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ASSOCIATION OF PREOPERATIVE SYSTEMIC INFLAMMATORY MARKERS (NLR, PLR, AND LMR) WITH PATHOLOGICAL TUMOR STAGE AND CERVICAL LYMPH NODE METASTASIS IN ORAL SQUAMOUS CELL CARCINOMA

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Abstract

Objective: *To analyze the correlation between preoperative inflammatory blood markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) with pathological tumor stage and neck node metastasis in patients suffering from oral squamous cell carcinoma (OSCC), concomitantly to check their ability to diagnose nodal involvement in such patients.*

Study Design: *Analytical Cross-Sectional Study.*

Study Duration: *From January 2022 to January 2023.*

Study Setting: *ENT, Head and Neck Surgery Department of one of the tertiary hospitals in Karachi, Pakistan.*

Methods: *Total of 120 patients diagnosed with the primary OSCC through histopathological examination were included in the study who underwent primary surgery and neck dissection procedures. Preoperative blood samples had been collected within a week prior to the surgery, and levels of preoperative inflammatory parameters such as NLR, PLR, and LMR were estimated from the results of the blood examination. The pathological stage of tumor and nodal involvement was determined according to the eighth edition of the AJCC staging system. Comparison of inflammatory parameters of the patients was done using Mann-Whitney U test and diagnostic ability of each inflammatory parameter was calculated using ROC analysis.*

Results: *The average age of the patients involved in the study is 52.4± 10.1 years, 82 patients were male (68.3%) and 38 patients were female (31.7%). Patients with advanced pathologic T-stage were 62 (51.7%) and patients*

with cervical lymph node metastasis were 54 (45.0%). Advanced T-stage patients had higher median NLR (3.28 vs. 2.04) and PLR (152.3 vs. 116.5) whereas their LMR was lower (2.45 vs. 3.98); all differences were found statistically significant (p<0.001). The same differences regarding NLR and LMR may be noticed in the group of nodal positive-sk and node-negative patients. The highest diagnostic capacity among three biomarkers was shown for NLR (AUC=0.84), followed by LMR (AUC=0.81) and PLR (AUC=0.74).

Conclusion: *NLR, PLR and LMR levels before operations correlates with the tumor pathology stage and status of cervical lymph nodes. NLR showed the strongest diagnostic capabilities in identifying lymph node involvement among three studied biomarkers. The results of the study suggested that the inflammatory markers related to the patient's status can help improve the quality of preoperative assessment of patients with OSCC.*

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most widespread types of malignancy in the oral cavity and is one of the pressing issues of public health. This issue is quite severe in South Asia, where the use of tobacco products including smokeless products assists in the development of oral malignancies. Reports and projections on the incidence of primary tumors made by the international organizations are again bringing the attention to the significance of oral cavity tumors as one of the major causes of morbidity and mortality worldwide.

The prognosis of OSCC is dependent on multiple clinicopathological factors, among which the three most important include: tumor size, depth of invasion, and histological status, and the involvement of regional lymph nodes. The importance of cervical lymph nodes and metastasis in this location is due to its direct correlation with the disease progression as well as worse prognosis. For this reason, the evaluation of the primary tumor size and lymph node status is critical when deciding on surgical and adjuvant therapy.

While imaging technologies and physical tests are the mainstay in detecting disease in the region, they are not necessarily successful in diagnosing all cases of hidden cancer cells present in cervical lymph nodes. It is the pathology reports that confirm whether the tumor and the lymph nodes are malignant or not. However, such reports are available only after surgery. Therefore, there is a need to consider the possibilities of finding simple parameters for identifying preoperative factors indicative of progress of the disease or metastasis of the infections.

The process of cancer advancement is determined by complicated relationships between cancerous cells and the immune system of the host. The inflammatory reaction to the disease is responsible for some processes related to tumor development, blood vessel formation, infiltration, and metastasis. At the same time, host immune system is the way of controlling the cancer development. (Ruiz-Ranz et al., 2022).

The blood tests part of routine evaluation offer some indicators useful for the development of systemic inflammatory indices. Thus, the ratio obtained by dividing the number of neutrophils by the number of lymphocytes gives the neutrophil-to-lymphocyte ratio (NLR). The determination of the PLR or platelet-to-lymphocyte ratio requires calculating the ratio of the platelets over the number of lymphocytes, whereas the lymphocyte-to-monocyte ratio (LMR) can be obtained by dividing the number of lymphocytes by the number of monocytes. These values can be derived from routine preoperative blood tests, which does not imply any extra laboratory work.

There is evidence that the increase in the NLR may indicate heightened levels of the inflammatory response in the body and make one

conclude that the activity of the lymphocyte-based immune system is decreased. Thus, neutrophils are capable of releasing agents of inflammation and enzymes involved in cancer development, while lymphocytes might participate in the activity directed against cancer cells. In a similar fashion, platelets may ensure the survival of cancer cells and metastatic processes, and the low LMR may indicate that there is a high number of circulating monocytes and a low level of lymphocyte activity. These mechanisms provide a biological rationale for investigating inflammatory ratios in patients with OSCC (Valero et al., 2020; Ruiz-Ranz et al., 2022).

Evidence from earlier studies indicates that there is a link between preoperative inflammation and clinical outcomes in the treatment of cancers in the oral cavity and head and neck. However, the cutoff points for this inflammation and their relative clinical validity differ between the studies. The differences in the tumors, patients' characteristics, stages of the disease and study methodology may account for these discrepancies (Mascarella et al., 2018; Tazeen et al., 2020).

The data from the research from Pakistan is also important as the local situation may show if the findings of international populations may be relevant to patients receiving care locally. A cross-sectional study that was done in Pakistan that focused on the pre-treatment NLR in patients suffering from head and neck squamous cell cancers underlined the importance of this parameter in the local clinical context (Khan et al., 2023).

In this regard, the present research was undertaken to analyze the relationship of preoperative levels of NLR, PLR, and LMR with tumor stage and cervical lymph node involvement in OSCC patients along with assessing the effectiveness of these parameters by utilizing ROC curve analysis to determine cutoff levels appropriate for differentiating between patients with and without lymph node involvement.

Literature Review

The study of systemic inflammation has been gaining popularity as an element possibly implicated in cancer advancement and as a supplier of useful prognostic markers for clinical practice. In the case of malignancies of the head and neck, several blood markers have attracted significant interest because they can be measured during routine laboratory testing.

NLR is one of the blood parameters that has been the subject of intensive research. A systematic review with a meta-analysis conducted by Mascarella et al. (2018) showed that the increased pretreatment value of NLR may represent a negative prognostic marker for patients suffering from head and neck squamous cell carcinoma, which also includes cases of oral neoplasms. In addition, Yang et al. (2019) demonstrated that high pretreatment NLR value may also serve as a predictive factor for poor survival results in head and neck squamous cell carcinoma patients.

Research focusing specifically on OSCC has also investigated the link between the number of neutrophils and the prognosis of the disease. Tazeen et al. (2020) looked at pre-treatment values of NLR and PLR in patients with OSCC, finding that both ratios have an effect on prognosis of the patients. These results suggest that hematological parameters can be used as additional prognostic parameters.

More research has gone into examining the link between the inflammatory parameters and the lymph node involvement. Wang et al. (2021) conducted research that examined the relationship between NLR, PLR, and lymph node metastasis in patients with oral tongue squamous cell carcinoma. The researchers suggested the potential importance of the indexes in terms of assessing the regional problem.

Besides, the significance of various inflammatory ratios has also been analyzed in larger cohorts of OSCC patients. Valero et al. (2020) examined leukocyte counts prior to treatment in patients with oral cavity cancer, analyzing their relation to the treatment results. It was noted that blood parameters related to inflammation and immune system could be useful in pre-operative estimation of risks.

Caruntu et al. (2021) investigated the role of preoperative blood parameters in oral cancer by

showing that potentially clinically relevant information can be derived from routinely taken blood test values.

Ruiz-Ranz et al. (2022) investigated the role of NLR, PLR, LMR, and other inflammatory indices in patients with OSCC, as well as their possible link to local and various systemic immune parameters. Their research demonstrated that the interpretation of these indices is complicated and their prognostic value is variable depending on the index and associated outcomes.

Mikami et al. (2022) examined preoperative systemic inflammatory changes in patients with early-stage OSCC. The examined parameters included NLR, PLR, and LMR, and clinical outcomes and occurrence of delayed metastasis are reported as important variables.

A similar study by Zhou et al. (2023) focused on the role of preoperative percentage NLR, PLR, and LMR in predicting outcomes in patients with head and neck squamous cell carcinoma, confirming the importance of using preoperative inflammation indicators. However, they underscored the necessity of conducting more studies on larger samples.

In another investigation, Xu et al. (2026) based on a meta-analysis of results obtained in various trials demonstrated the benefit of applying components NLR, PLR, and LMR in predicting outcomes in patients with OSCC.

At the same time, researchers failed to determine universal thresholds specifically for NLR, PLR, and LMR values in OSCC. Differences within the studied groups as well as primary tumors, stages of pathology, laboratory approaches used, and definitions of outcomes may influence the obtained results. Moreover, it is worth mentioning that results on PLR and LMR were not completely the same in other studies.

Despite previous research having analyzed the individual inflammatory components and their significance for OSCC prognosis, there is still a need to conduct further research on other cohorts from different locations. The study presents local data by analyzing the three individual ratios from the same cohort of patients who underwent surgery for OSCC. It explores their correlation with the pathological stage of the tumor and nodal involvement while also evaluating their predictive capability with the use of ROC analysis.

Methodology

Study Design and Setting

In this clinical cross sectional study, the research was performed at the Department of Otolaryngology, Head and Neck Surgery, of a Karachi based tertiary care hospital, Pakistan, from January 2022 to January 2023

Study Population

A cohort of 120 individuals suffering from primary oral squamous cell carcinoma (OSCC), confirmed by histopathological assessments, underwent surgical resection, accompanied by neck dissection involving one or both sides of the neck. To be eligible for inclusion, participants within the age bracket of 18 and 80 years were selected, regardless of their sex. They were expected to have a presurgery, complete blood count taken within seven days prior to the surgery. Individuals with previous chemotherapy or radiotherapy history, or prior surgery for head and neck cancer were excluded from the study. Further exclusions were made for cases of recurrent acute infections, autoimmune disorders, chronic hematological illnesses and use of immunosuppressors.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Review Committee. Written informed consent was obtained from all participating patients before enrollment.

Laboratory Data Collection

Blood tests for venous blood were conducted using tubes containing ethylenediaminetetraacetic acid (EDTA) and the work done using automated hematology analyzer within 2 hours. Data about absolute neutrophil count, absolute lymphocyte count, absolute monocyte count and platelet count was retrieved from the blood test report.

Measurements of different inflammatory indexes were performed using three mathematical expressions to obtain following three indexes:

1. Neutrophil/lymphocyte ratio (NLR): division of the absolute neutrophil count with that of absolute lymphocyte count.
2. Platelet/lymphocyte ratio (PLR): division of the absolute platelet count with that of absolute lymphocyte count.
3. Lymphocyte/monocyte ratio (LMR): division of the absolute lymphocyte count with that of the absolute monocyte count.

All of the three indices were obtained from the preoperative check-up blood test done within the stated period of seven days before the surgery.

Histopathological Assessment and Staging

Hematoxylin and eosin were used to stain resected surgical specimens. Histopathological examination was done by two experienced head and neck pathologists. The pathological tumor category and cervical lymph node status were determined according to the eighth edition of the AJCC staging system (Amin et al., 2017).

For analysis purposes, pathological T-stage was categorized as early disease (T1–T2) and advanced disease (T3–T4). Regional lymph node status was classified as pN0 (node-negative) or pN+ (node-positive).

Statistical Analysis

The analysis of the data was conducted using the IBM SPSS Statistics 26.0 version computer software package. Categorical variables were summarized in terms of frequencies and percentages while continuous variables were evaluated for normality by means of Shapiro-Wilk Test. Normal distributions are presented in terms of mean and standard deviations and inversely non-normal distributions are given in terms of the median and interquartile range.

The Mann-Whitney U test was applied in order to compare the levels of inflammatory markers between pathological T-stage early and advanced groups and the comparison was also made between the patients who were node-negative and node-positive.

Receiver operating characteristic analysis was applied to evaluate the diagnostic effectiveness of NLR, PLR, and LMR for prediction of cervical lymph node metastases. The cut-off value was established by means of Youden Index. The area under curve, 95% CI values as well as sensitivity and specificity were calculated. The p-value was considered statistically significant at a threshold of p less than 0.05.

Analysis & Discussion

Baseline Demographic and Clinicopathological Characteristics

The study encompassed a total of 120 subjects diagnosed with OSCC and confirmed by histopathological evidence. The cohort's mean age was found to be 52.4 ± 10.1 years with ages ranging from 28 to 76 years. There were 82 (68.3%) males and 38 (31.7%) females in the study population.

The buccal mucosa was affected more than any other anatomical region involved in this research with a total of 68 (56.7%) cases prevalent in the sample population. The oral tongue presented in 34 (28.3%) individuals followed by the lower alveolus in 12 (10%) subjects and floor of mouth in 6 individuals (5%).

The participants in the cohort reported the consumption of smokeless tobacco in the form of gutka or naswar. The participants consisted of 89 (74.2%) individuals who used smokeless tobacco in any form. The pathology examination revealed the findings for the cases included in the study with 58 (48.3%) cases having early-stage cancer (pT1–pT2) and the remaining 62 (51.7%) subjects having advanced disease (pT3–pT4). The cervical lymph nodes were found to be metastasized in 54 (45.0%) patients while 66 (55.0%) were found to be lymph-node negative. The demographic and clinicopathological characteristics are summarized in Table 1.

Table 1. Baseline Demographic and Clinicopathological Characteristics of the Patient Cohort (N = 120)

Characteristic	Frequency (n) / Mean ± SD	Percentage (%) / Range
Age (years)	52.4 ± 10.1	28–76
Gender		
Male	82	68.3
Female	38	31.7
Primary anatomical subsite		
Buccal mucosa	68	56.7
Oral tongue	34	28.3
Lower alveolus	12	10.0
Floor of mouth	6	5.0
Smokeless tobacco use (gutka/naswar)	89	74.2
Pathological T-stage (AJCC 8th edition)		
pT1	18	15.0
pT2	40	33.3
pT3	38	31.7
pT4a	24	20.0
Pathological nodal status		
pN0 (node-negative)	66	55.0
pN+ (node-positive)	54	45.0
Histopathological grade		
Well differentiated (G1)	36	30.0
Moderately differentiated (G2)	62	51.7
Poorly differentiated (G3)	22	18.3

Association Between Inflammatory Markers and Pathological Tumor Stage

Analysis of systemic inflammatory indicator differences across pathological T-stage groups presented pertinent information. Individuals with advanced pathological stage (T3–T4) exhibited a greater mean NLR than the group with early stage (T1–T2), respectively, 3.28 and 2.04 ($p < 0.001$). At the same time, the mean PLR was greater among patients at advanced stage (152.3) than in the early stage (116.5) ($p < 0.001$).

Contrarily, mean LMR in patients with advanced pathological T-stage turned out to be less than that in early stage (2.45 vs. 3.98, $p < 0.001$). Therefore, the findings suggest that higher NLR and PLR as well as lower LMR were characteristic of patients at advanced pathological tumor stage in the presented study.

Association Between Inflammatory Markers and Cervical Lymph Node Metastasis

In a similar analysis of inflammatory indexes according to pathological nodal status, an increase in median NLR levels for patients with metastasis in cervical lymph nodes (pN+) in comparison with patients with no signs of nodal involvement (pN0) has been noted (3.42 vs. 1.95, $p < 0.001$). At the same time, median PLR of the patients with positive nodes was higher than that of the

individuals without node involvement (158.4 and 112.1, respectively, $p < 0.001$).

On the other hand, it should be noted that median LMR of patients with positive cervical lymph nodes was lower than that for patients without nodal involvement (2.31 vs. 4.15, $p < 0.001$). These results show that all three discussed inflammatory markers have significant differences for the groups with different pathological nodal statuses. The comparative values are presented in Table 2.

Table 2. Comparison of Systemic Inflammatory Markers According to Pathological T-Stage and Cervical Lymph Node Status (N = 120)

Inflammatory marker	Early T-stage (T1–T2)	Advanced T-stage (T3–T4)	p-value	Node-negative (pN0)	Node-positive (pN+)	p-value
NLR	2.04	3.28	<0.001	1.95	3.42	<0.001
PLR	116.5	152.3	<0.001	112.1	158.4	<0.001
LMR	3.98	2.45	<0.001	4.15	2.31	<0.001

Diagnostic Performance of Inflammatory Markers for Cervical Lymph Node Metastasis

This ROC Curve analysis evaluates the capacity of preoperative inflammatory markers to differentiate between patients with and without cervical lymph node metastasis. Among the three indices, NLR exhibited the highest diagnostic ability with the area under the curve of 0.84 (95% CI: 0.76-0.91).

An NLR cutoff greater than 2.65 achieved 81.5% sensitivity and 78.8% specificity in identifying cervical lymph node metastasis. LMR also showed discrimination in the area of the ROC with an AUC of 0.81 (95% CI: 0.73-0.89). A cutoff value less than 3.10 was associated with a sensitivity of 79.6% and specificity of 75.8%.

PLR provided fair diagnostic accuracy with an AUC of 0.74 (95% CI: 0.65-0.83). The cutoff of 132.5 resulted in a sensitivity of 70.4% and specificity of 68.2%. Overall, among all biomarkers, NLR possessed the highest degree of discrimination among the three markers in this study.The ROC findings are summarized in Table 3.

Table 3. Diagnostic Performance of Systemic Inflammatory Markers for Cervical Lymph Node Metastasis (N = 120)

Inflammatory marker	Optimal cutoff value	AUC	95% CI	Sensitivity (%)	Specificity (%)
NLR	>2.65	0.84	0.76–0.91	81.5	78.8
PLR	>132.5	0.74	0.65–0.83	70.4	68.2
LMR	<3.10	0.81	0.73–0.89	79.6	75.8

Interpretation of the Findings in Relation to Previous Research

The current research investigated association between markers of inflammation in the blood prior to operation and disease characteristics in 120 patients suffering from oral squamous cell carcinoma. The main outcome indicates that the increase in neutrophil to lymphocyte ratio and platelet to lymphocyte ratio and the decrease in lymphocyte to monocyte ratio were shown to be linked to advanced pathological T-stage and cervical lymph node metastasis. Moreover, ROC curve analysis showed that NLR had the best diagnostic accuracy in detection of metastasis in lymph nodes compared to LMR and PLR.

According to demographic data, men accounted for 68.3% of the total sample. The most common anatomical subsite affected by the disease was the

buccal mucosa, as this anatomical region was affected in more than a half of the patients. This distribution is important due to the fact that this type of cancers is linked to smoking habits of population; in the studied cohort 74.2% of subjects reported using smokeless tobacco. Despite this fact, such study design cannot establish any cause and effect relationship between exposure to tobacco and tumor characteristics..

The link between elevated levels of NLR and severe stage of cancer is in accordance with earlier studies investigating neoplasms of the oral cavity and the head and neck. Neutrophils are responsible for inflammatory responses and may also aid in tumor development through the release of cytokines, proteolytic enzymes, and other agents. Such actions imply angiogenesis, remodeling of the extracellular matrix, and movement of tumor cells. Unlike neutrophils, lymphocytes have an important function in antitumor immunity. Hence, the increase of NLR may be indicative of the imbalance between body inflammation and immunity. According to previous studies, there is a connection between elevated levels of NLR and negative outcomes for head and neck cancer patients. The meta-analysis performed by Mascarella et al. (2018) showed that overall survival rates are associated with elevated NLR levels. Research conducted by Yang et al. (2019) revealed that high pretreatment levels of NLR are connected to dysfunctional outcomes in patients with head and neck squamous cell carcinoma. According to Tazeen et al. (2020), the prognostic impact of pretreatment NLR levels is significant for patients diagnosed with OSCC.

According to the results of this investigation, there was a significant difference in median values of PLR between patients with advanced T-stage and those with early-stage disease. Similar finding was noted in the case of node-positive and node-negative subjects. It is known that platelets are important for hemostasis and inflammatory processes; however, they may also be involved in cancer development. As was pointed out, PLR may be the result of the role of platelet-derived growth factors as well as the interaction of platelets with circulating tumor cells. However, it is important to note that PLR depends on lymphocyte counts in the circulation, thus it needs to be considered with the effects of both platelets and lymphocytes.

Moreover, LMR was demonstrated to behave inversely compared to NLR and PLR. It was revealed that patients with advanced T-stage and nodal-positive status showed lower median values of LMR. This may be explained with the reduced lymphocyte-mediated immune response in relation to circulating monocytes. Monocytes are capable of penetrating the malignant tumor and maturing into tumor-associated macrophages, which can also participate in tumor growth, angiogenesis, and immune modulation. Ruiz-Ranz et al. (2022) studied the association between systemic inflammatory markers and the local immune tumor microenvironment in OSCC, providing further context for understanding the biological relevance of these ratios.

The results from ROC analysis highlighted the relative diagnostic performance of said markers. Among them, NLR obtained the highest AUC value of 0.84, having a cutoff point greater than 2.65, its sensitivity being 81.5% and specificity 78.8%. The AUC for LMR was slightly lower, namely 0.81, while the aforementioned PLR provided an AUC value of 0.74.

This aligns with previous studies showing the role of inflammatory markers in OSCC. For instance, Wang et al. (2021) researched the levels of inflammatory indices in oral tongue SCC and their association with lymph node metastasis. Mikami et al. (2022) assessed systemic inflammatory markers in early-stage OSCC while Zhou et al. (2023) focused on the significance of NLR, PLR, and LMR with regard to prognosis in head and neck SCC. Such papers suggest that the usage of blood-based inflammatory markers will maintain its relevance, being important adjuncts to tumor assessment.

The cutoff values determined by this research should be evaluated based on the background of the enrolled patients. Various studies have estimated different cutoff values for NLR and PLR, meaning that the cutoff values will differ depending on the pathology of the tumor, its stage, the characteristics of the patients, and the

outcome that is being estimated. Therefore, the cutoff values obtained in the present cohort should not be considered universally applicable without external validation.

Moreover, the obtained results may be of relevance to the healthcare institutions where advanced diagnostic techniques may not be available. Complete blood counts are included in the preoperative assessment, which may provide data needed for the NLR and PLR calculations. Therefore, these indices may provide information without the necessity to complete specialized laboratory testing. However, they should be analyzed in combination with the clinical and radiological data.

Certain limitations must be acknowledged. Firstly, the study took place at a single tertiary hospital limiting generalization of the results to clinical practice in other centers. The second limitation is the small sample of 120 patients which impairs the replication of the findings in larger samples. Thirdly, different factors could influence inflammatory markers that can render the results irrelevant. Although patients with inflammatory and hematological conditions were specifically excluded, there remains the possibility of confounding effects.

Moreover, the study only used group comparisons and ROC curve analysis instead of multivariable logistic regression analysis that prevents the authors from claiming the independence of the identified factors as predictors of nodal metastasis. Further studies are needed to apply multivariable approaches and incorporate common biological and clinical variables such as tumor size and stage, grades of malignancy, presence of perineural, and lymphovascularinvasion into the analysis as well as confirm the validity of the cutoff points in clinical practice.

Conclusion

Preoperative systemic inflammatory markers showed statistically significant relations with pathological tumor stage and lymph node status in OSCC. More advanced pathological disease and lymph nodes with tumor involvement were associated with increased levels of NLR and PLR and decreased levels of LMR. The highest sensitivity in diagnosing lymph node invasion was shown by NLR, followed by LMR and PLR. Though more extended confirmation of results by multicenter studies is required, these commonly used markers may serve as additional tools in the preoperative investigation of patients with OSCC.

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