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Baseline Haemoglobin as an Independent Marker for Survival Outcomes in Head and Neck Cancers: A retrospective cohort study

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ABSTRACT: **Objective:** To assess baseline haemoglobin (Hb) as an independent marker for early tumour response and survival outcomes in squamous cell carcinoma of the head and neck (HNC).
Methods: A retrospective review was conducted using the institutional database from 2016 to 2018. Data from 100 patients treated with definitive radiotherapy (RT) with or without chemotherapy were analysed. Patients were divided into two groups based on baseline Hb levels: Group A (≤ 12.5 gm/dl) and Group B (> 12.5 gm/dl). Overall survival (OS) and relapse-free survival (RFS) were evaluated.
Results: Baseline Hb levels significantly influenced local disease control and survival. Low baseline Hb (≤ 12.5 gm/dl) was a poor prognostic marker for OS and RFS.
Conclusion: Baseline Hb is a significant prognostic marker for survival outcomes in HNC patients treated with definitive RT with or without chemotherapy.
KEYWORDS: Haemoglobin, headandneckcancer, tumor hypoxia, prognosticfactors, radiotherapy

I. INTRODUCTION

Background/Rationale

Head and neck cancers (HNC) are the second most common malignancies in India. Despite combined modality treatment, locoregionalrecurrence remains a significant concern, with 50- 60% of patients experiencing local disease recurrence within two years of diagnosis. Anaemia is common in HNC patients and correlates with intra-tumoral hypoxia, influencing prognostic outcomes. Haemoglobin (Hb), a critical component of blood, is responsible for transport of oxygen from the lungs to the tissues. Several studies have demonstrated that anaemia, indicated by low Hb levels, adversely affects local control and survival in patients undergoing radiotherapy (RT) or concurrent chemoradiotherapy (CCRT).[1,2,3] The present retrospective analysis is aimed at evaluating pre-treatment Hb values as a prognostic factor in patients with head and neck squamous cell carcinoma (HNSCC) treated with RT or CCRT. The proposed hypothesis is that higher pre-treatment Hb levels correlate with better survival.

Objectives

To investigate whether baseline Hb levels can serve as a prognostic marker for early tumour response and survival outcomes in HNC patients.

II. METHODS

In this retrospective cohort study conducted at an Indian tertiary cancer hospital, we reviewed the institutional database between January 2016 to December 2018 for patients with head and neck cancers. Selection criteria included: newly diagnosed primary cancers of the head and neck region (including the oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx subsites), squamous cell carcinoma (SCC) histology, local or loco-regional disease, Eastern Cooperative Oncology Group (ECOG) performance score ≤ 2, patients who were treated with radical treatment with either RT alone or CCRT. The following patients were excluded from the study: Patients undergoing upfront surgery, non-squamous histology, metastatic disease, recurrent/ second primary disease, and history of prior CT or RT for head and neck malignancies. A total of 122 patients were identified to fulfill the inclusion criteria, however, 100 patients were analysed, selected based on availability of complete data. Using 12.5 gm/dl as a cut-off for baseline haemoglobin, the patients were divided into two groups: Group A

(with a Hb value ≤ 12.5 gm/dl) and Group B (with a Hb value > 12.5 gm/dl).

Statistical Analyses:

Baseline patient clinical and tumour characteristics were summarised by Hb cut-off (≤ 12.5 gm/dl and > 12.5 gm/dl). Categorical variables were expressed as frequencies along with respective percentages and continuous variables were presented as mean and standard deviation (SD) or median (range). These characteristics were compared between the two groups. The primary endpoints of this study were overall survival (OS) and relapse-free survival (RFS). OS was calculated as the time from the date of diagnosis to the date of death. RFS was calculated as the time from the date of diagnosis to the date of local/ regional recurrence.

These were calculated using the Kaplan–Meier product-limit method. Log-rank test was used for comparison between the two groups. Univariate analysis for OS and RFS was performed on the clinicopathological factors. Multivariate Cox proportional hazards regression analysis was performed to estimate the impact of known relevant prognostic factors. Potential biases were addressed by including all eligible patients and performing logistic regression to control for confounding variables. All statistical analyses were performed using a statistical package for the social science system (SPSS version 20, SPSS Inc, Chicago, IL, USA), and a p-value <0.05 was considered statistically significant. All p-values reported represent two-sided tests. Details of last follow-up and patient's status at that time were assessed using hospital records. Patients who were lost to follow up were contacted telephonically.

III. RESULTS

A total of 100 patients were found eligible for this study and analysed. Of these, 29 (29.0%) patients were in Group A with a baseline haemoglobin level ≤ 12.5 gm/dL and 71 (71.0%) in Group B with a baseline haemoglobin level > 12.5 gm/dL. The comparison of patients and the various disease-related characteristics between the two groups are shown in Table 1.The baseline and treatment characteristics were comparable between two groups except for gender, smoking and clinical nodal staging. The overall mean Hb level was 10.65 gm/dL. In Group A, it was found to be 8.4 gm/dL, while in Group B it was 12.9 gm/dL.

The median follow-up was 49 months (1 – 104 months) for the entire cohort. The median RFS for group A and B was found to be 7 months (95% CI: 3.92 - 10.08) and 50 months (95% CI: 6.36 - 93.64), respectively (p = 0.001). The median OS was 70 months for patients in Group A whereas it was not reached for Group B patients (p = 0.044). This is depicted in Figure 1 (A) and (B).

The results of univariate and multivariate analysis for OS and RFS are summarised in Table 2 and 3 respectively. A logistic regression was performed to ascertain the effect of Hb on the likelihood that patients were surviving. The results showed, for each unit reduction in the Hb level, the odds of surviving decreases by a factor of 0.231 (Odd Ratio 0.794; CI: 0.680 - 0.926; p = 0.003). On univariate analysis, T staging, N staging, tobacco usage, smoking and groups were significant predictors for RFS. However, only low Hb and N staging were significant predictors for OS on univariate analysis. The effect of HB on RFS and OS have been demonstrated in the Kaplan Maier curves given in Fig. 1 (a) and (b).

IV. DISCUSSION

Hb plays a crucial role in maintaining adequate oxygenation in tissues. Anaemia reduces the oxygen carrying capacity of blood and induces tumour hypoxia where tumour tissues are deprived of oxygen. Anaemia is a known adverse prognostic factor in cancer therapy.[4] Hb levels influence the oxygen-carrying capacity of the blood; thus, anaemia can exacerbate hypoxic conditions within tumours.[1] This decreased cellular oxygenation leads to radio-chemotherapy resistance via oxygen deprivation, ultimately leading to poorer treatment outcomes.[5]

Cancer related anaemia (CRA) has been reported in approximately in 58% of patients with solid tumours and 84% with lymphoid malignancies by Rodgers et al.[6] European Cancer Anaemia Survey (ECAS), found anaemia to be present in 39.3% of patients being treated for malignant tumours.[7] Anaemia is a problem that affects a large percentage of patients with head and neck cancer. The common causes of anaemia in HNC include chronic inflammation, nutrient (commonly iron and vitamin B12) deficiencies, and repeated episodes of bleeding.[8]

The prognostic significance of haemoglobin levels in HNC patients can be attributed to several factors. Firstly, lower haemoglobin levels are associated with increased tumour hypoxia, leading to decreased radiosensitivity. Secondly, anaemia can impair the overall health and performance status of patients, further compromising treatment efficacy. Studies have consistently shown that maintaining adequate haemoglobin levels before and during treatment can significantly improve treatment response and

survival rates. Retrospective data generally are inconclusive. Some studies suggested improved local response in patients receiving transfusions, whereas others showed no significant positive effect.[9,10] An increase of Hgb by 20% produces a theoretic decrease in hypoxic tissue volume of approximately 30%.[11]

World Health Organisation (WHO) defines anaemia as a haemoglobin concentration <12 gm/dL in women and <14 gm/dL in men.[12] Low pre-radiation Hb, even when ranging from 12 to 14 gm/dL, poses a substantial risk of poor locoregional control and survival. The threshold for Hb level versus outcome may vary across different tumour sites, making an exact definition of anaemia or hypoxia difficult. Since it is unclear as to exactly what the threshold should be for low Hb, thus our clinically defined thresholds may serve as guidelines rather than firm definitions. Previous studies conducted in this regard have used thresholds ranging from 9–14.5 gm/dL.[1, 3, 5] Most studies have used a haemoglobin cut-off of 12.5 gm/dL and have also recommended to use this as a reference for further studies.[13, 14] The authors of the current study have also used a cut-off of 12.5 gm/dL.

Our study has shown a decrease in the odds of survival by a factor of 0.23 for a drop of every one-unit Hb in HNSCC patients. It was also found that low Hb levels are associated with poorer OS and RFS.

The impact of haemoglobin levels on treatment outcomes has been evaluated through various clinical trials and retrospective studies. These have emphasized the prognostic value of pre-RT Hb levels in patients with locally advanced HNSCC. Numerous studies have that anaemia negatively impacted locoregional control and survival in head and neck cancer patients.[5, 15, 16] Narayanaswamy et al. found that patients with pre-radiotherapy Hb levels ≥ 10.7 gm/dL had significantly better loco-regional control (LRC), higher performance status, fewer treatment interruptions, and lower grades of mucositis compared to those with Hb levels < 10.7 gm/dL.[1] Kumar et al. found that patients with anaemia had a nearly 50% lower two-year survival rate compared to non-anaemic patients.[15] Study showed that anaemia not only impacts OS but also affects the effectiveness of RT in HNC patients.[16] In their systematic review, Caro et al. identified low Hb as an independent prognostic factor for poorer survival outcomes, regardless of cancer type.[17]

Despite the well-established link between anaemia and poor treatment outcomes, haemoglobin monitoring was infrequently performed in clinical practice.[18] It is important to monitor Hb levels before, during, and after RT. This underlines the need for standardized protocols to manage anaemia in HNC patients undergoing RT.Timely interventions to correct anaemia before initiating RT and the concept of Hb concentration modification as a therapeutic strategy have also been suggested.[5] Interventions for correction of anaemia include oral or intravenous iron supplements for iron deficiency anaemia, erythropoiesis-stimulating agents (ESAs) like erythropoietin (EPO), blood transfusions, nutritional support, and management of underlying causes of anaemia.

The evidence supporting the prognostic value of haemoglobin levels in head and neck cancer patients underscores the importance of regular monitoring and management of anaemia. Clinical guidelines should incorporate routine haemoglobin assessments before and during treatment to identify and correct anaemia early. Moreover, interdisciplinary collaboration between oncologists, haematologists, and radiation therapists is essential to develop and implement effective management protocols for anaemia. This collaborative approach can ensure that patients receive comprehensive care that addresses all aspects of their condition, thereby improving treatment outcomes. The findings are relevant to other similar clinical settings, given the commonality of the conditions and treatments evaluated. This study, however, is limited by its retrospective nature and the potential for missing data.

V. CONCLUSION

Low baseline Hb is a poor prognostic marker for overall and relapse-free survival in HNC patients treated with definitive RT with or without chemotherapy. Baseline Hb can be used as a simple and accessible marker to guide treatment decisions and improve prognostic stratification in HNC patients. Early correction of mild-to-moderate anaemia in the radiation oncology setting has the potential to enhance the efficacy of cancer treatments and improve the overall prognosis for patients.

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Table 1: Comparison of patient and disease-related characteristics between the two groups

Characteristic	Category	Group A N (%)	Group B N (%)	p-value	Effect Size
Total patients		**29 (29%)**	**71 (71%)**		
Site	Oral Cavity	6 (20.6%)	5 (7.0%)	0.083	
	Oropharynx	15 (51.7%)	27 (38.0%)		
	Larynx	4 (13.7%)	26 (36.6%)		
	Hypopharynx	3 (10.3%)	10 (14.0%)		
	Nasopharynx	1 (3.4%)	3 (4.2%)		
Gender	Male	18 (62.0%)	71 (100 %)	<0.001	
	Female	11 (37.9%)	0 (0 %)		
Clinical Tumor Stage	</=T2	3 (10.3%)	19 (26.7%)	0.072	
	>T2	26 (89.6%)	52 (73.2%)		
Clinical Nodal Stage	</=N2b	17 (58.6%)	59 (83.0%)	0.009	
	>N2b	12 (41.3%)	12 (16.9%)		
Comorbidities	Absent	20 (68.9%)	55 (77.4%)	0.259	
	Present	9 (31.0%)	16 (22.5%)		
Tobacco	Absent	20 (68.9%)	58 (81.6%)	0.163	
	Present	9 (31.0%)	13 (18.3%)		
Smoking	Absent	12 (41.3%)	9 (12.6%)	0.001	
	Present	17 (58.6%)	62 (87.3%)		
Alcohol	Absent	22 (75.8%)	39 (54.9%)	0.051	
	Present	7 (24.1%)	32 (45.0%)		

Table 2: Univariate and multivariate analysis for prognostic factors affecting OS

	Univariate Analysis			**Multivariate Analysis**	
Variable	**HR (95% CI)**	**p-value**		**HR (95% CI)**	**p-value**
Haemoglobin level (Group A vs Group B)	0.506 (0.256-0.998)	0.049		0.637 (0.310 – 1.309)	0.220
Tobacco (Absent vs Present)	1.199 (0.544 – 2.646)	0.133			
Smoking (Absent vs Present)	0.506 (0.242 – 1.056)	0.07			
Alcohol (Absent vs Present)	0.570 (0.274 - 1.187)	0.133			
Tumour Stage (</=T2 vs >T2)	1.292 (0.564 – 2.96)	0.545			

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Nodal Stage (</=N2b vs >N2b)	2.586 (1.291 – 5.154)	0.07		2.233 (1.079 – 4.645)	0.03

Table 3: Univariate and multivariate analysis for prognostic factors affecting RFS

	Univariate Analysis			**Multivariate Analysis**	
Variable	**HR (95% CI)**	**p-value**		**HR (95% CI)**	**p-value**
Haemoglobin level (Group A vs Group B)	0.410 (0.240 - 0.702)	0.001		0.563 (0.317 – 0.983)	0.049
Tobacco (Absent vs Present)	2.269 (1.295 – 3.975)	0.004		1.984 (0.981 – 4.831)	0.08
Smoking (Absent vs Present	0.497 (0.279 – 0.884)	0.017		0.838 (0.349 – 1.32)	0.738
Alcohol (Absent vs Present)	0.821 (0.048 – 1.380)	0.456			
Tumour Stage (</=T2 vs >T2)	2.838 (1.344 – 5.99)	0.006		2.41 (0.981 – 4.58)	0.091
Nodal Stage (</=N2b vs >N2b)	3.609 (2.025 – 6.27)	<0.001		2.962 (1.643 – 5.341)	0.001

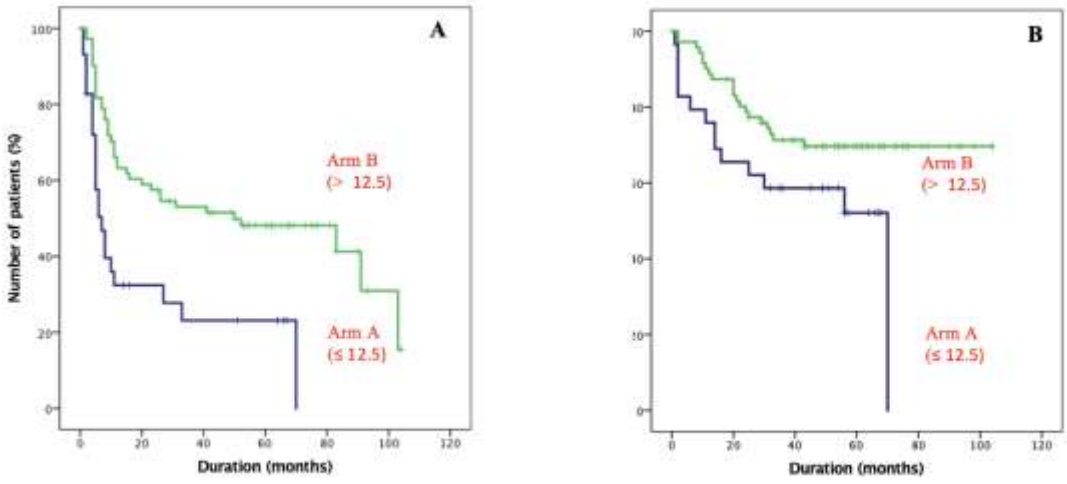

Fig 1: (A) Effect on Hb on relapse-free survival (RFS); and (B) overall survival (OS)

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