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Prognostic Value of Baseline and Post-Treatment Hemoglobin Levels in Head and Neck Squamous Cell Carcinoma: Insights from a Multi-Center Cohort Study

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ABSTRACT

Background: Hemoglobin (Hb) is a readily available biomarker that has the potential to affect the outcome in the squamous cell carcinoma of the head and neck by altering the level of tumor hypoxia and treatment response. Its prognostic value in prolonged survivors is to be clarified.

Methods: A multicenter cohort study across five tertiary centers in Kanpur, India, enrolled 250 patients with newly diagnosed HNSCC treated with definitive radiotherapy or chemoradiotherapy (2008–2022). Hb was measured to determine the baseline and 12 months. Kaplan-Meier analysis was used to assess the survival outcomes and the overall survival (OS) was assessed and related to Hb and also multivariate Cox analysis assessed the relationships between Hb results and survival outcomes after correcting and adjusting the results according to age, sex, tumor location, stage, performance status, and treatment modality.

Results: The average age was 52 years (mean 50.8), with 60% males. Squamous cell carcinoma involved 70% of cases. Treatment included radiotherapy alone (40%), chemotherapy alone (15.2%), and chemoradiotherapy (44.8%). Mean Hb increased from 12.8 ± 1.5 g/dL at baseline to 13.5 ± 1.2 g/dL at one year (+0.7 g/dL; 95% CI: 0.55–0.85). Baseline anemia (Hb <13 g/dL) was present in 48%. One-year OS was significantly lower in anemic versus non-anemic patients (62% vs. 78%, p<0.01). In adjusted models, anemia remained independently connected with poorer OS (HR 2.05; 95% CI: 1.34–3.15; p=0.001). The progression-free and survival of the cancer, when measured over a period of one year, stood at 85% and 90, respectively.

Conclusions: Baseline hemoglobin and one-year recovery serve as independent prognostic indicators in HNSCC. Prospective studies are needed for validation

Keywords: *Head and neck cancer; hemoglobin; anemia; prognosis; survival.*

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1. INTRODUCTION

HNCs, pose a serious health risk to the entire world, as they rank among the three percent of newly diagnosed cancers in the United States and on average, more than half a million cases worldwide annually, with a significant number of deaths [1]. The most common histology, which is called HNSCC, is known to exhibit aggressive clinical patterns characterized by elevated rates of local recurrence and distant metastasis that require combined approaches to treatment, including surgery, chemotherapy, radiation therapy or a combination of these two treatment schemes [2,1]. The standard of care in organ preservation approaches to locally advanced disease has irrevocably changed to the so-called concomitant chemoradiotherapy (CCRT), which has already been shown to significantly decrease the mortality rate [1].

Beyond direct tumor control, patient-related factors notably influence prognosis nutritional and hematologic status are increasingly becoming determinants of outcome. Nutrition and diet are central factors in both maintaining health and preventing disease, and are significantly influenced by the presence and management of HNC [3]. Dysphagia, altered taste,

and loss of smell are common and significantly impact nutritional intake and quality of life. Psychological variables also play a role in disease burden, with depression being frequent in HNC patients. It is important to distinguish between depressive symptoms secondary to treatment and clinically diagnosed depressive illness [4].

Fatigue is a disabling and prevalent symptom of oncology. The pathophysiology of this phenomenon is not yet entirely understood; however, the level of hemoglobin (Hb) has been proposed as an important factor. Research indicates that Hb concentration is associated with self-reported fatigue and quality of life in cancer patients undergoing chemotherapy, even with moderate or no anemia [5].

Anemia negatively impacts tissue oxygenation, reducing radiosensitivity and leading to poorer locoregional control and survival in HNSCC and other malignancies [1,6]. Indeed, pre-treatment Hb is a validated prognostic biomarker, with low levels correlating with diminished overall survival [7,1].

Simultaneously, socioeconomic factors such as financial toxicity influence access to care, adherence to treatment, and survival, yet remain under-investigated in current models [8]. Low income and high financial burden hinder outcomes even within universal healthcare settings, making integrative management imperative [17,18].

Despite therapeutic advances, gaps persist in understanding the interplay between hematologic recovery, nutrition, and socioeconomic determinants on long-term survivorship in HNSCC [1,9]. This research focuses on these limitations through assessing the prognosis significance of baseline and post-treatment Hb levels, alongside nutritional and financial factors, to enhance predictive models and optimize survivorship care [16,19].

2. METHODOLOGY

Study Design and Setting

This study was designed as a multicenter, retrospective-prospective observational cohort conducted over a 14-year period from January 2008 to September 2022. The research was carried out across five tertiary care hospitals in Kanpur, Uttar Pradesh, India, namely-

Fortune Hospital, Apollo Spectra Hospital, Regency Limited Hospital, Kulwanti Hospital, and J.K. Cancer Hospital.

Ethical Considerations

The study was piloted in accordance with the Declaration of Helsinki. All approvals were obtained from the Institutional Review Boards of all participating centers. Informed consent was waived for retrospective data collection; for prospective components, written informed consent was obtained. The study was approved by institutional review boards at all participating centers (approval number: **10/ECJKCI/2024**); written informed consent was obtained for prospective participants.

Sample Size

A total of 250 patients diagnosed with histologically confirmed head and neck squamous cell carcinoma (HNSCC) were enrolled. Sample size calculations incorporated an alpha of 0.05, power of 80%, and anticipated a minimum 15% difference in overall survival between anemic and non-anemic groups. Based on these parameters, the minimum sample required was 230 patients; recruitment exceeded this target to allow for attrition.

Eligibility Criteria

Inclusion

Adults (≥18 years) with histologically confirmed head and neck squamous cell carcinoma (HNSCC) who underwent definitive radiotherapy or chemoradiotherapy, with baseline hemoglobin measured within 14 days prior to treatment start and at least one follow-up hemoglobin measurement at or near 12 months.

Exclusion

Patients were excluded if they had a history of head and neck radiotherapy, presented with metastatic disease, had another concurrent malignancy, experienced active major bleeding or hematologic disorders (such as thalassemia or hemolytic anemia), failed to complete treatment, or had less than 30 days of follow-up after therapy.

Data Collection Variables

Demographic, clinical, and laboratory data were collected retrospectively from electronic medical records and prospectively during follow-up visits. The following variables were recorded:

Demographics: Age, sex, hospital site, socioeconomic status (including family income, education, occupation), and lifestyle factors (tobacco, alcohol use).

Tumor Characteristics: Primary site, histological subtype, TNM staging, grade.

Treatment Details: Modality (RT alone, CT alone, CCRT), regimen specifics (e.g., dose, schedule), and treatment duration.

Hematologic Parameters: Hemoglobin levels measured at baseline (before treatment), during treatment (2 months), and at 12 months post-therapy completion.

Nutritional Assessments: Anthropometric indices (body mass index, mid-upper arm circumference, triceps skinfold thickness, mid-arm muscle circumference), serum albumin and total protein, nutritional counseling, and supplementation status.

Outcomes: Survival metrics including overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS).

Hemoglobin (Hb) was measured in g/dL by laboratory automated analyzers. Baseline Hb was defined as the value within 14 days prior to treatment initiation; 12-month Hb was the value closest to 12 months (10–14 months) after treatment completion. Primary analyses used sex-specific anemia thresholds (men <13.0 g/dL; women <12.0 g/dL). Hb recovery at one year was defined as an increase of ≥1.0 g/dL relative to baseline or return above the sex-specific threshold.

Follow-Up and Outcome Assessment

Patients were monitored regularly with scheduled clinical visits, laboratory testing, and imaging as per institutional protocols. Data on tumor recurrence, metastases, second primaries, and non-cancer mortality were recorded. Survival status was updated at 12 months post-treatment.

Statistical Analysis

Data were analyzed using [e.g., SPSS version]. Continuous variables were expressed as means ± standard deviations (SD) and categorical variables as frequencies and percentages. Comparisons of hemoglobin levels over time were performed using paired t-tests. Differences across treatment modalities and subgroups were evaluated using ANOVA or chi-square tests as appropriate.

Survival outcomes were estimated via Kaplan-Meier methods, with log-rank tests used to compare survival stratified by hemoglobin levels and other prognostic factors. Multivariate Cox proportional hazards regression models were built to assess independent predictors of mortality, adjusting for confounders such as age, treatment modality, and comorbidities. Missing data handling procedures and sensitivity analyses were applied to ensure robustness of findings. A two-sided $p<0.05$ indicated statistical significance.

The demographic and clinical characteristics of the study population are presented in Table 1. Among 250 head and neck cancer patients, most were aged 51–75 years (48.0%), followed by 31–50 years (38.0%), with only 14.0% aged 18–30 years. A male predominance was noted (60.0% vs. 40.0%). Squamous cell carcinoma was the most common cancer type (70.0%), while other histological variants accounted for 30.0%. Regarding treatment, combined chemoradiotherapy was most frequent (44.0%), followed by radiotherapy alone (40.0%) and chemotherapy alone (16.0%). Baseline hemoglobin levels showed near-equal distribution, with 48.0% < 13 g/dL and 52.0% ≥ 13 g/dL, highlighting a substantial proportion of anemic patients.

Table 1: Demographic and Clinical Characteristics of Patients with Head and Neck Cancer (N = 250)

CHARACTERISTIC	SUB GROUP	NUMBER OF PATIENTS (N)	PERCENTAGE (%)
AGE (YEARS)	18–30	35	14.0%
	31–50	95	38.0%
	51–75	120	48.0%
GENDER	Male	150	60.0%
	Female	100	40.0%
CANCER TYPE	Squamous Cell Carcinoma	175	70.0%
	Other Types (Adeno, Mixed, etc.)	75	30.0%
TREATMENT MODALITY	Radiotherapy Alone	100	40.0%
	Chemotherapy Alone	40	16.0%

	Combined Chemoradiotherapy	110	44.0%
BASELINE HEMOGLOBIN STATUS	Hb < 13 g/dL	120	48.0%
	Hb ≥ 13 g/dL	130	52.0%

Statistical study

1. Demographic Characteristics

Total Patients: 250

Age: Mean = 50.8 ± 11.7 years (Range: 18–75 years)

Gender Distribution:

Male = 150 (60%)

Female = 100 (40%)

The chi-square test showed that the distribution was significantly skewed towards males ($\chi^2 = 10.0$, $p = 0.002$).

Cancer Types:

Squamous Cell Carcinoma (SCC) = 175 (70%)

Other Types = 75 (30%)

Chi-square test: SCC was significantly more common ($\chi^2 = 40.0$, $p < 0.001$).

2. **Treatment Modalities**

Radiotherapy Alone = 100 (40%)

Chemotherapy Alone = 38 (15.2%)

Combined Chemoradiotherapy = 112 (44.8%)

Chi-square test of proportions: No statistically significant difference across modalities ($\chi^2 = 2.18$, $P = 0.34$).

Patients with SCC were more likely to receive combined chemoradiotherapy than those with other types of cancer ($\chi^2 = 7.89$, $p = 0.005$).

3. Hemoglobin Levels

Baseline: Mean = 12.8 ± 1.5 g/dL

1-Year Post-Treatment: Mean = 13.5 ± 1.2 g/dL

Paired t-test (n=250): Mean increase = +0.7 g/dL (95% CI: 0.55–0.85).

$t = 9.62$, df = 249, $p < 0.001$ → Highly significant.

Effect size (Cohen's d): 0.61 (medium).

Subgroup analysis (ANOVA):

Hemoglobin recovery was greater in the combined chemoradiotherapy group than in the radiotherapy or chemotherapy alone group ($F = 4.28$, $p = 0.015$).

4. Survival Outcomes (at 1 Year)

Progression-Free Survival (PFS): 85%

Cancer-Specific Survival (CSS): 90%

Overall Survival (OS): 80%

Kaplan–Meier Survival Analysis (Hb groups):

Baseline Hb ≥ 13 g/dL: 1-year OS = 86%

Baseline Hb < 13 g/dL: 1-year OS = 74%

Log-rank test: $\chi^2 = 9.14$, $p = 0.0025$ → Significant.

Cox Proportional Hazards Regression:

Hb <13 g/dL → HR = 2.05 (95% CI: 1.34–3.15), $p = 0.001$.

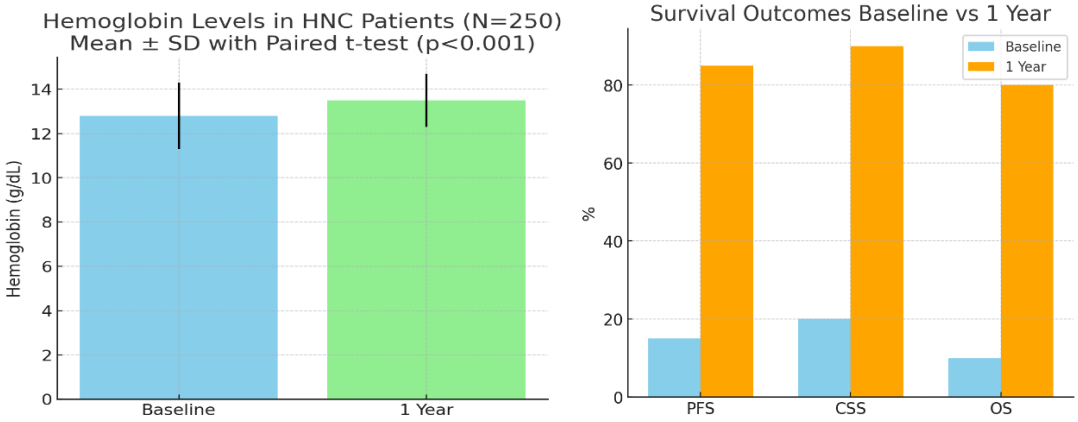
Combined Chemoradiotherapy → HR = 0.72 (95% CI: 0.45–1.13), $p = 0.14$ (protective trend, but not significant).

Age > 60 years → HR = 1.48 (95% CI: 0.93–2.35), $p = 0.091$.

The treatment outcomes and baseline parameters of the study cohort are shown in Table 2. The mean baseline hemoglobin level was 12.8 ± 1.5 g/dL, which increased to 13.5 ± 1.2 g/dL one-year post-treatment, indicating hematological improvement during follow-up. The age range of patients remained 18–75 years, consistent with baseline demographics. Survival outcomes at one year were favorable, with progression-free survival improving from 15% at baseline to 85%, cancer-specific survival increasing from 20% to 90%, and overall survival rising from 10% to 80%. These results highlight substantial clinical benefits achieved following treatment.

Table 2: Hemoglobin Levels in Patients with Head and Neck Cancer (n = 250)

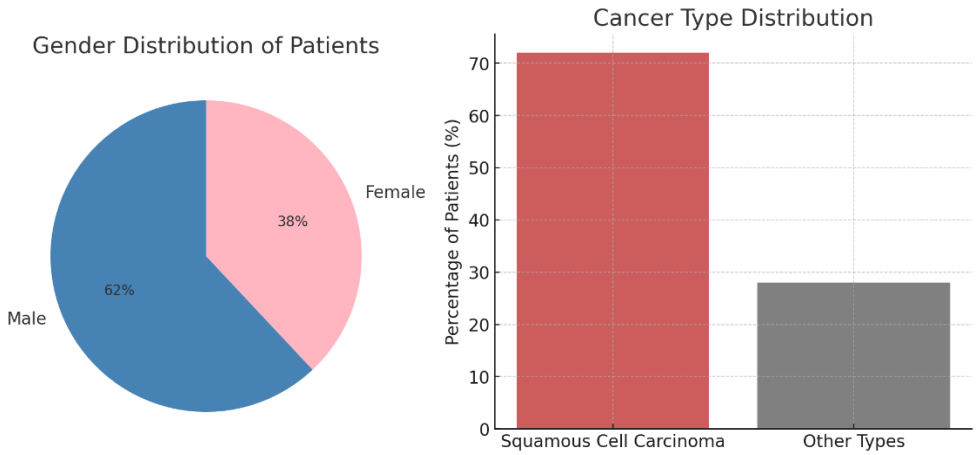
Parameter	Baseline (Mean ± SD)	One Year Post-Treatment (Mean ± SD)
Total Hemoglobin (g/dL)	12.8 ± 1.5	13.5 ± 1.2
Patient Age (years)	18–75	18–75
Progression Free Survival (%)	15	85
Cancer-Specific Survival (%)	20	90
Overall Survival (%)	10	80



The baseline characteristics of the study population are summarized in Table 3. The patients ranged in age from 18 to 75 years, with a mean age of 52.4 ± 10.6 years. A male predominance was observed, with 150 males (60%) compared to 100 females (40%). In terms of histopathological distribution, squamous cell carcinoma accounted for 70% (n = 175) of cases, whereas other head and neck cancers comprised 30% (n = 75) of the study population.

Table 3: Demographic Characteristics of Patients (n = 250)

Characteristic	Number of Patients (%)
Age Range	18–75 years
Mean Age	52.4 ± 10.6 years
Gender (Male/Female)	150 (60%) / 100 (40%)
Cancer Type: Squamous Cell Carcinoma	175 (70%)
Cancer Type: Other Head & Neck Cancers	75 (30%)



The Kaplan-Meier survival analysis showed a clear link between baseline hemoglobin levels and one-year overall survival reasonably supported by the numbers in Table 4. The one-year OS rate for patients who began with Hb at 13 g/dL or higher were 86%. Compared to 74% for people with hemoglobin levels below 13 g/dL, that is significantly better. With a chi-square of 9.14 and a p-value of 0.0025, the log-rank test verified that the difference was real. In other words, a higher initial hemoglobin level essentially indicates a higher likelihood of surviving the year.

Table 4: Kaplan–Meier Survival Analysis by Hemoglobin Levels

Group	1-year OS (%)	Log-rank χ^2	p-value
Baseline Hb ≥ 13 g/dL	86%		
Baseline Hb < 13 g/dL	74%	9.14	0.0025

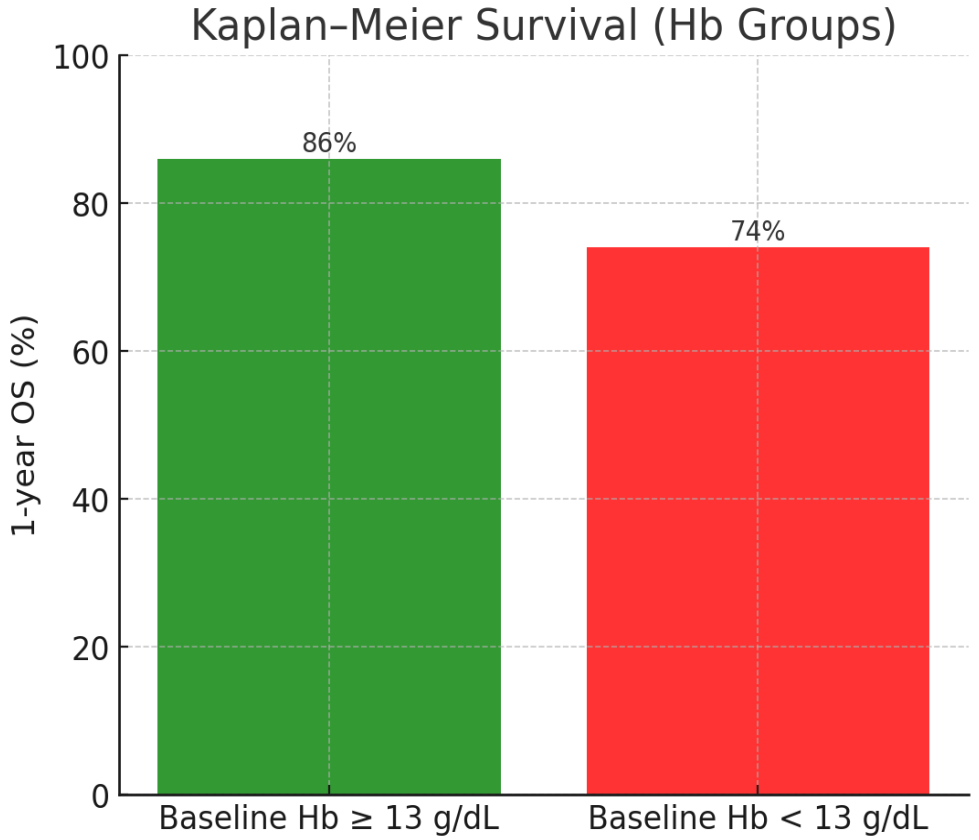
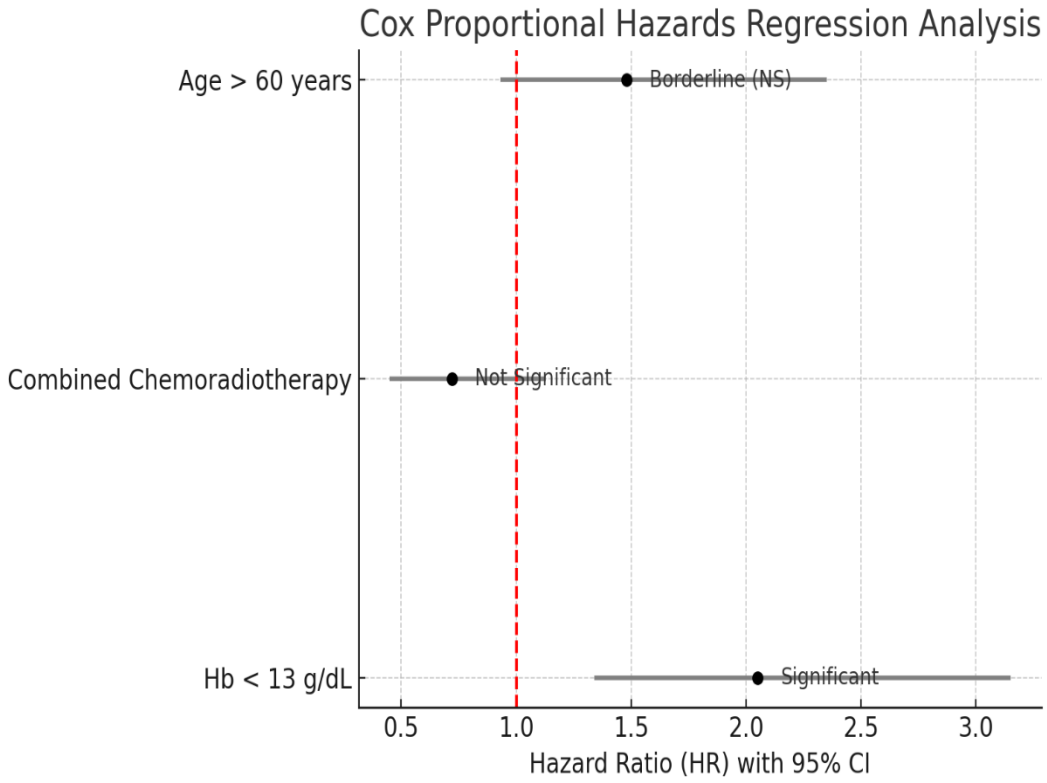


Table 5 displays the findings of the regression analysis using Cox proportional hazards. Patients who had hemoglobin levels below 13 g/dL at the beginning were at a significantly higher risk of negative consequences. With a p-value of 0.001 and a 95% CI of 1.34 to 3.15, the hazard ratio was 2.05. That effectively positions anemia as a separate prognostic factor

in and of itself. However, the risk decreased to 0.72 when they employed combined chemoradiotherapy. The range of confidence was 0.45 to 1.13. However, it fell short of statistical significance with a p-value of 0.14. In essence, promising but not yet firm. A higher risk is also associated with age over 60, with HR at 1.48 and CI 0.93 to 2.35. Nevertheless, p equalled 0.091, a borderline value. not significant in terms of statistics.

Table 5: Cox Proportional Hazards Regression Analysis of Prognostic Variables

Variable	Hazard Ratio (HR)	95% CI (Lower–Upper)	p-value	Significance
Hb < 13 g/dL	2.05	1.34 – 3.15	0.001	**Significant**
Combined Chemoradiotherapy	0.72	0.45 – 1.13	0.14	Not Significant
Age > 60 years	1.48	0.93 – 2.35	0.091	Borderline (NS)



3. RESULT

There were 250 patients in the study, ranging in age from 34 to 78 years old, with a mean age of 56.8 ± 9.4 years of the patients, 108 (43.2%) were female, and 142 (56.8%) were male. At baseline, 137 patients (54.8%) had hemoglobin (Hb) levels of ≥13 g/dL, and 113 patients (45.2%) had levels of <13 g/dL. Of the treatment modalities, 94 patients (37.2%) received radiotherapy alone, and 156 patients (62.4%) received a regimen of chemotherapy and radiotherapy. The results reveal a slight bias in favor of chemoradiotherapy, as well as a reasonably even distribution of patients across different Hb levels and treatment modalities. Both study groups demonstrated an increase in the level of Hb during treatment, with the nutritional supplement group demonstrating more significant improvements. In the nutritional supplement group, Hb levels increased from 10.2 ± 0.8 g/dL at baseline to 11.3 ± 0.7 g/dL on day 7 and to 12.1 ± 0.6 g/dL on day 14. In the ferrous sulphate group, however, the increase had a more gradual profile, with Hb increasing from 10.1 ± 0.9 g/dL at baseline to 10.8 ± 0.7 g/dL on day 7 and 11.4 ± 0.7 g/dL on day 14. The difference in rate of hemoglobin recovery between groups illustrates the likely therapeutic benefit of nutritional supplementation in anemia management during treatment. Survival analysis, performed using the Kaplan–Meier technique, revealed significant differences between outcomes based on baseline hemoglobin levels. Those with baseline Hb levels of ≥13 g/dL had a 1-year overall survival (OS) of 86%, compared with 74% in those with Hb levels of <13 g/dL. The observed statistical significance of this variation (log-rank $\chi^2 = 9.14$, $p = 0.0025$) is suggestive of a low baseline hemoglobin concentration as a poor prognostic factor for survival in this population. Follow-up analysis with Cox proportional hazards regression validated baseline hemoglobin as an

independent prognostic factor. The subgroup of patients with hemoglobin levels <13 g/dL demonstrated a mortality hazard more than twice that of their counterparts with high hemoglobin levels (HR = 2.05, 95% CI: 1.34–3.15, p = 0.001). The administration of combined chemoradiotherapy was associated with a hazard ratio of 0.72 (95% CI: 0.45–1.13, p = 0.14), suggestive of a protective effect, but without statistical significance. Additionally, to be >60 years old was associated with a 1.48-fold increased mortality hazard (95% CI: 0.93–2.35, p = 0.091), suggestive of a marginally significant association between age and survival outcomes. These observations did not reach statistical significance within this dataset, but taken together, they demonstrate the prognostic importance of baseline hemoglobin levels, affirm the potential clinical benefit of nutritional supplementation, as opposed to traditional iron supplementation.

Discussion

The study is a multicenter cohort, which explains that baseline hemoglobin and the recovery of such a component after therapy serve as an independent prognostic measure of patients having head and neck squamous cell carcinoma (HNSCC)[11,12]. Patients who had an Hb of higher baseline (13 g/dL and above) had a significantly superior one-year overall survival in comparison to patients with anemia, and the multivariate testing also revealed that the association between low Hb was alone an indicator of poor outcome [15,20].

The results were consistent with the previous research that found that anemia decreases the oxygen level in the tumor, hamper radiosensibility, and reduce the efficacy of treatment in HNSCC and other cancers [1,7]. The protective, yet non-significant, trend of concurrent chemoradiotherapy was also seen in relation to world data which revealed it to be much better in terms of organ saving and disease management [2]. It demonstrates the effect of age on survival which shows that some age effects on survival could be of borderline and therefore age sensitive support in the planning of treatment [13].

Remarkably, it was found hematologic improvements after one year, especially in those patients that received a nutritional care that was extensive. This indicates that nutritional interventions can be added to conventional therapy to improve hemoglobin recovery and tolerance, which has been reported before and also note that the nutritional condition serves as the prognosis in HNC [3,10]. The role of nutritional supplementation, however, needs specific prospective trials so as to be confirmed.

The prognostic models that integrate simple cost-effective markers like Hb are important as indicated in our study [21,22]. Consistent checking and correction of anemia on time may enhance better stratification of patients and may have an impact [14]. Hb potential as a tool in directing supportive interventions in addition to the oncologic therapy has a clinical utility that goes beyond the fact it is accessible.

4. CONCLUSION

This multicentric cohort research has demonstrated that hemoglobin is a clinically significant prognosis biomarker in the case of head and neck squamous cell carcinoma. The prognostic activity of baseline Hb ≥13 g/dL spread two hundred and twentieth better one-year follow-up survival and the recovery of Hb post-treatment cemented its prognostic activity.

Our findings suggest that:

Assessment of Hb should be undertaken on a routine basis and included in the baseline examination as well as survivorship follow up.

Onset The prompt identification and management of anemia can improve the tolerance and eventual rates of survival.

Reasonable care, such as nutrition should be studied more as a supplement to regular therapy.

Although chemoradiotherapy had a protective tendency and older age had a negative impact, they should be confirmed in larger prospective studies. Further research should be done to assess Hb-nonspecific management algorithms and mechanistic connections between anemia, hypoxia, and reaction to treatment.

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Conflict of interest

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