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Assessment of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and mean platelet volume levels in oral squamous cell carcinoma and their correlation with histological grading and TNM staging

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ABSTRACT

Objectives: The inflammatory response of the host plays a role in the prognosis of oral squamous cell carcinoma (OSCC). We studied the levels of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) in OSCC patients and correlated them with TNM staging and histopathological grade to assess their role in prognosis.

Materials and Methods: The study included 30 cases of OSCC and 30 controls. The mean NLR, PLR, and MPV of patients with OSCC were compared to the control group. Differences between different variables were analyzed using one-way analysis of variance test and unpaired *t*-test. Spearman's rho test was used to determine the correlation between NLR, PLR, and MPV values in OSCC cases.

Results: Mean PLR and NLR were higher, and mean MPV was lower in the OSCC group than in the control group. There was a statistically significant relationship between PLR and clinical TNM stage of cancer. Furthermore, there was a statistically significant relationship between PLR and NLR and histological stages of cancer. A statistically significant positive correlation between NLR and PLR was also observed.

Conclusion: NLR and PLR, two inflammatory blood markers, have a significant prognostic impact on OSCC. MPV levels were not as important in predicting prognosis in OSCC as NLR and PLR. PLR and NLR are simple to incorporate into medical care and, when combined with other prognostic indicators, can help in the prognosis of OSCC.

Keywords: Mean platelet volume, Neutrophil-lymphocyte ratio, Oral squamous cell carcinoma, Platelet-lymphocyte ratio, Inflammatory response

INTRODUCTION

Oral squamous cell carcinomas (OSCCs) are malignant neoplasms that commonly affect adults and the elderly. It is ulcerated and has an elevated rolled border around a necrotic central area. The most common sites of occurrence are buccal mucosa and tongue.[1] OSCC is the eighth most common cancer globally and one of the top three in the Indian subcontinent.[2] While males are more affected, females are experiencing an increased number of cases.[3]

Major causes of oral cancer include smoking, drinking, ultraviolet rays, human papillomavirus, candida infections, nutrition deficiencies, and genetics.[4] Early detection can prevent oral cancers. Numerous factors, including age, sex, level of socioeconomic status, race, daily habits, tumor location, size, shape, histology, and treatment modalities, affect the prognosis. The inflammatory response of cancer cells can predict cancer prognosis and impact clinical outcomes in OSCC, influenced by tumor histological properties and the host's response.[5] Different types of peripheral blood cells, including neutrophils, lymphocytes, monocytes, and platelets, and their ratios, such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), can significantly impact the prognosis of certain tumors, such as esophageal squamous cell carcinoma, cervical carcinoma, and renal carcinoma.[6-8]

Platelet activation is a crucial biological process in cancer occurrence and metastasis, promoting angiogenesis, extracellular matrix disintegration, adhesion molecule release, and growth factors essential for tumor growth and spread.[9,10] Therefore, evaluating platelet index, such as mean platelet volume (MPV) levels, may correlate with prognosis in OSCC.

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To the best of our knowledge, no studies are highlighting the prognostic implications of NLR, PLR, and MPV together in OSCC in India, where many people have a habit of chewing tobacco, which leads to oral cancer. Therefore, we conducted the study on the assessment of NLR, PLR, and MPV levels in OSCC and correlated them with histological grading and TNM staging.

MATERIALS AND METHODS

The present study followed a prospective study design. This study was conducted in August–September 2022 in our college. It included 30 patients with OSCC and 30 age- and sex-matched controls. The study was approved by the Institutional Ethical Committee, and patients with other malignancies, pre-operative chemotherapy history, systemic infection, inflammation, or hematological disease were excluded from the study. Controls were selected based on the absence of systemic illness and inflammatory lesions.

The patients were explained about the procedure and informed consent was taken from all the participants in both the groups. A detailed case history was taken. Blood samples of oral cancer subjects were collected preoperatively and a complete hemogram was done using a Sysmex automatic hematology analyzer XT 2000i (Sysmex Corporation, Kobe, Japan). The pre-operative platelet count, absolute lymphocyte count, absolute neutrophil count, and MPV levels were recorded. PLR and NLR values were then calculated. PLR is the absolute platelet count divided by the absolute lymphocyte count. NLR is the absolute neutrophil count divided by the absolute lymphocyte count. The lesion was clinically examined, and staging was done according to the American Joint Committee on Cancer (AJCC) 8th edition. Formalin-fixed paraffin-embedded tissue blocks were used for histopathological examination, with hematoxylin and eosin staining performed on sections. Histopathological grading was done by two oral pathologists using the World Health Organization grading system.

Data were analyzed using the Statistical Package for the Social Sciences software version 26. Data were expressed as mean ± standard deviation. Differences between different variables were analyzed using a one-way analysis of variance (ANOVA) test and an unpaired *t*-test.

$P \leq 0.05$ was considered to be significant. Spearman's rho test was used to determine the correlation between NLR, PLR, and MPV values in OSCC cases. $P \leq 0.01$ was considered to be significant.

RESULTS

The mean age of patients was 49.6 years, and there was male predominance (86.6%). The majority of (63.3%) patients consumed smokeless tobacco; 20% consumed smoked tobacco, while the remaining consumed both smoked and smokeless forms of tobacco. Alveolar mucosa was the most common (40%) site of involvement, followed by buccal mucosa (33.3%), gingiva (10%), labial mucosa (6.6%), lateral border of the tongue (6.6%), and palate (3.3%). Based on AJCC Cancer Staging 8th edition, 60% of patients had TNM Stage IVa cancer, 23.3% were TNM Stage II cancer, 6.6% were TNM Stages III and IVb, and 3.3% were TNM Stage I cancer. There were 17 (56.6%) patients with well-differentiated squamous cell carcinoma (Grade I), 12 (40%) with moderately differentiated OSCC (Grade II), and 1 (3.3%) with poorly differentiated OSCC (Grade III). All other results are mentioned in Tables 1-3.

A statistically significant positive correlation ($r = 0.623$, $P < 0.001$) was seen between NLR and PLR. PLR was negatively correlated with MPV while NLR was positively correlated but it was not significant statistically [Figure 1].

The association of clinical characteristics such as size and habit with NLR, PLR, and MPV was also seen, but it was statistically insignificant.

DISCUSSION

Inflammation significantly impacts tumor development and therapy, with key factors including NLR, PLR, and MPV mediating immune-cancer cell dialogue. The present study evaluated the predictive potential of inflammatory markers such as NLR, PLR, and MPV in OSCC patients.

Nikolić *et al*. found a mean NLR of 3.63 and a mean PLR of 171 for the cancer group and a mean NLR of 2.07 and a mean PLR of 115 for the control group in lung cancer patients.[11] These results were similar to our study in which the mean PLR and NLR were higher in the OSCC group as compared to the control group [Table 1]. It was also seen that the differences between PLR and NLR of lung cancer patients and control groups were statistically significant ($P < 0.001$). In our study, only PLR showed a significant difference ($P = 0.002$) using one-way ANOVA. However, in a study by Anand *et al*., although the mean PLR in OSCC patients was higher than in controls, it was statistically insignificant.[12] High pre-operative PLR and a poor prognosis are associated, but the exact mechanisms are unclear. Sabrkhany *et al*. highlighted the potential significance of platelets in tumor angiogenesis and proliferation in cancers.[13] According to them, platelets get activated and adhere to the tumor's endothelial cells causing them to release angiogenic and angiostatic material, promoting angiogenesis.[13] Kim *et al*. state that platelets expressing P-selectin have the ability to attach to big mucin molecules found on the surface of tumor cells, which have P-selectin binding sites.[14] Tumor-induced platelet activation arcs form when platelets become activated by a tumor through their P-selectin and integrin, causing thrombosis and starting a reciprocating loop.[15] These activated platelets produce a number of growth factors

Table 1: Comparison of mean PLR, NLR, and MPV between Group I and Group II using Unpaired *t*-test.

Groups	Mean	*P*-value
PLR		
Group-1	121.536	**0.002* (<0.05)**
Group-2	72.48	
NLR		
Group-1	2.961	0.113
Group-2	2.431	
MPV		
Group-1	11.24	0.306
Group-2	11.58	

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, MPV: Mean platelet ratio, Group I: OSCC patient group, Group II: Control group. *: This symbol and bold values means that p value is less than 0.05 and is significant. OSCC: Oral squamous cell carcinoma.

Table 2: Comparison of mean PLR, NLR, and MPV with histological grade of OSCC cases and controls using one-way ANOVA.

Histological grade	Mean	SD	F value	*P*-value
PLR				
Grade I	123.11	48.20	3.254	**0.028* (<0.05)**
Grade II	120.67	70.06		
Grade III	105.00	0		
Controls	72.48	63.70		
NLR				
Grade I	2.911	1.09	2.843	**0.046* (<0.05)**
Grade II	2.79	1.64		
Grade III	5.87	0		
Controls	2.43	1.12		
MPV				
Grade I	11.41	1.05	0.641	0.592
Grade II	10.98	1.47		
Grade III	11.500	0		
Controls	11.580	1.277		

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, MPV: Mean platelet ratio, SD: Standard deviation, OSCC: Oral squamous cell carcinoma, ANOVA: Analysis of variance. Bold values with '*' symbol means p value is less than 0.05 and is significant.

that induce angiogenesis, metastasis, and tumor growth. This vicious cycle leads to the spread of cancer.[15]

In our study, the mean NLR of oral cancer patients was higher than the control group but the findings were not statistically significant (P = 0.113). This is in contrast to a study by Düzlü *et al.*, where NLR was significantly higher in OSCC patients as compared with control groups.[16] This difference in statistical findings could be due to our smaller sample size.

Table 3: Comparison of mean PLR, NLR, and MPV with clinical stage (cTNM) of OSCC cases and controls using one-way ANOVA.

Clinical stage	Mean	SD	f-value	*P*-value
PLR				
Stage I	239.70	0	2.954	**0.020* (<0.05)**
Stage II	119.49	64.18		
Stage III	87.01	9.70		
Stage Iva	118.88	54.27		
Stage Ivb	127.9500	5.74		
Controls	72.4820	63.70		
NLR				
Stage I	3.20	0	0.843	0.526
Stage II	2.88	1.47		
Stage III	1.99	0.23		
Stage Iva	3.13	1.54		
Stage Ivb	2.50	0.97		
Controls	2.43	1.12		
MPV				
Stage I	9.10	0	1.301	0.277
Stage II	11.42	1.08		
Stage III	12.35	0.49		
Stage Iva	11.25	1.17		
Stage Ivb	10.55	2.05		
Controls	11.58	1.27		

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, MPV: Mean platelet ratio, cTNM: Clinical TNM stage, SD: Standard deviation, OSCC: Oral squamous cell carcinoma, ANOVA: Analysis of variance, Bold values with '*' symbol means p value is less than 0.05 and is significant.

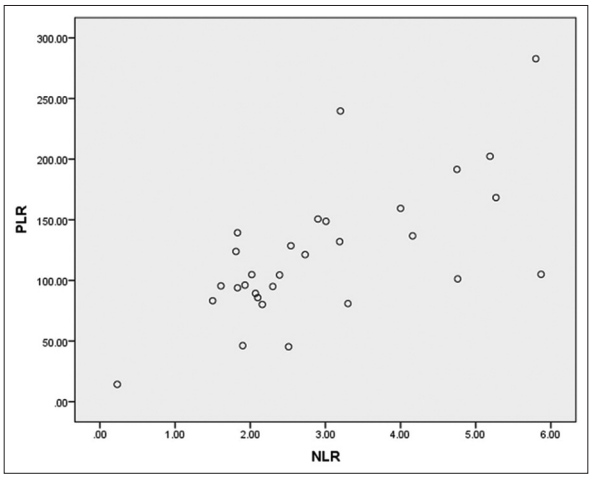

Figure 1: X-axis – Neutrophil-lymphocyte ratio (NLR), Y-axis – Platelet-lymphocyte ratio (PLR).

The relationship between NLR and worse outcomes in cancer is not fully understood but may be influenced by neutrophils' ability to secrete vascular endothelial growth factor, according to a study by Kusumanto *et al*.[17] For recurrent or metastatic head-and-neck squamous cell carcinoma, NLR derived from a blood sample at the time of the initial diagnosis of the metastatic disease or during recurrence may be a helpful laboratory measure.[18]

Our study demonstrates the statistically significant relationship between PLR and clinical TNM stage of cancer (P = 0.020). The mean PLR values decreased from TNM Stage I to TNM Stage III and then increased in TNM Stages IVa and IVb. This can be due to a lower sample size. Lu *et al*. found that advanced tumor characteristics, including poorer differentiation, deeper depth, and advanced TNM stages, were significantly associated with elevated PLR, suggesting that PLR could be a new parameter in the current TNM staging system for colorectal cancer prognosis.[19]

In our study, we discovered a statistically significant relationship between PLR and NLR and histological stages of cancer**.** This is in contrast to a study by Seetohul *et al*. in 2020, as they saw a non-significant rise in NLR and PLR with an increase in the histological grade of cancer.[20]

Furthermore, NLR decreased from well-differentiated to moderately differentiated and then increased from moderately differentiated to poorly differentiated OSCC. These results are inconclusive and may need further research with a larger sample size. However, poor tumor differentiation was associated with high NLR (P = 0.019) and PLR (P = 0.019) in a study by Zou *et al.*[21]

We also saw a statistically significant positive correlation between NLR and PLR, which was in concurrence with a finding in the study by Ari and Gunver, who also showed a strong and statistically significant positive correlation between NLR and PLR in thyroid cancer.[22]

Another finding of our study was that the mean MPV levels in the oral cancer group were lower than the control groups but the result was not statistically significant [Table 1]. In a study by Düzlü *et al*., they also found MPV levels significantly decreased in OSCC as compared to control groups.[16] Some studies have given the opposite results. In a study conducted by Anand *et al*., mean MPV levels in OSCC patients were higher than controls but there was no statistical association seen between them.[12] Therefore, the role of MPV in the prognosis of OSCC patients remains controversial.

CONCLUSION

We conclude that inflammatory hematological markers such as NLR and PLR act as significant prognostic factors in OSCC. MPV levels were not as significant as NLR and PLR in determining prognosis in OSCC. Furthermore, NLR and PLR are quick and easily measurable parameters that can be used as clinical biological markers to predict the prognosis of cancer.

As the present study was conducted on only 30 patients at one institution, this study has a sample size limitation. Our research, therefore, requires confirmation by larger prospective studies.

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