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Leucocytosis: A Potential Prognosis Biomarker in Head and Neck Malignancies

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Abstract

Recent research has highlighted the role of inflammation in cancer development, with white blood cell (WBC) count being linked to various malignancies. Studies have shown that elevated WBC counts, particularly leucocytosis, are associated with overall survival and disease-free survival in patients with different types of cancer,including head and neck cancers. This mini review aims to explore the latest findings on the significance of white blood cell counts in the prognosis and progression of head and neck malignancies.

Keywords: Leucocytosis in head and neck cancer, raised WBC count in oral cancers, HNSCC, Neutrophil leucocyte ratio

Abbreviations: WBC: White Blood Cell; TLC: Total Lymphocyte Count; HNSCC: Head and Neck Squamous Cell Carcinoma; PML: Pre-Malignant Lesion; NLR: Neutrophil Lymphocyte Ratio; NK cell: Natural Killer Cell; OS: Overall Survival; PFS: Progression Free Survival; DFS: Disease Free Survival; LSCC: Laryngeal Squamous Cell Carcinoma

Introduction

Cancer is a group of diseases which develops due to uncontrolled division of cells in any body tissue [1]. There are many factors associated with tumorigenesis like genetic factors, lifestyle factors, infections, inflammation etc. Infection, chronic irritation and inflammation are important components of tumor progression and are major causes for many types of cancer like head and neck cancers [2]. In 2020, about 562,328 people were diagnosed and 277,597 people died with head and neck cancer worldwide [3]. Most of the head and neck cancers, especially oral cancers are derived from precancerous lesions such as leukoplakia, oral submucous fibrosis [4]. Inflammation can result in leucocytosis and presence of leukocytes has been observed in tumor tissue [5]. WBC count has been used as predictor in many cancers [6]. So, WBC count can be a simple and cost effective predictor of head and neck cancers also.

Mechanism

Multiple studies have found a negative correlation between leukocytosis and thrombocytosis and treatment outcomes in patients with head and neck cancer. In head and neck cancer patients, high preoperative neutrophil and lymphocyte ratios are associated with worse disease outcomes, including shorter disease-free survival and overall mortality. It appears that published data offer further useful recommendations for assessing the disease trajectory in individuals with head and neck cancer. Because it responds to a variety of acute and long-term stressors, white blood cell count is very unpredictable. Infection, stress, and long-term irritant exposures like smoking all increase it [7]. Numerous investigations have been carried out for malignancies other than those of the head and neck.

According to Grimm et al. [8], the WBC count was substantially correlated with the probability of dying from cancer. Additionally, WBC count and overall cancer mortality were linked by Erlinger et al. [9]. A correlation between a high WBC count and cancer mortality was also discovered by Shankar et al. [10]. The increased number of neutrophils and monocytes seen in the HNSCC patients are supported by previous reports showing similar findings in other types of cancer [11,12]. The increase could be a result of an increased leukocyte turnover, which could lead to greater inflammation and greater bone marrow-derived immature neutrophil and monocyte infiltration. Therefore, the high neutrophil-lymphocyte ratio found in HNSCC patients points to persistent systemic inflammation [13].

Additionally, a high systemic inflammation may be related to the patient's prognosis because a high neutrophil-lymphocyte ratio seems to be correlated with a lower survival probability. According to recent findings, this ratio may serve as a prognostic indicator for a number of cancer types [14]. The role of neutrophils

in cancer has recently drawn more attention. They are believed to be pro-tumorigenic due to the release of pro angiogenic molecules that promote angiogenesis and the inhibition of the adaptive immune system [15]. Activated neutrophils may induce antitumor activity, according to Gregory and Houghton.

The current data shows that HNSCC patients who have a higher frequency of activated neutrophils live longer, which is evidence in favor of this finding [16]. The increased immune activation that is evident from the high levels of activated T cell subsets and NK cells in HNSCC patients-and particularly in those with confirmed lymph node metastasis-corresponds well with the elevated neutrophil-lymphocyte ratio. Both show a heightened leukocyte turnover and an accelerated systemic immunological response [17]. NK cells are thought to contribute to tumor immune surveillance and have cytolytic properties [28]. Therefore, it is tempting to assume that the increased number of activated NK cells currently found is a result of improved immune surveillance against the tumor. But it must be remembered that in HNSCC, NK cells have also been linked to diminished anti-tumor activity [18,19].

Discussion

Research on the connection between inflammation and malignancy has been sparked by knowledge of the presence of inflammation in the tumor microenvironment. Inflammation leads to increased TLC which can be used as a predictor for tumor progression and disease outcome. As documented in the table below, many studies have been done to know the correlation between high TLC and head and neck cancers. Most of the studies have resulted in significant connection between TLC and disease outcome except Kruse et.al. which failed to show any correlation between head and neck cancer and TLC levels. Rest of the trials have proved high TLC levels are associated with poorer OS and PFS and also it is a good predictor for progression of PMLs to cancer. High NLR (both preoperative and post treatment)is associated with more aggressive disease and poorer outcomes (Table 1).

Table 1.

Study	Patient profile	Discussion	Result
Millrud et al. [20]	20 patients with head and neck squamous cell cancer (HNSCC) Median age 69 years	HNSCC patients display increased numbers of total leukocytes, neutrophils and monocytes, and accordingly a higher neutrophil/lymphocyte ratio than control subjects.	There is an increased systemic inflammation in HNSCC patients, determined by an increased activation of leukocytes.
Schernberg et al. [21]	193 patients HNSCC, all treated with concurrent cisplatin-based chemoradiotherapy.	24% and 20% patients displayed baseline leukocytosis or neutrophilia. Mean leukocyte count were significantly more elevated in current smokers, patients with performance status (PS) >0, T4 and less in HPV + t	locally advanced HNSCC treated with concurrent cisplatin and radiation, baseline leukocytosis predicts OS and PFS.
Singh et al. [22]	150 patients	TLC count, neutrophil count and lymphocyte count showed statistically significant difference while other parameters such as hemoglobin percentage, bleeding time, clotting time, eosinophil count, monocyte count and basophil count were statistically non-significant.	TLC count, neutrophil count and lymphocyte count might prove as useful determinant factor in oral squamous cell carcinoma and oral potentially malignant disorders.
Cho et al. [23]	621 patients who received definitive RT for nasopharyngeal, oropharyngeal, hypopharyngeal, and laryngeal cancer	The patients with a high Neutrophil/ lymphocyte ratio (NLR) (68%) had a significantly lower 5-year PFS and OS than their counterparts with a low NLR (32%) (PFS: 39.2% vs. 75.8%, $p < 0.001$; OS: 50.9% vs. 83.8%, $p < 0.001$).	Head and neck cancer tends to be more aggressive in patients with a high NLR, leading to a poorer outcome after RT.
Kruse et al. [24]	543 patients of HNSCC	It establishes absolute levels of neutrophils and lymphocytes measured in circulation as independent prognostic variables in cancers of the oral cavity, pharynx, and larynx. the numbers of neutrophils and lymphocytes were inversely correlated and that NLR was an indicator of poor prognosis.	Neutrophil and lymphocyte counts are strong biomarkers with opposing prognostic significance and the NLR is a robust predictor of overall survival in oral, pharyngeal, and laryngeal squamous cell carcinomas.

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Kim et al. [25]	104 patients treated with definite CRT	This study evaluated the correlation of pretreatment NLR and posttreatment NLR with recurrence and survival in head and neck cancer patients who have undergone definite CRT.	A univariate analysis revealed that T,N-stage, the pre- and posttreatment NLRs were significant predictors of progression after the chemoradiotherapy. However, the posttreatment NLR remained an independent predictor of PFS in the multivariate analysis (HR = 2.23, 95% CI 1.15–2.321; P = 0.001). A high posttreatment NLR was significantly associated with an increased risk of death (HR = 1.87, 95% CI 0.89–3.31; P = 0.037).
Sun et al. [26]	251 patients of nasopharyngeal carcinoma	Neutrophil counts, lymphocyte counts, platelet counts, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) were adopted as potential prognostic biomarkers	NLR ≥2.7 (hazard ratio [HR] = 2.01; 95% confidence interval [CI] = 1.23–3.29; p = .005) and PLR ≥167.2 (HR = 2.12; 95% CI = 1.35–3.33; p = .001) were significantly associated with shorter PFS, whereas PLR ≥163.4 (HR = 2.64; 95% CI = 1.25-5.60; p = .011) was correlated with poor OS.
Tu et al. [27]	141 Laryngeal SCC patients	The impact of the NLR and other potential prognostic factors on disease-free survival (DFS) and overall survival (OS) was assessed using the Kaplan-Meier method and multivariate Cox regression analysis.	elevated preoperative NLR was an independent predictor of poor prognosis for patients with LSCC after surgical resection
Kruse et al. [28]	278 patients the preoperative WBC count was compared with the clinicopathological information: age, gender, T-status, N-status, recurrence, metastases, follow-up time, and time till recurrence or metastases appeared.	No significant correlation could be found between WBC count and the development of recurrence or metastases	elevated WBC count does not seem to be a predictor for recurrence or for further metastases

Table 1: Summary of Studies Demonstrating the Prognostic Significance of Leucocytosis in Head and Neck Malignancies.

This table compiles findings from multiple studies that highlight the correlation between elevated white blood cell counts (leucocytosis) and clinical outcomes in patients with head and neck cancers, including its impact on overall survival, diseasefree survival, and tumor progression.

‘Conclusion

Pretreatment leucocytosis is a clinically significant indicator for overall survival and Progression free survival in individuals with locally progressed HNSCC. In head and neck cancer patients, high preoperative neutrophil and lymphocyte ratio ratios are associated with worse disease outcomes, including shorter disease-free survival and overall mortality. Published data appear to offer additional useful recommendations for assessing the course of the disease in patients with head and neck cancer. Further research is warranted to explore treatment avenues that can further explore the relationship between inflammation and aggressiveness in head and neck cancers.

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