

# A new inflammation index is useful for patients with esophageal squamous cell carcinoma

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**Background:** The prognostic value of inflammation indexes in esophageal cancer has not been established. Recent studies have shown that the advanced lung cancer inflammation index (ALI) is a useful predictive factor. The purpose of the current study was to determine whether the ALI is useful for predicting long-term survival in patients with esophageal squamous cell carcinoma (ESCC).

**Patients and methods:** A total of 293 patients who had undergone esophagectomy for ESCC were included. The ALI was calculated as body mass index  $\times$  serum albumin/neutrophil-to-lymphocyte ratio. Then, patients were divided into two groups: ALI  $\geq 18$  and ALI  $< 18$ . The Kaplan–Meier method was used to calculate the cancer-specific survival (CSS), and the difference was assessed by the log-rank test. Univariate and multivariate analyses were performed to evaluate the prognostic factors.

**Results:** In our study, there were 120 patients with ALI  $< 18$  and 173 patients with ALI  $\geq 18$ . ALI was significantly higher in patients with large tumors ( $P=0.028$ ), poor differentiation ( $P=0.010$ ), deep invasion ( $P=0.009$ ), and nodal metastasis ( $P=0.004$ ). The 5-year CSS was 34.5% in our study. Patients with ALI  $< 18$  had a significantly poorer 5-year CSS compared to ALI  $\geq 18$  (21.7% versus 43.4%,  $P<0.001$ ). On multivariate analysis, we showed that the ALI was a significant predictive factor of CSS ( $P=0.024$ ).

**Conclusion:** The ALI is still a useful predictive factor for long-term CSS in patients with ESCC. However, the prognostic value of the ALI is yet to be formally tested within randomized trials.

**Keywords:** esophageal squamous cell carcinoma, neutrophil-to-lymphocyte ratio, body mass index, albumin, survival

## Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide.<sup>1</sup> In the People's Republic of China, EC was the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in 2008.<sup>1</sup> Esophageal squamous cell carcinoma (ESCC) is the most common pathological type of ECs in the People's Republic of China, in contrast to the predominance of esophageal adenocarcinoma in the Western countries.<sup>2,3</sup> Because there are vital biological differences between ECs in the People's Republic of China and Western countries, a prognostic model that takes into account the predominance of ESCC in the People's Republic of China is necessary for deciding on a postoperative strategy that will prolong the survival. Thus, assessing the prognostic factors in ESCC is more and more important.

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Recently, systemic inflammatory response (SIR) plays a vital role in the progression of cancer.<sup>4,5</sup> Previous reports have shown that systemic inflammation, indicated by an elevated level of serum C-reactive protein (CRP), strongly influenced the prognosis in patients with gastrointestinal carcinomas.<sup>6</sup> Moreover, the Glasgow prognostic score (GPS), which is based on the serum CRP and hypoalbuminemia, has been demonstrated as an indicator for the prognosis in various types of cancers, including ECs.<sup>7-9</sup> In addition, there is increasing evidence that neutrophil to lymphocyte ratio (NLR) can be used for prognostication in several types of cancer.<sup>10,11</sup> Recently, Jafri et al<sup>12</sup> evaluated a novel inflammation-based prognostic system, named advanced lung cancer inflammation index (ALI; based on body mass index, serum albumin [Alb] and NLR). The results showed that ALI was considered as a useful predictive factor in lung cancer.<sup>12</sup> To our knowledge, however, no studies regarding ALI in patients with ECs are available. Therefore, the purpose of the current study was to determine whether the ALI is still useful for predicting long-term survival in patients with ESCC.

## Materials and methods

A retrospective analysis was performed on 293 patients with ESCC in our department from January 2006 to December 2008. All patients were diagnosed as ESCC. Patients who had received preoperative neoadjuvant therapy (chemotherapy and/or radiotherapy) were excluded. Based on the medical records, the following data were collected for each patient: age, sex, height, weight, differentiation, tumor length and location, laboratory examination, depth invasion, nodal metastasis, and other miscellaneous characteristics. Ethical approval was obtained from the Ethical Committees of Zhejiang Cancer Hospital. In our institute, the patients were followed up in the outpatient department. Either X-ray or computed tomography of the chest was performed during the follow-up. The cancer-specific survival (CSS) was analyzed in this study. The last follow-up time was November 2011. All patients were staged according to the 7th edition of the American Joint Committee on Cancer Cancer Staging.<sup>13</sup>

All of the patients were treated with esophagectomy. The standard surgical approach included the Ivor Lewis and the McKeown procedure.<sup>2</sup> The lymphadenectomy included two-field (thoracoabdominal) and three-field (cervical-thoracoabdominal) lymphadenectomy. Most of the patients underwent two-field lymphadenectomy. Three-field lymphadenectomy was used only if the cervical nodes metastasis.

As the role of postoperative adjuvant chemoradiotherapy was controversial during that period, postoperative adjuvant therapy was not mandatory. Cisplatin and 5-fluorouracil were the most frequent chemotherapy. Postoperative radiation was initially performed through the anteroposterior field to 36 Gy, then through the parallel opposing oblique fields to 14 Gy, in order to avoid the spinal cord.

## Statistical analysis

Statistical analysis was conducted with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The ALI was calculated using the following formula:  $\text{body mass index (BMI)} \times \text{Alb}/\text{NLR}$ , and it was categorized into two groups: ( $\text{ALI} \geq 18$  and  $\text{ALI} < 18$ ).<sup>12</sup> The  $\text{BMI} = \text{body weight (kg)}/\text{height}^2 (\text{m}^2)$ , and it was categorized into two groups: ( $\text{BMI} > 18.5 \text{ kg/m}^2$  and  $\text{BMI} \leq 18.5 \text{ kg/m}^2$ ).<sup>14</sup> The Alb was categorized into two groups: ( $\text{Alb} > 3.5 \text{ g/dL}$  and  $\text{Alb} \leq 3.5 \text{ g/dL}$ ).<sup>15</sup> The NLR was categorized into two groups: ( $\text{NLR} < 5$  and  $\text{NLR} \geq 5$ ).<sup>10,11</sup> The Kaplan–Meier method was used to calculate the CSS, and the difference was assessed by the log-rank test. Univariate and multivariate analyses were performed to evaluate the prognostic factors. A  $P < 0.05$  was considered to be statistically significant.

## Results

Among the 293 patients, there were 34 (11.6%) women and 259 (88.4%) men. The mean age was  $59.5 \pm 7.9$  years (range from 38 to 78 years). There were 120 (41.0%) patients with  $\text{ALI} < 18$ , and 173 (59.0%) patients with  $\text{ALI} \geq 18$ .

The relationships between the ALI and clinicopathological characteristics of the 293 patients for ESCC are shown in Table 1. Our study showed that ALI was significantly higher in patients with large tumors ( $P=0.028$ ), poor differentiation ( $P=0.010$ ), deep invasion ( $P=0.009$ ), and nodal metastasis ( $P=0.004$ ).

The 5-year CSS was 34.5% in our study. Patients with  $\text{ALI} < 18$  had a significantly poor 5-year CSS compared to  $\text{ALI} \geq 18$  (21.7% versus 43.4%,  $P < 0.001$ ) (Figure 1). By univariate analysis, tumor length, vessel involvement, depth invasion, nodal metastasis, BMI, Alb, NLR, and ALI were significant association with the 5-year CSS. On multivariate analysis, we showed that ALI was a significant predictive factor of CSS ( $P=0.024$ ) (Table 2).

## Discussion

To our knowledge, this is the first study to show ALI as an independent prognostic factor in patients with ESCC. Our study demonstrated that ALI is still a useful predictive factor for CSS in patients who underwent esophagectomy for ESCC.

**Table 1** The relationship between ALI and clinicopathological characteristics

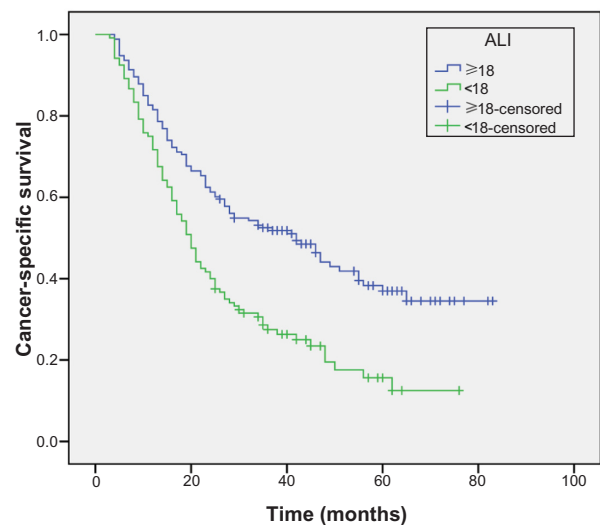
	Cases (n, %)	ALI <18 (n, %)	ALI ≥18 (n, %)	P-value
Age (years)				0.483
≤60	161 (54.9)	63 (52.5)	98 (56.6)	
>60	132 (45.1)	57 (47.5)	75 (43.4)	
Sex				0.475
Female	34 (11.6)	12 (10.0)	22 (12.7)	
Male	259 (88.4)	108 (90.0)	151 (87.3)	
Tumor length (cm)				<b>0.028</b>
≤3	76 (25.9)	23 (19.2)	53 (30.6)	
>3	217 (74.1)	97 (80.8)	120 (69.4)	
Tumor location				0.304
Upper	16 (5.5)	5 (4.2)	11 (6.4)	
Middle	143 (48.8)	54 (45.0)	89 (51.4)	
Lower	134 (45.7)	61 (50.8)	73 (42.2)	
Differentiation				<b>0.010</b>
Well	43 (14.7)	11 (9.2)	32 (18.5)	
Moderate	188 (64.2)	75 (62.5)	113 (65.3)	
Poor	62 (21.1)	34 (28.3)	28 (16.2)	
Vessel involvement				0.808
Negative	246 (84.0)	100 (83.3)	146 (84.4)	
Positive	47 (16.0)	20 (16.7)	27 (15.6)	
Depth invasion				<b>0.009</b>
T1	49 (16.7)	13 (10.8)	36 (20.8)	
T2	46 (15.7)	17 (14.2)	29 (16.8)	
T3	163 (55.6)	68 (56.7)	95 (54.9)	
T4a	35 (12.0)	22 (18.3)	13 (7.5)	
Nodal metastasis				<b>0.004</b>
Negative	149 (50.9)	49 (40.8)	100 (57.8)	
Positive	144 (49.1)	71 (59.2)	73 (42.2)	
Adjuvant therapy				<b>0.010</b>
No	196 (66.9)	70 (58.3)	127 (73.4)	
Yes	97 (33.1)	50 (41.7)	47 (26.6)	

**Note:** Statistically significant P-values are shown in bold.

**Abbreviation:** ALI, advanced lung cancer inflammation index.

ALI <18 had a hazard ratio (HR) of 1.433 (95% confidence interval [CI]: 1.048–1.959;  $P=0.024$ ) for CSS. In our study, we analyze the potential prognostic role of ALI in ESCC patients without neoadjuvant chemoradiotherapy, mainly because chemotherapy or radiation will have an important impact on the systemic inflammation.

BMI is a steady nutritional indicator. BMI levels may vary between healthy and diseased conditions or obese and non-obese persons or even healthy condition and malnutrition. Thus, the importance of BMI with regard to cancer progression can have different implications. Previous published studies have shown that BMI is a predictor of survival in several cancers, such as breast cancer, gynecologic cancer, and lymphoma.<sup>16–18</sup> However, due to the inconsistent results, its role in EC is still controversial. Engeland et al<sup>14</sup> reported that low BMI increased the risk of ESCC. However,



**Figure 1** Patients with ALI <18 had a significantly poor 5-year cancer-specific survival compared to ALI ≥18 (21.7% versus 43.4%,  $P<0.001$ ).

**Abbreviation:** ALI, advanced lung cancer inflammation index.

Skipworth et al<sup>19</sup> demonstrated that BMI did not demonstrate as an independent predictive factor of survival in EC patients undergoing radical esophagectomy. Grotenhuis et al<sup>20</sup> also showed that BMI did not have prognostic role for short- or long-term survival in EC patients. In our study, although BMI was not a significant predictor in patients with ESCC, patients with BMI ≤18.5 kg/m<sup>2</sup> had a significantly poor 5-year CSS compared to BMI >18.5 kg/m<sup>2</sup> (24.5% versus 40.4%,  $P<0.001$ ).

It has been reported that Alb participate in the SIR. Hypoalbuminemia is a useful prognostic factor for survival in patients with various cancers. Uppal et al<sup>21</sup> reported that preoperative hypoalbuminemia is an independent predictor of poor outcomes in gynecologic cancers. Chandrasinghe et al<sup>22</sup> also showed that hypoalbuminemia predicts poor survival in patients with rectal cancer. In ECs, Ikeda et al<sup>23</sup> demonstrated that hypoalbuminemia was significantly associated with poor survival in EC patients. In addition, recent studies reported that hypoalbuminemia was predictive of the response to adjuvant chemoradiotherapy for EC.<sup>24,25</sup> In our study, however, hypoalbuminemia was not a significant predictor in patients with ESCC.

NLR is another prognostic factor for survival in various cancers, such as lung cancer, colorectal cancer, and urinary cancer.<sup>26,27</sup> However, its role in EC is still controversial. Sharaiha et al<sup>10</sup> and Sato et al<sup>11</sup> reported that NLR >5 correlated with poor survival in EC patients. However, Rashid et al<sup>28</sup> and Dutta et al<sup>29</sup> revealed that NLR did not associate with survival in patients with EC. In our study, however, we have demonstrated that BMI, Alb, and NLR did not have prognostic value for patients

**Table 2** Univariate and multivariate analyses of CSS in ESCC patients

	CSS (%)	Chi-square	P-value	HR (95% CI)	P-value
Age (years)		0.005	0.940	–	–
≤60	33.5				
>60	35.6				
Sex		0.001	0.980	–	–
Female	35.3				
Male	34.4				
Tumor length (cm)		17.494	<b>&lt;0.001</b>		0.219
≤3	52.6			1.000	
>3	28.1			1.294 (0.858–1.952)	
Tumor location		0.548	0.459	–	–
Upper/middle	37.1				
Lower	31.3				
Differentiation		2.781	0.095	–	–
Well/moderate	35.8				
Poor	29.5				
Vessel involvement		8.543	<b>0.003</b>		0.395
Negative	37.4			1.000	
Positive	19.1			1.174 (0.811–1.701)	
Depth invasion		24.961	<b>&lt;0.001</b>		<b>0.036</b>
T1-2	56.5			1.000	
T3-4a	24.4			1.527 (1.027–2.271)	
Nodal metastasis		54.063	<b>&lt;0.001</b>		<b>&lt;0.001</b>
Negative	53.0			1.000	
Positive	15.3			2.101 (1.507–2.930)	
Adjuvant therapy		0.100	0.752	–	–
No	36.7				
Yes	29.9				
Alb (g/dL)		23.484	<b>&lt;0.001</b>		0.160
>3.5	40.4			1.000	
≤3.5	15.7			1.285 (0.905–1.824)	
BMI (kg/m <sup>2</sup> )		10.370	<b>0.001</b>		0.741
>18.5	40.4			1.000	
≤18.5	24.5			1.060 (0.752–1.494)	
NLR		11.407	<b>0.001</b>		0.096
<5	38.2			1.000	
≥5	10.3			1.436 (0.938–2.198)	
ALI		19.847	<b>&lt;0.001</b>		<b>0.024</b>
≥18	43.4			1.000	
<18	21.7			1.433 (1.048–1.959)	

**Note:** Statistically significant P-values are shown in bold.

**Abbreviations:** CSS, cancer-specific survival; ESCC, esophageal squamous cell carcinoma; NLR, neutrophil to lymphocyte ratio; Alb, serum albumin; BMI, body mass index; ALI, advanced lung cancer inflammation index; CI, confidence interval; HR, hazard ratio.

with ESCC. Thus, we used a new inflammation index, named ALI, based on BMI, Alb and NLR. Our study demonstrated that ALI was a significant predictive factor of CSS ( $P=0.024$ ).

In conclusion, ALI is still a useful predictive factor in patients with ESCC. ALI is an easy method to assess the systemic inflammation in ESCC patients. High systemic inflammation as judged by ALI  $<18$  had a significantly poor 5-year CSS compared to ALI  $\geq 18$ . However, the prognostic value of the ALI remains to be formally tested within the randomized trials.

## Disclosure

The authors report no conflicts of interest in this work.

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