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Clinical significance of the C-reactive protein-to-albumin ratio for the prognosis of patients with esophageal squamous cell carcinoma

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Abstract. The aim of the present study was to investigate the prognostic value of the C-reactive protein-to-albumin ratio (CAR) and compare it with other inflammation-based prognostic scores (Glasgow prognostic score, modified Glasgow prognostic score, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, prognostic nutritional index and prognostic index) in patients with esophageal squamous cell cancer (ESCC). A database of 116 patients with primary ESCC who underwent treatment at the Division of Surgical Oncology at Nagasaki University Hospital between January 2007 and August 2014 was retrospectively reviewed and the correlations between CAR and overall survival (OS) were investigated. Kaplan-Meier and Cox regression analyses were used to assess independent prognostic factors. The area under the curve (AUC) was used to compare the prognostic value of different scores. According to the receiver operator characteristics analysis, the recommended cut-off value for CAR was 0.042, with an AUC of 0.678 (sensitivity 31.1%, specificity 66.7%). Thus, patients were dichotomized into low (<0.042) and high (≥0.042) CAR groups. On multivariate analysis, CAR was found to be significantly associated with OS in patients with ESCC [hazard ratio (HR)=2.350; 95% confidence interval (CI): 1.189-4.650; P=0.014], as was tumor-node-metastasis stage (HR=3.059; 95% CI: 1.422-6.582; P=0.004). In addition, CAR had a higher AUC value (0.678) compared with several other systemic inflammation-based prognostic scores (P<0.001). This study suggested that CAR is a novel and promising inflammation-based prognostic score in patients with ESCC. Due to its simplicity, affordability and availability, CAR may be important for improving clinical decision-making and may contribute to more rational study design and analyses.

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Introduction

Esophageal cancer is the eighth most common type of cancer and the sixth most common cause of cancer-related mortality worldwide (1). In the United States and other Western countries, ~50% of esophageal cancers are adenocarcinomas. However, in Asian countries, including Japan, ~90% of esophageal cancers are squamous cell carcinomas (SCCs), which is the predominant histological subtype of esophageal cancer, comprising ~80% of all esophageal cancers worldwide (2). Thus, there is continuing interest in new and useful biological serum markers that may enable more accurate stratification of patients with esophageal SCC (ESCC), improve clinical decision-making, and possibly contribute to a more rational study design and analysis.

Recently, inflammation-based scoring systems that measure the state of the systemic inflammatory response, such as the Glasgow prognostic score (GPS), modified GPS (mGPS), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), have been reported to have prognostic value in patients with various types of cancer, including ESCC (2-5). In addition, several studies have indicated that C-reactive protein (CRP)-to-albumin ratio (CAR) is a risk factor for patients with several types of cancer (6-8). However, whether CAR is associated with outcome in patients with ESCC has not yet been elucidated. Therefore, the aim of the present study was to investigate the prognostic value of CAR and compare its prognostic value with other inflammation-based prognostic scores in patients with ESCC.

Patients and methods

Patients. A database of 116 patients with primary ESCC who underwent treatment in the Division of Surgical Oncology at Nagasaki University Hospital (Nagasaki, Japan) between January 2007 and August 2014 was retrospectively reviewed. Written informed consent was obtained from each patient.

No patients had received preoperative radiotherapy. The study protocol complied with the standards of the Declaration of Helsinki and the current ethical guidelines and was approved by the Institutional Ethics Board of Nagasaki University Hospital. The following factors were examined: Age, sex, Charlson comorbidity index (CCI), clinical status based on the 7th edition of esophageal cancer tumor-node-metastasis (TNM) classification, tumor site, tumor depth, carcinoembryonic antigen (CEA) level, SCC antigen (SSCA) and type of treatment. Six inflammation-based prognostic scores were evaluated, namely CAR, GPS, mGPS, NLR, PLR, prognostic nutritional index (PNI) and prognostic index (PI). Clinical staging in our hospital was performed with X-rays, computed tomography (CT), esophagogastroduodenoscopy, barium enema and positron emission tomography (PET)/CT scanning. The assessment of lymph node involvement was performed routinely and was radiographically confirmed in lymph nodes with a short axis of <1 cm on CT and no accumulation of fluorodeoxyglucose on PET/CT.

Values of inflammation-based prognostic scores (CAR, GPS, mGPS, PNI, NLR, PLR and PI), CEA and SCCA. Routine laboratory measurements including albumin, serum CRP and tumor markers, such as CEA and SCCA, were performed on the same day to exclude any inflammatory effects of sequential preoperative examinations, such as esophagogastroduodenoscopy or barium enema. According to the manufacturers, the cut-off values for serum CEA and SCCA are 5.0 ng/ml and 1.5 U/ml, respectively. The GPS was estimated as previously described (9). Briefly, patients with both elevated CRP levels (>1.0 U/ml) and hypoalbuminemia (<3.5 g/dl) were assigned a score of 2. Patients with only one of these biochemical abnormalities were assigned a score of 1. Patients with neither of these abnormalities were assigned a score of 0. The mGPS, NLR, PLR, PI and PNI were all calculated as previously described (10). CAR was calculated as the ratio of serum CRP (mg/dl) to serum albumin (g/dl) (11).

Statistical analysis. The significance of differences between groups was determined using the Chi-squared test, paired t-test, or Mann-Whitney U-test, depending on the type of data. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated by uni- and multivariate analyses using Cox proportional hazard models. A continuous variable was categorized by generating a receiver operating characteristics (ROC) curve to identify the optimal cut-off value. Kaplan-Meier analysis and the log-rank test were used to compare survival curves between groups. Deaths prior to December 31, 2015 were included in this analysis. The discriminatory ability of the factors to predict overall survival (OS) was assessed using the area under the curve (AUC). All the data were statistically analyzed using JMP®10 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. A total of 116 patients were enrolled in the present study. The median age of the patients was 66 years (range, 44-83 years), and the male:female ratio was 5.4:1. A total of 42 (36.2%) patients had succumbed to the disease and 74 (63.8%) remained alive at the last follow-up (December 31, 2015). To investigate the correlation among markers of the systemic inflammatory response, ROC curves were constructed to further assess their discriminatory ability (Fig. 1). According to the ROC analysis, the recommended cut-off value for CAR was calculated to be 0.042 with an AUC of 0.678 (sensitivity 31.1%, specificity 66.7%), which was higher compared with that of other markers (Table I). Thus, patients were dichotomized into low (<0.042) and high (≥0.042) CAR groups. The association between CAR and the clinicopathological characteristics in ESCC patients is shown in Table II. Significant differences were found between the low and high CAR groups in terms of PNI, PLR, treatment, tumor depth, TNM stage, CEA and SCCA (Table II).

Table I. Comparison of the AUCs for seven inflammation-based prognostic scores.

Prognostic scores	AUC	95% CI	P-value
CAR	0.678	0.588-0.768	<0.001
PNI	0.582	0.503-0.661	0.041
NLR	0.568	0.503-0.634	0.041
PLR	0.559	0.466-0.651	0.212
PI	0.594	0.514-0.674	0.022
mGPS	0.608	0.529-0.686	0.007
GPS	0.606	0.525-0.687	0.011

AUC, area under the curve; CAR, C-reactive protein to albumin ratio; CI, confidence interval; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; PI, prognostic index; PNI, prognostic nutrition index; PLR, platelet to lymphocyte ratio.

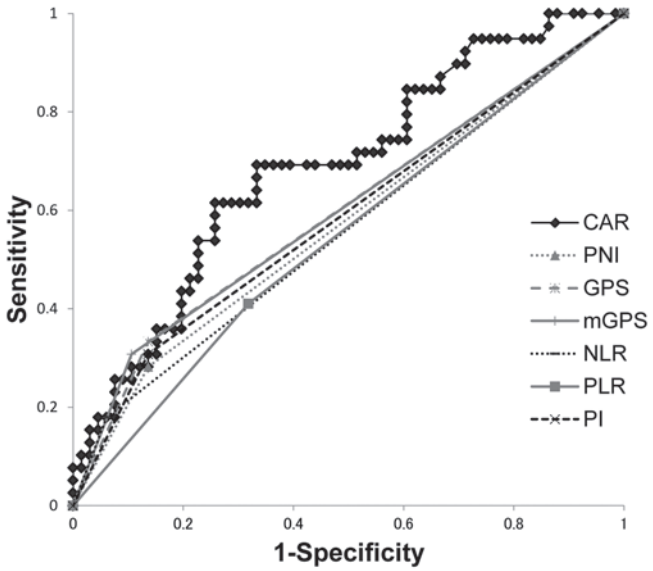

Figure 1. Predictive ability of the seven inflammation-based prognostic scores was compared by receiver operating characteristics curves. CAR, C-reactive protein-to-albumin ratio; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PI, prognostic index.

Table II. Clinicopathological characteristics of the patients.

Characteristics	CAR ≤0.042 n=65 (56%)	CAR >0.042 n=51 (44%)	P-value
Age: <65/≥65 years	31/34	19/32	0.260
Sex: Male/female	53/12	45/6	0.323
CCI: 0, 1/≥2	34/31	24/27	0.575
GPS: 0/1, 2	64/1	29/22	NA
mGPS: 0/1, 2	65/0	31/20	NA
PNI: 0/1	59/6	36/15	0.010
NLR: 0/1	63/2	41/10	NA
PLR: 0/1, 2	49/16	26/25	0.006
PI: 0/1, 2	65/0	29/22	NA
Tumor site: Ce-Ut/Mt/Lt-Ae	15/31/19	11/26/14	0.940
Treatment: Operation/other	41/24	10/41	<0.01
Tumor depth: cT1-2/cT3-T4	36/29	17/34	0.018
TNM: cStage 0-II/III-IV	36/29	15/36	0.005
CEA: <5/≥5/unknown ng/ml	62/3/0	34/15/2	0.001
SCC: <1.5, ≥1.5 U/ml	45/20	22/29	0.005

CAR, C-reactive protein to albumin ratio; CCI, Charlson comorbidity index; CEA, carcinoembryonic antigen; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; NA, not available; NLR, neutrophil to lymphocyte ratio; PI, prognostic index; PNI, prognostic nutrition index; PLR, platelet to lymphocyte ratio; SCC, squamous cell carcinoma antigen; TMN, tumor-node-metastasis.

The clinicopathological factors of age, sex, CCI, treatment, tumor depth, TNM stage, GPS, mGPS, PNI, NLR, PI, CAR, CEA and SCCA were investigated. The findings from the univariate and multivariate analyses on post-treatment mortality are summarized in Table III. Of the patient factors, CCI was not significant, but age and sex were significant for OS. Of the tumor factors, treatment, tumor depth and TNM classification were significant for OS. Of the inflammation factors, PLR was not significant, but GPS, mGPS, PNI, NLR, PI and CAR were significant for OS. CAR was the most sensitive inflammation factor for post-treatment mortality (HR=3.361; 95% CI: 1.762-6.410; P<0.001). Of the tumor markers, CEA was not significant, but SCCA was associated with post-treatment mortality. The significant variables (age, sex, TNM classification, SCCA and CAR) were tested in the multivariate analysis. Multivariate analysis of the OS of ESCC patients revealed that CAR (HR=2.350; 95% CI: 1.189-4.650; P=0.014) and TNM stage (HR=3.059; 95% CI: 1.422-6.582; P=0.004) were significant prognostic factors for a worse outcome (Table III). The median and minimum follow-up times for survivors were 1,092 and 70 days, respectively. The disease-specific 5-year survival was significantly longer in the low CAR group compared with that in the high CAR group (73 vs. 49%, respectively, P<0.01; Fig. 2A). The 5-year OS was significantly longer in the low CAR group compared with that in the high CAR group (56 vs. 44%, respectively, P<0.01; Fig. 2B).

Discussion

Although advances have been made in medical technology, such as endoscopic surgery and early detection and treatment by endoscopy, ESCC is frequently associated with a high mortality rate resulting from late diagnosis and rapid recurrence. The clinical utility of new diagnostic markers of malignancies must be evaluated to identify potentially useful methods for prognosis and treatment monitoring. In recent years, accumulating evidence has elucidated the role of inflammation-based prognostic scores, including PNI, NLR, PLR, PI, mGPS and GPS in cancer patient prognosis (12-15). Although several studies have identified CAR as a prognostic factor for patients with various types of tumors (6-8), the prognostic value in patients with ESCC remained unclear (16). GPS was first introduced by Forrest *et al*, who investigated its prognostic value in advanced cancer patients (17). McMillan *et al* proposed adopting mGPS, which may be a more sensitive prognostic predictor in various malignancies (18).

ESCC patients often suffer from cancer cachexia, as they have difficulty eating, which leads to dystrophy. Complications such as diarrhea occurring after chemoradiation and surgery may further aggravate dystrophy. Low serum albumin levels, as a state of malnutrition, are associated with various cancer survival outcomes (19,20). Thus, CAR, which is calculated from CRP and albumin, is particularly suitable for the evaluation of ESCC patients.

In this study, the usefulness of inflammation-based scoring, particularly CAR, was exclusively evaluated in patients with ESCC. Serum CRP, an acute-phase protein, is produced in hepatocytes, predominantly under the control of interleukin-6, and is a very sensitive prognostic indicator of inflammation in various cancers (21,22). Based on our current observations, it is suggested that CAR, which is calculated from both serum CRP concentrations and albumin levels, may better predict cancer outcome. Interestingly, our results demonstrated that CAR may be a more sensitive prognostic factor in patients with

Table III. Uni- and multivariate analyses of survival using Cox proportional hazard models.

Variables	HR	95% CI	Favorable/unfavorable	P-value
Univariate analysis				
Age	3.239	1.579-6.645	<65/≥65 years	0.001
Sex	4.715	1.133-19.620	Male/female	0.033
CCI	1.077	0.588-1.974	0, 1/≥2	0.811
GPS	2.639	1.387-5.024	0/1, 2	0.003
mGPS	2.554	1.326-4.919	0/1, 2	0.005
PNI	2.361	1.202-4.640	0/1	0.013
NLR	3.184	1.434-7.070	0/1	0.004
PLR	1.631	0.884-3.011	0/1, 2	0.118
PI	2.17	1.127-4.178	0/1, 2	0.021
CAR	3.361	1.762-6.410	Low/high	<0.001
Treatment	3.153	1.580-6.292	Operation/other	0.001
Tumor depth	3.981	1.948-8.134	cT1-2/cT3-T4	<0.001
TNM	4.332	2.065-9.089	cStage 0-II/III-IV	<0.001
CEA	2.104	1.001-4.424	<5/≥5 ng/ml	0.05
SCC	2.854	1.530-5.323	<1.5/≥1.5 U/ml	0.001
Multivariate analysis				
Age	2.192	0.963-4.991	<65/≥65 years	0.062
Sex	3.904	0.873-17.447	Male/female	0.075
TNM	3.059	1.422-6.582	cStage 0-II/III-IV	0.004
SCC	1.375	0.663-2.851	<1.5/≥1.5 U/ml	0.392
CAR	2.35	1.189-4.650	Low/high	0.014

CAR, C-reactive protein to albumin ratio; CCI, Charlson comorbidity index; CEA, carcinoembryonic antigen; CI, confidence interval; GPS, Glasgow prognostic score; HR, hazard ratio; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; PI, prognostic index; PNI, prognostic nutrition index; PLR, platelet to lymphocyte ratio; SCC, squamous cell carcinoma antigen; TMN, tumor-node-metastasis.

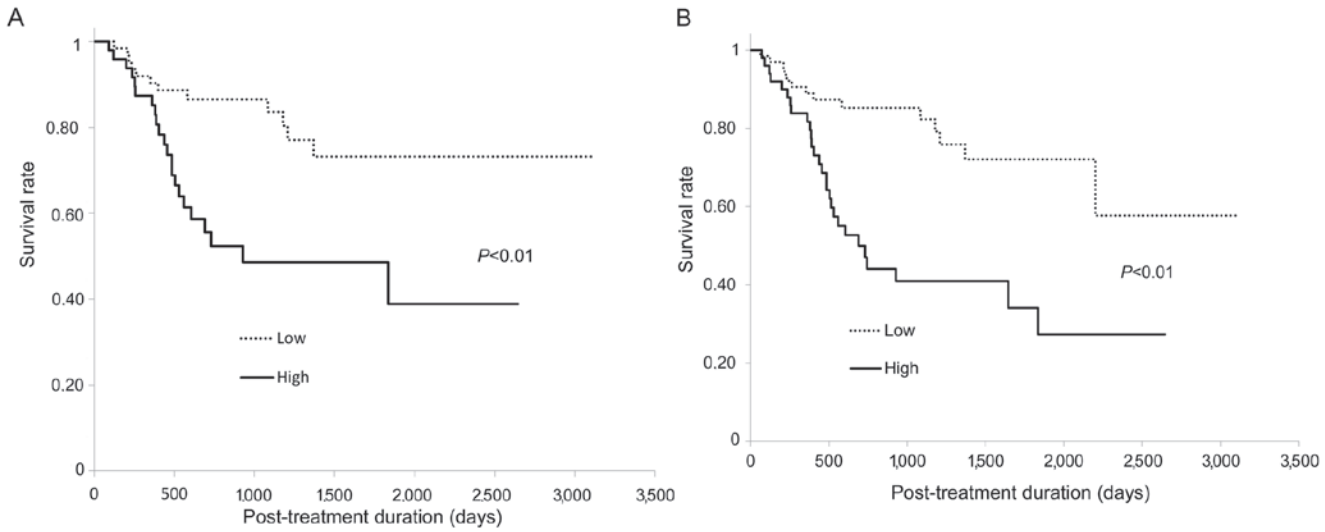

Figure 2. Comparison of (A) disease-specific survival and (B) overall survival curves between the low and high CAR groups. The 5-year survival rates differed significantly between the two groups (73 vs. 49; and 56 vs. 44%, respectively). Both P-values <0.01. CAR, C-reactive protein-to-albumin ratio.

ESCC when it is defined by a cut-off level of 0.042 in survival analysis (Table I). In ROC analysis, our findings indicated that CAR may be superior to other inflammation-based scores in terms of its prognostic ability in patients with ESCC (Fig. 1). Our results are in accordance with the results of a recently published study using a different cut-off for CAR in ESCC, which was higher compared with that in our study (16).

In the present study, CAR was found to be significantly correlated with OS, and Cox regression analysis revealed that high CAR was an independent prognostic factor for

survival in our ESCC patients (Table III). Kaplan-Meier analyses demonstrated significant differences in 5-year disease-specific survival and 5-year OS between patients in the low and high CAR groups (Fig. 2A,B). CAR may thus serve as an independent prognostic biomarker for ESCC and may enable a more accurate stratification of ESCC patients. Moreover, its prognostic ability is superior to that of other inflammation-based prognostic scores. CAR in particular is a useful, simple, objective, reproducible and cost-effective prognostic indicator that may be used in routine clinical laboratory tests of patients with ESCC. In addition, patients with high CAR may benefit from anti-inflammatory therapy or nutritional support.

The present study had several important limitations. First, this was a retrospective, single-center study and the results must be replicated in multicenter and prospective studies. Second, the biological mechanisms underlying the prognostic roles of systemic inflammation factors are unknown. Third, variable treatments were used for patients with ESCC in this study. Finally, our cut-off value for CAR was likely biased, as it was selected using ROC analysis. Therefore, these results must be validated independently.

In summary, CAR is a novel and promising inflammation-based prognostic score in patients with ESCC. Due to its simplicity, affordability and availability, CAR may be an important factor leading to improved clinical decision-making, and may contribute to more rational study design and analysis.

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