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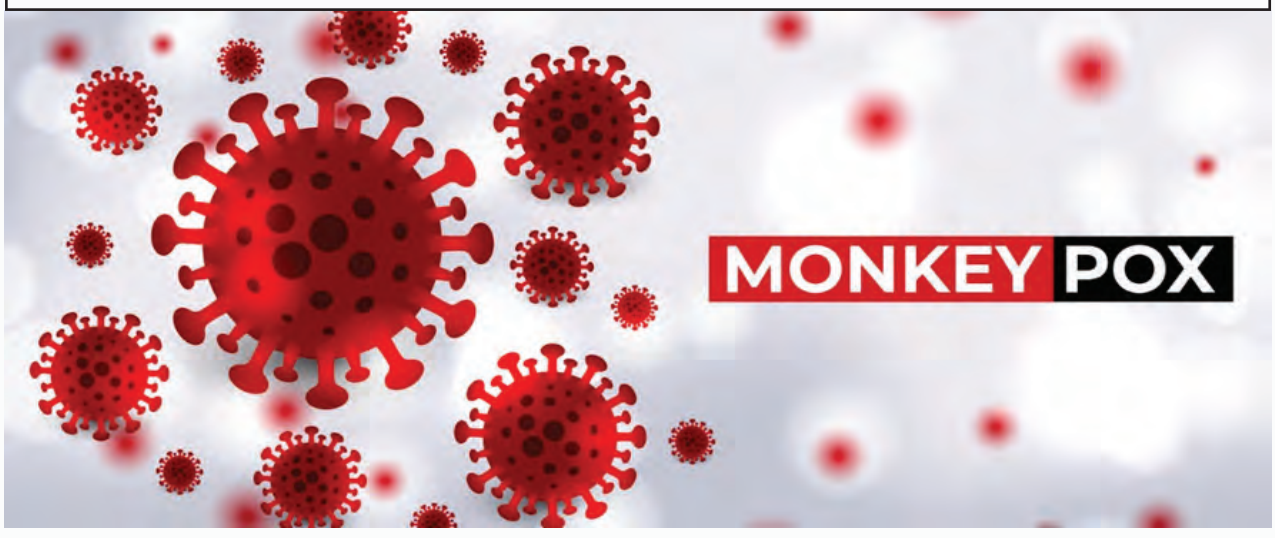


The International Tobacco Control Conference on

The Scourge of Smoking and Conflicts of Interest

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Original Article

Survival Outcomes and Predictive Factors to Evaluate the Efficacy of Neoadjuvant Chemoradiation in Carcinoma Esophagus: An Institutional Experience from India

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Abstract

Aim & Objectives: Although NCRT (Neoadjuvant Chemo Radiation Therapy) followed by surgery demonstrates an increase in overall survival (OS) in locally advanced operable esophageal cancer, there is a lack of a reliable predictive factor to identify patients who are more likely to be affected by treatment toxicities or natural history of the disease. In this study, we have studied various indices like pre–treatment serum albumin, hemoglobin, Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), Platelet to Albumin Ratio (PAR), Systemic Immune Index (SII) as independent prognostic factors in esophageal cancer, with respect to the outcomes and tumor response.

Material & Methods: A total of 83 patients of esophageal cancer who were treated with Neoadjuvant Chemoradiation from 2016–2021 were evaluated in this study. All the patients were treated with 41.4 Gy / 23 # External Beam Radiation Therapy with concurrent weekly Paclitaxel & Carboplatin (CROSS Protocol). Baseline hematological parameters like PLR, NLR, PAR, SII, Serum Albumin and Hemoglobin were obtained from laboratory records. Survival outcomes were analyzed using the Kaplan–Meier method and log rank test. Chi square test was used to analyze the association with pathological complete response after NCRT.

Results: The median follow–up time of the study was 42.50 months, and the median age of patients was 55 years (IQR – 45–63). The majority of the patients were squamous cell carcinoma (92.8%), and 7.2% of the patients were adenocarcinoma of the esophagus.

Amongst this study group, 41 patients (49.4%) underwent surgery following chemoradiation, the rest of the patients couldn't undergo surgery. Amongst the 41 operated patients, 21 (51.2%) had pathological complete response, 13 (31.7%) had partial response, 7 (17.1%) had poor/no response to neoadjuvant chemoradiation. The median OS of a group of patients who underwent surgery (44.7 Months) was found to be significantly higher ($p<0.001$) than that of patients who were not operated (17.8 Months).

Kaplan Meir analysis and log–rank test revealed that high pretreatment albumin and hemoglobin had statistically significant association with better OS.

High PLR, low NLR, low PAR and high SII had a correlation trend with better OS. However, statistical significance couldn't be demonstrated owing to our smaller sample size. Patients with high PLR (> 180) were found to have a higher rate of pathologic complete response compared to the patients with low PLR (< 180).

Conclusion: NCRT when offered to a selected subgroup of patients having operable carcinoma esophagus can give excellent survival outcomes. Patient selection should incorporate factors that look into the biology, systemic inflammatory response and baseline status of these patients. The evaluation of these factors on a larger scale prospective multicentric trials is warranted.

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As predictive factors become more accurate, treatments may become more tailored for individual patients to minimize treatment toxicities without compromising survival outcomes.

Keywords: Carcinoma Esophagus, neoadjuvant chemoradiation, prognostic markers, survival outcomes

Introduction

Owing to its insidious onset, individuals with oesophageal cancer are frequently diagnosed at advanced local stages upon presentation, making upfront primary resection unfeasible. Neoadjuvant Chemoradiation (NCRT) has been widely adopted as the standard of care for locally advanced oesophageal cancer in the last decade. [1] The goal of neoadjuvant concurrent chemoradiotherapy is to downstage the tumour, resulting in a greater chance of complete resection. Although NCRT improved the survival outcome of the majority of patients, a substantial number of patients may be affected by a plethora of treatment–related toxicities, which results in premature termination of treatment or death due to treatment–related toxicities. Amongst the patients who have achieved complete remission of the disease, there is a high risk of recurrence in around half the patients undergoing resection after NCRT. [2] Although there has been an improvement in advanced treatment modalities, the 5–year overall survival rates are typically in the range of 20–30%. [3,4]

While NCRT followed by surgery demonstrated an increase in overall survival (OS) in locally advanced oesophageal cancer, there is a lack of a reliable predictive factor to identify patients who are more likely to be overwhelmed by CCRT side effects and to help predict the clinical outcomes. [5] Recently published literature consists of attempts to identify various hematologic parameters at baseline as surrogate markers of treatment response and to predict treatment toxicities. [6]

As predictive factors become more accurate, treatments may become more tailored

for individual patients to minimize treatment–related adverse events without compromising survival outcomes. In this study, we aimed to evaluate multiple haematological indices as independent prognostic factors in determining the clinical outcomes of oesophageal cancer patients treated with neoadjuvant chemoradiation.

Materials & Methods

Study Population

We evaluated the clinical and laboratory data records of 83 patients who had locally advanced oesophageal cancer treated with NCRT in our institution between 2016 and 2021.

Patients who satisfied the following criteria were included in this study: (a) histologically confirmed oesophageal cancer, (b) stage II or higher non–metastatic oesophageal cancer according to the TNM Classification of Malignant Tumors based on AJCC 8th Edition, 2017 [7], (c) no active malignant neoplasm other than oesophageal cancer at the point of start of the treatment course, (d) availability of blood test data. Clinical information, including information on sex, age, histology, performance status, tumour location, tumour stage and treatment details, was obtained from clinical records. The cell counts and hematologic parameters were obtained from the electronic laboratory records in our institution.

Radiotherapy

All the patients were treated with Neoadjuvant Chemoradiation, dose 41.4Gy / 23#, and concurrent weekly chemotherapy, i.e., Inj. Paclitaxel 50mg/m2 & Inj. Carboplatin AUC–2 (CROSS Protocol). [8] Target volume delineation, prior to dosimetric planning, was according to standard international consensus–based contouring guidelines proposed by Abraham et al.. [9] Radiotherapy planning was done using Eclipse Treatment Planning System (TPS) (Varian Medical, Palo Alto, CA). Volumetric Modulated Arc Therapy (VMAT) / Intensity Modulated Radiation Therapy (IMRT) was delivered with 6–MV Acuros–XB algorithm photon beams generated from the Varian Clinac–iX linear accelerator equipped with a 120–leaf Millenium multi–leaf collimator.

Toxicities during treatment were managed according to standard protocols. Dose reduction was done as per the British Columbia Cancer Agency (BCCA) chemotherapy protocol whenever necessary. [10] After the completion of the radiotherapy course, patients who were fit underwent surgery after 4–6 weeks. The patients who were unfit for surgery were given a boost with external beam radiotherapy to the locoregional tumour.

Prognostic Indices

The baseline parameters were obtained around 7–10 days prior to the initiation of the radiotherapy course. The optimal cut–offs for each parameter were designated according to existing literature. [11–13]

a. **Platelet Lymphocyte Ratio (PLR) –** PLR is defined as the ratio of the platelet count to the absolute lymphocyte count. A PLR of ≥ 180 is considered a high PLR.

b. **Neutrophil Lymphocyte Ratio (NLR) –** NLR is defined as the ratio of the absolute neutrophil count to the absolute lymphocyte count. An NLR of ≥ 2.62 is considered a high NLR.

c. **Platelet Albumin Ratio (PAR) –** PAR is defined as the ratio of the platelet count to the serum albumin. A PAR of ≥ 5.7 x 10^9 is considered a high PAR.

d. **Systemic Immune Index (SII) –** SII is calculated as the product of platelet count and absolute neutrophil count divided by the absolute lymphocyte count. An SII of 577.7 is considered a high SII.

e. **Serum Albumin –** A high serum albumin is considered as ≥ 3.5 g/dL, and low serum albumin is considered to be <3.5 g/dL.

f. **Serum Hemoglobin –** A high serum haemoglobin is considered as ≥ 10 g/dL, and a low serum haemoglobin is considered to be <10 g/dL (anaemia).

Statistical Analysis

The follow–up data comprised endoscopy reports, computed tomography (CT) reports, or 18F–FDG PET/CT reports. Patient data are summarized as frequency (%) for categorical variables and as median with interquartile range (IQR) or range for continuous variables. Overall survival (OS) was determined for each patient based on the time from the date of registration to the date of death or last follow–up. Survival outcomes were analyzed using the Kaplan–Meier method. Log–rank tests were used to determine significant differences between survival curves. A Cox regression model was used to estimate the hazard ratio (HR) for the variables associated with OS. The chi–square test was used to analyze the association of pathologic complete response with other variables. A p–value < 0.05 was considered statistically significant. All statistical tests were performed using SPSS version 19.0. (SPSS, Chicago, IL).

Results

Baseline characteristics of study patients

A total of 83 patients were analyzed in this study between 2016 and 2021. The baseline characteristics of these patients are summarized in Table 1.

The median age of the study population is 55 years (IQR = 45,63). Forty patients (48.2%) were male and 43 patients (51.8%) were female. The majority of the patients were squamous cell carcinoma (92.8%), and 7.2% of the patients were adenocarcinoma of the oesophagus. Stage

Variable	N
Age	
<65 years	65 (78.3%)
≥65 years	18 (21.7%)
Sex	
Female	43 (51.8%)
Male	40 (48.2%)
ECOG Performance Status	
1	41 (49.4%)
2	35 (42.2%)
3	7 (8.4%)
Smoking	
No	56 (67.5%)
Yes	27 (32.5%)
Alcohol intake	
No	51 (61.4%)
Yes	32 (38.6%)
Comorbidities	
DM	6 (7.2%)
DM & SHTN	7 (8.4%)
SHTN	7 (8.4%)
NIL	56 (67.6%)
Others	7 (8.4%)
Location	
Gastroesophageal Junction	18 (21.7%)
Lower–Thoracic	28 (33.7%)
Mid–Thoracic	34 (41.0%)
Upper–Thoracic	3 (3.6%)
Histology	
Adenocarcinoma	6 (7.2%)
Squamous cell carcinoma	77 (92.8%)
Grade	
Moderately Differentiated	57 (68.7%)
Poorly Differentiated	2 (2.4%)
Well Differentiated	24 (28.9%)
T–Stage	
T2	5 (6.0%)
T3	50 (60.2%)
T4A	12 (14.5%)
T4B	16 (19.3%)

N–Stage	
0	32 (38.7%)
1	35 (42.2%)
2	16 (19.3%)
Stage Group	
II	26 (31.4%)
III	29 (34.9%)
IVA	28 (33.7%)
Surgery	
No	42 (50.6%)
Yes	41 (49.4%)
Serum Haemoglobin	
<10 g/dL (Anaemia)	43 (51.8%)
≥10 g/dL (Non–anaemic)	40 (48.2%)
Serum Albumin	
High (≥3.5 g/dL)	46 (55.4%)
Low (<3.5 g/dL)	37 (44.6%)
Systemic Immune Index (SII)	
High SII	64 (77.1%)
Low SII	19 (22.9%)
Neutrophil Lymphocyte Ratio (NLR)	
High NLR	56 (67.5%)
Low NLR	27 (32.5%)
Platelet Albumin Ratio (PAR)	
High PAR	48 (57.8%)
Low PAR	35 (42.2%)
Platelet Lymphocyte Ratio (PLR)	
High PLR	31 (37.3%)
Low PLR	52 (62.7%)

Table 1: Baseline characteristics of study population including oesophageal cancer patients who underwent neoadjuvant chemoradiation

ECOG – Eastern Cooperative Oncology Group; DM – Diabetes Mellitus; SHTN – Systemic Hypertension; SII – Systemic Immune Index; NLR – Neutrophil Lymphocyte Ratio, PAR – Platelet Albumin Ratio, PLR – Platelet Lymphocyte Ratio

III comprised the majority of the study population (34.9%), followed by Stage II (33.7%). Based on anatomical location, most of the patients had a Mid–Thoracic oesophageal tumour (41%), followed by Lower–Thoracic oesophagus (33.7%), Gastro–oesophageal junction (21.7%) and Upper–Thoracic oesophagus (3.6%).

Amongst this study group, 41 patients (49.4%) underwent surgery following chemoradiation. The remaining patients couldn't undergo surgery due to the following reasons: 5 (6%) deaths during chemoradiation, 10 (12%) died while awaiting surgery, 12 (14.5%) did not consent to surgery, 8 (9.6%) progressed after chemoradiation, 7 (8.5%) were deemed medically unfit for surgery. Amongst the 41 operated patients, 21 (51.2%) had a pathological complete response, 13 (31.7%) had a partial response, and 7 (17.1%) had poor/no response to neoadjuvant chemoradiation.

Survival Analysis

The median follow–up period of the study population was 42.5 months.

The one–year and three–year overall survival of the entire study population is 61.4% and 19.2%, respectively. The median overall survival is 22.37 Months (IQR = 14.1,30.56)

The median overall survival of the group of patients who underwent surgery (44.7 Months) was found to be significantly higher ($p<0.001$) than that of patients who were not operated (17.8 Months). (Figure 1)

Sex, T–stage, N–stage, stage group, surgical intervention, serum haemoglobin and serum albumin were found to have statistically significant associations on univariate analysis with overall survival. On multivariate analysis, smoking habit, comorbidities, N–stage, surgical intervention, and Platelet Albumin Ratio were found to have statistically significant associations with overall survival.

Anaemic patients (<10 g/dL) were also found to have poorer survival outcomes than non–anaemic patients (≥ 10 g/dL), with a hazard ratio of 2.51 (95% CI = 1.44–4.38); $p<0.01$. (Figure 2) The overall survival of patients with high serum albumin (≥ 3.5g/dL) was better than that of low serum albumin (< 3.5 g/dL), with a hazard ratio of 0.52 (95% CI = 0.30–0.88); $p=0.02$. (Figure 3)

Patients with a high PAR ($\geq 5.7 \times 10^9$) had lower overall survival compared to those with a low PAR ($< 5.7 \times 10^9$) with a hazard ratio of 3.22 (95% CI = 1.35–7.66); $p=0.01$. High PLR, low NLR, and high SII had a correlation trend with better OS. However, statistical significance couldn't be demonstrated owing to our smaller sample size. The univariate & multivariate analyses of overall survival with various variables are summarized in Table 2.

Pathologic Response

A chi–square test was performed to determine the association of pathologic response in the subgroup of oesophageal cancer patients (N=41) who underwent

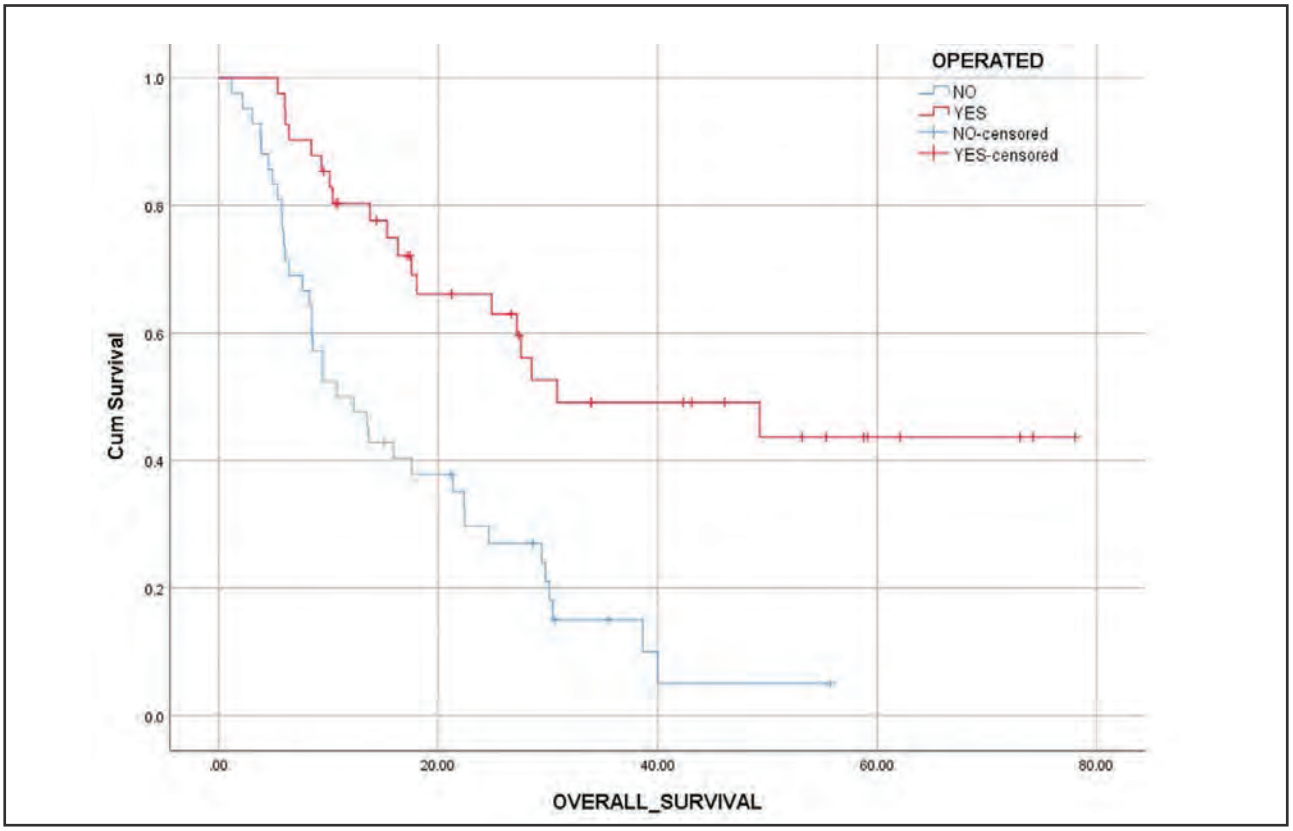


Figure 1: Kaplan Meir curve depicting the difference in the overall survival between the groups of oesophageal cancer patients who underwent surgery and who did not undergo surgery after neoadjuvant chemoradiation (Red Line – Operated, Blue Line – Not operated)

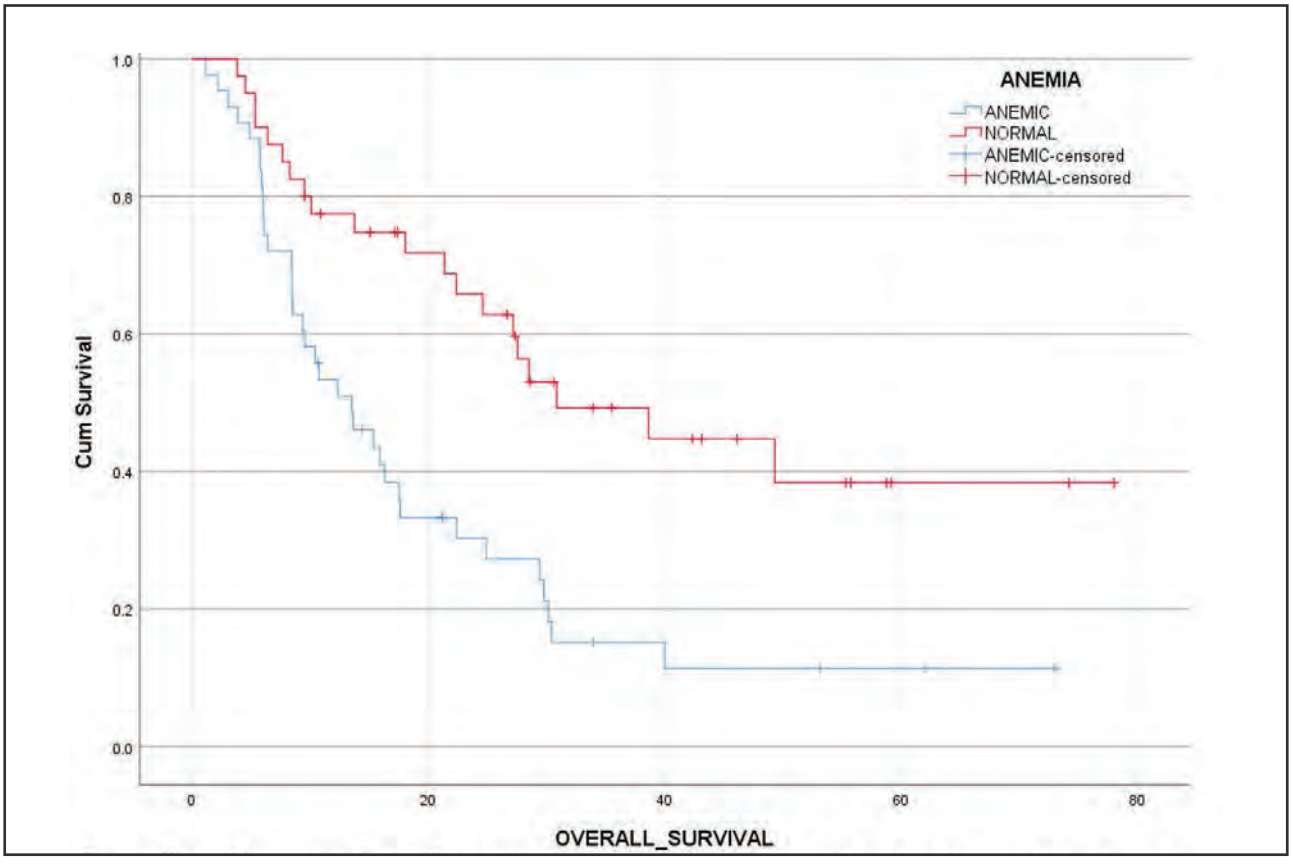


Figure 2: Kaplan Meir curve depicting the difference in the overall survival between the groups of oesophageal cancer patients with anaemia (serum hemoglobin <10g/dl) and normal haemoglobin (serum haemoglobin >10g/dl) (Red Line – Normal haemoglobin group, Blue Line – Anaemic group)

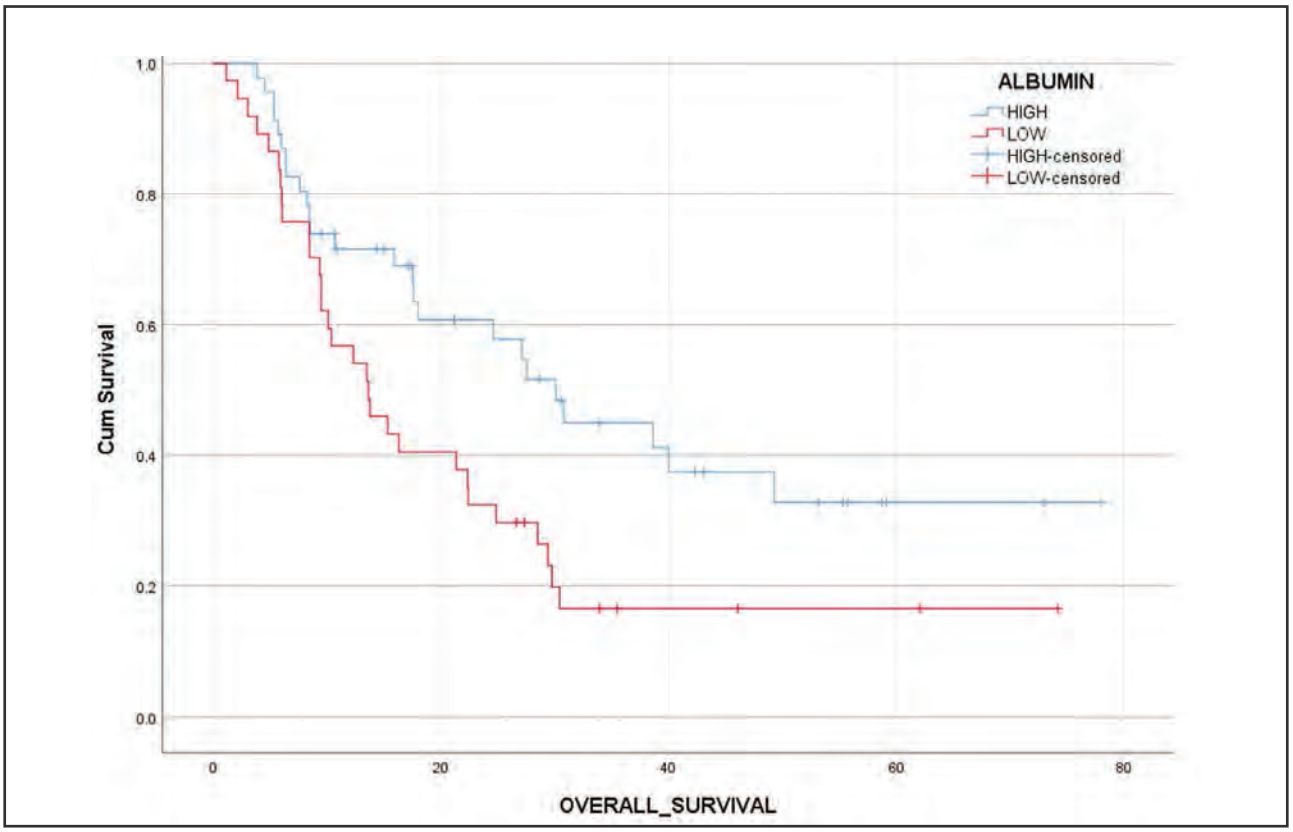


Figure 3: Kaplan Meir curve depicting the difference in the overall survival between the groups of oesophageal cancer patients with high serum albumin (>3.5g/dl) and with low serum albumin (<3.5g/dl) (Red Line – Low Serum Albumin group, Blue Line – High Serum Albumin group)

surgical resection after neoadjuvant chemoradiation (complete vs non–complete) with various variables. Sex, Alcohol intake, Histology, and Platelet Lymphocyte Ratio were found to have statistically significant associations with pathologic response.

Patients with high PLR (≥ 180) were found to have a higher rate of pathologic complete response compared to the patients with low PLR (< 180); p=0.02.

The results of the chi–square test for association of variables with pathologic response in the subgroup of oesophageal cancer patients who underwent surgical resection after Neoadjuvant Chemoradiation are summarized in Table 3.

Discussion

The findings of this study shed light on the potential prognostic significance of various haematological indices in locally advanced oesophageal cancer patients treated with neoadjuvant chemoradiation. The management of oesophageal cancer poses significant challenges due to its insidious onset and often advanced stage at diagnosis.

A study by Zhang et al. in 2014 retrospectively reviewed the outcomes of 103 patients with oesophageal squamous cell carcinoma and correlated it with baseline serum haemoglobin. The study identified anaemia as a highly significant prognostic factor and helped predict 3–year overall survival (hazard ratio 1.916; p = 0.012 and 3–year disease–free survival (hazard ratio 1.973; p = 0.007). [13] In our study, the presence of anaemia (<10 g/dL) was also associated with poorer survival outcomes, consistent with previous studies linking anaemia to adverse outcomes. Anaemia reflects both disease severity and compromised physiological reserve, which may contribute to poorer treatment tolerance and outcomes.

A study by Takeda et al. in 2018 analyzed the association of serum albumin with the clinical outcomes of 183 oesophageal cancer patients. It was found that high baseline serum albumin level (3.6 g/dL) and change in serum albumin from baseline to Day 105 (+ 0.3 g/dL) were independent predictors for overall survival, in addition to other factors like T–stage and overall treatment time (OTT). [14] These findings were coherent with our study wherein high serum albumin levels (>3.5g/dL) were associated with better overall survival, supporting the established role of serum albumin as a marker of nutritional status and overall health of the patient.

Hsueh et al., in 2022, prospectively studied the association of pretreatment albumin and neutrophil–lymphocyte ratio (NLR), Albumin–NLR Score (ANS) in comparison to the prognostic nutrition index (PNI) in 123 patients of oesophageal cancer who received neoadjuvant

		Univariate Analysis			Multivariate Analysis		
Variable	**N**	**HR**	**95% CI**	**p–value**	**HR**	**95% CI**	**p–value**
Age							
<65 years	65 (78.3%)	0.59	0.32–1.08	0.09	0.43	0.17–1.09	0.07
≥65 years	18 (21.7%)	1			1		
Sex							
Female	43 (51.8%)	0.40	0.23–0.69	<0.01	0.25	0.05–1.19	0.08
Male	40 (48.2%)	1			1		
ECOG Performance Status							
1	41 (49.4%)	0.176	0.07–0.44	0.44	0.35	0.07–1.61	0.18
2	35 (42.2%)	0.282	0.11–0.69	0.69	0.69	0.14–3.31	0.64
3	7 (8.4%)	1			1		
Smoking							
No	56 (67.5%)	0.62	0.35–1.07	0.08	4.06	1.42–11.6	0.01
Yes	27 (32.5%)	1			1		
Alcohol intake							
No	51 (61.4%)	0.40	0.23–0.69	<0.01	0.38	0.09–1.68	0.20
Yes	32 (38.6%)	1			1		
Comorbidities							
DM	6 (7.2%)	2.56	0.74–8.92	0.14	27.46	3.99–188.7	<0.01
DM & SHTN	7 (8.4%)	1.12	0.32–3.90	0.85	0.60	0.07–5.42	0.65
SHTN	7 (8.4%)	1.20	0.35–4.15	0.77	3.40	0.53–21.89	0.20
NIL	56 (67.6%)	0.87	0.34–2.23	0.77	0.94	0.23–3.86	0.93
Others	7 (8.4%)	1			1		
Location							
Gastroesophageal Junction	18 (21.7%)	1.13	0.25–5.17	0.87	10.38	0.87–123.49	0.06
Lower–Thoracic	28 (33.7%)	1.28	0.30–5.54	0.74	10.43	0.86–126.96	0.07
Mid–Thoracic	34 (41.0%)	1.18	0.28–5.06	0.82	7.66	0.62–94.29	0.11
Upper–Thoracic	3 (3.6%)	1			1		
Histology							
Adenocarcinoma	6 (7.2%)	1.6	0.69–3.77	0.27	1.22	0.28–5.4	0.79
Squamous cell carcinoma	77 (92.8%)	1			1		
Grade							
Moderately Differentiated	57 (68.7%)	0.99	0.55–1.77	0.96	0.49	0.18–1.36	0.17
Poorly Differentiated	2 (2.4%)	1.03	0.14–7.87	0.97	0.07	0.00–1.48	0.09
Well Differentiated	24 (28.9%)	1			1		
T–Stage							
T2	5 (6.0%)	0.21	0.05–0.95	0.04	1.50	0.15–14.99	0.73
T3	50 (60.2%)	0.50	0.25–0.99	0.05	1.65	0.56–4.89	0.37

T4A	12 (14.5%)	0.79	0.34–1.84	0.58	3.49	0.7–17.29	0.13
T4B	16 (19.3%)	1			1		
N–Stage							
0	32 (38.7%)	0.22	0.10–0.46	<0.01	0.06	0.01–0.44	0.01
1	35 (42.2%)	0.73	0.40–1.47	0.44	0.58	0.21–1.64	0.31
2	16 (19.3%)	1			1		
Stage Group							
II	26 (31.4%)	0.25	0.11–0.52	<0.01			
III	29 (34.9%)	0.94	0.52–1.62	0.82			
IVA	28 (33.7%)	1					
Surgery							
No	42 (50.6%)	3.02	1.71–5.33	<0.01	4.17	1.57–11.09	<0.01
Yes	41 (49.4%)	1			1		
Serum Haemoglobin							
<10 g/dL (Anaemia)	43 (51.8%)	2.51	1.44–4.38	<0.01	0.71	0.31–1.61	0.41
≥10 g/dL (Non–anaemic)	40 (48.2%)	1			1		
Serum Albumin							
High (≥3.5 g/dL)	46 (55.4%)	0.52	0.30–0.88	0.02	0.48	0.2–1.17	0.10
Low (<3.5 g/dL)	37 (44.6%)	1			1		
Systemic Immune Index (SII)							
High SII	64 (77.1%)	0.80	0.44–1.44	0.45	0.34	0.09–1.21	0.10
Low SII	19 (22.9%)	1			1		
Neutrophil Lymphocyte Ratio (NLR)							
High NLR	56 (67.5%)	1.12	0.64–1.97	0.69	1.27	0.29–5.61	0.76
Low NLR	27 (32.5%)	1			1		
Platelet Albumin Ratio (PAR)							
High PAR	48 (57.8%)	1.30	0.76–2.23	0.34	3.22	1.35–7.66	0.01
Low PAR	35 (42.2%)	1			1		
Platelet Lymphocyte Ratio (PLR)							
High PLR	31 (37.3%)	0.84	0.48–1.50	0.56	1.24	0.46–3.33	0.66
Low PLR	52 (62.7%)	1			1		

Table 2: Univariate & Multivariate analysis of association of variables with overall survival in oesophageal cancer patients who underwent neoadjuvant chemoradiation

ECOG – Eastern Cooperative Oncology Group; DM – Diabetes Mellitus; SHTN – Systemic Hypertension; SII – Systemic Immune Index; NLR – Neutrophil Lymphocyte Ratio, PAR – Platelet Albumin Ratio, PLR – Platelet Lymphocyte Ratio

Variable	N (%)	Pathologic Response		
		Non–complete Response (20)	Complete Response (21)	p–value
Age				
<65 years	34 (82.9%)	15 (75%)	19 (90%)	0.29
≥65 years	7 (17.1%)	5 (25%)	2 (10%)	
Sex				
Female	26 (63.4%)	6 (30%)	20 (95%)	<0.01
Male	15 (36.6%)	14 (70%)	1 (5%)	
ECOG Performance Status				
1	23 (56.1%)	10 (50%)	13 (62%)	0.70
2	15 (36.6%)	8 (40%)	7 (33%)	
3	3 (7.3%)	2 (10%)	1 (5%)	
Smoking				
No	31 (75.6%)	13 (65%)	18 (86%)	0.10
Yes	10 (24.4%)	7 (35%)	3 (14%)	
Alcohol intake				
No	27 (65.9%)	8 (40%)	19 (90%)	<0.01
Yes	14 (34.1%)	12 (60%)	2 (10%)	
Comorbidities				
DM	2 (4.9%)	0 (0%)	2 (10%)	0.79
DM & SHTN	5 (12.2%)	3 (15%)	2 (10%)	
SHTN	3 (7.3%)	2 (10%)	1 (5%)	
NIL	28 (68.3%)	13 (65%)	15 (71%)	
Others	3 (7.3%)	2 (10%)	1 (5%)	
Location				
Gastroesophageal Junction	7 (17.1%)	3 (15%)	4 (19%)	0.33
Lower–Thoracic	18 (43.9%)	11 (55%)	7 (33%)	
Mid–Thoracic	14 (34.1%)	5 (25%)	9 (43%)	
Upper–Thoracic	2 (4.9%)	1 (5%)	1 (5%)	
Histology				
Adenocarcinoma	5 (12.2%)	5 (25%)	0 (0%)	<0.01
Squamous cell carcinoma	36 (87.8%)	15 (75%)	21 (100%)	
Grade				
Moderately Differentiated	29 (70.7%)	15 (75%)	14 (67%)	0.67
Poorly Differentiated	0 (0%)	0 (0%)	0 (0%)	
Well Differentiated	12 (29.3%)	5 (25%)	7 (33%)	
T–Stage				
T2	4 (9.8%)	1 (5%)	3 (14%)	0.14
T3	26 (63.4%)	11 (55%)	15 (71%)	
T4A	5 (12.2%)	5 (25%)	0 (0%)	
T4B	6 (14.6%)	3 (15%)	3 (14%)	

N–Stage				
0	19 (46.3%)	7 (35%)	12 (57%)	0.20
1	17 (41.5%)	9 (45%)	8 (38%)	
2	5 (12.2%)	4 (20%)	1 (5%)	
Stage Group				
II	16 (39.0%)	5 (25%)	11 (52%)	0.13
III	14 (34.1%)	7 (35%)	7 (33%)	
IVA	11 (26.8%)	8 (40%)	3 (14%)	
Serum Haemoglobin				
<10 g/dL (Anaemia)	17 (41.5%)	10 (50%)	7 (33%)	0.10
≥10 g/dL (Non–anaemic)	24 (58.5%)	10 (50%)	14 (67%)	
Serum Albumin				
High (≥3.5 g/dL)	25 (61.0%)	12 (60%)	13 (62%)	0.60
Low (<3.5 g/dL)	16 (39.0%)	8 (40%)	8 (38%)	
Systemic Immune Index (SII)				
High SII	32 (78.0%)	15 (75%)	17 (81%)	0.88
Low SII	9 (22.0%)	5 (25%)	4 (19%)	
Neutrophil Lymphocyte Ratio (NLR)				
High NLR	26 (63.4%)	11 (55%)	15 (71%)	0.39
Low NLR	15 (36.6%)	9 (45%)	6 (29%)	
Platelet Albumin Ratio (PAR)				
High PAR	22 (53.7%)	10 (50%)	12 (57%)	0.67
Low PAR	19 (46.3%)	10 (50%)	9 (43%)	
Platelet Lymphocyte Ratio (PLR)				
High PLR	15 (36.6%)	3 (15%)	12 (57%)	0.02
Low PLR	26 (63.4%)	17 (85%)	9 (43%)	

Table 3: Chi–square analysis for association of variables with pathologic response in the subgroup of oesophageal cancer patients (N=41) who underwent surgical resection after Neoadjuvant Chemoradiation

ECOG – Eastern Cooperative Oncology Group; DM – Diabetes Mellitus; SHTN – Systemic Hypertension; SII – Systemic Immune Index; NLR – Neutrophil Lymphocyte Ratio, PAR – Platelet Albumin Ratio, PLR – Platelet Lymphocyte Ratio

chemoradiation. The trial reported that pretreatment ANS was significantly associated with NCRT safety profiles, CCRT completion rate, and survival outcome in patients with oesophageal cancer with excellent performance compared to PNI and NLR.[15]

The results of our study indicate that several biomarkers, including high Platelet–to–Lymphocyte Ratio (PLR), low Neutrophil–to–Lymphocyte Ratio (NLR), low Platelet–to–Albumin Ratio (PAR), and high Systemic Immune–Inflammation Index (SII), exhibited a correlation trend with improved Overall Survival (OS) among the study population. Our findings are consistent with the study by Hsueh et al., which proved the association of pretreatment albumin and neutrophil–lymphocyte ratio (NLR) score with outcomes in patients with oesophageal cancer receiving neoadjuvant chemoradiation. These results collectively suggest that biomarkers related to inflammation, immune response, and nutritional status may serve as valuable prognostic indicators and potentially guide treatment decisions in patients with oesophageal cancer undergoing neoadjuvant chemoradiation.

In 2022, Aoyama et al. evaluated the clinical impact of the preoperative platelet–to–albumin ratio (PAR) in 168 resectable oesophageal cancer patients who received

curative treatment. There was a significant difference in OS (p=0.005), favouring the low–PAR (<80×10^3) group. [16] Conversely, a study by Huang et al. in 2022 reviewed 470 patients with oesophageal cancer who underwent definitive radiotherapy with or without chemotherapy. Patients with high PAR were associated with poorer OS and PFS than patients with low PAR. [11] In our study, notably, a high Platelet Albumin Ratio (PAR) was associated with lower overall survival rates, suggesting its potential utility as a prognostic marker in oesophageal cancer. This finding aligns with previous research like Aoyama et al., which also found a correlation between low PAR and improved survival, highlighting the role of PAR as an independent predictor of survival outcomes in oesophageal cancer.

Our study identified several haematological indices as potential prognostic factors in predicting clinical outcomes. The underlying mechanisms linking elevated PAR to poorer prognosis warrant further investigation but may involve inflammatory processes and tumour progression.

While our study provides valuable insights into the prognostic significance of haematological indices in oesophageal cancer, several limitations should be acknowledged. Firstly, the retrospective nature of the study introduces inherent biases and limits the generalizability of findings. Additionally, the relatively small sample size may have influenced the statistical power to detect significant associations, particularly for certain haematological indices. Moreover, the study's single–center design may limit the extrapolation of findings to broader patient populations.

Future research should focus on validating our findings in larger, multicenter cohorts to enhance generalizability and robustness. Prospective studies are warranted to elucidate the underlying biological mechanisms linking haematological indices to oesophageal cancer prognosis. Furthermore, incorporating multimodal biomarker panels may enhance predictive accuracy and facilitate personalized treatment approaches in oesophageal cancer.

Conclusion

In conclusion, our study highlights the potential utility of haematological indices as prognostic factors in locally advanced oesophageal cancer patients undergoing neoadjuvant chemoradiation. Elevated Platelet Albumin Ratio (PAR) and anaemia were associated with poorer survival outcomes, while high serum albumin levels were indicative of a better prognosis. These findings underscore the importance of incorporating readily available haematological parameters into clinical decision–making to optimize risk stratification and treatment planning in oesophageal cancer. Further research is warranted to validate these findings and elucidate underlying biological mechanisms, with the ultimate goal of improving outcomes for oesophageal cancer patients.

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