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The crucial role of high C-reactive protein interval and Glasgow prognostic score for predicting prognosis in esophageal cancer patients undergoing chemoradiotherapy

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ABSTRACT

Background: Our aim was to draw attention to the dominant role of C-reactive protein (CRP) on prognosis by examining the effect of the high CRP interval, Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS) and CAR (CRP to albumin ratio) in patients undergoing chemoradiotherapy (CRT). ***Materials and Methods***: 85 patients, with the diagnosis of esophageal cancer and who were scheduled for neoadjuvant or definitive CRT, were included in the study. CRP levels of each patient during the follow-up period were determined separately, and the total number of days for which serum CRP levels were > 5 mg/L was expressed as "days when CRP>5". The effects of the GPS, mGPS, CAR, and''days when CRP>5'' on the prognosis and survival of these patients with esophageal cancer were analyzed in this retrospective study. ***Results:*** In the survival analysis, CAR (p=0.007), GPS (p<0.001), mGPS (p<0.001) and ''days when CRP > 5'' (p=0.002) were determined to be independent predictive factors for mortality. In the long-rank test results, it was observed that the patients with GPS 0 and mGPS 0 had longer overall survival than the others (p < 0.001). In addition, with the increase in ''days when CRP>5'', disease recurrence also increased significantly (p = 0.01). Similarly, in the ROC analysis, the area under the curve (AUC) was significant for the ''days when CRP>5'' (AUC: 0.956, 95% CI: 0.915–0.998; P < 0.001). ***Conclusions:*** In patients diagnosed with esophageal cancer, beginning from the pretreatment period and throughout the follow-up period, serum CRP levels are an independent factor in predicting survival, both in terms of the number of days it is high and in terms of the scoring systems it is associated with.

INTRODUCTION

Preoperative chemoradiotherapy (CRT) compared to surgery alone resulted in higher overall survival (OS), disease-free survival (DFS), pathologic complete response (pCR), and R0 resection rates in locally advanced esophageal cancers [1]. However, despite the advances in technical developments and current trimodal treatment approaches, esophageal cancer still results in high morbidity and mortality and is among the top ten causes of cancer-related death [2].Therefore, factors affecting the survival of patients with esophageal cancer continue to be investigated with respect to clinical, biochemical, molecular, and immunohistochemical profiles.

The role of acute-phase reactants is increasingly emphasized in the recurrence and progression of patients who experience rapid weight loss throughout treatment. In this respect, the predictive value of the Glasgow Prognostic Score (GPS), which is based on serum C-reactive protein (CRP) and albumin values, and of the CAR, which is based on the CRP and albumin ratio, is under investigation for many solid cancer types [3-6].

Albumin, synthesized by the liver, is the most abundant protein in the blood and plays an essential role in the transport of essential nutrients and hormones. Increased vascular permeability is associated with inflammation, sepsis, chronic diseases, organ failure, trauma, and carcinogenesis, leading to hypoalbuminemia [7]. CRP has a wide range of biological properties and functions and is an inflammation marker. It has been detected at measurably high levels in many other pathological conditions with tissue damage.

Most infections, major traumas, inflammatory diseases, and malignancies are associated with high CRP levels. In many types of cancer, an increase in serum CRP levels due to systemic inflammation, nutritional disorder, or tumor secretion may be associated with a poor prognosis independent of all other factors. In some studies, the good prognostic effect of low CRP levels, even independent of albumin, contributed to developing the modified

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Glasgow Prognostic Score (mGPS) [8].Similarly, many studies support that CRP plays an active role in survival independently of all other markers [9-10]. Inspired by this effect of CRP on prognosis, in this study, the effect of "high CRP interval" on survival was tried to be investigated throughout the entire disease course.

MATERIALS AND METHODS

Patient selection

The study protocol was approved by the Ethics Committee of Istanbul Prof. Dr. Cemil Taşcıoğlu City Hospital (04.04.2022, E-48670771-514.99). Additional informed consent was obtained from all patients for which identifying information is included in this article. Among the patients treated in our center between 2013 and 2021, with esophageal cancer diagnosis histopathologically confirmed as adenocarcinoma or squamous cell carcinoma (SCC), clinical stage 2–3, 85 patients who were scheduled for neoadjuvant or definitive CRT were included in the study. The staging of the patients was done with endoscopic examination, positron emission tomography and computed tomography (PET-CT), and the treatment decision was planned by a multidisciplinary team for each patient.

Patients with distant metastases or who could not receive chemotherapy initially were excluded from the study. CRP, albumin, CEA, and CA19.9 levels, as well as complete blood count parameters of all patients before and after CRT, were evaluated retrospectively. Neoadjuvant chemotherapy was administered as weekly paclitaxel (taxol, China) and carboplatin (Kocak,Turkey).

The Glasgow Prognostic Score was determined as follows: score 0 if serum CRP level is ≤10 mg/L and albumin level is ≥3.5 g/dL; score 1 if either CRP or albumin is at an abnormal level; score 2 based on the abnormal levels of both CRP and albumin.

The modified Glasgow Prognostic Score was determined as follows: score 0 when CRP levels were normal, (independent of albumin!) score 1 when only CRP levels were abnormal, and score 2 when both CRP and albumin levels were abnormal (table 1).CAR is the ratio of CRP (mg/L)/albumin (g/dL). In addition, the CRP levels of each patient before and after CRT were examined, and the total number of days when serum CRP levels were above ≥5 mg/L was expressed as "days when CRP > 5".

Simulation, volume definition, and radiotherapy technique

All patients underwent computed tomography (CT) simulation with a Philips Brilliance (Amsterdam, Switzerland) scanner in the supine position with a slice thickness of 3 mm. These simulation CT images were fused with PET CT images, and target volume delineation was carried out using a Varian Eclipse TPS station (Varian Medical Systems, Palo Alto, CA).

RT target treatment volumes were designed with a safety margin of 3-4 cm in the craniocaudal plane and 1-1.5 cm in the axial plane. This included the metabolic tumor volume observed in PET-CT and the regional lymph node area, including the involved lymph node area. According to tumor location, bilateral supraclavicular lymph node area in cervical and upper thoracic tumors, paraesophageal lymphatic area in mid-thoracic tumors and celiac area in distal localized tumors were included in the treatment area.

Table 1. Prognostic scoring.

	CRP	Albumin	SCORE
GPS	≤10 mg/L	≥3.5 g/dL	0
	≤10 mg/L	< 3.5 g/dL	1
	>10 mg/L	≥3.5 g/dL	1
	>10 mg/L	< 3.5 g/dL	2
mGPS	≤10 mg/L	any	0
	>10 mg/L	≥3.5 g/dL	1
	>10 mg/L	< 3.5 g/L	2

CRP; C-reactive protein, GPS; Glasgow Prognostic Score, mGPS; modified Glasgow Prognostic Score.

Depending on tumor location, organs at risk were contoured as the brachial plexus, medulla spinalis, lung, heart, liver, and kidneys. Treatment planning was made using the volumetric modulated arc therapy (VMAT) technique, paying attention to the dose tolerance limits of healthy tissues at risk.

Treatment protocol

Neoadjuvant or definitive CRT was planned for all patients, and surgery was performed on eligible patients after neoadjuvant therapy. Treatments were administered concomitantly with weekly paclitaxel (50 mg/m2) - carboplatin (area under the curve [AUC] 2) using the Rapidarc–Trilogy (Varian Medical Systems, Inc., Palo Alto, CA, ABD) linear accelerator device. Radiotherapy was planned as 60–66 Gy / 1.8-2 Gy and 50.4 Gy /1.8 Gy for cervical and non-cervical esophageal tumors respectively. The patients were followed up 1–3 times a week during the RT treatment, and enteral and/or parenteral nutrition support was provided if necessary. In the fourth week after neoadjuvant CRT, CT and endoscopic examinations were performed, the multidisciplinary team evaluated the response, and the surgical decision was accordingly made. Adjuvant chemotherapy was performed on patients with residual tumor and/or lymph node positivity in the postsurgery pathological evaluation. Posttreatment follow-up was done every 3–4 months for the first two years and then every 6 months for 5 years.

Statistical methods

The data for continuous variables were expressed as the median (range), and categorical variables were reported as number and percentage. Data

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distribution was assessed by the Kolmogorov–Smirnov test. In consideration of the sample size, the non-normal distribution of variables was assumed, and nonparametric tests were used for between-group comparisons. Univariate and multivariate survival analyses were carried out using the Cox proportional hazards regression model. Multivariate cox regression analysis was performed to determine the predictors of mortality; including sex, CAR, GPS, mGPS, and ''days when CRP > 5'' as covariates. Kaplan -Meier curves were generated for OS, and significance was assessed using the log-rank test. Receiver operating characteristic (ROC) curves were also used to analyze the ''days when CRP >5'' for predicting the OS. Statistical analyses were performed using SPSS 25 software (SPSS Inc., Chicago, IL, USA). A probability value of p<0.05 was considered significant.

RESULTS

Patient characteristics

The numbers of male and female patients in the study were similar, and the median age was 62 years (range: 22–82). While 82.4% of the cases were SCC, 17.6% were observed to be adenocarcinoma. The median follow-up period was 20 months (range: 3–162). Clinical lymph node positivity was observed in 53% of the patients. Tumor localization was cervical and upper thoracic in 24.7% of patients, middle thoracic in 26%, and lower thoracic/distal esophagus in 49.3% of the patients. The median dose of RT administered was 50.4 Gy (45–68 Gy). Surgery was performed on 25 (29.4%) patients, and pCR was observed in 10 (40%) patients who underwent surgery (table 2).

Survival analysis

After a median follow-up period of 20 months, disease recurrence was observed in 21 (25%) of 85 patients, and 30 (35%) patients died. Two-year DFS and OS rates were 54% and 63%, respectively. Gender (p=0.02), albumin (p<0.001), CRP (p<0.001), lymphocyte (p=0.09), platelet (p<0.001), GPS (p<0.001), mGPS (p<0.001), CAR (p<0.001), and ''days when CRP > 5'' (p<0.001) were found to be predictive factors for mortality. In univariate and multivariate cox regression analyses, CAR (hazard ratio: 1.04, 95% confidence interval: 1.01–1.08, p=0.007), GPS (hazard ratio: 4.77, 95% confidence interval: 2.66–8.56, p<0.001), mGPS (hazard ratio: 3.72, 95% confidence interval: 2.19–6.3, p<0.001), and ''days when CRP > 5'' (hazard ratio: 1.01, 95% confidence interval: 1.0–1.02 , p=0.002) were independent predictors of mortality (table 3).

Prognostic impact of GPS 0-1-2 and mGPS 0-1-2 on OS

Kaplan- Meier survival analysis was performed to evaluate the differences in prognostic impact between GPS 0-1-2 and mGPS 0-1-2. Patients with a GPS of 0 demonstrated significantly longer OS values than patients with a GPS of 1 or 2 (p < 0.001 for both GPS 1 and 2 according to the log-rank test). Similarly, patients with an mGPS of 0 demonstrated significantly longer OS values than patients with an mGPS of 1 or 2 (p < 0.001 for both mGPS 1 and 2 according to the log-rank test) (figures 1 and 2).

Predictive impact of "days when CRP > 5"

In addition, as the number of days for which the CRP value was above the normal level (days when CRP > 5) increased, the recurrence of the disease also increased significantly (p = 0.01). In the ROC analysis, the (AUC) was found to be significant for the ''days when CRP > 5'' (AUC: 0.956, 95% CI: 0.915–0.998; p < 0.001). An optimal cutoff point of 34 days when CRP > 5 was found to predict overall survival with 90% sensitivity and 92.7% specificity (figure 3).

Table 2. Patient characteristics and basic statistical findings.

	Patients (n:85 , %)
Age	62 (22-82)
Gender	
Female	43 (%50,6)
Male	42 (%49,4)
BMI (kg/m^2)	23,1 (17,8-35,6)
Histoloji	
Squamous cell carcinoma	70(%82,4)
Adenocarcinoma	15(%17,6)
Location of tumor	
Upper	21(%24,7)
Middle	22(%25,9)
Lower	42(%49,3)
Clinical stage	
II	40(%47,1)
III	45(%52,9)
Histological Grade	
I	20(%23,5)
II	44(%51,8)
III	21(%24,7)
Surgery	
Yes	25(%29,4)
No	60(%70,6)
Pathological stage	
I	11(%44)
II	4(%16)
III (A/B)	10(%40)
Pre- neoadjuvant chemoradiotherapy	
CEA (ng/mL)	2,5(0,4-22,3)
CA 19-9 (U/mL)	10(0,8-38,4)
Albumin (g/dl)	3,9(2,9-4,7)
CRP	6,4(0,4-189)
Hemoglobin (g/dL)	13(8,9-16)
WBC count (x10^3/µL)	7(8,2-)
Lymphocyte (x10^3/µL)	1,7(0,6-3)
Neutrophil (x10^3/µL)	4,9(1-20)
Platelet (10^9/L)	253(117-517)
CAR	1,6(0,09-55,6)
GPS	
0	53 (%62,4)
1	20 (%23,5)
2	12 (%14,1)
mGPS	
0	57 (%67,1)
1	16 (%18,8)
2	12 (%14,1)
Days when CRP >5	17 (0-285)

BMI; body mass index, WBC; white blood cell, CAR; CRP to albumin ratio, CRP; C-reactive protein, GPS; Glasgow Prognostic Score , mGPS; modified Glasgow Prognostic Score.

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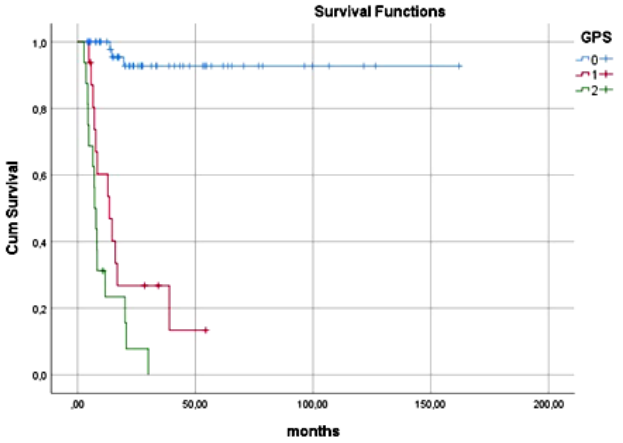

Figure 1. Survival curve for GPS 0-1-2.

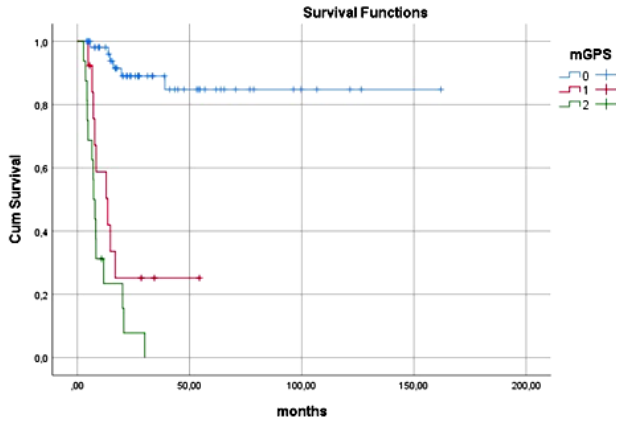

Figure 2. Survival curve for mGPS 0-1-2.

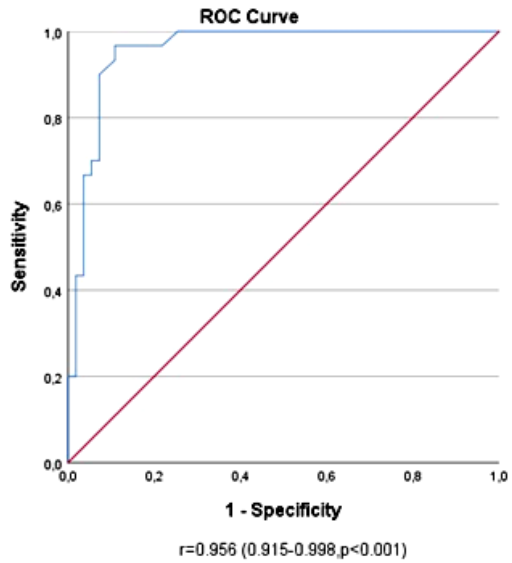

Figure 3. Area under the curve of 'Days when CRP>5'.

DISCUSSION

Many studies have explored the effects of various markers of inflammation on survival and prognosis in different cancer types. Among these inflammation markers, some scoring systems based on CRP and albumin have been developed and in the light of the data, survival and prognosis have been tried to be predicted both in the chemo radiotherapy process in inoperable patients [10], in the surgical treatment process in operable patients [11] and in the terminal period supportive care patients [12-13]. Wei *et al.* demonstrated the relationship of CAR with tumor size, tumor differentiation, nodal stage, TNM stage, and survival in squamous cell esophageal cancer [14]. Wang *et al.* also examined the predictive role of GPS (calculated based on albumin and CRP) in survival of patients with esophageal cancer in a meta-analysis [15]. McMillan *et al.* concluded that CRP was a good prognostic indicator, independent of albumin, and they modified the GPS score according to CRP levels, as CRP had a greater influence on other prognostic factors [16]. Ibuki *et al.* investigated the relationship between survival and CRP levels on postoperative days 1, 2, 3, 5, and 7 in 202 patients operated on for esophageal cancer. They evaluated the increased CRP levels measured on the postoperative 3, 5 and 7 days to be associated with recurrence-free survival. In addition, they categorized the patients into low-risk (0.67-5.16), moderate-risk (5.21–8.60), and high-risk (8.61-36.1) groups according to the CRP levels measured on the seventh postoperative day and found a significant effect of the high levels of CRP on recurrence-free survival [17].

All these findings were crucial for establishing the hypothesis of our study and prompted us to examine CRP more closely from the beginning to the end of the treatment process, especially in terms of the relationship between the "high CRP interval" and survival. From this point of view, unlike previous studies, in this study, the relationship between the total number of days in which CRP remained at high levels during the follow-up of each patient and survival was examined. The "days when CRP > 5" were determined for each patient and found to be significantly higher in patients who died than in those who survived. Days when CRP > 5 were also a significant, independent predictive factor in univariate and multivariate survival analyses and were significantly higher in patients with local recurrence.

Moreover, in patients with more than 34 for days when CRP > 5, the days when CRP > 5 factor was observed to predict mortality with 90% sensitivity and 92.7% specificity. This CRP increase, which we have determined from the diagnosis in patients with esophageal cancer who underwent CRT, can be attributed to different mechanisms. Inflammatory response in the tumor microenvironment with increasing tumor size in healthy tissue, the local and systemic response of the organism due to the direct effects of chemotherapy and radiotherapy, the development of malnutrition and cachexia in patients with reduced oral nutrition and weight loss, the perioperative process in patients undergoing surgery, weakening of the immune system after chemotherapy and all the infective processes may have caused this

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"days of CRP >5" increase. Based on studies conducted on many solid cancer types [18-21], our results emphasize that, regardless of the cause, increased CRP levels are associated with a poor prognostic course and mortality. At the same time, similar to other studies, CAR, GPS, and mGPS—all of which are based on CRP levels—had significant effects on prognosis and survival in our study.

Limitations of the study

Not all patients in the study had the same histology. Although SCC cases constitute the majority, 17.6% of the patients had a histological profile indicating adenocarcinoma. Inoperable cases with cervical esophageal localization who treated with curative doses were combined with tumors that located in the upper-middle-lower thoracic and distal thoracic junction which surgically had different topographical features. CRP follow-up was not standardized because each patient had a different clinical course. So more and longer CRP follow-ups were performed in patients if clinically necessary. In addition, the study design was retrospective, and the number of cases was small.

CONCLUSION

In patients with esophageal cancer for whom a multimodal approach is an irreplaceable treatment, CRP emerges as an effective prognostic parameter, both in terms of the duration for high CRP levels and the different scoring systems based on CRP levels. For this reason, it may be beneficial to consider CRP levels in these group of patients, who still have high morbidity and mortality due to esophageal cancer.

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