PRE-TREATMENT HAEMATOLOGIC MARKERS OF INFLAMMATION IN MUCOSAL HEAD AND NECK SQUAMOUS CELL CARCINOMA AT THE KENYATTA NATIONAL HOSPITAL, NAIROBI, KENYA

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ABSTRACT

Background: Head and Neck Squamous Cell Cancers (HNSCC) are among the commonest cancers encountered in clinical practice, constituting a significant public health problem. Diagnosis, and management of these cancers remains challenging to clinicians especially in resource limited settings. Use of simple and affordable biomarkers of inflammation like the Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR) and the Red Cell Distribution Width (RDW) may highlight the role of inflammation in patients with mucosal HNSCC in this setting.
Objective: The aim of this study was to investigate the effect of mucosal HNSCC on the levels of haematologic markers of inflammation viz, NLR, PLR and RDW, at the Kenyatta National Hospital (KNH), Nairobi, Kenya.
Design: This was a cross-sectional case control study.
Methods: The study involved 61 mucosal cancer patients and 61 gender-matched and age-matched controls at KNH. Convenience sampling technique was used to recruit participants. Our data collection tool captured the demographic, clinical and disease specific characteristics of the respondents. The NLR, PLR, and RDW were computed from the Complete Blood Count (CBC) result slips.
Data management and analysis: Data was expressed as means and standard deviations. Differences between variables in case and control groups were analysed using the Pearson's Chi-squared test and mean levels of PLR, NLR and RDW were correlated with clinico-demographic variables by one-way analysis of variance (ANOVA). A two tailed P-value of <0.05 was our cut off for statistical significance.
Results: A total of 61 cases and 61 controls were recruited into this study. Males constituted 41 (67.2%) of both study arms. The mean age for cases was 45.30±17.17 years and 43.00±15.45 for controls. Mean values of NLR between cases and controls were 4.1±4.8 and 1.3±0.7 respectively (P<0.001). Values of PLR for cases and controls were 238.4±138.5 and 117.8±44.0 (P<0.001). Similarly, cases had a higher RDW (CV) value compared to controls, 14.8±3.5 and 13.8±1.2 respectively, p= 0.04. When values of NLR and PLR were dichotomized, the odds ratio for having mucosal HNSCC and having a raised NLR, PLR and RDW were 5.55 (CI: 2.60-11.85, P<0.001), 3.25 (CI: 2.01-5.25, P<0.001) and 1.57(CI: 0.89-2.74, p=0.08) respectively. There was a non-significant increase of NLR with T-stage of mucosal HNSCC.
Conclusion: The NLR, PLR and RDW levels are significantly higher in mucosal HNSCC patients than in healthy individuals. We recommend appropriate studies to correlate these indices with treatment outcomes, mortality, and prognosis of mucosal HNSCC in this setting.

Key words: Haematologic markers, Complete blood count, Neutrophil lymphocyte ratio, Platelet lymphocyte ratio, Red cell distribution width

INTRODUCTION

Mucosal HNSCCs (HNCs) are cancers arising within the mucosal surfaces of the hypopharynx, nasal cavities and sinuses, nasopharynx, larynx, and oral cavity, the most common histological variant being squamous cell carcinoma[1]. HNCs are the fifth most common cancers globally and are responsible for more than 600,000 new cases diagnosed yearly and more than 300,000 deaths per year[2]. Recently, there have been many studies exploring the relationship between inflammation and carcinogenesis [3-8]. Markers of inflammation and immunity such as Neutrophil-to-Lymphocyte Ratio (NLR) and the Platelet-to-Lymphocyte Ratio (PLR) have been found useful as prognostic indicators in patients with HNCs. The red cell distribution width, a reliable marker of chronic inflammation in malnourished patients[8,9], has

been associated with poor outcomes in patients with malignancies and has shown positive correlation with cancer stage in patients with lung cancer[10].

Use of NLR, PLR, and RDW, which could all be drawn from the Complete Blood Count (CBC), could be an affordable approach in deciding on patient management, monitoring response to treatment and for prognostication in patients with mucosal HNSCCs. The full blood count is routinely performed before, during and after treatment of many disease conditions in clinical practice including mucosal HNSCCs. This investigative modality roughly estimates the patient's anaemic, inflammatory, immunologic, and nutritional status and could therefore provide benefit in this subset of patients. The main objective of the present study was to investigate the effect of mucosal HNSCCs on the levels of NLR, PLR and RDW among patients. Determination of pre-treatment levels of NLR, RDW and PLR will provide useful information for establishment of reference values for these parameters in evaluating the extent of mucosal HNSCC patients. This will also form a substantive basis for the use of these markers in monitoring of treatment response and for prognostication in our patients. These parameters may also aid in deciding on the therapeutic choices in mucosal HNSCC patients and will form a basis for further research on the applicability of inflammation in designing therapies for cancers.

MATERIALS AND METHODS

This was a cross-sectional case control study conducted at the Kenyatta National Hospital, Nairobi Kenya. This study was approved by the ethics and research committee of the University of Nairobi/ Kenyatta National Hospital, protocol number P34/01/2019. Data collection tool was a specially designed questionnaire that captured demographic characteristics of the study population, cancer characteristics and the complete blood count result slip. Cases were patients aged 18 years and above, presenting with a histological diagnosis of mucosal HNSCC. Controls were healthy individuals, aged 18 years or older who were not being followed up regularly for any disease condition. They were sampled among blood donors who had undergone assessment for fitness to donate and individuals with conditions like refractive errors or cataract followed up at KNH. They were matched with cases based on gender and age ranges established on 10 year intervals. We excluded patients who have had or are currently on treatment for mucosal HNSCC such as surgery, radiotherapy, or chemotherapy and participants with diagnosed cancers of other body regions apart from mucosa of the head and neck region. Individuals with history of long-term steroid use were also excluded. Complete blood count was analysed with an automated analyser (SYMEX™, MODEL: XN500).

Data was expressed as mean, standard deviation and 95% Confidence Interval (CI). Comparative analysis of quantitative data was achieved with Student T test whereas qualitative data was evaluated by using Chi-square and Fishers exact tests. Normally distributed data was analysed with one- way ANOVA test. Dichotomization of markers of inflammation to high and low values was based on the following cut offs; NLR-<3.5 and ≥3.5, PLR-≥350 and <350, RDW-≥15 and <15. A two tailed P-value of <0.05 was our cut-off for statistical significance.

RESULTS

A total of 122 participants (61 cases and 61 controls) met the inclusion criteria. Males constituted 41 (67.2%) of each study arm. The mean age for cases was 45.30±17.17 years and 43.00±15.45 for controls, (P=0.44). The age distribution of the study population is depicted in Figure 1 and the gender distribution is presented in Table 1.

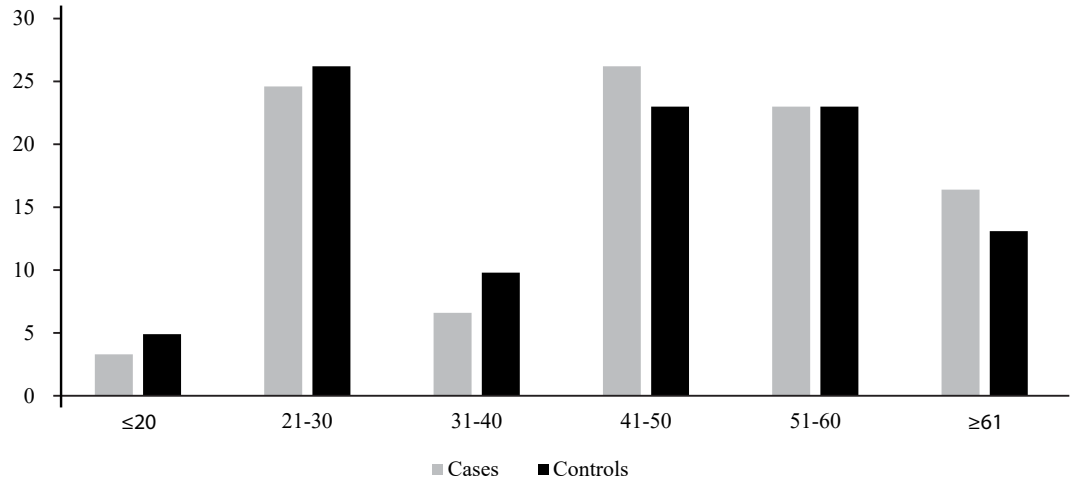

Figure 1: Age distribution of the study population

Table 1: Gender distribution

Characteristic	Case	Control	P-value
Gender			
Male	41(67.2%)	41(67.2%)	1.00
Female	20(32.8%)	20(32.8%)	
Age (years) Mean	45.30±17.17	43.00±15.45	0.44

Laryngeal carcinoma was the most common cancer (31.1%) among our participants (Figure 2). Most participants (91.8%) were at advanced stage (T3 and T4) at the time of recruitment into the study. Early stage presentations were relatively rare. Cervical nodal stage, N2, disease was the most encountered (49.2%) in our population. Distant metastases were found in only seven (11.5%) of the participants. Well differentiated squamous cell carcinomas were seen in 31 (50.8%) patients (Table 2).

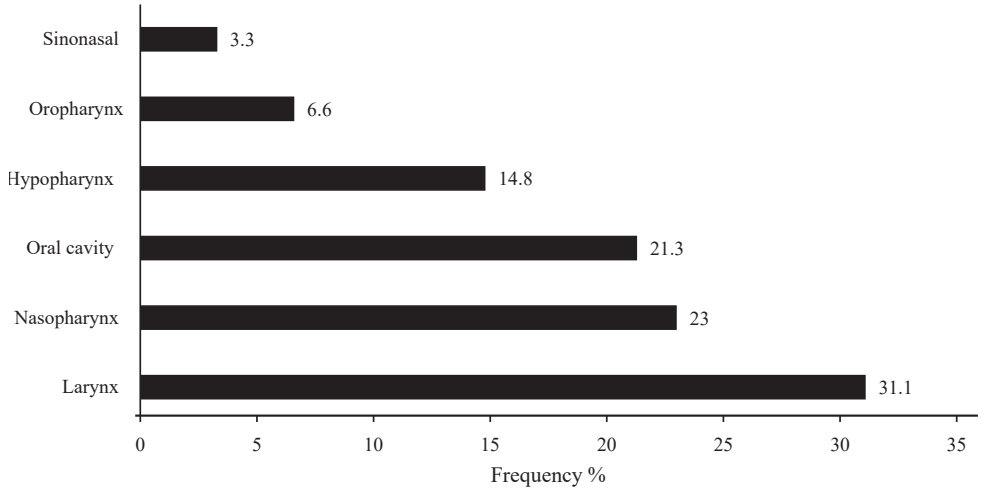

Figure 2: Distribution of cancers based on anatomical location

Table 2: Cancer characteristics

Characteristics		Frequency (%)
Location	Nasopharynx	14 (23)
	Sinonasal	2 (3.3)
	Oropharynx	4 (6.6)
	Oral cavity	13 (21.3)
	Hypopharynx	9 (14.8)
	Larynx	19 (31.1)
T-stage	T1	1 (1.6)
	T2	4 (6.6)
	T3	13 (21.3)
	T4	43 (70.5)
N-stage	N0	13(21.3)
	N1	6 (9.8)
	N2	30 (49.2)
	N3	12 (19.7)
M-stage	M0	54 (88.5)
	M1	7 (11.5)
Histological grade	Grade 1	31 (50.8)
	Grade 2	16 (26.2)
	Grade 3	2 (3.3)
	Grade 4	11 (18.0)

The complete blood count and markers of inflammation

Total white blood cell counts were significantly higher in mucosal HNSCC patients than the general population (10.0±8.31 vs 5.5±1.5 respectively, P<0.001). Differential neutrophil counts likewise were significantly higher in cases than in controls (7.1±8.1 vs 2.7±1.1 respectively, P<0.001). Lymphocyte counts however were higher among controls than cases (2.2±0.6 vs 1.7±0.6, P=0.02). Significant differences were also observed in total platelet counts between cases and controls (409.5±139.7 vs 247.8±76.1 respectively, P<0.001). Significantly higher values of the red cell distribution width coefficient variation value were observed in cases than in controls (14.8±3.5 vs 13.8±1.2 respectively, P=0.03).

Markers of inflammation were similarly higher in head and neck mucosal squamous cell carcinoma patients than in the general population. Mean values of NLR between cases and controls were 4.1±4.8 and 1.3±0.7 respectively (P<0.001) likewise, values of PLR for cases and controls were 238.4±138.5 and 117.8±44.0 (P<0.001).

When values of NLR and PLR were dichotomized, the odds ratio for having head and neck mucosal squamous cell carcinoma and having a raised NLR, PLR and RDW were 5.55 (CI: 2.60-11.85, P<0.001), 3.25 (CI: 2.01-5.25, P<0.001) and 1.57(CI: 0.89-2.74, p=0.08) respectively (Table 3).

Table 3: The complete blood count and markers of inflammation

Parameter	Normal values	Cases	Controls	P-values
WBC	4.6 -10.2	10.0±8.31	5.5±1.5	<0.001
Neutrophils	2 -6.9	7.1±8.1	2.7±1.1	<0.001
Lymphocytes	0.6 -3.4	1.7±0.6	2.2±0.6	0.02
Platelets	142 -424	409.5±139.7	247.8±76.1	<0.001
RDW (CV)	11.6-14.8	14.8±3.5	13.8±1.2	0.04
NLR		4.1±4.8	13.8±1.2	<0.001
PLR		238.4±138.5	117.8±44.0	<0.001

Correlations between markers of inflammation and clinicodemographic parameters

Higher values for NLR were found among male cases than female cases**,** 4.7±5.6 vs 3.1±2.4 but similar in controls across both gender categories. This relationship was not however significant, P=0.28. On the contrary, among the cases, females had higher values of PLR and RDW than males, 242.7±107 and 15.2±3.6 vs 236.2±152.7 and 14.6±3.4 for controls, females had higher values for PLR than males, 127.8±44.2 vs 113.0±42.6 but similar values for RDW, 13.8±1.4 vs 13.8±1.0. The relationship between PLR and RDW with gender was not significant, P=0.64 and P=0.52, respectively. The NLR, PLR and RDW were therefore, similarly distributed across both gender categories (Table 4).

Table 4: Correlation between gender and markers of inflammation

Characteristics	Gender	Case	Control	P-value
NLR	Male	4.7±5.6	1.3±0.8	0.28
	Female	3.1±2.4	1.3±0.5	
PLR	Male	236.2±152.7	113.0±42.6	0.64
	Female	242.7±107	127.8±44.2	
RDW	Male	14.6±3.4	13.8±1.4	0.52
	Female	15.2±3.6	13.8±1.0	

Highest values for NLR were recorded in the 31-40-year age group for both cases and controls, 5.5±7.2 and 1.9±1.7, respectively, P=0.92. There was no predictable relationship between PLR, RDW and age and no statistical differences existed between both groups.

Table 5: Correlation between markers of inflammation and age of participants

Marker	Ages (years)	Case	Control	P-value
NLR	≤20	5.0±1.6	0.7±0.3	0.92
	21-30	3.4±2.8	1.1±0.4	
	31-40	5.5±7.2	1.9±1.7	
	41-50	4.0±2.3	1,4±0.4	
	51-60	5.1±8.6	1.3±0.4	
	≥61	3.4±2.6	1.2±0.4	
PLR	≤20	362.7±39.8	117.9±36.7	0.30
	21-30	216.1±119.8	103.0±41.8	
	31-40	260.8±98.6	139.9±72.9	
	41-50	297.8±203.3	124.0±35.0	
	51-60	220.4±70.8	119.9±38.0	
	≥61	168.3±98.4	116.7±60.6	
RDW	≤20	16.2±1.7	12.7±1.4	0.55
	21-30	15.8±4.6	13.7±1.1	
	31-40	13.4±1.8	13.5±1.3	
	41-50	15.7±4.9	13.6±1.4	
	51-60	15.6±4.9	14.7±3.6	
	≥61	14.4±0.9	14.0±1.1	

There was a non-significant increase of NLR with T-stage of mucosal HNSCC. Oral cavity and oropharyngeal tumours had the highest levels of NLR. This relationship was however not significant. Highest levels of PLR were found in oropharyngeal cancers and oral cavity tumours had the highest values of RDW. None of these were statistically significant. T4 cancers had higher levels of NLR and PLR than the other stages. There were no predictable associations between N-stage, M-stage and histological differentiation of mucosal HNSCCs and the markers of inflammation (Table 6).

Table 6: Correlation between cancer characteristics and markers of inflammation

Characteristic		Mean NL-R±SD	P-value	Mean PLR±SD	P-value	Mean RD-W(CV) ±SD	P-value
Tumour location	Nasopharynx	4.3±2.9	0.35	274.6±92.3	0.59	15.3±3.2	0.55
	Sinonasal	3.0±1.7		257.7±54.8		12.2±0.5	
	Oral cavity	6.1±8.6		204.3±98.8		15.8±5.9	
	Oropharynx	6.0±3.4		322.8±333.1		15.2±1.2	
	Hypopharynx	5.0±4.7		246.7±134.4		15.1±3.3	
	Larynx	2.4±2.0		213.7±146.5		13.8±1.5	
T-stage	T1	2.7	0.62	242.9	0.30	12.7	0.68
	T2	2.6±1.4		216.2±106.3		15.9±3.5	
	T3	3.2±3.2		176.3±93.7		14.0±1.4	
	T4	4.8±5.4		260.2±151.0		15.0±4.0	
N-stage	N0	5.3±8.9	0.71	175±89.4	0.05	15.2±5.0	0.35
	N1	2.7±1.0		151.0±33.0		13.4±1.4	
	N2	3.8±3.2		266.8±140.6		13.4±2.4	
	N3	5.1±3.0		283.6±177.9		16.2±4.5	
M-stage	M0	4.3±5.1	1.00	236.7±147.3	0.71	14.5±3.1	0.06
	M1	4.3±1.4		257.8±53.5		17.2±5.8	
Histological grade	Grade 1	3.6±2.5	0.65	235.7±170.3	0.46	15.0±3.4	0.91
	Grade 2	5.5±8.3		207.6±99.8		14.7±4.4	
	Grade 3	3.7±0.5		263.0±47.3		13.3±2.1	
	Grade 4	4.4±3.2		293.4±92.9		14.7±2.3	

DISCUSSION

Mucosal HNSCCs constitute a growing problem worldwide with heavy burden in terms of morbidity and mortality especially in developing countries. In this study, we sought to compare the pre-treatment levels of haematologic markers of inflammation in mucosal HNSCC patients to that of the healthy population.

This study had a predominantly male population which is consistent with the worldwide gender specific incidence rates of mucosal HNSCCs showing highest values among males than females. This is mainly attributable to cigarette smoking and alcohol consumption behaviours which are more prevalent among males than females[11].

The most prevalent subtype of mucosal HNSCC was laryngeal cancer. This finding is supported by the findings of Onyango *et al*[12] in the same study setting. This is however different from other settings especially in Asia pacific region where oral cavity cancers are the most frequently encountered[11]. The difference is mainly related to the variances in risk factor exposures, where betel quid chewing is the most common form of tobacco exposure contrary to our setting where cigarette smoking predominates. Late presentation to hospital in mucosal HNSCCs is common in our setting. Our findings are similarly reported by Onyango *et al*[12] and Oburra[13] in which studies, late presentation stemmed from misdiagnosis at primary health care settings and the inefficiency of the referral system in the most part. However, presentation to health facility of mucosal HNSCCs is variable with respect to the subsite involved. Oral cavity (tongue) and glottic carcinomas generally cause early symptoms whereas pharyngeal and supraglottic tumours usually present at an advanced stage nonetheless differences in presentation times still exist from region to region[15]. Despite advanced tumour stage and lymph node metastasis at diagnosis, distant metastasis at presentation is generally uncommon as shown in our population.

Neutrophil-lymphocyte ratio and platelet-lymphocyte ratios were significantly higher in mucosal HNSCC patients compared to healthy individuals. This finding has been reported similarly by Kuo *et al*[16]. These markers generally reflect the balance between pro-tumour inflammation and host immunity. High levels therefore suggest that mucosal HNSCCs in this study setting engender higher levels of peritumoral inflammation than can be surmounted by host immunity. Seetohul *et al*[17] showed among 170 cases of mucosal HNSCC patients and 80 controls, that the NLR and the PLR were significantly higher in the cases than the controls (2.76 ± 1.82 and 113.20 ± 60.36, P=0.005 vs 2.15 ± 0.90 and 91.41 ± 38.62, p=0.030) respectively. These values are lower than those in this present study. The difference is mainly because most of our cases presented at an advanced stage contrary to their study in which a majority of were early cancers (T2, N0). In their study among 65 laryngeal cancer patients and 42 controls, laryngeal cancer patients, Duzlu *et al*[18] demonstrated a statistically significant difference (p = 0.004) in NLR between larynx carcinoma (2.70 ± 1.25) and control group (2.04 ± 0.90). Similarly, Ciftci *et al*[19] showed among 53 laryngeal cancer patients and 50 controls, the median NLR was higher in the malignant group (1.9455) compared to the control group (1.5404) and the difference was statistically significant (p = 0.01). Rasoulli *et al*[20] showed that head and neck squamous cell carcinoma patients with higher values of these inflammatory markers have increased mortality and an associated increased incidence of recurrent disease. Furthermore, Sun *et al*[21] and Turri-Zanoni *et al*[22] showed that nasopharyngeal cancer patients with high pre-treatment levels NLR and PLR had shorter overall and disease-free survival and these findings have been similarly reported in sinonasal carcinoma.

Red cell distribution width (coefficient of variation) levels was significantly higher in mucosal HNSCC patients than healthy individuals. Peri-tumoral inflammation has been shown to disrupt the maturation process of red blood cells through membrane disruption leading to high RDW[23]. The magnitude of this disruption therefore mimics the level of systemic inflammatory response. Bozkurt *et al*[24] found that patients with laryngeal cancer had higher pre-treatment levels of RDW and this subgroup of patients had poorer survival and a higher incidence of locoregional recurrence. Though the relationship between RDW and cancer progression, treatment and outcomes is still poorly understood, inflammation and nutritional factors may be implicated as RDW has been shown to be elevated in malnutrition.

Contrary to Rassouli *et al*[20] who found significant increase in NLR and PLR with advancing T stage, our study did not find any significant relationship between clinicodemographic parameters and levels of inflammatory markers. The differences may be attributed to differences in study designs and sample sizes. Rassoulli *et al*[20] conducted a retrospective cohort study in 319 head and neck mucosal cancer patients while the present study was a case control study and comparably had a smaller sample size. Nevertheless, the findings in this present study are in keeping with other studies by Seetohul *et al*[17] and Duzlu *et al*[18].

CONCLUSIONS

We have shown in this case control study design that the NLR, PLR and RDW levels are significantly higher in mucosal HNSCC patients than in healthy individuals. There was no significant relationship between the pre-treatment levels of these markers and other clinicodemographic variables explored in this study.

RECOMMENDATION

Appropriate studies are recommended to correlate these indices with treatment outcomes, mortality, and prognosis of mucosal HNSCC in this setting.

Conflict of interest: The authors declare no conflict of interest related to this work

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