

Prognostic value of lactate dehydrogenase to albumin ratio (LAR) in patients with resectable esophageal squamous cell carcinoma

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Ji-Feng Feng^{1,2}
Liang Wang¹
Xun Yang¹
You-Hua Jiang^{1,2}

¹Department of Thoracic Surgery, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou 310022, People's Republic of China; ²Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology, Hangzhou, Zhejiang Province 310022, People's Republic of China

Background: We firstly identified a combination of lactate dehydrogenase (LDH) along with albumin (ALB), which was defined as LAR (LDH/ALB ratio). The purpose of our study here was initially to explore the prognostic role of LAR in patients with esophageal squamous cell carcinoma (ESCC) undergoing esophagectomy.

Patients and methods: A retrospective study was conducted including 346 resectable ESCC patients. Patients who received curative surgery without any neoadjuvant therapy were included in the current study. The X-tile program was performed to calculate the optimal cut-off values for LDH, ALB and LAR. The Kaplan-Meier methods, Cox regression univariate and multivariate analyses were utilized to analyze the prognostic factors for cancer-specific survival (CSS).

Results: There were 76 (22.0%) women and 270 (78.0%) men in all 346 patients. The mean value for serum LDH, ALB and LAR were 180 ± 62 U/L (range 28–473 U/L), 40.3 ± 5.3 g/L (range 26.6–52.4 g/L) and 4.6 ± 1.8 (range 0.64–14.97), respectively. According to the X-tile program, the optimum cut-off points were 220 (U/L), 40.5 (g/L), and 5.5 for LDH, ALB, and LAR, respectively. The 5-year CSS was 31.8%. Patients with a high level of LAR (>5.5) were associated with poor CSS (13.3% vs 38.3%, $P < 0.001$). Multivariate analyses revealed that LAR was an independent predictor in resectable ESCC patients ($P = 0.038$).

Conclusion: Our retrospective observations indicate that LAR is a useful potential prognostic biomarker in resectable ESCC patients who received curative surgery without any neoadjuvant therapy with the optimal cut-off value of 5.5.

Keywords: esophageal squamous cell carcinoma, lactate dehydrogenase, albumin, prognosis

Introduction

Esophageal cancer (EC) is the main cancer worldwide (the 8th incidence and the 6th cause of death). The incidences vary widely in different countries and regions. To date, approximately 53.8% and 51.9% of all ECs occurred and died in China.¹ The major kind of pathological type (90%–95%) is esophageal squamous cell carcinoma (ESCC) in China.^{2,3}

Lactate dehydrogenase (LDH) is an important enzyme in energy production in various cell types. Recent studies revealed that serum LDH is related to prognosis in a variety of malignancies, such as renal cell carcinoma, breast cancer, non-small cell lung cancer, pancreatic cancer, nasopharyngeal carcinoma and so on.^{4–8} In EC, however, the prognostic role for serum LDH remains controversial.^{9–11} It has been also reported that albumin (ALB) participate in systemic inflammatory response.

Correspondence: Ji-Feng Feng;
You-Hua Jiang
Department of Thoracic Surgery, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, No. 38 Guangji Road, Hangzhou 310022, People's Republic of China
Tel +86 05 718 812 8072
Email fengjf@zjcc.org.cn;
jiangyh@zjcc.org.cn

Over the past few years, studies have revealed that ALB is still a controversial prognostic biomarker for prognosis, including EC.^{12–14}

It is commonly recognized that LDH and ALB are both cheap and simple serum biomarker which could be conducted in daily clinical practices. In this study, we have firstly identified that a combination of LDH along with ALB, which defined as LAR (LDH/ALB ratio). To the best of our knowledge, no study regarding the prognostic role of LAR so far has assessed. Therefore, the purpose of our study here was initially to explore the prognostic role of LAR for predicting prognosis with the optimal cut-off value in resectable ESCC patients.

Patients and methods

Patients

From January 2007 to December 2010 in the Department of Thoracic Oncological Surgery, Zhejiang Cancer Hospital, a retrospective study was conducted including 346 resectable ESCC patients. The eligibility criteria were included: 1) ESCC was confirmed by histopathology; 2) surgery was performed with curative esophagectomy; and 3) preoperative levels of serum LDH and ALB were obtained before surgery within one week. The exclusion criteria were as follows: 1). patients who received preoperative neoadjuvant therapy; 2). patients who had any form of acute or chronic inflammatory diseases or infections; 3). patients who had any form of systemic diseases, and 4) those diagnosed with distant metastases. Written informed consent for the collection of specimen and other medical information were obtained from all patients before surgery. The current study was approved by the Ethics Committees of our hospital (IRB Approval No. IRB-2018–130).

Surgery and follow-up

All patients underwent curative esophagectomy. The standard esophagectomy includes the Ivor Lewis procedure (ESCC in the middle or lower third) and McKeown procedure (ESCC in the upper third). The two-field (thoracoabdominal lymphadenectomy) was the major method of lymphadenectomy. Follow-up was performed in regular intervals, and the follow-up results were obtained through reviews of the hospital records and outpatient visit.

Data collection

The main clinical characteristics, such as age, gender, tumor length and location, vessel invasion, differentiation, TNM stage, preoperative weight loss (WL), performance status

(PS), serum levels of LDH and ALB, were extracted in retrospective medical records. The TNM in this study was accordance with the AJCC/UICC TNM staging system (the 7th edition).¹⁵ The PS was accordance with the criteria of Eastern Clinical Oncology Group (ECOG).¹⁶ Malnutrition was usually defined as a WL >5% of baseline.^{17,18} Preoperative WL in the current study was defined as unintentional WL during the 3 months before diagnosis.

Statistical analysis

The X-tile program was performed to calculate the optimal cut-off values for LDH, ALB and LAR.¹⁹ The chi-squared tests and an independent-sample *t*-test were used to compare the clinical characters grouped by LAR. The Kaplan-Meier methods, Cox regression univariate and multivariate analyses were utilized to analyze the prognostic factors for CSS. Statistical analyses were conducted with SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

There were 76 (22.0%) women and 270 (78.0%) men in all 346 patients. The mean value for serum LDH, ALB and LAR were 180 ± 62 U/L (range 28–473 U/L), 40.3 ± 5.3 g/L (range 26.6–52.4 g/L) and 4.6 ± 1.8 (range 0.64–14.97), respectively. According to the X-tile program, the optimum cut-off points for LDH, ALB and LAR were 220 U/L, 40.5 g/L and 5.5, respectively (Figure 1). Patients then were divided into 2 groups for further analyses (LAR ≤ 5.5 and LAR > 5.5).

The clinicopathologic characters regarding LAR and other clinical characters were shown in Table 1. LAR was significantly associated with differentiation ($P=0.033$) and TNM stage ($P=0.042$). The levels of LAR were significantly correlated with the levels of ALB ($P<0.001$) and LDH ($P<0.001$). However, there were no significant differences between the LAR groups in terms of PS ($P=0.329$) and WL ($P=0.383$). In addition, no correlations were found between the levels of ALB and LDH ($r=-0.086$, $P=0.109$). However, LAR was significantly correlated with LDH ($r=0.934$, $P<0.001$) and ALB ($r=-0.413$, $P<0.001$) (Figure 2).

Cancer-specific survival analyses

A high LAR level (>5.5) was associated with poor CSS ($P<0.001$) in the CSS analyses by the Kaplan-Meier method. To be more specific, the 5-year CSS was 13.3%

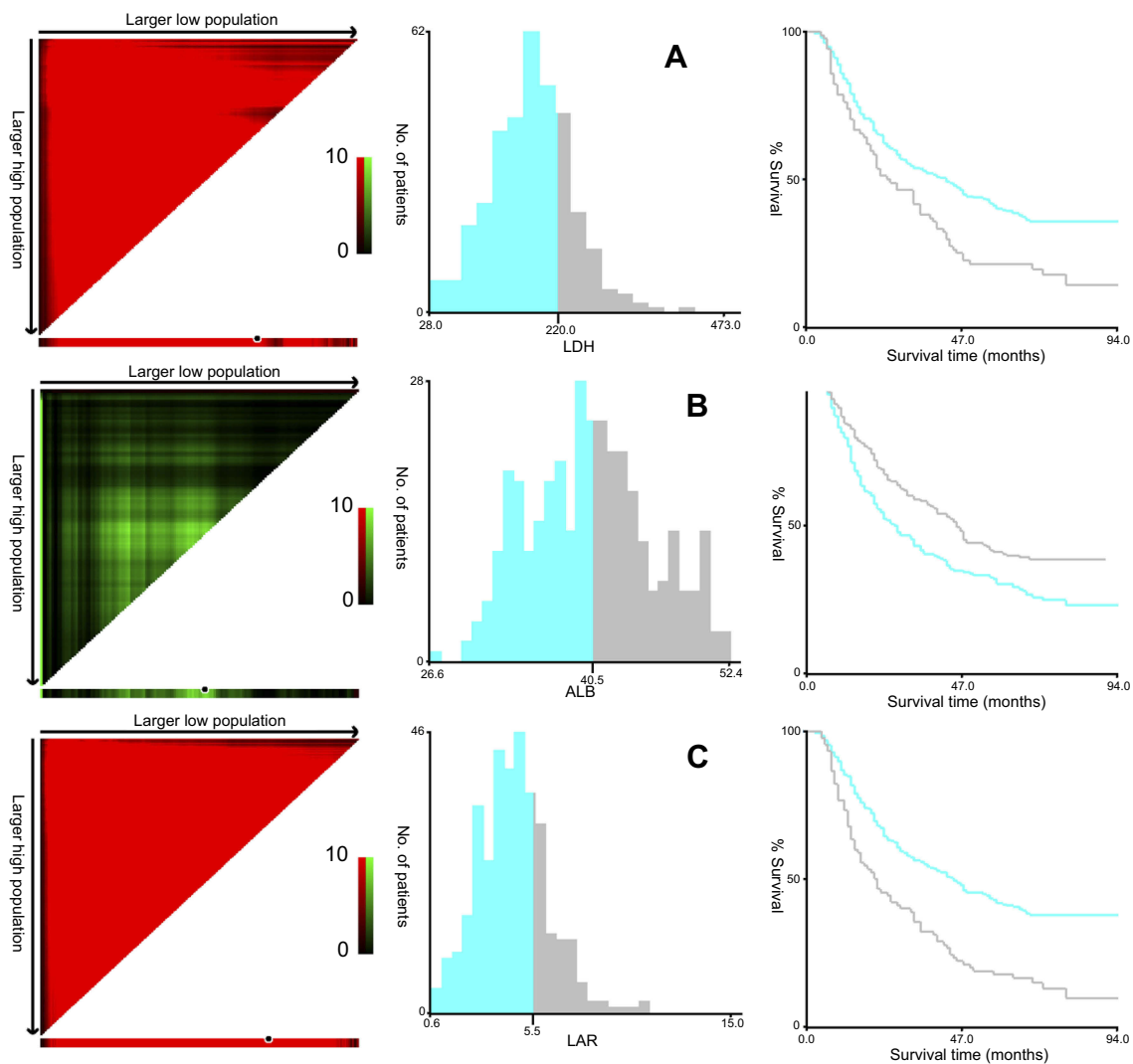


Figure 1 X-tile analyses. The optimum cut-off points for LDH, ALB and LAR were 220 U/L (**A**), 40.5 g/L (**B**) and 5.5 (**C**) according to the X-tile program. **Abbreviations:** LAR, lactate dehydrogenase to albumin ratio; LDH, lactate dehydrogenase; ALB, albumin.

in patients with $\text{LAR} > 5.5$ and 38.3% in those with $\text{LAR} \leq 5.5$ (Figure 3A). In subgroup analyses based on TNM stage, we revealed that LAR was also significantly correlated with CSS (Figure 3B–D).

Cox regression univariate and multivariate analyses

In univariate analyses, several factors (tumor length, vessel invasion, LAR, LDH, ALB, TNM and WL) were significantly associated with CSS (Table 2). However, we found that $\text{LAR} (> 5.5 \text{ vs } \leq 5.5, P=0.038)$, but not for LDH ($> 220 \text{ vs } \leq 220, P=0.322$) or ALB ($> 40.5 \text{ vs } \leq 40.5, P=0.300$), was an independent predictor for CSS by multivariate analyses. In addition, we confirmed that TNM stage ($P<0.001$) and WL ($P=0.012$) were other significant prognostic variables by multivariate analyses (Table 2).

Discussion

Our study demonstrated some important findings: (1) LAR was a strong predictor of CSS; (2) LAR, but not LDH or ALB, was a useful predictive indicator. In this study, we have firstly identified that a combination of LDH along with ALB, which defined as LAR (LDH to ALB ratio). It is generally recognized that LDH and ALB may be influenced by a variety of other non-cancer related conditions, the potential basis could be decreased by the LDH to ALB ratio (LAR). Therefore, the role of the LAR would be more reliable than the effect of either LDH or ALB.

It is demonstrated that various malignancies express a higher level of LDH than normal cells. Serum LDH was associated with systemic inflammatory response.⁷ Recent studies revealed that LDH is related to cancer prognosis.^{4–8} In EC, however, the prognostic role for

Table I Comparison of baseline clinical characteristics based on LAR

	Cases (n, %)	LAR (mean \pm SD)	P-value	LAR ≤ 5.5 (n, %) >5.5 (n, %)	P-value
Age (years)			0.825		0.493
≤ 60	199 (57.5)	4.5 \pm 1.8		150 (58.6) 49 (54.4)	
>60	147 (42.5)	4.6 \pm 1.8		106 (41.4) 41 (45.6)	
Gender			0.162		0.945
Female	76 (22.0)	4.8 \pm 2.1		56 (21.9) 20 (22.2)	
Male	270 (78.0)	4.5 \pm 1.7		200 (78.1) 70 (77.8)	
Tumor length (cm)			0.803		0.277
≤ 3.0	96 (27.7)	4.6 \pm 1.8		75 (29.3) 21 (23.3)	
>3.0	250 (72.3)	4.5 \pm 1.8		181 (70.7) 69 (76.7)	
Tumor location			Reference		0.169
Upper	18 (5.2)	4.9 \pm 1.7	0.556	11 (4.3) 7 (7.8)	
Middle	164 (47.4)	4.6 \pm 1.7	0.429	117 (45.7) 47 (52.2)	
Lower	164 (47.4)	4.5 \pm 1.9		128 (50.0) 36 (47.4)	
Vessel invasion			0.155		0.473
Negative	289 (83.5)	4.5 \pm 1.7		216 (84.4) 73 (81.1)	
Positive	57 (16.5)	4.9 \pm 2.2		40 (15.6) 17 (18.9)	
Differentiation			Reference		0.033
Well	47 (13.6)	4.2 \pm 1.4	0.170	40 (15.6) 7 (7.8)	
Moderate	230 (66.5)	4.6 \pm 1.9	0.025	172 (67.2) 58 (64.4)	
Poor	69 (19.9)	4.8 \pm 1.6		44 (17.2) 25 (27.8)	
TNM stage			Reference		0.042
I	88 (25.4)	4.5 \pm 1.7	0.587	70 (27.3) 18 (20.0)	
II	116 (33.5)	4.3 \pm 1.6	0.150	91 (35.5) 25 (27.8)	
III	142 (41.1)	4.9 \pm 2.0		95 (37.2) 47 (52.2)	
LDH (U/L)			<0.001		<0.001
≤ 220	262 (75.7)	3.9 \pm 1.2		238 (93.0) 24 (26.7)	
>220	84 (24.3)	6.7 \pm 1.6		18 (7.0) 66 (73.3)	
ALB (g/L)			<0.001		<0.001
≤ 40.5	179 (51.7)	5.2 \pm 1.9		106 (41.4) 73 (81.1)	
>40.5	167 (48.3)	3.9 \pm 1.3		150 (58.6) 17 (18.9)	
PS (ECOG score)			0.241		0.329
0	323 (93.4)	4.6 \pm 1.8		237 (92.6) 86 (95.6)	
I	23 (6.6)	4.1 \pm 1.3		19 (7.4) 4 (4.4)	
WL (%)			0.121		0.383
≤ 5.0	179 (51.7)	4.4 \pm 1.7		136 (53.1) 43 (47.8)	
>5.0	167 (48.3)	4.7 \pm 1.9		120 (46.9) 47 (52.2)	
Adjuvant therapy			0.641		0.900
No	244 (70.5)	4.5 \pm 1.7		181 (70.7) 63 (70.0)	
Yes	102 (29.5)	4.6 \pm 2.0		75 (29.3) 27 (30.0)	

Abbreviations: ESCC, esophageal squamous cell carcinoma; LAR, lactate dehydrogenase to albumin ratio; LDH, lactate dehydrogenase; ALB, albumin; TNM, Tumor Node Metastasis; PS, performance status; ECOG, Eastern Clinical Oncology Group; WL, weight loss.

serum LDH remains controversial. Furthermore, the optimum cut-off point for LDH to predict prognosis for EC is still controversial.^{9–11} Recent published

studies have showed that ALB was a systemic inflammatory response-related factor, which reflected both nutritional and chronic inflammatory status. However,

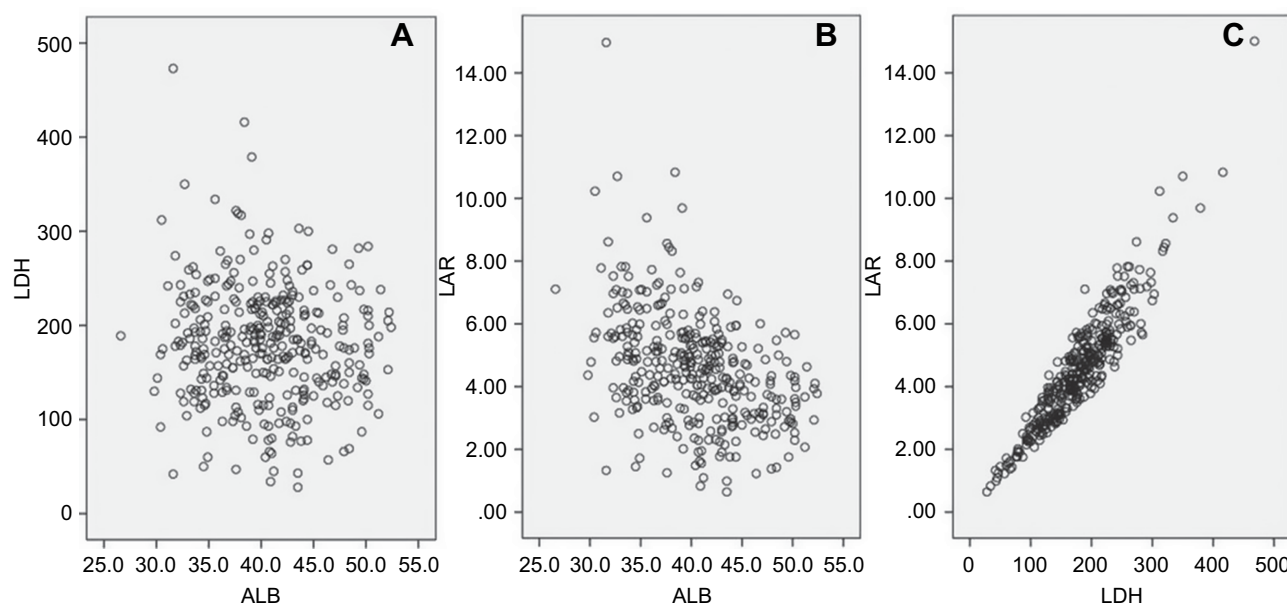


Figure 2 Correlation analyses. No correlations were found between LDH and ALB ($r=-0.086$, $P=0.109$; [A]). However, LAR was significantly correlated with ALB ($r=-0.413$, $P<0.001$; [B]) and LDH ($r=0.934$, $P<0.001$; [C]).

Abbreviations: LAR, lactate dehydrogenase to albumin ratio; LDH, lactate dehydrogenase; ALB, albumin.

ALB is still a controversial prognostic biomarker for prognosis, including EC.^{12–14}

LDH and ALB are both routinely tested serum enzymes in clinical practice, which makes them easily available. In this study, we have firstly identified that a combination of LDH along with ALB, which defined as LAR (LDH/ALB ratio). As everyone knows, LDH and ALB may be influenced by a variety of other non-cancer related conditions, the potential basis could be decreased by the LAR. In our study, patients with a high level of LAR (>5.5) were associated with poor CSS (13.3% vs 38.3%, $P<0.001$). We found that LAR (>5.5 vs ≤ 5.5 , $P=0.038$), but not for LDH (>220 vs ≤ 220 , $P=0.322$) and ALB (>40.5 vs ≤ 40.5 , $P=0.300$), was an independent predictor for CSS by multivariate analyses.

Malnutrition is usually defined as a WL of more than 5% during the whole treatment.^{17,18} However, the prognostic role of preoperative WL in EC patients remains controversial.^{20,21} Van Der Schaaf et al.²⁰ have reported that a $>10\%$ preoperative WL leads to decrease of 5-year overall survival in patients with EC, whereas Skipworth et al.²¹ have revealed that preoperative WL does not influence the perioperative mortality rate and prognosis in EC. To investigate the prognostic value of WL in patients with ESCC, patients were divided into two groups based on their rate of WL before surgery in the current study (WL $\leq 5.0\%$ and WL $>5.0\%$). Our results revealed that preoperative WL was an independent predictor for CSS by multivariate analyses ($P=0.012$).

Serum ALB is commonly used as an important marker of nutrition. However, the relation between ALB and WL remains controversial. Kuo et al.²² reported WL was significantly associated with ALB in colon cancer patients. However, Unal et al.²³ revealed that there was no significant difference between the WL and ALB in patients with head and neck cancer. In the current study, we further explored the association between LAR and nutritional status. We found that it was not significantly associated with preoperative WL ($P=0.383$), although LAR reflected not only inflammation but also nutritional status of cancer patients. The results in our study concluded that systemic inflammatory response exerted more potent prognostic value than nutritional status. In addition, a study from Unal et al.²³ revealed that if malnutrition develops in a short time, ALB is not a clinically relevant nutritional marker, which might also explain part of the reason.

The role of preoperative neoadjuvant chemotherapy and/or radiotherapy followed by surgery compared to surgery alone has been addressed by several randomized control trials.^{24–26} The most promising CROSS trial revealed that neoadjuvant chemoradiotherapy improved survival among patients with potentially curable EC.²⁵ In contrast to the results of the CROSS trial, the French trial (FFCD 9901) reported that preoperative chemoradiotherapy did not improve survival in patients with stage I or II EC.²⁶ Recently, two meta-

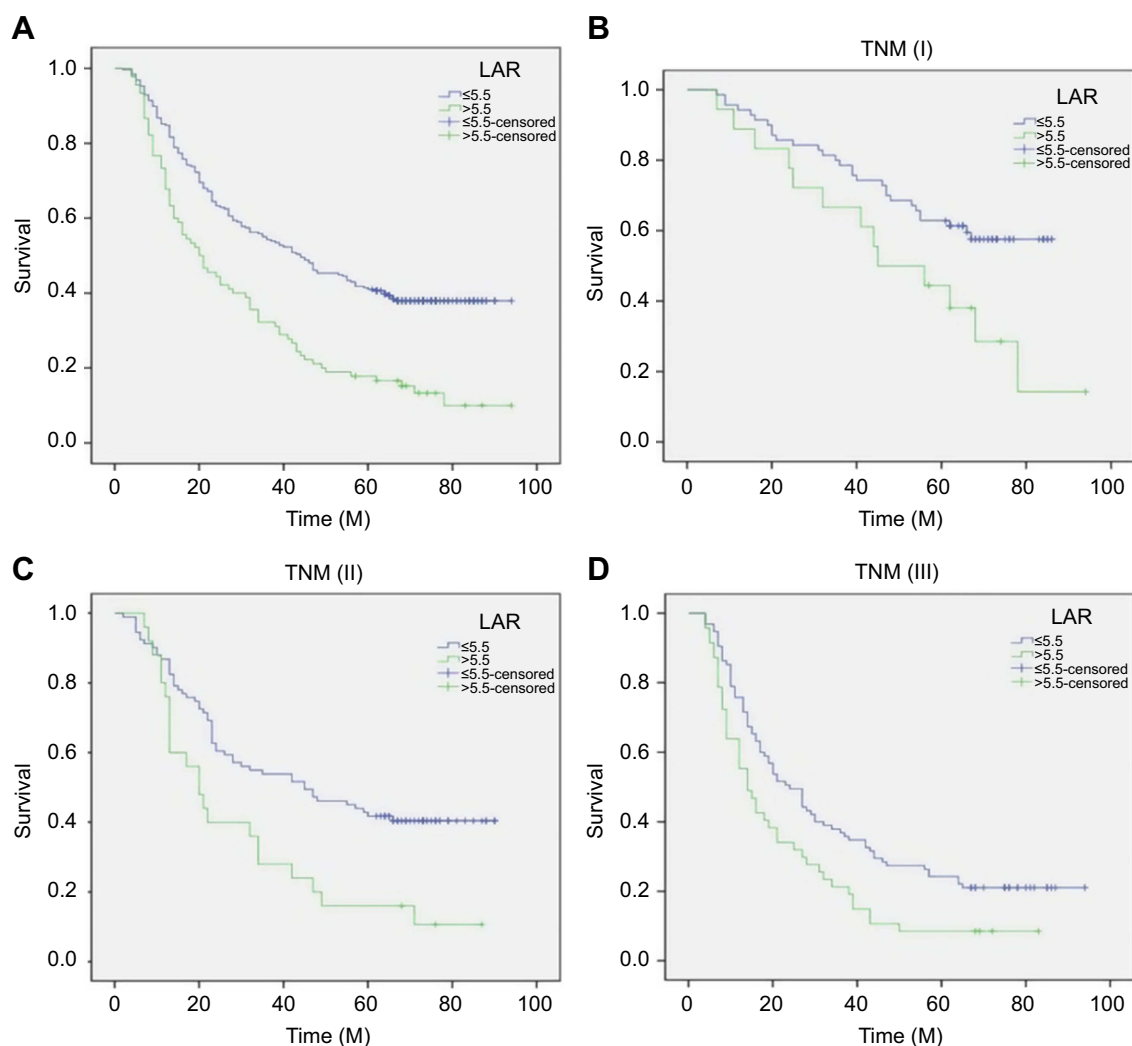


Figure 3 Kaplan-Meier CSS curves. Patients with LAR ≤ 5.5 had a significantly better 5-year CSS than patients with LAR > 5.5 (38.3% vs 13.3%, $P < 0.001$; **[A]**). Subgroup analyses revealed that LAR was also significantly correlated with CSS (TNM I: 58.6% vs 27.8%, $P = 0.023$, **(B)** TNM II: 40.7% vs 12.0%, $P = 0.003$, **(C)** TNM III: 21.1% vs 8.5%, $P = 0.007$, **(D)**). **Abbreviations:** CSS, cancer-specific survival; LAR, lactate dehydrogenase to albumin ratio; TNM, Tumor Node Metastasis.

analyses concluded a survival benefit of neoadjuvant chemoradiotherapy or chemotherapy compared to surgery alone in patients with EC.^{27,28} However, patients who received preoperative treatment were excluded in the current study because neoadjuvant treatment might have a side effect on LDH and ALB. Currently, there is no general consensus on the role of adjuvant treatment in patients with locally advanced EC. A phase III trial performed by Ando et al.²⁹ (JCOG9204) revealed that patients with ESCC receiving surgery plus post-operative adjuvant chemotherapy with two courses of cisplatin and 5-fluorouracil showed superior 5-year disease-free survival than those receiving surgery alone. In another randomized trial (JCOG9907), moreover, they indicated that preoperative chemotherapy

with cisplatin plus 5-fluorouracil can be regarded as standard treatment for patients with stage II/III ESCC.³⁰ A meta-analysis of 11 randomized controlled trials and nonrandomized studies revealed that patients with stage III-IV ESCC are most likely to benefit from adjuvant chemotherapy.³¹ Furthermore, a network meta-analysis was performed to assess the efficacy of surgery with different adjuvant therapies for patients with EC.³² They concluded that patients with surgery plus adjuvant chemoradiotherapy have the best prognosis including long-term survival and low risk of recurrence compared to the other adjuvant therapies. In the current study, however, no significant differences were found regarding 5-year CSS in adjuvant therapy (32.4% vs 30.4%, $P = 0.324$). Three possible

Table 2 Univariate and multivariate analyses of CSS in ESCC patients

	Univariate analysis HR (95% CI)	P-value	Multivariate analysis HR (95% CI)	P-value
Age (years)		0.584		
≤60	1.000			
>60	0.930 (0.717–1.206)			
Gender		0.530		
Female	1.000			
Male	1.105 (0.809–1.510)			
Tumor length (cm)		0.001		0.969
≤3.0	1.000		1.000	
>3.0	1.634 (1.208–2.211)		1.007 (0.713–1.423)	
Tumor location		0.845		
Upper	1.000			
Middle	1.160 (0.624–2.156)	0.638		
Lower	1.197 (0.644–2.222)	0.569		
Vessel invasion		0.003		0.224
Negative	1.000		1.000	
Positive	1.636 (1.187–2.255)		1.226 (0.883–1.704)	
Differentiation		0.075		
Well	1.000			
Moderate	1.247 (0.834–1.864)	0.282		
Poor	1.660 (1.045–2.638)	0.032		
LDH (U/L)		0.001		0.322
≤220	1.000		1.000	
>220	1.611 (1.215–2.135)		1.221 (0.823–1.811)	
ALB (g/L)		0.002		0.300
≤40.5	1.000		1.000	
>40.5	0.669 (0.517–0.867)		0.860 (0.646–1.144)	
LAR		<0.001		0.038
≤5.5	1.000		1.000	
>5.5	1.993 (1.516–2.619)		1.528 (1.025–2.277)	
Adjuvant therapy		0.329		
No	1.000			
Yes	1.149 (0.870–1.517)			
TNM stage		<0.001		<0.001
I	1.000		1.000	
II	1.804 (1.237–2.631)	0.002	1.769 (1.179–2.654)	0.006
III	3.067 (2.150–4.373)	<0.001	2.699 (1.794–4.060)	<0.001
PS (ECOG score)		0.488		
0	1.000			
I	1.197 (0.720–1.989)			
WL (%)		<0.001		0.012
≤5.0	1.000		1.000	
>5.0	1.160 (1.245–2.083)		1.397 (1.076–1.815)	

Abbreviations: ESCC, esophageal squamous cell carcinoma; LAR, lactate dehydrogenase to albumin ratio; LDH, lactate dehydrogenase; ALB, albumin; TNM, Tumor Node Metastasis; PS, performance status; ECOG, Eastern Clinical Oncology Group; WL, weight loss; CI, confidence interval; HR, hazard ratio.

reasons were as follows: Firstly, the postoperative adjuvant therapy was not mandatory in our study. Secondly, ESCC with stage I-III was included in the current study while patients with stage I did not receive adjuvant therapy. Thirdly, although adjuvant therapy was followed by surgery for stage II-III, the survival of locally advanced ESCC was poor.

It is worth noting that our results can be considered relevant with potential applications in the clinical practice in the therapy of ESCC. With an elevated LAR, patients with early-stage ESCC may need closer follow-up, and those with local advanced ESCC may require more aggressive adjuvant chemotherapy and/or radiotherapy. However, the results of our study are expected more large-sample trials to confirm in future.

Limitations should be acknowledged in this study. The major limitations of this study are its retrospective character and the relatively small samples. Moreover, patients who received preoperative treatment, such as chemotherapy and/or radiotherapy were excluded, which might have influenced the result in this study. On the one hand, neoadjuvant treatment will have a side effect on LDH and ALB. On the other hand, neoadjuvant treatment can improve cancer survival for locally advanced ESCC, but not for early-stage ESCC.^{25,26,33} Therefore, the potential applications of these findings can be limited due to the fact that these patients were treated with surgery alone and, in many countries, the standard of treatment in these patients is preoperative chemoradiotherapy. However, the results of our study are expected more large-sample trials to confirm in future.

Conclusion

This study is the first for us to identify LAR and to determine its prognostic value in ESCC patients undergoing esophagectomy without any neoadjuvant therapy. LAR was an effective and independent predictor in resectable ESCC patients who received curative surgery without any neoadjuvant therapy with the optimum cut-off point of 5.5.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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