# CHAPTER-7

# SUMMARY

## 7.1. Study aims

i. To study the nutritional profile and systemic immunity in patients with Head and Neck Squamous Cell Carcinoma (HNSCC).
ii. To study the correlation between the nutritional status and systemic immunity with outcome of treatment in patients being treated for HNSCC.
iii. To develop a low cost model for early prognosis using nutritional status and systemic immunity marker in patients being treated for HNSCC.

## 7.2. Hypothesis

$H_0$ - There is no correlation between nutritional status and systemic immunity in patients with HNSCC.

$H_1$ - there is a positive correlation between nutritional status and systemic immunity in patients with HNSCC.

## 7.3. Study design and methodology

This was a prospective cohort study, conducted at Cancer Research Institute (CRI), SRHU, Dehradun. The patients starting treatment for HNSCC at CRI, were enrolled in the study after a written informed consent, they were evaluated for nutrition status and systemic immunity before starting, during, and at completion of planned treatment. The disease status and overall survival were assessed upto 6 months of completion of planned treatment. The primary end points of the study were Nutritional status, Systemic Immunity before and after treatment, and Disease status, Overall survival at 6 months of completion of treatment. Taking the correlation coefficient between nutritional status and systemic immunity as 0.5(unknown), α at 0.5, β at 90%, design effect 1.5 the sample size was calculated to be 55 in node positive group and 55 in node negative group. Taking the loss to follow up rate as 20 % the final sample size was 66 in each group (total of 132 patients).

## 7.4. Statistical analysis

MS Excel 2010 was used for data entery, SPSS software version 22 was used for statistical analysis. The normality of distribution was tested using the “one-sample Kolmogorov-Smirnov Test”. Parametric tests were used to analyse normally distributed data, non-parametric tests for non-normally distributed data andChi square test for the categorical data. The level of significance was taken as $p<0.05$.

“Pearson chi square test” was used for categorical variables. “Unpaired Student t test” and “Paired-sample ttest”used to test difference in mean; non-parametric tests used were “Related-Samples Wilcoxon Signed Rank test, Related-samples Marginal Homogeneity test, Independent-Samples Mann-Whitney U test and Independent-Samples Kruskal-Wallis test”. “Cochran's and Mantel-Haenszel Statistic” was used to calculate Risk Ratio (RR). Correlation was tested with Pearson's coefficient and Spearman’s coefficient. Multivariate analysis was performed using the Multi-nominal Logistic Regression model. ROCs were generated to get cut-off values and their sensitivity and specificity to predict the outcome. Survival curves were generated using “Kaplan-Meier method and Cox-Regression model”and were used to calculate the Hazard Ratio (HR) for outcomes, i.e., Progression Free Survival (PFS) and Overall Survival (OS). Using the variables significantly associated with the outcome, RR and ROC cut-off values novel risk stratification models were developed to predict outcomes such as failure to complete planned treatment, disease recurrence 6months and death at 6 months.

## 7.5. Results

i. Out of total 161 patients there were 73 in N- and 88 in N+ cohorts with no significant differences in variables like gender, age, ECOG PS and co-morbidities; but N+ cohort had higher proportion of patients with T3/4 stage(68.2% v/s 52%, p=0.000), tumor subsite oropharynx (30.7% v/s 13.7%; p=0.003) and poorly differentiated tumors (14.8% v/s 6.8%; p=0.018) as compared to N- cohort.

ii. At baseline, mean weight, BMI and Hb were similar in N- and N+ cohorts; however, median pre-treatment weight loss and median SGA score were significantly higher in N+

cohort; higher proportion of patients had ≥10% pre-treatment weight loss (28.4% v/s 13.7%; p=0.034), low MUAC (22.8% v/s 9.6%; p=0.036), ≥40 SGA score (58% v/s 34.2%; p=0.015) and Bitot spots (18.2% v/s 4.1%; p=0.006) in N+ cohort.

iii. At baseline, the mean NLR was similar (3.83±4.42 SD, 3.93±3.89 SD and 3.8±5.16 SD) in the overall, N- and N+ cohorts (p=0.992).

iv. Treatment details-54.8% patients in N- group and 73.9% in N+ group were planned for multi-modality treatment, but only 50.7% in N- and 67% in N+ finally received multi-modality treatment. Grade III complications occurred in 23.6% patients (same for both cohorts). Failure to complete all planned treatment occurred in 13%, 4.1% and 20.5% patients in overall, N- and N+ group cohorts (p=0.002).

v. During treatment, at the end of first, second modality, and completion of treatment, the mean reduction in weight was 4.69%, 7.48% and 9.17% in the overall group; 6.2%, 6.7% and 8.9% in the N- cohort; was 3.6%, 8% and 9.4% in the N+ cohort.

vi. During treatment, at the end of first, second modality, and completion of treatment, the mean reduction in BMI was 1.45, 2.71 and 2.09 in the overall group; 1.52, 2.83 and 2.01 in the N- cohort; and 1.39, 2.62 and 2.16 in the N+ cohort.

vii. During treatment, at the end of first, second modality, and completion of treatment, the proportion of patients with ≥10% weight loss from baseline was 27.2%, 38.1% and 45.3% in the overall group; it was 26.4%, 37% and 41.1% in the N- cohort; and it was 27.9%, 38.9% and 48.8% in the N+ cohort.

viii. At completion of treatment, the proportion of patients with low BMI increased from 22.8% to 43.4% in overall group; 20.9% to 35.5% in the N- cohort; and 24.4% to 50% in N+ cohort.

ix. At completion of treatment, the proportion of patients with low MUAC increased from 16.8% to 30.8% in overall group; 9.6% to 20.5% in the N- cohort; and from 22.7% to 39.5% in N+ cohort.

x. At completion of treatment, the proportion of patients with SGA score ≥40 increased from 47.2% to 87.4% overall group; 34.3% to 79.5% in the N- cohort; and 58% to 94.2%

in N+ cohort. The median SGA score increased from 39 to 50, 34 to 48 and 42 to 53 in overall, N- and N+ cohorts.

xi. Comparing nutritional profile in patients having received single versus multi-modality treatment, mean weight was significantly lower with single modality treatment in N+ group (47.85 v/s 52.44 kg); mean reduction in BMI was higher with multi-modality treatment in overall, N- and N+ groups (1.29 v/s 2.57, 1.44 v/s 2.66 and 1.1 v/s 2.52 respectively); median increase in SGA score was higher with multi-modality treatment in overall, N- and N+ groups (6 v/s 13, 8 v/s 15 and 4 v/s 12 respectively).

xii. Comparing nutritional profile in patients having received single versus multi-modality treatment, mean %weight loss was significantly higher with multi-modality treatment in overall, N- and N+ groups (6.26% v/s 11.01%, 6.79% v/s 10.86%, and 6.95% v/s 11.12% respectively). Proportion of patients with ≥10% weight loss was higher with multi-modality treatment in overall, N- and N+ groups (28.6% v/s 56.3%, 30.6% v/s 51.4%, and 26% v/s 59.3% respectively).

xiii. During treatment, the median NLR (IQR) increased from 3(2-4), 4(3-7), 5.86(4-9) and 5(3.8-8.4) in overall group; 3(2-4.13), 3.8(2.6-6), 5.52(3.81-9.63) and 4.5(3.02-8.23) in N- cohort; 3(2-4), 4.72(3.01-8), 6.3(3.91-7.64) and 6.08(4.8-7.8) in N+ cohort at baseline, end of first, second modality, and completion of treatment respectively.

xiv. Comparing systemic immunity in patients having received single versus multi-modality treatment- median NLR was not significantly different in N- group (4 v/s 5), but significantly higher after single modality treatment in N+ group (8 v/s 5.82). There was no significant difference noted in mean or median change in NLR with single versus multi-modality treatment in any group.

xv. Association between NLR and PS at baseline – Theproportion of patients with **NLR > 6** was significantly higher in patients with PS >2 v/s 0-2 in overall (30.77% v/s 8.9%; p=0.046; RR=2.171) and N- cohort (66.67% v/s 8.7%; p=0.031; RR=2.203) but not in N+ cohort;

xvi. Association between NLR and PS at treatment completion – The proportion of patients with **NLR > 6** was significantly higher in patients with PS >2 v/s 0-2 in overall (53.3% v/s

30.8%; p=0.013; RR=2.878) and N+ cohort (62% v/s 32.3%; p=0.014; RR=1.911) but not in N- cohort.

xvii. Association between NLR and nutritional parameters at baseline– The proportion of patients with **NLR > 6** was not different with weight ≤50 v/s >50kg and low v/s normal BMI in all groups; significantly higher for pre-treatment weight loss ≥10% v/s <10% in overall (14.3% v/s 9.7%; p=0.057; RR=2.008) and N+ group (16% v/s 8%; p=0.015; RR=2.478) but not in N- cohort; significantly higher for MUAC ≤21 v/s >21cm in N+ cohort (14.3% v/s 9.1%; p=0.006; RR=-3.253), but not in N- cohort; significantly higher with SGA score ≥40 v/s <40 in overall group (17.33% v/s 4.76%; p=0.014; RR=2.806) and N+ cohort (16% v/s 2.7%; p=0.010; RR=2.935) but not in N- cohort.

xviii. Association between NLR and nutritional parameters at treatment completion – The proportion of patients with **NLR > 6** was significantly higher in patients with PS >2 v/s 0-2 in overall and N+ cohorts; with weight ≤50 v/s >50kg in only N- cohort; no significant association was found with BMI, change in weight during treatment, MUAC, Hb, SGA score or change in SGA score during treatment in any groups.

xix. Correlation between nutritional parameters and NLR at baseline – A statistically significant moderate positive correlation was found for SGA score and pre-treatment % weight loss; moderate negative correlation for weight and BMI; mild negative correlation for PS and hemoglobin in the overall group. Similar findings were noted for the N+ cohort, but no significant correlation was found in the N- cohort.

xx. Correlation between nutritional parameters and NLR at baseline – There was a statistically significant mild positive correlation for PS only in overall and N+ cohort; significant negative mild correlation was found for weight, MUAC, and positive mild correlation for SGA score in N- cohort.

xxi. The baseline variable like age, gender, primary tumor subsite, cT stage, tumor grade and PS were not found to be associated with *FailureTxCompletion.*

xxii. Proportion of patients with *FailureTxCompletion* was significantly higher with single versus multi-modality treatment in overall (20% v/s 4%; p=0.035; RR=2.75) and N+ group (34.5% v/s 13.46%; p=0.028; RR=3.35), but not in N- group.

xxiii. Nutrition parameters were found to be significantly associated with *FailureTxCompletion* in N+ group and systemic immunity in N- group.

xxiv. In N+ cohort, proportion of patients who had *FailureTxCompletion* was significantly higher with low BMI (40.9% v/s 13%; p=0.002; RR=4.385) ≥10% pre-treatment weight loss (44% v/s 11.1%; p=0.001; RR=6.25) and low MUAC (46% v/s 16%; p=0.002; RR=4.5).

xxv. In N- cohort, proportion of patients who had *FailureTxCompletion* significantly increased with rising NLR ≤3, >3 ≥6 and >6 (0%, 1.92% and 25%; p=0.035).

xxvi. The variables like age, gender, tumor grade, treatment modality, PS, nutrition parameters and systemic immunity were not associated with Grade III complications. In N- cohort only primary tumor subsite and cT stage were significantly associated with Grade III complications, but this was not seen in N+ cohort.

xxvii. The overall median follow up was 182 days (range 0 to 640), 4.3% patients were lost to follow up. Disease progression at 6 months was seen in 36.02%, 23.3%, and 46.6% patients; death at 6 months in 14.9%, 8.2% ,and 20.5% patients overall, N- and N+ groups respectively.

xxviii. On multivariable analysis factors associated with poor 6 months PFS were as follows –

cT3/4 stage(HR 4.06; 95%CI 0.53-21.22; p=0.021), single modality treatment (HR 2.67; 95%CI 1.46-4.97; p=0.001), *FailureTxCompletion* (HR 2.88; 95%CI 1.32-6.29; p=0.008), high pre and post-treatment NLR (HR 1.28; 95%CI 0.55-2.97; p=0.559) and (HR 2.54; 95%CI 1.3-4.92; p=0.006), high post- treatment SGA score (HR 1.83; 95%CI 1.08-3.09; p=0.025). In the N- cohort only high post-treatment NLR associated with poor PFS.

xxix. On multivariable analysis factors associated with poor 6 months OS were –

cT3/4 stage (HR 2.47; 95%CI 1.16-5.23; p=0.018), pre-treatment PS>2, single modality treatment (HR 5.56, 95%CI 1.75-17.69, p=0.004), *FailureTxCompletion* (HR 7.31; 95%CI 2.13-25.11; p=0.002), high pre-treatment SGA score (HR 2.97; 95%CI 0.92-9.57; p=0.068), high pre and post-treatment NLR (HR 7.94; 95%CI 2.83-27.8; p=0.001). No

factors were significantly associated with poor OS in N- cohort, probably due to the low event rate.

xxx. On ROC plotting ≥90% specificity for *FailureTxCompletion* was found with the following cut-off values – Pre-treatment weight ≤45.5kg; MUAC ≤20.5cm, 21.5cm and 20.5cm; BMI ≤17kg/$m^2$; pre-treatment %weight loss ≥15.5%, 14.5% and 18%; SGA score ≥53, 51, 56.5; NLR ≥7, 6.5, 7.5 in overall, N- and N+ cohorts respectively.

xxxi. On ROC plotting ≥90% specificity for 6 months PFS was found with the following cut-off values – Pre-treatment NLR ≥5.49, 6.46, 4.16; post-treatment NLR ≥10; post-treatment SGA score ≥59.5, 58.5, 60.5 in overall, N- and N+ cohorts respectively.

xxxii. On ROC plotting ≥90% specificity for 6 months PFS was found with the following cut-off values – Pre-treatment SGA score ≥55.5, 54, 55.5; pre-treatment NLR ≥6.08, 6.96, 4.39; post-treatment NLR ≥11.04, 11.04, 11.13 in overall, N- and N+ cohorts respectively.

xxxiii. The novel low risk stratification model to predict *FailureTxCompletion* comprised of pre-treatment weight, BMI, MUAC, pre-treatment %weight loss, Bitot spots, SGA score and modality of treatment. Internal validation in overall group, 45.5%, 27.6% and only 6.6% patients stratified as high, medium and low risk had *FailureTxCompletion* (p=0.000)*;* in N+ cohort, it was 62.5%, 35% and only 10% respectively (p=0.001).

xxxiv. The novel low risk stratification model to predict 6 months PFS comprised of- cT stage, modality of treatment, *FailureTxCompletion,* pre- and post-treatment NLR and post-treatment SGA score. Internal validation in overall group, 85.7%, 47.2% and 16.9% patients stratified as high, medium and low risk had disease progression*;* similar finding were noted in both N- and N+ cohorts (p=0.000, 0.014, 0.000).

xxxv. The novel low risk stratification model to predict 6 months OS comprised of cT stage, modality of treatment, *FailureTxCompletion,* pre- and post-treatment NLR and post-treatment SGA score. Internal validation in overall group, 57.9%, 18.8% and only 4.4% patients stratified as high, medium and low risk had mortality (p=0.000)*;* in N+ cohorts it was 66.7%, 20.7% and only 5% respectively (p=0.000).

## 7.6. Conclusions

i. Malnutrition (defined as either ≥10% weight loss or BMI <18.5 or SGA score ≥40) was found in 47.1% patients pre-treatment and this proportion increased to 87.6% patients post-treatment. The median NLR (IQR) was 3 (2-4) pre-treatment and increased to 5 (3.8-8.4) post-treatment. There was statistically significant moderate positive correlation between NLR and SGA score, pre-treatment percent weight loss; moderate negative correlation between NLR and weight, BMI.

ii. Malnutrition was significantly associated with failure to complete planned treatment in node positive patients and raised NLR in node negative patients. On multivariate analysis, Cox-Regression and survival analysis with Kaplan-Meier curves, both poor nutritional status and raised NLR were associated with poor six months progression frre and overall survival.

iii. The novel low cost risk stratification models, developed in this study using clinical parameters, nutritional status and the NLR were successfully tested for internal validation as predictive for poor clinical response (failure to complete planned treatment, early disease recurrence and mortality) in patients being treated for HNSCC.

## 7.7. Clinical recommendations

i. Apart from the regular clinical and disease parameters (like PS, clinical stage, pathological features, subsite etc.) patients' baseline *nutritional status* and systemic immunity marker *NLR* should be taken into account while planning the oncological management for HNSCC patients.

ii. A patient with malnutrition at the start of oncological treatment for HNSCC should be offered structured nutritional advice and regular nutritional monitoring during the ongoing active treatment to improve clinical outcomes of these patients.

iii. Systemic immunity marker NLR, as calculated from the peripheral blood sample, is a cost effective and easily available tool and should be utilized routinely to prognosticate HNSCC patients planned for treatment into high risk groups for poor clinical outcomes.

iv. The novel low cost risk stratification models developed in this study were validated internally to prognosticate patients as low, medium and high risk for poor clinical outcomes, and now need to be validated externally on different HNSCC patient populations by other researchers.