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Research Article

C-Reactive Protein-Albumin Ratio's Prognostic Importance in Esophageal Cancer for Survival

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Abstract

Objectives: This study is designed to show the importance of C-reactive protein (CRP) to albumin ratio (CAR) in esophageal cancer (EC) prognosis.

Methods: 39 patients with stage I-III EC, who were treated between 2012–2019 in Erzurum Regional Training and Research Hospital Oncology Clinic, are scanned retrospectively. The relationship between CAR and overall survival (OS) is evaluated. CAR cut-off value is calculated as 0.5; the patients are categorized and analyzed in two groups as <0.5 and ≥0.5.

Results: 39 patients' evaluation with Cox Regression Analysis showed that CAR has statistically significant effect on survival (p=0.005). Increase in CAR is observed with a decline in patient survival. Sex, histology, localization, smoker or non-smoker groups had no statistically significant effect on survival between <0.5 and ≥0.5 subgroups.

Conclusion: This study made us think that CAR can be a new and promising inflammation based prognostic score in operable EC patients. An easy, cheap, easily accessible marker CAR, supported with large patient series and prospective studies, may prove to have contribution in clinical decision process.

Keywords: C-reactive protein/albumin ratio, esophageal cancer, survival

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A frequent digestive system neoplasm esophageal cancer (EC) is the sixth leading cause of cancer deaths worldwide. EC can be mainly grouped in two, as adenocarcinomas and squamous cell carcinomas (SCC). 80 percent of cases consists of SCCs.[1] Despite multimodal approaches in EC therapy, long term survival results are not satisfying. Because of that, biomarkers to predict the prognosis are needed to evaluate clinical therapies.[2]

In cancer related upper digestinal system tumors, oral intake deteoriation and dyspepsia symptoms on the contrary of increased metabolic demand cause malnutrition.[3] Moreover, intense multimodal therapies and long therapy duration in EC contribute to that malnutrition.[4] It is observed that 60–80% of EC cases had malnutrition.[5]

A correlation is observed between nutrition status and postoperative morbidities, response rate to clinical treat-

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ments, prognosis, also life quality.[3,5] Albumin is accepted as an efficient biomarker showing nutritional status, and albumin level is observed to have a relation with comorbidity and prognosis in certain cancers.[6] C-reactive protein (CRP) is an acute phase protein, produced mainly in hepatocytes under interleukin-6 control, and is a very precise prognostic factor for inflammation in various cancers.[7,8]

Recently, nutrition based and/or inflammation based prognostic markers like Glasgow Prognostic Score (GPS), Modified GPS (mGPS), neutrophil-lymphocyte ratio (NLR), and thrombocyte-lymphocyte ratio (PLR) are used to calculate systemic inflammatory response's severity, and they proved to have prognostic value in patients with various cancer types including EC.[1,9–11] C-reactive protein-albumin ratio (CAR) is found out to be the new inflammation based prognostic score, proved to be a very efficient prognostic value in hepatocellular carcinoma.[12]

In our study with stage I-III esophageal cancer patients, we try to evaluate the prognostic value of this easy, cheap, and easily accessible marker CAR for overall survival (OS).

Methods

Clinically and radiologically stage I-III 39 patients, histopathologically diagnosed as EC with endoscopy, and are followed by Erzurum Regional Training and Research Hospital Oncology Clinic, are included in this study. Esophageal small cell cancers and carcinosarcomas, patients with no CRP and albumin values before treatment, and patients with chronic inflammatory diseases except ES which should increase inflammation markers, such as vasculitis, connective tissue disorders, rheumatologic diseases, acute infections, are excluded. CAR is calculated as CRP (mg/dl)/albumin (mg/dl). This ratio is calculated before any therapy, like chemotherapy, radiotherapy or surgery.

CAR's optimal cut-off value is set as 0.5 for highest sensitivity and specificity with ROC analysis. Overall survival (OS) is calculated as the time interval between EC diagnosis and exitus, or last outpatient visit.

Statistical Analysis

Differences between patient features are compared in groups of patients having different treatment modalities for esophageal cancer. Categorical variables, patient count and patient percentage in each category are set, and to evaluate statistical difference between therapy groups Chi-Square or Fisher's Exact test is used. Survival ratios are calculated with Kaplan-Meier method, and Log-rank test is used to compare OS ratios between groups. Relationships between survival and equivalent variables, single variable and multiple variables are evaluated with Cox regression analysis. Hazard ratios (HR) are calculated with 95% confidence interval (CI). In comparison of numerical data, Student T Test was used for normally distributed data, and Mann Whitney U test was used for non-normally distributed data. Receiver operating characteristic (ROC) curve analysis was used for the effect of the variable in predicting patient survival and cut-off point. In the presence of significant limit values, the sensitivity, specificity and positive predictive and negative predictive values of these limits were calculated. The significance level was accepted as 0.05 for all tests. Analyzes were made using SPSS version 22 statistical software (IBM Corporation, Somers, New York, USA).

Results

Median diagnostic age was 62.6. 8 patients were female, 21 patients were male. Histologically 33 patients were squamous cell carcinoma, 6 patients were adenocarcioma. 2 patients were stage I, 7 patients were stage II, and 30 patients were stage III. According to tumor localization, 3 patients had proximal (cervical) tumor, 8 patients had middle esophagus tumor, and 28 patients had distal esophagus tumor. 16 patients had surgical resection, 23 patients had definitive chemoradiotherapy. 9 patients received induction chemoterapy, 15 patients received neoadjuvant chemoradiotherapy. Clinical, pathological and demographical characteristics of the patients are listed at Table 1.

Median OS was 22.07 months (Fig. 1). Univariate Cox regression analysis is done and it showed CAR's statistically significant effect on survival as a decrease in OS with increasing CAR ratio (p=0.005, HR:1.746–95.0% CI; 1.182–2.578).

Student T-test showed that overall CAR value of exitus and surviving patients are 1.27 and 0.78 respectively.

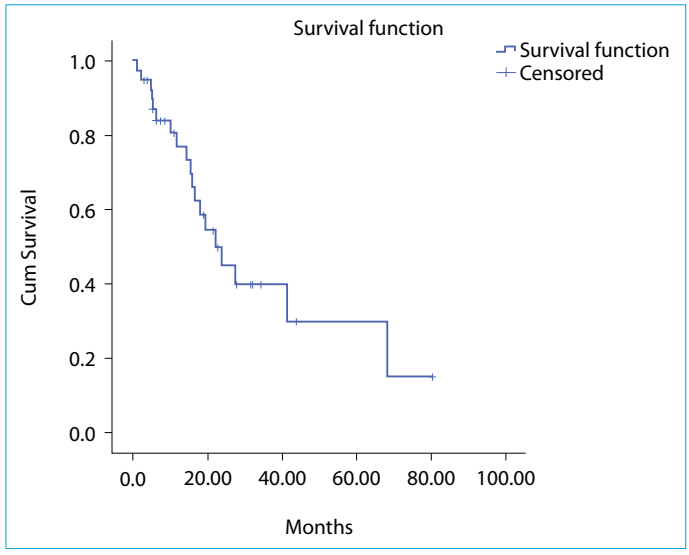

Figure 1. Overall survival.

Overall CAR values for Stage I, stage II and stage III were 0.92 (std:0:10), 0.51 (std:0.35), and 1.13 (std:1.26) respectively. There was no statistically significant relation between stages (p=0.5).

In the analysis made by categorizing CAR <0.5 and ≥0.5; between women and men, <0.5, ≥0.5 subgroups did not have any statistically significant difference.

In the analysis made by histological type, the median OS in the squamous cell cancer group was 41.2 months for <0.5, and the median OS for ≥0.5 was 16.4 months (p=0.2). In the adenocarcinoma group, there was not any survival difference between subgroups.

According to the localization of the tumor, the median OS was 27.3 months in the proximal and thoracic localized tumor for <0.5, and the median OS for ≥0.5 was 4.7 months (p=0.22). In distal tumors, no difference in survival was observed between subgroups.

Between smoker and non-smoker groups, there was not any statistically significant difference among <0.5 and ≥0.5 subgroups. All analysis results are given at Table 2.

Discussion

Inflammation is accepted as a regulatory factor for progression and metastasis in cancer.[13,14] Inflammatory factors are secreted not only by systemic reactions, but also acute phase proteins like CRP , chemokines , cytokines like interleukin 6 (IL-6) are secreted from tumor cells.[15–17] For this reason, inflammatory components' levels have a prognostic value in cancer, and this theory is proved by comprehensive studies.[12,18] Also, insufficient nutrition is correlated with low performance condition and low survival.[19] Low serum albumin level as a result of insufficient nutrition is related with worse survival in a variety of cancers.[20,21] Because of that, CAR, which is calculated from CRP and albumin, is a suitable marker to evaluate EC patients.

In Wei et al.'s[22] study with 423 stage I-IV esophageal SCC patients, with median age 58, optimal cut-off value for CAR was calculated as 0.095. 85% of patients had surgery. All stages are included in the study and grouped as curative (85%) and palliative (15%) therapy groups. Patients' median OS value was 60.5 months, and they found no statistically significant OS difference according to the CAR cut-off value. Multivariate analysis for CAR showed significant prognostic value for young age (<54), moderately differentiated tumors, and for patients receiving palliative therapy for stage IV disease and male patients. CAR, age, stage, therapy purpose (curative or palliative), body mass index (BMI) are found to be independent prognostic factors for OS.In our study, all patients received surgery or definitive chemoradiotherapy, and stage IV patients are not included. On the contrary of Wei et al.'s study, in our curative therapy receiving EC patients, Univariate Cox regression analysis showed CAR's strong statistically significant prognostic value in OS. In our study's subgroup analysis, there was no statistical significance between genders. Even though proximal and middle esophagus tumors showed numerical differences, a statistical significance cannot be reached, prob-

Table1. Clinical parameters of patients included in this study

Characteristics	Patients n (%)
Overall	39 (100)
Median age	62.6
Gender	
Female	18 (46.2)
Male	21 (53.8)
Stage	
I	2 (5)
II	7 (18)
III	30 (77)
Tumor location	
Proximal (Cervical)	3 (7.7)
Midle (Thoracic)	8 (20.5)
Distal (Abdominal)	28 (71.8)
Operation	
Yes	16 (41)
No	23 (59)
Histology	
Squamous cell carcinom	33 (84.6)
Adenocarcinom	6 (15.4)
Cigarette	
Yes	8 (20.5)
No	11 (28.2)
Unknown	20 (51.3)

n: Number; %: Percent

Table 2. Univariate analysis for overall survival (OS) in 39 patients with stage I-III esophageal carcinoma

Variables	n	<0.5 (m)	≥0.5 (m)	p
Female	18	27.3	15.7	0.2
Male	21	23.7	18.1	0.6
Proximal (Cervical)+ Midle (Thoracic)	11	27.3	4.7	0.22
Distal (Abdominal)	28	24.1	15	0.12
Squamous cell carcinom	33	41.2	16.4	0.2
Adenocarcinom	6	19.4	14.3	0.8
Cigarette				
Yes	8	30.2	10.2	0.12
No	11	41.2	16.4	0.3

n: Number; m: Month

ably because of low patient count. Wei et al. only included SCC tumors, in our study, when we analyzed SCC patients separately, there was numerically strong difference in OS according to CAR, but that was statistically not significant.

Kunizaki et al.[23] evaluated CAR and other inflammatory parameters' prognostic importance in 116 patients with stage I-IV SCC esophagus cancer. ROC analysis calculated cut-off value for CAR as 0.042. CAR is found to be the most sensitive inflammation factor for mortality after therapy (HR=3.361; 95% CL: 1.762-6.410; p<0.001). Multivariate analysis showed that stage and CAR are the most important factors predicting survival. Low CAR group compared with high CAR group had significantly longer disease specific 5-year disease free survival (DFS) (respectively 73% vs 49%, p<0.01), and 5-year OS (respectively 56% vs 44%, p<0.01). On the other hand, in our study, we did not observe any statistically significant difference between stages according to CAR, it may be thought that this is because we did not include stage IV patients and have lower patient count.

Ling-Xu et al.[24] chose 468 stage I-III SCC esophagus cancer patients for their study. Median age was 58, tumor locations were mainly middle (%43.6) and distal (%53.2) esophagus. Like our study, CAR cut-off value was 0.50. According to cut-off value they had two subgroups (<0.50, n=381; >0.50, n=87), in univariate analysis, CAR>0.50 group's and CAR<0.50 group's 5-year OS was %43.4 vs %17.7 (p<0.0001), in multivariate analysis, CAR>0.50 (HR:2.44; 95% GA: 1.82–3.26; p<0.0001) group showed worse survival results than CAR<0.50 group.The results are similar to our study. Our cut-off value was also the same, and we also found CAR is statistically significant in predicting OS.

Our limitations for this study was to have a small patient count in a single institution. Also, because of the retrospective design, we had lack of data for evaluating disease-free survival.

In conclusion, our study had a more homogeneous patient group in comparison with the literature's many studies which have heterogeneous patient groups receiving both curative and palliative therapies. CAR proved to have predictive value in EC. In addition, even though we could not reach statistical significance, proximal-thoracic esophagus tumor, and squamous cell tumor patients had numerically prominent different survivals. Lack of statistical significance may also be because of our low patient count. Accordingly, CAR is a useful, easy, objective, repeatable and cheap prognostic marker for EC patients, which can be used routinely with laboratory tests. Also, patients with high CAR value may benefit from anti-inflammatory therapy and nutrition supplement.

Disclosures

Ethics Committee Approval: The ethics committee of Health Sciences University Erzurum Regional Training and Research Hospital provided the ethics committee approval for this study (20.05.2020-2020/10-107).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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