in vivo *36*: 1930-1936 (2022)
doi:10.21873/invivo.12914

Pre-treatment CRP and Albumin Determines Prognosis for Unresectable Advanced Oesophageal Cancer

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Abstract. *Background/Aim: Nutritional disorders due to cancer-related weight loss, such as cancer-impaired food passage, are prominent in many cases of advanced oesophageal cancer. Here, we investigated the nutritional factors that most affect the therapeutic effect and prognosis of unresectable oesophageal cancer. Patients and Methods: One hundred four patients diagnosed with cT4b oesophageal squamous cell carcinoma were included in this study. The values of C-reactive protein/albumin ratio, Glasgow Prognostic Score, prognostic nutritional index, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were calculated from the pre-treatment blood sampling results of the patients who received chemoradiotherapy, and the therapeutic effect and prognosis were analysed. Results: High- C-reactive protein/albumin group and Glasgow Prognostic Score 1 or 2 group correlated with a significantly worse prognosis compared with the low- C-reactive protein/albumin group and Glasgow Prognostic Score 0 group regarding both disease-specific survival and overall survival. Conclusion: Evaluation of pre-treatment CRP and albumin levels in locally advanced oesophageal cancer leads to useful prognostic prediction.*

Oesophageal cancer is the 6th leading cause of death from cancer and the 6th most common cancer in the world (1). Oesophageal cancer is a cancer that has a strong tendency to invade adjacent organs including the trachea, lungs, heart, and aorta because there is no serosa in the oesophagus anatomically. In general, the nutritional disorders of cancer patients are classified into cancer-related weight loss and cancer-induced body weight loss (2). Especially in advanced oesophageal cancer, nutritional disorders due to cancer-related weight loss, such as cancer-impaired food passage, are prominent in many cases. Furthermore, in advanced cancer, the weight loss of cancer derivatives and inflammation caused by the host–tumour interaction have a strong influence on the general condition of patients and following therapeutic effect. Therefore, evaluating the accuracy of pre-treatment nutrition is needed to predict the therapeutic and prognostic effects. Although the prognosis of oesophageal cancer has improved due to advances in perioperative management and treatment, advanced cancer still has a poor prognosis. Therefore, identifying prognostic markers and therapeutic effect predictors from pre-treatment nutritional evaluation is important in advanced oesophageal cancer. Increasing evidence has shown that systemic inflammatory responses and nutritional status are involved in tumour development and are important factors associated with clinical prognosis in various types of gastrointestinal cancers (3, 4). Hypoalbuminemia and elevated C-reactive protein (CRP) are associated with a poor prognosis in cancer patients (5). The Glasgow Prognosis Score (GPS), a combination of albumin and CRP, indicates risk stratification for the prognosis of clinical outcomes in cancer patients. This scoring system has been validated in colorectal, lung, and ovarian cancer (6-8). For oesophageal cancer, GPS is a useful tool to predict survival in patients with oesophageal carcinoma (9). Xu XL *et al*. (10) reported that the C-reactive protein/albumin ratio (CAR) predicted the prognosis of patients with operable oesophageal squamous cell carcinoma. A meta-analysis also showed that a higher CAR indicated worse long-term overall survival in oesophageal cancer (11). Furthermore, preoperative GPS and CAR predicted long-term survival in stage T1N0 oesophageal squamous cell carcinoma patients who underwent esophagectomy (12). The prognostic nutritional index (PNI) has also been reported as a prognostic

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Key Words: CRP, albumin, oesophageal cancer, prognosis.

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factor of many tumours and oesophageal cancer (13). A meta-analysis by Xue *et al*. (14) found that PNI was associated with tumour stage and lymph nodes metastases and was an independent prognostic factor of oesophageal cancer.

Moreover, the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), reported as inflammatory and immunologic-based scores, have also been identified as prognostic indicators in oesophageal cancer (15, 16). Many reports have been made on the progression and prognosis of inflammation and nutrition, but few on the most useful nutritional factors to predict prognosis for locally advanced oesophageal cancer alone. Here, we sought to determine the nutritional factors that most affect the prognosis of unresectable advanced oesophageal cancer.

Patients and Methods

This study is single-centre, retrospective study of 104 patients (85 male and 19 female) diagnosed with cT4b oesophageal squamous cell carcinoma without distant organ metastasis treated at the Department of General Surgical Science, Gunma University between May 2004, and December 2016. Clinical staging and pathological examination for resected specimens were performed according to the Guidelines for Clinical and Pathological Studies on Carcinoma of the Oesophagus of the Japanese Society for Oesophageal Diseases (17). TNM classification was evaluated using the 7th edition of the AJCC Cancer Staging System (18). This study was approved by the institutional review board of our hospital (HS2021-185), and all patients provided written informed consent to the use of their data for analysis.

Outcome measures. Patient characteristics, clinicopathological factors, treatment course, pre-treatment plasma CRP and albumin levels, platelet count, neutrophil count, lymphocyte count, total cholesterol, and postoperative survival were recorded for each case. Each nutritional index was calculated as described in a previous study, as shown below. The CAR was calculated by dividing the serum CRP level by the serum albumin level (19). NLR and PLR were calculated from complete blood counts by dividing the absolute neutrophil or platelet count, respectively, by the absolute lymphocyte count (20). For GPS, CRP 10 mg/l and albumin 35 g/l were determined as the cut-off points, and the GPS was determined from 0-2, as described previously (21). PNI was calculated using the following formula:

PNI=(10×albumin (g/l)+(0.005×total lymphocyte count) (22).

The cut-off values for CAR, PNI, NLR, and PLR were the average values obtained for each (0.33, 47.1, 3.98, and 195, respectively). PNI, NLR, and PLR were examined except for three cases with lack of data.

Treatment and follow-up. Oesophagoscopy, computed tomography, endoscopic ultrasonography and positron emission tomography were performed for evaluation of all patients. These were performed at the time of diagnosis and preoperatively, or whenever disease recurrence was suspected.

CRT was performed as initial treatment for unresectable oesophageal cancer with infiltration of surrounding organs without distant metastasis. Following 40 Gy radiation, all patients were evaluated to determine whether surrounding invasion had resolved and whether surgical resection was an option. If curative resection was judged possible and the patient was able to tolerate surgery, CRT was stopped, and conversion surgery was performed after approximately 4 weeks and after obtaining adequate informed consent. Conversely, if curative resection was impossible because of residual infiltration of a surrounding organ or because the patient declined surgery, patients underwent continued CRT (60 Gy). Salvage surgery was performed on patients with residual tumour or local recurrence after CRT. A total of 32 (30.8%) of 104 patients underwent conversion surgery, and 72 (69.2%) underwent definitive CRT. In addition, 14 cases underwent salvage surgery after CRT.

Statistical analysis. We performed all statistical analyses using the JMP Pro Version 15 software (SAS Institute Japan, Tokyo, Japan). We assessed continuous data using Student's *t*-test or the Mann-Whitney *U*-test and categorical data using Person's χ^2 test, Fisher's exact test, or the Mann-Whitney *U*-test as appropriate. *p*-Values <0.05 were considered statistically significant.

Results

Examination of each index and patients' background and prognosis. Table I presents patient characteristics and each index. No significant differences were found between each index of CAR, GPS, PNI, NLR, and PLR and age, sex, location, and tumour progression.

In the examination of each index and its prognostic value, the high-CAR group showed significantly worse prognosis compared with the low-CAR group regarding both disease-specific survival (DSS) (p=0.029, Figure 1A) and overall survival (OSS) (p=0.031, Figure 1B). In addition, regarding GPS, the prognosis for both DSS and OS was significantly worse for GPS 1 and GPS 2 than for GPS 0 (p=0.032, p=0.037, respectively, Figure 2A and B). Regarding PNI, NLR and PLR, no significant difference was found in the prognosis between the high-value and low-value groups (data not shown). Moreover, multivariate analysis of DSS and OSS including lymph node metastasis, stage, CAR, and GPS was performed only for unresectable advanced cancer, but no independent prognostic factors were found in this study (data not shown).

Progress and prognosis of conversion cases and definitive CRT cases.

Conversion surgery cases. Examination of each index and postoperative complications revealed no significant difference between each index and each complication. The relationship between each index and prognosis was investigated only in conversion surgery cases, and no correlation with prognosis was found with any of the indices.

Definitive CRT (dCRT) cases. The effect of each index on the therapeutic effect was evaluated, but no significant difference was found between each index and the therapeutic

Table I. *Comparison between patients characteristics and each index.*

Variable	CAR		*p*-Value	GPS			*p*-Value	PNI(n=101)		*p*-Value	NLR(n=101)		*p*-Value	PLR(n=101)		*p*-Value
	Low (n=76)	High (n=28)		0 (n=73)	1 (n=20)	2 (n=11)		Low (n=47)	High (n=54)		Low (n=70)	High (n=31)		Low (n=63)	High (n=38)	
Age (mean±SEM)	65.7±0.72	68.3±1.18	0,069	65.7±0.73	66.6±1.39	70.6±1.88	0,057	66.4±0.94	66.4±0.87	0,99	66.1±0.77	67.0±1.15	0,552	66.4±0.81	66.3±1.04	0,922
Sex																
Male	62	23	0,947	61	15	9	0,695	35	48	0,058	56	27	0,379	53	30	0,513
Female	14	5		12	5	2		12	6		14	4		10	8	
Location																
Ce	9	2		9	2	0		5	6		7	4		6	5	
Ut	16	9	0,63	15	7	3	0,616	8	15	0,534	16	7	0,98	13	10	0,78
Mt	44	14		42	9	7		28	29		40	17		38	19	
Lt	7	3		7	2	1		6	4		7	3		6	4	
TNM (pre CRT)																
cN0	10	2	0,374	9	3	0	0,228	6	5	0,573	7	4	0,67	5	6	0,227
cN1	66	26		64	17	11		41	49		63	27		58	32	
cM (lymph)																
0	63	19	0,106	60	15	7	0,365	39	41	0,381	54	26	0,434	47	33	0,132
1	13	9		13	5	4		8	13		16	5		16	5	
cStage																
3	63	19	0,106	60	15	7	0,365	39	41	0,381	54	26	0,434	47	33	0,132
4	13	9		13	5	4		8	13		16	5		16	5	

SEM: Standard error of the mean.

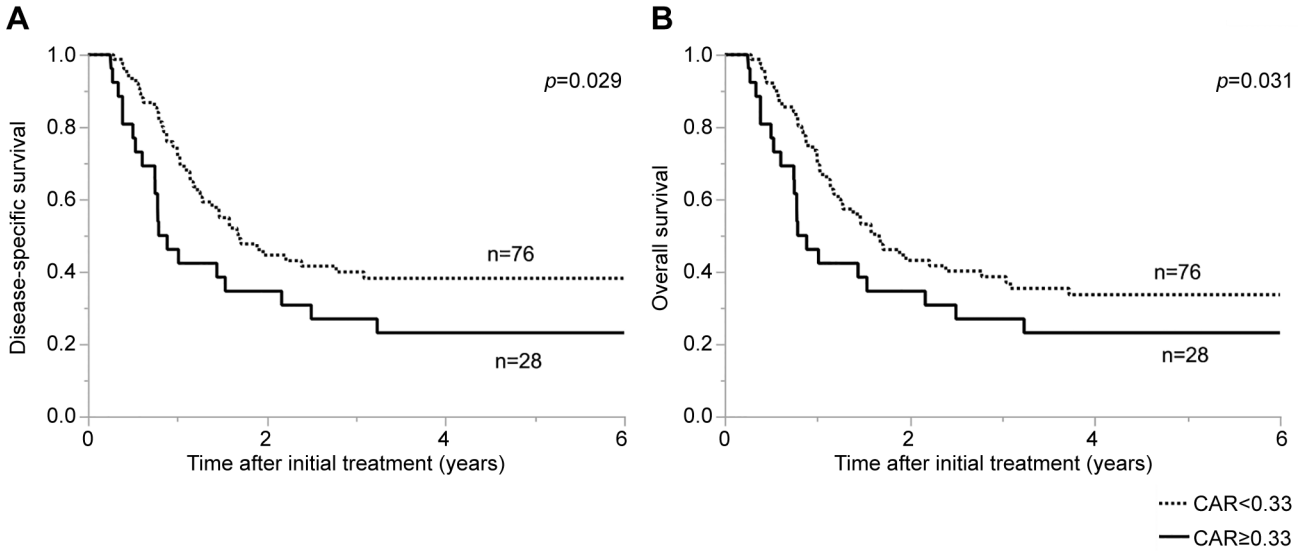

Figure 1. *Survival comparison between high-CAR group and low-CAR group in all patients. A) Five-year disease-specific survival in low-CAR group and high-CAR group was 38.15% and 23.08%, respectively (p=0.029). B) Five-year overall survival in low-CAR group and high-CAR group was 33.60% and 23.08%, respectively (p=0.031). CAR: C-reactive protein/albumin ratio.*

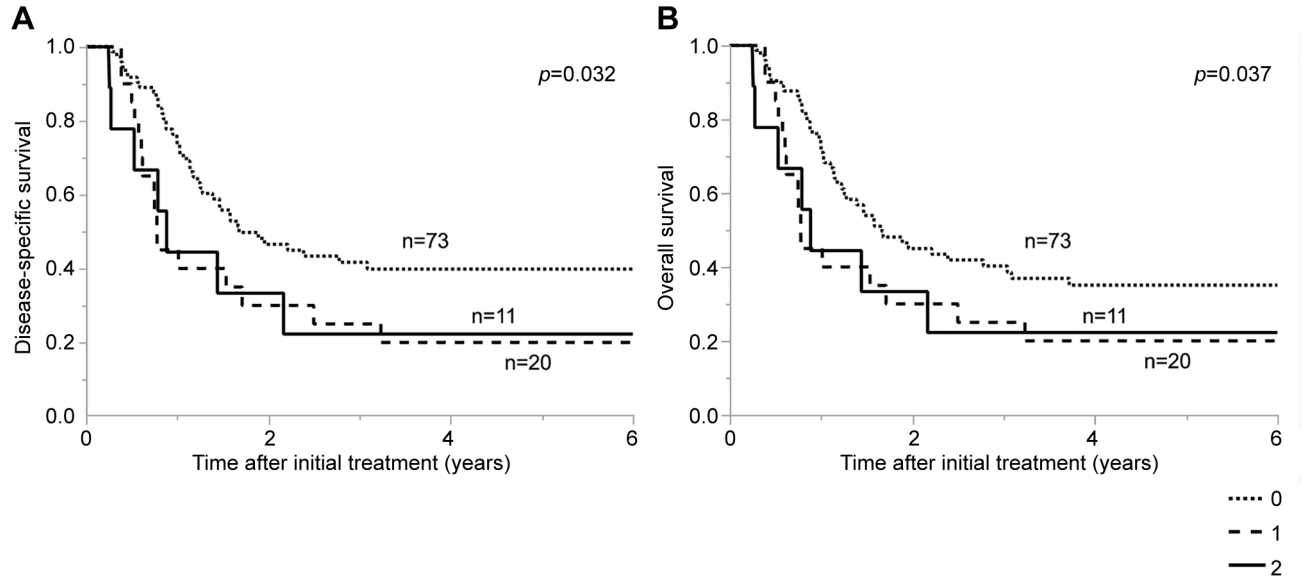

Figure 2. *Survival comparison based on GPS score in all patients. A) Five-year disease-specific survival in GPS 0, 1, and 2 was 39.85%, 20.00% and 22.22%, respectively (p=0.032). B) Five-year overall survival in GPS 0, 1 and 2 was 35.06%, 20.00% and 22.22%, respectively (p=0.037). GPS: Glasgow Prognosis Score.*

effect. In the examination of the prognosis of dCRT cases, significant difference was observed for CAR. The high-CAR group showed a poorer prognosis compared with the low-CAR group regarding both DSS and OS (p=0.030, p=0.035, respectively, Figure 3A and B). However, no significant differences were found between each of GPS, PNI, NLR, and PLR and prognosis.

Discussion

In this study, prognostic factors for advanced oesophageal cancer were examined based on various nutritional evaluations before initial treatment. Although the prognostic value of many indices for oesophageal cancer have been reported previously, no reports have identified the most

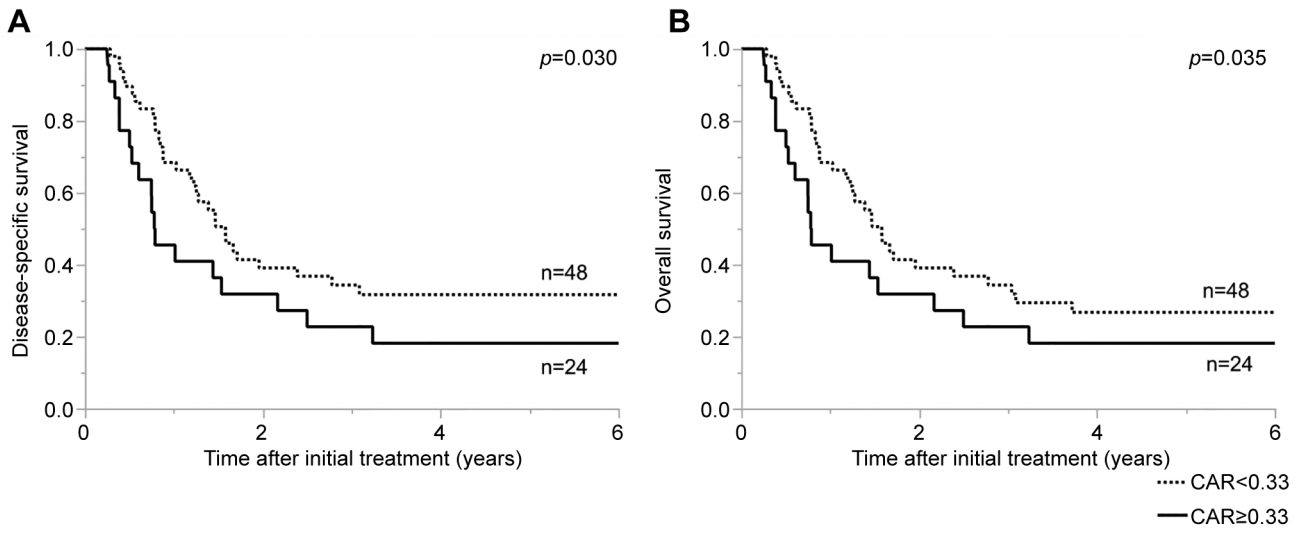

Figure 3. *Survival comparison between high-CAR group and low-CAR group in definitive CRT group. A) Five-year disease-specific survival in low-CAR group and high-CAR group was 31.67% and 18.18%, respectively (p=0.030). B) Five-year overall survival in low-CAR group and high-CAR group was 26.74% and 18.18%, respectively (p=0.035). CAR: C-reactive protein/albumin ratio.*

useful ones in only advanced oesophageal cancer. Since many nutritional indices depend on the degree of tumour progression, this study is most useful in predicting prognosis and therapeutic efficacy by focusing on unresectable advanced oesophageal cancers without distant metastases. Since many nutritional and inflammatory factors can be affected by the degree of tumour progression, it is important to examine the degree of progression in a uniform manner. The results of this study indicate CAR and GPS as significant prognostic factors. Thus, for unresectable locally advanced oesophageal cancer without distant metastasis, the prognosis can be predicted by measuring pre-treatment CRP and albumin levels. The CRP level in patients with cancer reflects the IL-6 levels in the circulating blood and the marked increase in CRP and, thus, increased IL-6 production, ultimately indicates the degree of inflammation in cancer tissue. Furthermore, the increase in IL-6 is directly reflected in the dynamics of acute phase proteins (APPs). Increasing APP is indicated by CRP levels, whereas decreasing APP is indicated by albumin levels. The prognostic significance of CRP was demonstrated in this study, especially in advanced cancers with large tumour volumes. In addition, the production of albumin is suppressed in a concentration-dependent manner by IL-6 produced by the tumours. In many cases, dietary intake is more difficult in advanced oesophageal cancer than in other digestive cancers, and many of these cases have low albumin levels. Therefore, it may be a natural result that CAR and GPS were prognostic indicators of unresectable advanced oesophageal cancer. Furthermore, they remain significant prognostic factors regardless of subsequent treatment intervention. CAR is a significant prognostic factor even for dCRT cases, as in all cases. However, CAR did not show a significant difference in the conversion cases. Based on these results, treatment strategies should be considered in light of the poor prognosis of patients with high CRP and low albumin, especially those with unresectable advanced oesophageal cancer who undergo dCRT. Therefore, performing a mid-term evaluation is an option, and surgery should be considered if conversion surgery is deemed feasible. This is also recommended because no significant difference was noted between CAR and postoperative complications in conversion surgery cases.

Josse *et al*. (23) found that NLR predicts postoperative complications in a study of colon cancer, and Sato *et al*. (24) reported that high pre-treatment NLR levels can predict the treatment effect of pre-treatment chemotherapy for oesophageal cancer. In the subgroup analysis of conversion cases and the examination of the therapeutic effects of dCRT, no significant difference was obtained in all indices, including NLR. Furthermore, a study of PLR in colorectal cancer by Wu *et al*. (25) showed that PLR is involved in the therapeutic effects, but the effects of PLR and chemotherapy were not significant in this study. Moreover, although low PNI values correlate with postoperative complications of pancreatic cancer (26) and gastric cancer (27), no correlation was found between each index before treatment and postoperative complications in conversion cases. Since this study was limited to unresectable advanced oesophageal cancer, the predictor of therapeutic effect could not be examined, and only a few conversion cases were included. Thus, the data may have been insufficient to evaluate complications.

In unresectable advanced oesophageal cancer, nutritional evaluation using blood cell components was not useful in predicting prognosis and therapeutic effect. However, the evaluation of CAR and GPS using blood protein components and inflammatory response helped predict the prognosis and therapeutic effects of CRT.

This study is limited to advanced oesophageal cancer, and the number of cases is small; thus, more cases need to be accumulated to obtain conclusive findings. Given the extremely poor prognosis for advanced oesophageal cancer and in order to improve the accuracy of therapeutic management, other better predictors need to be identified and evaluated, especially indices that were not examined in this study.

Conflicts of Interest

The Authors have no financial conflicts of interest to disclose concerning this study.

Authors' Contributions

Makoto Sohda: Substantial contributions to the conception or design of the work. Arisa Yamaguchi, Takayoshi Watanabe, Nobhiro Nakazawa, Yasunari Ubukata, Kengo Kuriyama, Makoto Sakai, Akihiko Sano and Takehiko Yokobori: Acquisition of data. Hiroomi Ogawa: Interpretation of data. Ken Shirabe: Interpretation of data and advice. Hiroshi Saeki: Interpretation of data and overall advice.

Acknowledgements

The Authors would like to thank Enago (www.enago.jp) for English language review.

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Received February 15, 2022
Revised May 9, 2022
Accepted May 10, 2022