

# Prognostic value of C-reactive protein-to-albumin ratio and inflammatory markers in esophageal cancer patients treated with chemoradiotherapy

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## Abstract

**Aim:** This retrospective research was aimed to evaluate disease-free survival using inflammatory markers in esophageal cancer patients who received chemoradiotherapy.

**Material and methods:** A total of 67 patients who received standard curative chemoradiotherapy for esophageal cancer were included in the study between 2011-2018. The patient, treatment characteristics, and pretreatment inflammatory markers were obtained from the patient's file.

**Results:** Median follow up time was 18 months (6-72 months). ROC curve analyses showed the C-Reactive Protein/Albumin cut-off value 0.9 for disease-free survival (AUC: 78.8%; sensitivity: 85%; specificity: 67.5%). 2-year disease free survival for C-Reactive Protein/Albumin  $\geq 0.9$  and C-Reactive Protein/Albumin  $< 0.9$  were 45.7% and 78%, respectively ( $P=0.035$ ). The radiation doses  $\geq 50$ Gy (versus  $< 50$ Gy,  $p=0.027$ ) and C-Reactive Protein/Albumin ratio  $< 0.9$  (versus  $\geq 0.9$ ,  $p=0.005$ ) appeared significant associates of better disease-free survival in univariate analyses, but the age, gender, stage, localization, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were no statistically significant ( $p>0.005$ ). On the multivariate logistic analysis, our results showed that C-Reactive Protein/Albumin  $< 0.9$  [hazard ratio 1.29; 95% confidence interval, 1.336-2.946;  $P=0.014$ ]; and radiation dose  $\geq 50$  Gy (hazard ratio 0.91; 95% confidence interval, 1.229-4.997;  $P=0.027$ ) independent prognostic indicators.

**Conclusion:** Our study found that the C-Reactive Protein/Albumin ratio is easy to apply and maybe a promising marker to predict disease-free survival in esophageal cancer patients who received chemoradiotherapy.

**Key words:** esophageal neoplasms, radiochemotherapy, C-reactive protein to albumin ratio

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## Introduction

Esophageal cancer is constituting 1.5-2% of all cancers and 5-7% of digestive system cancers. It is one of the cancer with the highest mortality despite surgery, chemotherapy, and radiotherapy treatments worldwide [1-2]. Esophageal cancer patients are usually at an advanced stage at the time of diagnosis, and early diagnosis is rare. Preoperative chemoradiotherapy (CRT) and CRT alone (trimodality therapy and bimodality therapy) are the standard treatment for locally advanced patients.

Despite novel treatment modalities, treatment responses and survival are still different in locally advanced esophagus cancer patients. For this reason, many studies try to predict the treatment response and survival more accurately by adding to the staging system in biochemical and hematological parameters [3-4]. These parameters that can be easily measured in the pre-treatment blood test and highly practical are most frequently used for survival estimation.

Many studies have shown that systemic inflammation is associated with progression and dissemination in some malignancies [5-8]. Today, many researchers start using inflammatory values in the blood as a biomarker for predicting prognosis and survival. The most well-known among them neutrophil-to-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), C-reactive protein albumin (CRP/Alb) ratio, and the Glasgow prognostic score (GPS) or the modified GPS (mGPS). These indicators have been widely researched and CAR has started to be used as a new prognostic biomarker compared to NLR and PLR. These biomarkers are generally used in studies to evaluate overall survival (OS) and treatment response. They have not been used before to assess disease-free survival (DFS) in patients with esophageal cancer receiving chemoradiotherapy. Therefore, our research was carried out to investigate the prognostic value of the CAR, NLR, and PLR in esophageal cancer patients who managed with definitive CRT, moreover association between CAR and other clinicopathological factors.

## Material and methods

### Patients characteristics

In this retrospective study, we evaluated 67 patients with a diagnosed esophageal cancer who were treated with CRT in from January 2011 to December 2018. All eligible patients underwent thoracic computed tomography (CT) and 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT to disease staging and detect probable distant metastasis. The criteria to be included in the study are the following: (1) histologically-proven esophageal cancer; (2) patients who were received CRT; (3) patient who had pretreatment hematological parameters and (4) Eastern Cooperative Oncology Group (ECOG) performance status 0-1. Patients had distant metastases or inflammatory conditions (such as ulcerative colitis, Crohn's) were excluded. While all related laboratory and pathology results were obtained from hospital data, data related to treatment follow-up were obtained from clinical files. After a thorough explanation of the study, the study was approved by the local ethics committee of our hospital, and informed consent was obtained from all patients (approval number: 2020-2233).

### Chemoradiotherapy data

All patients received CRT. All patients received external beam RT in 1.8 to 2.0 Gy daily fractions with 18 MV photon, five days a week. A total dose of radiotherapy was 40-50.4 Gy. 21 patients received neoadjuvant CRT after then underwent surgery. Radiation treatment was carried out using field-in field IMRT and 3-Dimension conformal technique. Gross tumor volume (GTV) included the primary tumor and involved regional lymph nodes. The clinical target volume (CTV) was defined as a primary tumor plus a 3-cm expansion superiorly and inferiorly and 1-cm radial margin.

The planning treatment volume (PTV) was the CTV with the addition of a 0.5-1 cm margin.

Chemotherapy protocol administered by the Medical Oncology Clinic. Concurrent chemotherapy protocols varied according to histopathology (Cisplatin 75mg/m<sup>2</sup>, 5-Fluorouracil 1200 mgr/m<sup>2</sup> day 1-4, infusion; Paclitaxel 50mg/m<sup>2</sup>, Carboplatin AUC 2/ weekly; 5-Fluorouracil 400 mgr/m<sup>2</sup>, Leucovorin 40 mgr/m<sup>2</sup> day 1-5).

### Hematological parameters and follow-up

In the blood sample taken one week before CRT treatment

and albumin count, C-reactive protein, lymphocyte count, neutrophil count, and platelet count were measured. Then, CRP/Alb ratio neutrophil/lymphocyte ratio and the platelet/lymphocyte ratio were calculated by division of the absolute values.

Treatment toxicity was evaluated with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [9]. During CRT, patients were assessed at least once a week with a clinical examination, and their blood counts and biochemistries were analyzed. The nutrition of the patients before and during the treatment is provided and followed by the nutrition team in our hospital. The treatment responses were evaluated using computed tomography (CT) scans and endoscopy one month later. Subsequent controls included physical examinations and radiological imaging every three months. Follow-ups were conducted every three months for the first two years and every six months for years 3 through 5. During the follow-up period, F-18 FDG PET/CT examination was requested in patients with suspected local or regional recurrence.

### Statistical analysis

Our primary endpoint was disease-free survival (DFS: Disease-free survival (DFS) was the period between the date of diagnosis and the time of any type of disease progression/ local tumor recurrence/metastasis) and outcome of the patients high versus low pretreatment CAR, NLR, and PLR value. Nominal and ordinal data were described with frequency analysis, whereas scale parameters were described with mean and standard deviations. Receiver operating characteristic (ROC) curves were also plotted to verify the accuracy of CAR, NLR, and PLR. Kaplan Meier analysis was used for disease-free survival analysis; the log-rank test was used for survival comparisons. The multivariate Cox proportional hazard model was used to evaluate interactions between these biomarkers, prognostic variable, and survival outcome. All analyses were performed at a 95% confidence level with a 0.05 significance level at SPSS 17.0 (SPSS Inc., Chicago, IL, USA) for the windows program.

### Results

In the study, which included a total of 67 patients. Some baseline parameters of patients and treatment features are given in Table 1. The median age was 56 (range 39-82) years for the entire study. The male patients were 27 (38%), female patients were 40 (56%). All of them had squamous cell carcinoma pathology. According to the 7th AJCC TNM staging system [3], 28 (41.7%) patients were stage IIB, 32 (47.7%) were stage IIIA, 1 (1.4%) were stage IIIB and 7 (9.9%) were stage IIIC. The biopsy was performed in 46 patients (64.8%) and received definitive chemoradiotherapy. The site of the tumor was located in the cervical region in 12 patients (16.9%) in the middle region in 20 patients (28.2%) and in the distal region in 35 patients (49.3%). CRT was applied to all patients. RT doses are generally preferred as 50.4 Gy (87.3%). Five patients received 41.4-45 Gy (12.7 %). Patients were re-evaluated by endoscopy and tomography 3 weeks after chemoradiotherapy. Patients with complete responses were followed up, while patients with partial responses were presented to the council for surgery. Twenty-one patients were operated on. Of these, 10 (14.5%) were performed total esophagectomy, while 11 (15.5%) patients were distal esophagectomy.

Patient follow-up time was 18.3 months (range 6-72), 35 (52.2%) patients were still alive and 32 (47.7%) patients

Table 1

Patient and treatment characteristics

Parameter	No of patients	%
<b>Sex</b>		
Female	27	38
Male	40	56
<b>Age,Median±Sd</b>	56±10,14(39-82)	-
<b>Stage</b>		
2B	17	23,9
3A	42	59,2
3B	1	1,4
3C	7	9,9
<b>Operation type</b>		
Esophagectomy	10	14,1
Distal esophagectomy	11	15,5
Biopsy	46	64,8
<b>Localization</b>		
Cervical	12	16,9
Middle	20	28,2
Distal	35	49,3
<b>Radiotherapy doses</b>		
50,4 Gy	62	87,3
45 Gy	4	5,6
41,4 Gy	1	1,4
<b>Concurrent chemotherapy regim</b>		
Cisplatin+5-FU	43	60,6
FUFA	18	25,4
Carboplatin+Taxol	6	8,5
<b>Metastasis</b>		
Lung	5	7,0
Liver	2	2,8
Bone	3	4,2
Local Recurrence	11	14,5
<b>Follow-up(month), Median±Sd</b>	18±13,67(6-72)	-
<b>Exitus</b>	32	45,1

died. during their follow-up. Local recurrence was observed in 11 patients (16.4%), distant metastasis in the lung in 5 patients (7%), the liver in 2 patients (2.3%), and bone in 3 patients (4.2%). The median 1-year and 3-year DFS time was 23.4, 7.2 months, 1-year, and a 3-year DFS ratio was 75% and 49%, respectively.

ROC curves were constructed for DFS. The optimal NLR, PLR, and CAR cut-off values for DFS were 3.2, 146, and 0.91, respectively. In addition to AUC was 0.617 (95% CI 0.460–0.774,  $P=0.152$ ) for NLR, 0.541 (95% CI 0.367–0.718,  $P=0.613$ ) for PLR and 0.788 (95% CI 0.675–0.854,  $P=0.010$ ) for CAR ratio, indicating that CAR ratio was superior to NLR and PLR as a predictive factor for DFS in patients with esophageal cancer (Figure 1).

Figure 1 -ROC curve analysis NLR, PLR and CAR for DFS

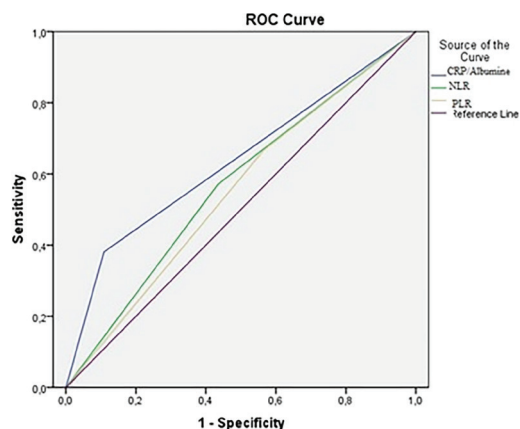


Figure 2A -Kaplan-Meier curve for NLR

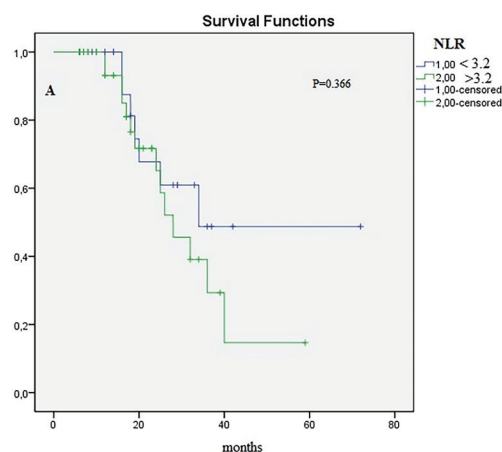


Figure 2B.-Kaplan-Meier curve for PLR

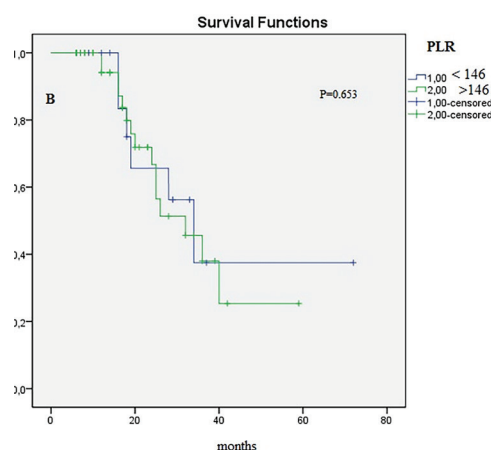
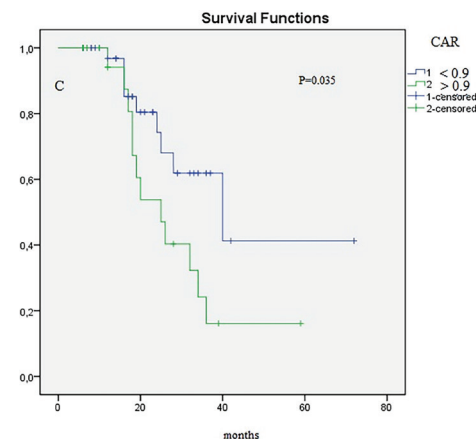


Figure 2C-Kaplan-Meier curve for CAR



The Kaplan-Meier curves CAR, NLR and PLR value evaluated. The 2-year DFS rates for CAR  $\geq 0.9$  and CAR  $< 0.9$  were 45.7% and 78%, respectively (Figure 2A,  $P=0.035$ ). Additionally the 2-year DFS rates for PLR  $\geq 146$  and PLR  $< 146$  were 74.7% and 85 %, respectively (Figure 2B,  $P=0.653$ ). Similarly, the 2-year DFS rates for NLR  $\geq 3.2$ , compared with NLR  $< 3.2$ , were 80% and 82%, respectively (Figure 2C,  $P=0.366$ ).

CAR of values and clinicopathological factors are compared in Table 2. Our study showed that higher radiation doses ( $\geq 50$ Gy vs.  $< 50$ Gy) and lower CAR ( $\geq 0.9$  vs.  $< 0.9$ ), value were associated with favorable DFS using the univariate analysis (Table 2). In addition, multivariate analysis discovered that CAR [hazard ratio (HR) 1.29; 95% confidence interval [CI], 1.336-2.946;  $P=0.014$ ]; and radiation dose (HR 0.91; 95% CI, 1.229-4.997;  $P=0.027$ ) were independent risk factors for DFS (Table 3).

Table 2

Comparison of CAR value.

Characteristics	All patients (N=67)	CAR<0.9 (N=54)	CAR≥0.9 (N=13)	P Value
Median age, years (range)	56 (39-82)	53 (40-75)	58 (39-74)	0,264
Age group (N;%)				
<50 years	32 (%47.7)	23 (%42.6)	9 (%69)	0,526
≥50 years	35 (%52.2)	31 (%57.4)	4 (%30)	
Gender (N;%)				
Female	27 (%40.2)	27 (%47.8)	0	0,058
Male	40 (%59.7)	27 (%47.8)	13 (%100)	
Stage (N;%)				
II	28 (%26.8)	22 (%22.2)	6 (%46.1)	0,958
III	39 (%73,1)	32 (%61.1)	7 (%53.8)	
Localization (N;%)				
Cervical+Thoracal	32 (%47.7)	24 (%44.4)	8 (%61.5)	0,192
Distal	35 (%52.2)	21 (%38.8)	5(%38.4)	
Radiation Doses(N;%)				
<50 Gy	5 (%7.5)	2 (%2)	4 (%30.7)	0.001
≥50 Gy	62 (%92.5)	52 (%98)	9 (% 69.2)	

Abbreviations:OS: overall survival; HR: hazard ratio; C/T: cervical/ thoracal; D:distal

## Discussion

Our results of 67 esophageal cancer patients treated with CRT demonstrated that pretreatment CAR ratio was related with significantly shorter DFS times. Moreover, we discovered that pretreatment  $\geq 0.9$  CAR ratio was poorer survival outcomes.

Firstly, the relationship between tumor and inflammation was investigated in the 1900s [10]. Inflammation has been shown to suppress apoptosis, improve angiogenesis, and contribute to tumor growth and metastasis. Then many studies have been done on this subject over the years [11-12]. Neutrophils, monocytes, lymphocytes, platelets, C-reactive protein, and cytokines are the best known. Novel indicators have been created by combining these cells, which show inflammation in the blood. CAR, GPS, mGPS, NLR, PLR, and SIRI (systemic inflammation response index) are used prognostic factors in various cancer [13-14]. Many articles showed that CAR better prognostic factor than GPS and mGPS [15-16]. When we reviewed the studies, we found that while these indicators were generally used to predict overall survival in patients receiving chemoradiotherapy for esophageal cancer, they were not used to predict relapse/metastasis. As a result of this information, we conducted this retrospective study.

The best treatment option for locally advanced esophageal cancer is still controversial. Radical CRT followed by surgery (trimodality) and postoperative RT/CRT being the treatment options. In 2002, INT 0123 trial [17], comparison high-dose radiotherapy (64.8 Gy) versus standard-dose (50.4 Gy) radiotherapy. They found that the standart radiation dose for patients treated with concurrent chemotherapy is 50.4 Gy. NCCN guidelines recommend that perioperative radiation dose 41.4-50.4 Gy and definitive radiotherapy dose 50-50.4 G. In the present study, we found the prognostic value of  $\geq 50$  Gy radiation doses. This discrepancy seems to be related to few patients received <50 Gy (5 patient) and 12 cervical esophagus patients received 64 Gy radiotherapy dose.

However, the most important finding of our study was the show of prognostic prediction of pretreatment CAR value on DFS of esophageal patients who received CRT. Shau et al. [18], Feng et al. [19], Liu et al. [20] used nomograms to estimate overall survival using various inflammatory markers and pathological parameters (NLR, GPS, mGPS, CAR and histological grade, T stage, modified N stage, tumor length(cm)). While NLR and PLR values were found as prognostic factors in some studies, CAR

Table 3

Outcomes of univariate and multivariate analysis for DFS

Factor	Univariate p value	Multivariate p value	HR
Aged group (<50 vs.≥50)	0.132	–	
Gender (female vs. male)	0.420	–	
Stage ( II vs.III)	0.244	–	
Tumor location(C/T vs.D)	0.277	–	
Radiation doses (<50 Gy vs.≥50Gy)	0.011	0.027	0.91
CAR (<0.9 vs. ≥0.9)	0.005	0.014	1.29
NLR ( <3.2 vs. ≥ 3.2)	0.285	–	–
PLR (< 146 vs. ≥146 )	0.810	–	–

and NLR values were found to be significant in some studies on multivariate analysis. It is not clear which inflammatory markers are more important in patients with esophageal cancer. In our study, a cutoff value of 0.9 and a value of <0.9 for CAR were shown to be associated with disease-free survival.

In the meta-analysis [21] published in 2019, 11 studies were examined and the relationship between inflammatory markers and long-term survival was examined. Higher NLR and CAR were found to be associated with lower overall survival (HR 1.47, 95% CI=1.32-1.63,  $P<.001$ ) and HR 1.88, 95% CI=1.28-2.77,  $P<.001$ , respectively).But, PLR was not found significant. The cut-off value for CAR in the studies was between 0.085 and 0.5 (median, 0.22). Our study showed that a cut-off value of 0.9 and a value of >0.9 for CAR were associated with disease-free survival. The 2-year disease-free survival was 45.7% in patients with  $\geq 0.9$  CAR, while the 2-year disease-free survival was 78% in patients with <0.9 CAR ( $P=0.035$ ). On the multivariate logistic analysis, our results showed that CAR [hazard ratio (HR) 1.29; 95% confidence interval [CI], 1.336-2.946;  $P=0.014$ ]; and radiation dose (HR 0.91; 95% CI, 1.229-4.997;  $P=0.027$ ) were independent risk factors for disease-free survival. The fact that both the close CAR cut-off value and the PLR value are insignificant reveals that our results are similar to the meta-analysis.

In our study, NLR and PLR were not found as independent prognostic factors in multivariate analysis. However, radiation doses and CAR were independent prognostic factors for DFS. It may be more accurate to create a nomogram with CAR and other pathological factors for performing a DFS analysis.

The limitations of our study are as follows: First, inflammatory parameters were limited. Interleukin-1,



interleukin-6, and tumor necrosis factor- $\alpha$  were not evaluated. The second significant limitation is the cut-off value for CAR, NLR, and PLR. While some studies used median value as a cut-off value, some studies determined this value with ROC analysis. The lack of a standard value for the cut of value is a significant disadvantage for our reviews.

## Conclusion

According to the results of the study, CAR can use an inflammation-based prognostic factor for esophageal cancer patients who received CRT to predict recurrence/metastasis. In the treatment of esophageal cancer, curative CRT decisions should be kept in the inflammatory markers together with the TNM system. In the future, more accurate and reliable survival nomograms will be created with various inflammatory biomarkers, TNM staging, genome sequencing, and RNA technologies.

## Abbreviations

RT: Radiotherapy

CRT: Concurrent radiotherapy

CT: Computerized tomography

F-18 FDG PET/CT: 8-Fluorodeoxyglucose Positron

Emission Tomography

PTV: The planning target volume

CTV: Clinical target volume

GTV: Gross tumor volume

CAR: CRP/Alb ratio

NLR: Neutrophil-to-lymphocyte ratio

PLR: Platelet-lymphocyte ratio

GPS: Glasgow prognostic score

mGPS: Modified Glasgow prognostic score

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**Authors contributions:** Berrin Inanc designed the research, Berrin Inanc and Ozlem Mermut performed the research, Berrin Inanc contributed analytic tools and Berrin Inanc wrote the paper.

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