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Original Article

Investigating the Prognostic Significance of Immune-Nutritional Indices in Esophageal Cancer Patients Following Esophagectomy

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ABSTRACT

Background: Esophageal cancer remains one of the most challenging malignancies to treat, with survival rates significantly influenced by various hematological and nutritional markers. Understanding these markers is critical in optimizing treatment approaches and improving patient outcomes.

Objective: This study aimed to investigate the prognostic significance of several markers, including Mean Corpuscular Volume (MCV), Red Cell Distribution Width (RDW), Mean Platelet Volume (MPV), C-Reactive Protein (CRP), Albumin, Total Lymphocyte Count (TLC), CRP Albumin ratio (CAR), and the Prognostic Nutritional Index (PNI), in patients with esophageal cancer undergoing esophagectomy.

Methods: A prospective observational study was conducted involving 43 patients diagnosed with esophageal carcinoma at Dr. Ruth K.M. Pfau Civil Hospital Karachi. Data collection included patient demographics, tumor characteristics, and laboratory results obtained from the Hospital Information and Management Security System (HIMSS). Statistical analysis was performed using SPSS version 25, with Kaplan–Meier survival curves and log-rank tests assessing the impact of hematological and nutritional markers on survival outcomes.

Results: The majority of patients presented with advanced disease (Stage III and IV) and tumor sizes ranging from 5 to 10 cm. Mean survival times and statistical comparisons were analyzed, but no significant differences in survival based on the markers were observed. For example, patients with low and high PNI values did not show significant differences in survival (Log-rank test p-value = 0.382).

Conclusion: The study did not demonstrate significant prognostic differences based on the evaluated hematological and nutritional markers. However, it highlights the importance of considering these factors in the overall management of esophageal cancer, suggesting further research with larger sample sizes and diverse populations is necessary.

Keywords: Esophageal Cancer, Prognostic Nutritional Index, Mean Corpuscular Volume, C-Reactive Protein, Esophagectomy, Oncology, Hematological Markers.

INTRODUCTION

Esophageal cancer ranks among the top ten most prevalent cancers worldwide, with a particularly high incidence and mortality rate in Pakistan, positioning it fourth in both categories nationally (1). Despite advances in therapeutic strategies, the prognosis for patients with esophageal cancer remains grim, primarily due to late-stage diagnosis, limited public awareness, and delays in referral to specialized centers. These systemic issues often restrict patients to palliative care, with survival rates further hampered by high recurrence rates and variable responses to chemoradiation (2, 3, 4). The traditional focus on tumor staging through the TNM classification system as the primary prognostic tool has been pivotal. However, it does not account for the significant variations in outcomes observed among patients with similar stages and treatment regimens, suggesting the influence of other factors (5).

Recent research has highlighted the significant role of the tumor's immune contexture, showing a strong correlation with both disease-free and overall survival, thus marking it as a critical prognostic factor (6). Concurrently, the impact of nutritional status on cancer progression has gained recognition, emphasizing the interaction between a patient's nutritional health and cancer outcomes.

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This connection suggests that a comprehensive approach to prognosis, which incorporates both immunological and nutritional factors, is essential (7).

To this end, various hematological and nutritional markers routinely assessed in clinical settings are being investigated for their prognostic significance. Mean Corpuscular Volume (MCV) has been identified as a potential marker for metastatic risk (8), while Red Cell Distribution Width (RDW) is indicative of anemia, inflammation, and nutritional deficits (9). Similarly, Mean Platelet Volume (MPV) highlights platelet activation, which plays a role in tumor progression (9). Total Lymphocyte Count (TLC) and serum albumin levels are indicative of a patient's immune status and nutritional health, respectively, with low albumin levels (hypoalbuminemia) signaling malnutrition (10, 11). Moreover, the CRP-albumin ratio has emerged as a significant prognostic indicator. Among these, the Prognostic Nutritional Index (PNI), which utilizes serum albumin levels and TLC, stands out as a robust immuno-nutritional marker that could significantly enhance prognostic assessments in esophageal cancer patients following esophagectomy (12). This shift towards integrating immune-nutritional indices in prognostic evaluations promises to refine therapeutic approaches and improve patient outcomes by providing a more nuanced understanding of individual prognostic landscapes.

MATERIAL AND METHODS

This research employed a prospective observational study design to explore the prognostic significance of various hematological and nutritional markers in patients with esophageal carcinoma. Conducted at the Surgical Unit 1: Department of Upper Gastrointestinal and Bariatric Surgery, Dr. Ruth K.M. Pfau Civil Hospital Karachi, the study began on 1st October 2022 and continued for one year. Participants included individuals diagnosed with esophageal carcinoma confirmed by biopsy. The study excluded patients with other ongoing cancer diagnoses, those with recurrent esophageal cancers, and those who were lost to follow-up or lacked complete staging investigations.

Patients eligible for the study were enrolled using a non-probability consecutive sampling method as they presented to the surgical unit during the one-year period following approval from the Institutional Review Board (IRB) at Dow University of Health Sciences (DUHS). Ethical approval was granted under the reference IRB-2673/DUHS/Approval/2022/1085 dated 26 October 2022, ensuring adherence to ethical standards, including those outlined in the Declaration of Helsinki.

Data collection involved recording detailed clinical information such as gender, age, addiction history, tumor site, type, histological grade, length, and clinical stage. This information was obtained through endoscopy, biopsy, computed tomography (CT) scans, and positron emission tomography (PET) scans. Preoperative laboratory data were accessed from the Hospital Information and Management Security System (HIMSS) to obtain results for the prognostic indices under investigation. Following the initiation of treatment, patients underwent regular follow-up, with appointments scheduled monthly for the first three months and subsequently every three months for a year. Overall survival was the primary endpoint, evaluated from the date of diagnosis to the date of last follow-up or recorded death.

Statistical analyses were performed using SPSS version 25. Descriptive statistics, including means, medians, frequencies, and proportions, were calculated and comparisons were made using Fisher's Exact test and Chi-square analysis. Survival probabilities were estimated using the Kaplan–Meier method, and differences in survival outcomes were assessed with the log-rank test. A p-value of less than 0.05 was considered statistically significant.

In accordance with ethical guidelines, prior to enrollment, informed written consent was obtained from each participant, ensuring they were fully aware of the study's nature, potential risks, and benefits. This consent process was designed to protect the participants' autonomy and adhere to the ethical standards prescribed by the IRB and international guidelines.

RESULTS

In our study, the clinical and hematological characteristics of 43 patients diagnosed with esophageal cancer were thoroughly evaluated to explore the prognostic significance of various markers. The mean age of patients was 43.74 ± 13.52 years, with no significant difference in age between those who were alive and those who had died during the study period (43.07 ± 12.71 vs. 44.88 ± 15.15, p = 0.678). The cohort predominantly consisted of female patients (58.1%) compared to males (41.9%), though the gender difference did not reach statistical significance in affecting survival outcomes (p = 0.084) (Table 1).

Analysis of addiction habits showed that the majority of patients (69.8%) did not have a history of addiction. There was no significant impact of addiction on survival rates, with both groups (addicted vs. non-addicted) showing similar survival patterns (p = 0.565). Tumor site distribution indicated that the lower thoracic region was the most commonly affected area (60.5%), followed by the mid-thoracic region (30.2%), and only a small fraction in the upper thoracic or mid and lower esophagus (4.7% each) (Table 1). Despite these differences, tumor site did not significantly affect patient outcomes (p = 0.605).

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Table 1: Characteristics and Survival in Esophageal Cancer Patients (n=43)

Characteristics	Total (n, %)	Alive (n, %)	Death (n, %)	p-value
Age (Mean±SD)	43.74±13.52	43.07±12.71	44.88±15.15	0.678*
Gender				0.084
Male	18 (41.9)	14 (51.9)	4 (25.0)	
Female	25 (58.1)	13 (48.1)	12 (75.0)	
Addiction				0.565
No	30 (69.8)	18 (66.7)	12 (75.0)	
Yes	13 (30.2)	9 (33.3)	4 (25.0)	
Tumor Site				0.605
Upper thoracic, 20 to 25cm	2 (4.7)	1 (3.7)	1 (6.3)	
Mid thoracic, 25 to 30cm	13 (30.2)	7 (25.9)	6 (37.5)	
Lower thoracic, 30 to 38cm	26 (60.5)	17 (63.0)	9 (56.3)	
Mid and lower esophagus	2 (4.7)	2 (7.4)	0 (0.0)	
Tumor Type				0.742
Squamous cell carcinoma	36 (83.7)	22 (81.5)	14 (87.5)	
Adenocarcinoma	5 (11.6)	3 (11.1)	2 (12.5)	
Undifferentiated	1 (2.3)	1 (3.7)	0 (0.0)	
Schwannoma	1 (2.3)	1 (3.7)	0 (0.0)	
Clinical Stage				0.019
II	9 (20.9)	9 (33.3)	0 (0.0)	
III	18 (41.9)	8 (29.6)	10 (62.5)	
IVA	16 (37.2)	10 (37.0)	6 (37.5)	
Histological Grade				0.396
Well differentiated	9 (20.9)	4 (14.8)	5 (31.3)	
Moderately differentiated	27 (62.8)	19 (70.4)	8 (50.0)	
Poorly differentiated	6 (14.0)	3 (11.1)	3 (18.8)	
None	1 (2.3)	1 (3.7)	0 (0.0)	
Tumor Length				0.756
<5 cm	16 (37.2)	11 (40.7)	5 (31.3)	
5-10 cm	23 (53.5)	14 (51.9)	9 (56.3)	
>10 cm	4 (9.3)	2 (7.4)	2 (12.5)	

Table 2: Laboratory Characteristics and Survival in Esophageal Cancer Patients (n=43)

Marker	Mean±SD (Total)	Mean±SD (Alive)	Mean±SD (Death)	p-value
MCV	82.90±8.54	83.69±8.52	81.58±8.69	0.439
RCDW	47.18±10.8	49.23±10.8	45.96±10.90	0.347
MPV	10.00±1.21	9.99±1.06	10.01±1.48	0.961
CRP	25.39±49.6	13.54±14.6	32.41±60.95	0.232
Albumin	3.53±0.57	3.62±0.59	3.40±0.53	0.225
TLC	6.94±3.39	6.88±3.83	7.03±2.61	0.892
PNI	38.26±17.0	38.06±19.3	38.58±12.97	0.924
CRP/Albumin (CAR)	8.04±16.40	10.21±20.15	4.39±5.11	0.782

The types of tumors observed were predominantly squamous cell carcinoma (83.7%), with a smaller representation of adenocarcinoma (11.6%) and very few cases of undifferentiated carcinomas or schwannomas (2.3% each). There was no significant variation in survival across these tumor types (p = 0.742). In terms of clinical staging, stages III (41.9%) and IVA (37.2%) were prevalent, with stage II comprising 20.9% of the cases. A notable finding was the significant difference in survival rates between different stages, with stage II patients having a 100% survival rate, which was significant (p = 0.019) (Table 1).

The histological grades ranged from well-differentiated to poorly differentiated, with the majority being moderately differentiated (62.8%). The histological differentiation did not show a significant correlation with survival outcomes (p = 0.396). Tumor length varied, with most tumors being between 5-10 cm (53.5%), but this factor did not significantly influence survival (p = 0.756).

Laboratory markers such as Mean Corpuscular Volume (MCV), Red Cell Distribution Width (RDW), Mean Platelet Volume (MPV), C-Reactive Protein (CRP), Albumin, Total Lymphocyte Count (TLC), Prognostic Nutritional Index (PNI), and CRP/Albumin ratio (CAR) were closely monitored. The MCV values ranged with a mean of 82.90 ± 8.54, but did not show a significant difference in survival analysis (p = 0.439) (Table 2). Similar non-significant results were observed for RDW, MPV, CRP, Albumin, TLC, PNI, and CAR, with their p-values demonstrating no significant impact on survival outcomes (Table 2).

The Kaplan-Meier survival plot provided (Figure 1) further illustrates the relationship between PNI levels and survival outcomes over the follow-up period of up to 50 months. Patients with a higher PNI (>43) showed a trend towards better survival compared to those with a lower PNI (≤43), although this was not statistically significant (Log-rank test p-value = 0.382). This indicates a potential prognostic value of PNI in esophageal cancer survival, warranting further investigation in larger cohort studies to substantiate these findings.

DISCUSSION

In our cohort of 43 patients, the study aimed to explore the prognostic value of several hematological and nutritional markers, including Mean Corpuscular Volume (MCV), Red Cell Distribution Width (RDW), Mean Platelet Volume (MPV), C-Reactive Protein (CRP), Albumin, Total Lymphocyte Count (TLC), CRP Albumin ratio (CAR), and the Prognostic Nutritional Index (PNI), for patients undergoing esophagectomy for esophageal cancer. The majority of these patients were diagnosed at advanced stages, primarily stages III and IV, and exhibited larger tumor sizes, ranging from 5 to 10 cm, highlighting the complexity and severity of the cases included in our study (Table-2).

Historically, MCV has been noted for its potential as an indicator of metastatic risk and survival in various cancers including colorectal, breast, liver, and esophageal cancers (8, 13-15). The prognostic relevance of MCV is particularly noteworthy as it has been linked not only to survival outcomes but also to the responsiveness to chemotherapy agents such as 5-Fluorouracil (5-FU) (13). Similarly, RDW has been associated with inflammation and malnutrition, which are significant for prognosis and overall patient management (16-22). Elevated RDW levels have been consistently linked to poorer survival across various cancers (18, 20). In addition, MPV and CAR have emerged as markers with potential prognostic significance in various malignancies, including esophageal cancer, indicating poor survival outcomes (23-27).

Nutritional status, assessed through parameters like the PNI, which is derived from serum albumin levels and lymphocyte counts, has been extensively documented as a significant prognostic factor across various cancers (12, 28-35). Despite the established importance of these indices in predicting patient outcomes, including overall survival, our study found that these markers did not show statistically significant differences in survival rates among patients with high and low PNI values, as illustrated in Figure 1, with a non-significant p-value of 0.382.

The absence of significant findings in our study could be attributed to several limitations. Firstly, the small sample size may have restricted our ability to detect significant differences. Additionally, the inherent heterogeneity of esophageal cancer, influenced by diverse demographics across different regions, may also contribute to the varied prognostic impacts observed in our study compared to others (4). Such variability underscores the complexity of reliably assessing prognostic markers in esophageal cancer.

CONCLUSION

Conclusively, while our investigation did not substantiate a strong prognostic influence of the evaluated markers, it contributes to the body of knowledge by offering insights that may explain variations seen in other studies. The findings emphasize the nuanced nature of esophageal cancer prognosis and highlight the potential influence of tumor heterogeneity on research outcomes. This study underscores the necessity for further research with larger cohorts and more diverse populations to refine our understanding of prognostic factors in esophageal cancer. Such studies would benefit from addressing these limitations by including a broader array of demographic and clinical variables to better understand the interplay between clinical outcomes and prognostic markers.

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