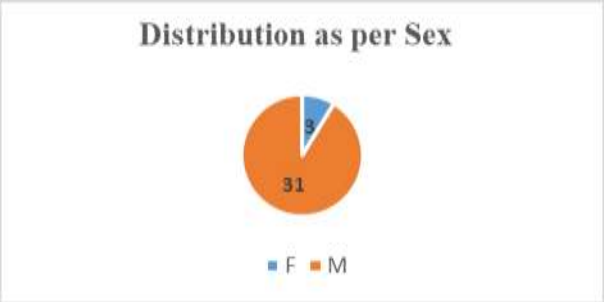

Table 5. Distribution as per site for the OSCC group

	Frequency	Percent
CA Buccal mucosa	11	32.4
CA Hard palate	2	5.9
CA lip + Floor of mouth	1	2.9
CA retromolar trigone	1	2.9
CA Tongue	18	52.9
CA tongue+ Buccal Mucosa	1	2.9
Total	34	100.0

Figure 5: Bar graph showing distribution as per site of malignancy

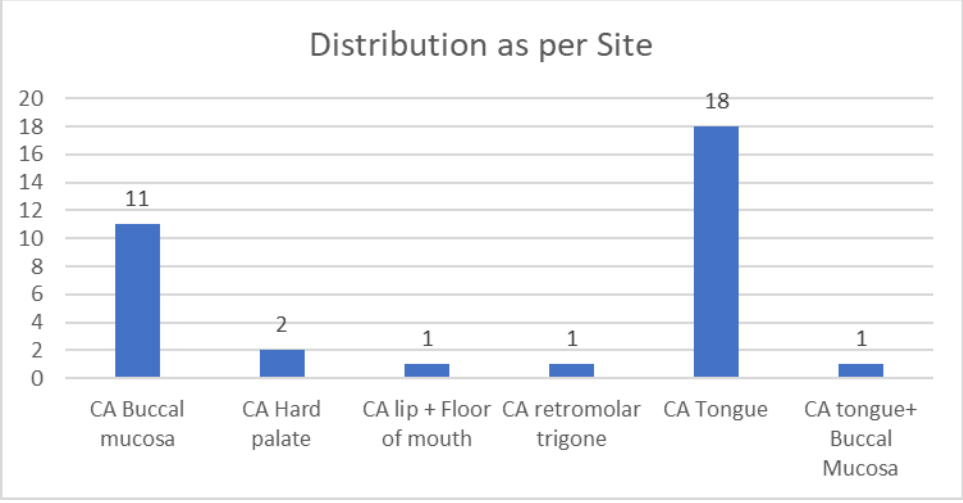

Table 6. Distribution as per H/P grading of OSCC

	Frequency	Percent
Moderately Differentiated Squamous Cell Carcinoma	29	85.3

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Well Differentiated Squamous Cell Carcinoma	5	14.7
Total	34	100.0

Figure 6: Pie diagram showing distribution as per H/P grading

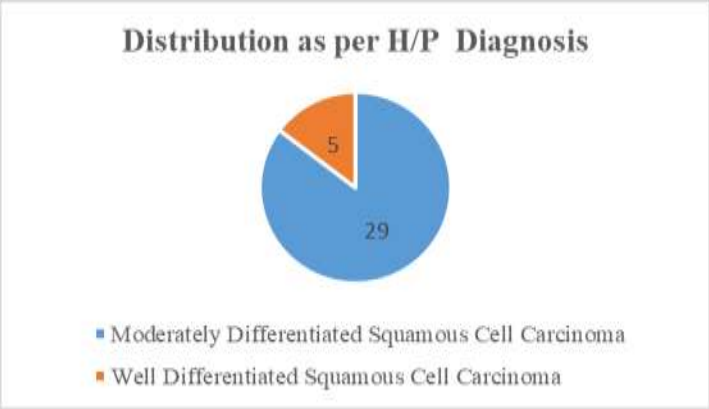

Table 7. Distribution as per Tumor (T) size for the OSCC group

	Frequency	Percent
T1	7	20.6
T2	18	52.9
T3	7	20.6
T4	2	5.9
Total	34	100.0

Figure 7: Bar graph showing distribution as per Tumor (T)

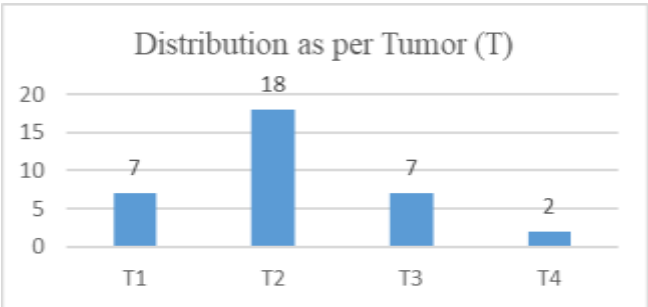

Table 8. Distribution as per Lymph node (N) metastasis in OSCC group

	Frequency	Percent
N0	1	2.9

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N1	15	44.1
N2	6	17.6
N2a	1	2.9
N2b	1	2.9
N2c	2	5.9
N3	5	14.7
Nx	3	8.8
Total	34	100.0

Figure 8: Bar graph showing distribution as per lymph node metastasis

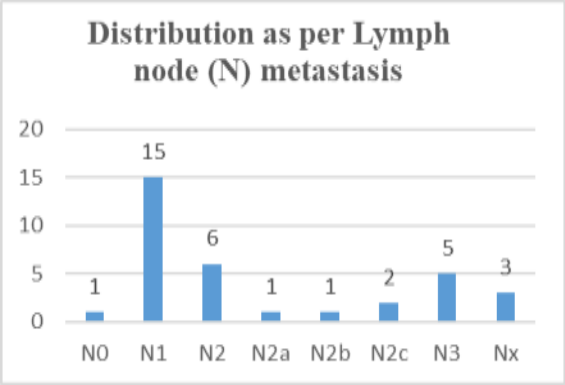

Table 9. Distribution as per Distant Metastasis (M) in OSCC group

	Frequency	Percent
M0	25	73.5
M1	9	26.5
Total	34	100.0

Figure 9: Pie diagram showing distribution as per distant metastasis

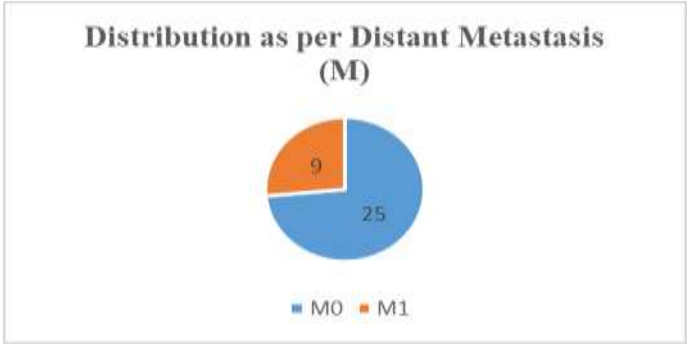

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Table 10. Clinical Staging of OSCC based on TNM classification

Clinical staging	N	Percent
Stage I	3	8.82
Stage II	1	2.9
Stage III	15	44.11
Stage IV	15	44.11

Table 11. Inter group comparison of values between the OSCC and the control group

	Group	N	Mean	Std. Deviation	Std. Error Mean	T value	p value of t test
Depth of invasion (DOI) mm	1	32	**7.09688**	3.121361	.551784	----	----
	2	0[a]	.	.	.		
Platelet Count (PC) (10 ^9/L)	1	34	344.26	82.425	14.136	2.473	**.016***
	2	30	302.90	42.471	7.754		
Mean Platelet Volume (MPV)	1	34	10.694	2.5596	.4390	6.068	**.000****
	2	30	7.813	.4740	.0865		
Platelet Distribution Width (PDW)	1	34	17.079	3.0812	.5284	2.604	**.012***
	2	30	15.593	.5420	.0990		

Figure 10: Bar graph showing intergroup comparison of different study variables

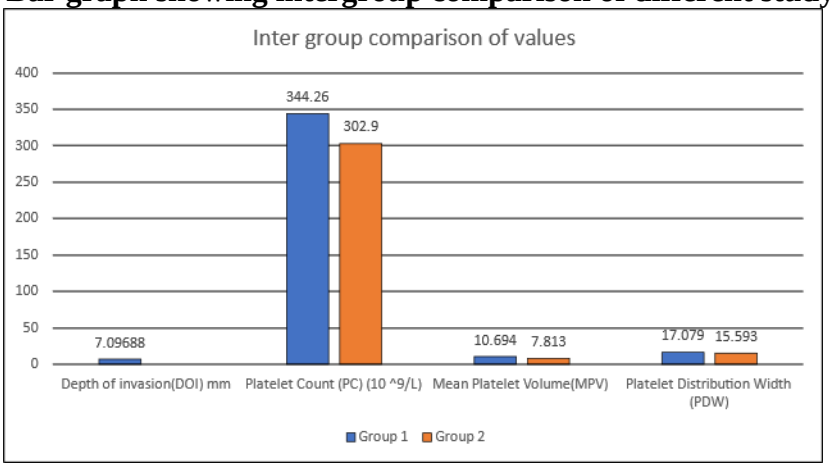

Table 11. Correlation of DOI with PC, MPV and PDW in the OSCC group

		Depth of invasion (DOI) mm

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Depth of invasion (DOI) mm	Pearson Correlation Sig. (2-tailed) N	
PC (10^9 /L)	Pearson Correlation Sig. (2-tailed) N	**0.531**** 0.002 32
MPV (fL)	Pearson Correlation Sig. (2-tailed) N	**0.705**** 0.000 32
PDW	Pearson Correlation Sig. (2-tailed) N	0.081 0.658 32

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed)

Figure 12.Line diagram depicting correlation between PC Vs DOI

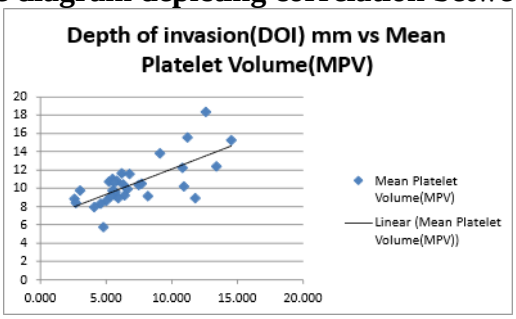
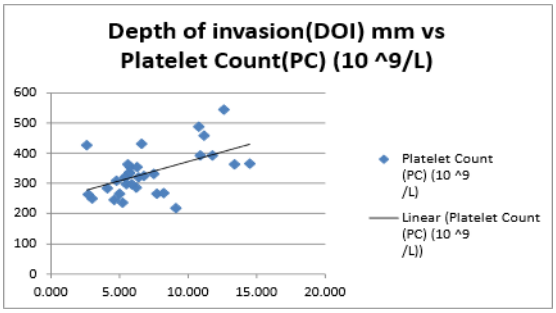


Figure 11:Line diagram depicting correlation between MPV Vs DOI



Discussion

India is well known for its high incidence of oral cancer cases. Many etiological factors like tobacco and areca nut and their different formulations, alcohol, low socioeconomic status are more prevalent in India. Oral potentially malignant disorders are more frequently the precursor lesions for most cases of OSCC. They have a higher rate of malignant transformation ranging from 7-30 %. [2] The incidence of oral cancer has been found to increase at

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the rate of 0.6% every year since last 10 years.[8]. TNM staging is the most widely accepted classification system that is clinically applicable in stratification of oral cancers helping its prognosis and treatment planning. The 8th edition of AJCC system (2017) has come up with certain modifications based on the tenets described by Groome et al. DOI in the T category of the primary tumor and extranodal extension in the N category are one of them especially for oral cancers. DOI has got the prognostic implications as deeper tumors are associated with high risk of nodal metastases and decreased survival rate. DOI can be clinically assessed either as thin (≤ 5 mm), intermediate (> 5 mm and ≤ 10 mm), and thick (> 10 mm) lesions and requires adequate palpation with supplementation of radiographic examination. Histopathologically it is expressed by measuring the line that begins from the basement membrane to the deepest point of invasion.[4,6,7]It significantly impacts the categorization of the tumor and predicts the nodal metastasis leading to poor survival in patients with OSCC.[1,3]

Some biomolecules are an important aid in injury, inflammation, cancer progression and metastasis. Cytokines and growth factors such as VEGF, PDGF, TGF beta are recognized as mediators of angiogenesis and even modulation of immune response, promoting carcinogenesis. Among several prognostic biomarkers platelet related markers are being evaluated more frequently because of their establishment in several malignancies. Thrombocytosis have been regarded as an independent paraneoplastic phenomenon and significantly associated with poor survival due to metastasis. Similarly studies reveal its association with DOI in OSCC. [1] Cancer cell induced platelet activation allows release of certain biomolecules, for example lysophosphatidic acid from platelets that boost up tumor invasiveness and vascular permeability. Platelets have a crucial role in coagulation for maintaining hemostasis after injury to the blood vessels. Platelet growth factors also allow cancer progression and distant metastasis. After detachment from the primary tumor, the cells migrate through the blood stream to first come in contact with the platelets. They protect the tumor cells from high shear rates and immune surveillance by enclosing them in a thrombus thus preventing their cytolysis by natural killer cells. Increased risk of thrombosis also have been reported in cancer patients. MPV, PC & PDW are important indexes of platelet activation are easy to obtain, reliable and repeatable as well.[5,8,10,12]

Demir B and Abuzaid G (2021) analyzed the pretreatment MPV, PDW and PC and stated their significant association with DOI in OSCC. Also elevated levels of MPV and PC predicted high DOI and worse prognosis whereas high PDW was associated with local recurrence.[1] This corresponds to the results of the present study in which high values MPV and PC were significantly associated with DOI. Whereas the PDW showed less correlation with DOI. Park J et al. (2017) reported that patients with high PC, MPV showed poorer prognosis as compared to the controls and hence considered significant prognostic factors.[3]These findings contradict to those stated by Shukla D et al (2022), Tham T.et al (2019) in which platelet parameters were poor prognostic markers of head and neck malignancy and alone are insignificant in determining the severity of disease.[5,10] Also Zang X. et al considered the MPV/PC ratio and PDW in nasopharyngeal carcinoma, benign nasopharyngeal tumors and controls. The results of the study concluded that these parameters can be utilized as indexes for nasopharyngeal cancer.[9] Ning Y et al revealed that preoperative MPV was significantly associated with advanced OSCC and is a novel prognostic factor. While MPV, PDW and PC were also found to significantly reduced following chemotherapy.[11] Platelet indexes like MPV, PDW, PC along with platelet large cell ratio (P-LCR) including some other parameters were studied by Anand A et al (2022) in patients of OSCC and controls. They found significant difference between cases and controls except MPV.[17] The results do correspond to our study with respect to PC but not with MPV and PDW. Thus in accordance with the literature our study also states that platelet indexes particularly MPV, PDW and PC can be considered as important prognostic factors.

Conclusion

Platelet indexes particularly MPV, PC and PDW can be easily determined in patients with OSCC prior to treatment. Their elevated levels in OSCC indicates active tumor associated thrombosis. They are independent prognostic factors and their association with DOI can also help to determine severity of

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disease and help judicious management of the cases. Though studies with larger sample size shall help determine exact pathogenesis behind it and their role in cancer causation can further be explored.

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