



Combination of neutrophil-to-lymphocyte ratio and albumin concentration to predict the prognosis of esophageal squamous cell cancer patients undergoing esophagectomy

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Background: Esophageal squamous cell cancer (ESCC) is an aggressive cancer with high incidence and mortality. It is crucial to predict prognosis of these patients individually. Neutrophil-to-lymphocyte ratio (NLR) has been reported as a prognostic indicator in several tumors, including esophageal cancer. Besides inflammatory factors, nutritional status can impact survival of cancer patients. Albumin (Alb) concentration is an easily obtained indicator to reflect nutritional status.

Methods: In this study, we retrospectively collected the data of patients with ESCC and used univariate and multivariate analysis to investigate the relationship between combination of NLR and Alb (NLR-Alb) and survival. Meanwhile, we compared clinical features among NLR-Alb cohorts.

Results: Univariate analysis showed that age ($P=0.013$), gender ($P=0.021$), surgical type ($P=0.031$), preoperative therapy ($P=0.007$), NLR-Alb ($P=0.001$), and tumor-node-metastasis (TNM) status ($P<0.001$) were associated with 5-year overall survival (OS). In multivariate analysis, NLR-Alb [hazard ratio (HR) =2.53, 95% confidence interval (95% CI): 1.38–4.63, $P=0.003$] and TNM status (HR =4.76, 95% CI: 3.09–7.33, $P<0.001$) were independent predictive factors for 5-year OS. The 5-year OS rates were 83%, 62%, and 55% for NLR-Alb 1, NLR-Alb 2, and NLR-Alb 3, respectively ($P=0.001$).

Conclusions: In summary, pre-operative NLR-Alb is a favorable and cost-effective index to predict prognosis of patients with ESCC individually.

Keywords: Neutrophil-to-lymphocyte ratio (NLR); albumin (Alb); esophageal squamous cell cancer (ESCC); prognosis

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Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer-related death and the eighth most common cancer worldwide (1). The 5-year survival of EC is approximately 15–25% (2). Esophageal squamous cell cancer (ESCC) is the predominant histological type, especially in China, where the incidence of ESCC is more than 100 cases/100,000 person-years (2,3).

In view of the high incidence and poor prognosis of ESCC, predicting the outcomes in individual patients is crucial. Many studies have suggested that age, gender, tumor differentiation, tumor-node-metastasis (TNM) status, pre-operative therapy, and molecular markers such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and p53 can predict prognosis (4-7). According to a meta-analysis, several tumor biomarkers such as cyclooxygenase-2 (COX-2), p21, p27, cyclin D1, human epidermal growth factor receptor-2 (HER-2), Ki67 can predict prognosis of EC (8). Circulating microRNAs and related microRNA family has been reported as potential prognostic biomarkers (9,10). However, these biomarkers cannot be obtained easily, which limit clinical practice.

Recently, neutrophil-to-lymphocyte ratio (NLR) has been reported as a prognostic indicator in several tumors including EC (11). As an inflammatory and immunological index, NLR can well reflect systemic inflammatory response (SIR), which is associated with tumor progression and

metastasis (12). Several meta-analyses have shown that higher NLR is significantly associated with poor outcomes in EC (13,14). Besides inflammatory factor status, nutritional status can also impact survival of cancer patients (15). Albumin (Alb) concentration is an easily obtained indicator to reflect nutritional status. It has been reported that neutrophil lymphocyte ratio/albumin ratio (NLR/Alb) was a prognostic index for ESCC (16,17). However, these studies did not stratify patients into different risk categories. A retrospective study reported Alb concentration combined with NLR (COA-NLR) can predict overall survival of patients with non-small cell lung cancer and stratify patients into 3 risk categories (18). Thus, in this paper we divided patients into 3 cohort via the combination of NLR and Alb (NLR-Alb), and we hypothesized that pre-operative NLR-Alb would be an available indicator to predict the prognosis of ESCC patients who underwent esophagectomy more accurately. We present the following article in accordance with the REMARK reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-333/rc>).

Methods

Participants

A total of 366 patients with ESCC who accepted esophagectomy at Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, China, from December 2007 to December 2010 were recruited to this study. All cases were diagnosed by pathology and classified via the 8th edition of the TNM classification (19). Patients with autoimmune disease, hematological disease, infection, and immunotherapy history were excluded (*Figure 1*). Some patients had received chemotherapy and/or radiotherapy before surgery. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent. The study was approved by the Ethics Committee of Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital (No. K2023-025-01).

Study design

This was a retrospective study. We collected the demographic data, pathologic findings, TNM stage, surgical type, blood cell count, and serum Alb concentration of 366 cases. The laboratory data within 1 week before surgery

Highlight box

Key findings

- Pre-operative NLR-Alb is a novel index to predict prognosis of patients with ESCC individually.

What is known and what is new?

- Neutrophil-to-lymphocyte ratio (NLR) has been reported as a prognostic indicator in several tumors including Esophageal cancer (EC). Several meta-analyses have shown that higher NLR is significantly associated with poor outcomes in EC.
- Besides inflammatory factor status, nutritional status can also impact survival of cancer patients. Albumin (Alb) concentration is an easily obtained indicator to reflect nutritional status. Thus, we hypothesized that the combination of NLR and Alb (NLR-Alb) would be an available indicator to predict the prognosis of ESCC and can stratify patients into different risk categories.

What is the implication, and what should change now?

- NLR-Alb is a favorable and cost-effective index to predict prognosis of patients with ESCC.

between 6 am and 10 am were collected. The survival data were collected via medical records or telephone, with 31 December 2016 being the deadline of the follow-up. Overall survival (OS) was defined as the time from the surgery to death or last follow-up. We investigated the relationship of NLR-Alb with survival via univariate and multivariate analysis. Moreover, we compared clinical features among NLR-Alb cohorts.

Definition

NLR was defined as absolute neutrophil count/absolute lymphocyte count. The NLR and Alb threshold were calculated based on the predominant point on receiver operating characteristic (ROC) curves. The 2 parameters threshold values were 1.9 [sensitivity: 0.678, specificity: 0.786, the area under ROC curve (AUC): 0.632] and 39 g/L (sensitivity: 0.977, specificity: 0.025, AUC: 0.652), respectively. The calculation of NLR-Alb is shown in Figure 2. Patients with a lower NLR (≤ 1.9) and a higher Alb

(>39 g/L) were allocated to the NLR-Alb 1 cohort. Patients with a higher NLR (>1.9) and a lower Alb (≤ 39 g/L) were allocated to the NLR-Alb 3 cohort. The remaining patients were allocated to the NLR-Alb 2 cohort.

Statistical analysis

The one-way analysis of variance (ANOVA) test was used to compare co-variables among the cohorts. Comparison of enumeration data used the chi-squared (χ^2) test. The cutoff values were set as the point on the ROC curves that was closest to the upper left-hand corner of the plot. Kaplan-Meier curve was used to analyze OS, and comparisons were determined by log-rank test. Each variable was assessed on the univariate analysis, and then calculated on the multivariable Cox proportional hazards model to validate their independent prognostic value. A P value <0.05 was considered statistically significant. Data were analyzed as of 2022 using the software SPSS 23.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

The baseline characteristics of 366 subjects are shown in Table 1. There were 285 (78%) males and 81 (22%) females with a median age of 56 (range, 35–86) years. The median body mass index (BMI) was 22.3 (range, 14.7–37.3) kg/m². More than half of the patients (53%) did not accept pre-operative therapy. A total of 194 (53%) patients were in TNM stage III–IV. There were no significant differences in age, gender, BMI, smoking, alcohol, pre-operative therapy, surgical type, tumor location, or tumor status among the

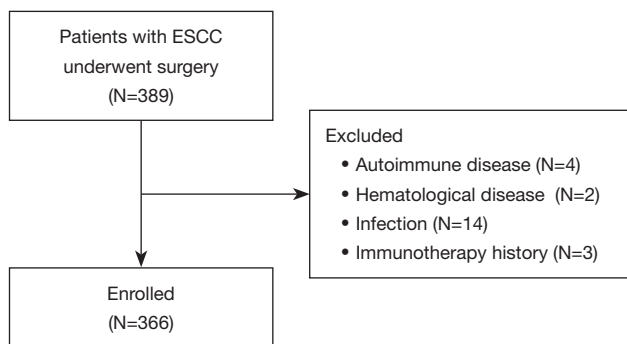


Figure 1 Flow of patients. ESCC, esophageal squamous cell carcinoma.

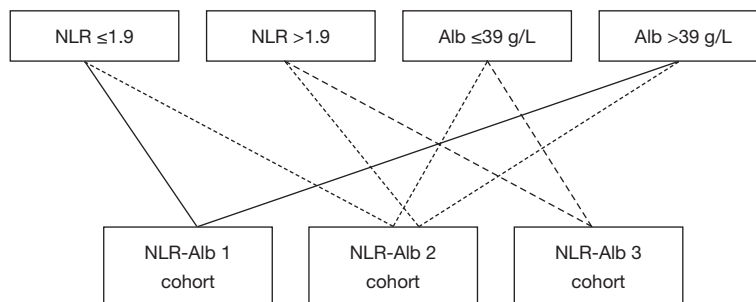


Figure 2 Calculation of NLR-Alb. NLR-Alb, neutrophil-to-lymphocyte ratio and albumin combined.

Table 1 Baseline characteristics of 366 subjects

Variables	Total =366	NLR-Alb 1 (n=70)	NLR-Alb 2 (n=220)	NLR-Alb 3 (n=76)	P value
Age, year (median, range)	56 [35–86]	54 [37–76]	57 [35–86]	57 [39–81]	0.06
Gender					0.97
Male	285 (78%)	54 (77%)	171 (78%)	60 (79%)	
Female	81 (22%)	16 (23%)	49 (22%)	16 (21%)	
BMI, kg/m ² (median, range)	22.3 (14.7–37.3)	22.3 (15.5–31.6)	22.2 (14.7–33.1)	23.2 (16.3–37.3)	0.23
Smoking	140 (38%)	27 (39%)	87 (40%)	26 (34%)	0.73
Alcohol	51 (14%)	8 (11%)	35 (16%)	8 (11%)	0.47
Preoperative therapy					0.38
Chemotherapy	124 (34%)	24 (34%)	76 (35%)	24 (32%)	
Radiotherapy	17 (5%)	1 (1%)	9 (4%)	7 (9%)	
Chemo-radiotherapy	27 (7%)	4 (6%)	20 (9%)	3 (4%)	
Else	3 (1%)	0	2 (1%)	1 (1%)	
None	195 (53%)	41 (59%)	113 (51%)	41 (54%)	
Surgical type					0.20
Three-field lymphadenectomy	286 (78%)	53 (76%)	171 (78%)	62 (82%)	
Two-field lymphadenectomy	68 (19%)	16 (23%)	38 (17%)	14 (18%)	
Left thorax	12 (3%)	1 (1%)	11 (5%)	0	
Tumor location					0.35
Upper third	65 (18%)	13 (19%)	34 (16%)	18 (24%)	
Middle third	264 (72%)	53 (76%)	161 (73%)	50 (66%)	
Lower third	37 (10%)	4 (6%)	25 (11%)	8 (11%)	
Tumor differentiation					0.48
Well	41 (11%)	5 (7%)	25 (11%)	11 (14%)	
Moderate	285 (78%)	56 (80%)	169 (77%)	60 (79%)	
Poor	40 (11%)	9 (13%)	26 (12%)	5 (7%)	
Pathologic N stage					0.38
N0	187 (51%)	42 (60%)	111 (51%)	34 (45%)	
N1	126 (34%)	22 (31%)	73 (33%)	31 (41%)	
N2	48 (13%)	6 (9%)	33 (15%)	9 (12%)	
N3	5 (2%)	0	3 (1%)	2 (3%)	
Pathologic T stage					0.92
T1	59 (16%)	13 (19%)	34 (16%)	12 (16%)	
T2	64 (18%)	10 (14%)	39 (18%)	15 (20%)	
T3	176 (48%)	36 (51%)	103 (47%)	37 (49%)	
T4	67 (18%)	11 (16%)	44 (20%)	12 (16%)	

Table 1 (continued)

Table 1 (continued)

Variables	Total =366	NLR-Alb 1 (n=70)	NLR-Alb 2 (n=220)	NLR-Alb 3 (n=76)	P value
Metastasis					1.00
M0	365 (99%)	70 (100%)	219 (99%)	76 (100%)	
M1	1 (1%)	0	1 (1%)	0	
TNM status					0.69
I-II	172 (47%)	36 (51%)	102 (46%)	34 (45%)	
III-IV	194 (53%)	34 (49%)	118 (54%)	42 (55%)	
OS, months (median, range)	76.4 (0.4–102.4)	82.8 (10.6–101.4)	76.3 (0.4–102.4)	62.5 (1.71–98.5)	<0.001

NLR-Alb, combination of neutrophil-to-lymphocyte ratio and albumin concentration; BMI, body mass index; TNM, tumor-node-metastasis; OS, overall survival.

NLR-Alb cohorts.

Prognostic analysis

Univariate analysis showed that age ($P=0.013$), gender ($P=0.021$), surgical type ($P=0.031$), preoperative therapy ($P=0.007$), NLR-Alb ($P=0.001$), and TNM status ($P<0.001$) were associated with 5-year OS. In multivariate analysis, NLR-Alb [hazard ratio (HR) =2.53, 95% confidence interval (95% CI): 1.38–4.63, $P=0.003$] and TNM status (HR =4.76, 95% CI: 3.09–7.33, $P<0.001$) were independent predictive factors for 5-year OS (Table 2).

Outcomes

The median OS of 366 cases was 76.4 months (range, 0.4–102.4 months), among them the NLR-Alb 1 cohort had the longest median OS, which was 82.8 months (range, 10.6–101.4 months) compared to 76.3 months (range, 0.4–102.4 months) in the NLR-Alb 2 cohort and 62.5 months (range, 1.71–98.5 months) in the NLR-Alb 3 cohort ($P<0.001$, Table 1). The 5-year OS rates were 83%, 62%, and 55% for NLR-Alb 1, NLR-Alb 2, and NLR-Alb 3, respectively ($P=0.001$, Figure 3A). The 5-year OS rates between TNM I–II and III–IV were 85% and 46% ($P<0.001$, Figure 3B).

Discussion

ESCC is an aggressive cancer with a high incidence and mortality. It is crucial to predict prognosis of these patients individually so they can receive appropriate treatment

and better outcomes. The emerging role of pre-operative inflammatory and nutritional status in prognosis is a popular topic in several solid tumors. Except for TNM status, NLR, platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), serum Alb, and BMI have been seen to be significant prognostic factors in survival of ESCC (20–23).

SIR plays an important role in the development and progression of tumors through tumor associated inflammation, chronic inflammation, and infection autoimmunity, moreover, SIR can suppress antitumor immunity and stimulate angiogenesis causing metastasis (12). CRP, procalcitonin (PCT), and cytokines can reflect status of SIR. However, they can be affected by many factors with low specificity. The NLR, as an easily calculated and cost-effective objective index, can reveal the status of SIR and be a marker of immunosurveillance failure. Many cytokines produced by neutrophils such as interleukin-6 (IL-6), IL-1, tumor necrosis factor (TNF) and VEGF may enhance tumor growth (24). The increased number of neutrophils can inhibit the antitumor activity of natural killer (NK) and activated T cells (25,26). In addition, cancer immunosurveillance is mediated by CD-4 helper lymphocytes and CD-8 suppressor lymphocytes. The decrease of CD-4 T cells and increase of CD-8 T cells lead to the depression of cancer cell destruction (27). The decreased number of lymphocytes result in immunosuppression causing production of inflammatory cytokines in the tumor microenvironment (28). A study which enrolled 68 ESCC patients who underwent definitive concurrent chemoradiotherapy showed that higher post-therapy NLR was associated with poorer OS (median 9.4 vs. 15.2 months, $P=0.03$) (29). Studies have shown that

Table 2 Univariate and multivariate analysis for 5-year OS

Variables	Univariate analysis for OS			Multivariate analysis for OS		
	HR	95% CI	P value	HR	95% CI	P value
Age, years						
<65	Ref	Ref		Ref	Ref	
≥65	1.622	1.108–2.374	0.013	1.392	0.928–2.087	0.110
Gender						
Male	Ref	Ref		Ref	Ref	
Female	0.572	0.355–0.920	0.021	0.719	0.445–1.163	0.179
BMI, kg/m ²						
<19.6	Ref	Ref				
≥19.6	0.790	0.527–1.182	0.251			
Surgical type			0.031			0.397
Three-field lymphadenectomy	Ref	Ref		Ref	Ref	
Two-field lymphadenectomy	0.549	0.325–0.929	0.025	0.748	0.439–1.274	0.285
Left thorax	1.667	0.733–3.793	0.223	1.407	0.596–3.324	0.436
Tumor location			0.246			
Upper third	Ref	Ref				
Middle third	0.834	0.535–1.300	0.423			
Lower third	1.273	0.688–2.358	0.442			
Preoperative therapy	1.784	1.259–2.530	0.007	1.335	0.912–1.954	0.137
Smoking	1.100	0.775–1.561	0.594			
Alcohol	1.123	0.690–1.827	0.641			
NLR-Alb			0.001			<0.001
NLR-Alb 1	Ref	Ref		Ref	Ref	
NLR-Alb 2	2.598	1.419–4.758	0.002	2.530	1.381–4.634	0.003
NLR-Alb 3	3.469	1.795–6.701	<0.001	3.795	1.962–7.339	<0.001
Alb, g/L						
<39	Ref	Ref				
≥39	0.866	0.590–1.272	0.866			
TNM						
I–II	Ref	Ref		Ref	Ref	
III–IV	4.645	3.019–7.146	<0.001	4.761	3.091–7.334	<0.001

OS, overall survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; NLR-Alb, combination of neutrophil-to-lymphocyte ratio and albumin concentration; TNM, tumor-node-metastasis.

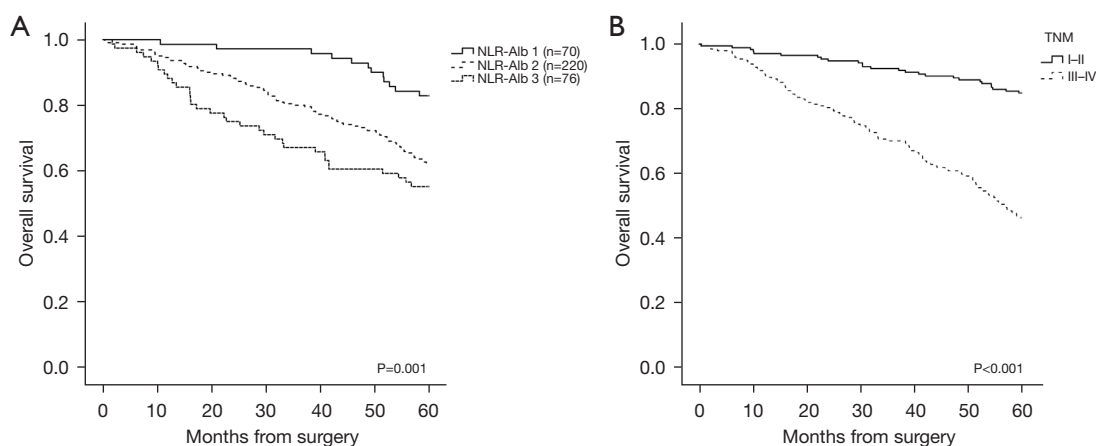


Figure 3 Overall survival. (A) Overall survival among NLR-Alb cohorts. (B) Overall survival between TNM stages cohorts. NLR-Alb, combination of neutrophil-to-lymphocyte ratio and albumin concentration; TNM, tumor-node-metastasis.

among patients with EC who underwent surgery, lower pre-treatment NLR was also associated with disease-free survival (DFS) or OS (30-32). Moreover, a study reported that preoperative NLR was an independent variable associated with the development of postoperative complications (33).

A low Alb concentration is associated with poor prognosis because hypoalbuminemia indicates a poor nutritional status and existence of SIR (34-36). However, the serum Alb concentration was not an independent prognostic factor in our study (HR =0.87, 95% CI: 0.59–1.27, P=0.866).

For predicting prognosis accurately and individually, we used the combination of NLR and Alb to investigate the outcome in patients with ESCC. NLR and serum Alb concentration can be obtained easily during routine blood test, and are cost-effective. NLR-Alb can reveal not only SIR status but also nutritional status. We classified cases into 3 cohorts via NLR-Alb score, and found that a low NLR-Alb score was relevant to a better outcome. Moreover, NLR-Alb was shown to be an independent prognostic indicator for patients with ESCC via multivariate analyses. As shown in *Table 1*, the 3 cohorts divided according to NLR-Alb had no significant differences in TNM status, therefore, NLR-Alb was an independent factor with little effect by TNM status to predict prognosis. In our study, univariate analysis showed that age, gender, surgical type, preoperative therapy, NLR-Alb, and TNM status were associated with 5-year OS. Multivariate analysis showed that the higher NLR-Alb score and TNM III–IV status were associated with poor outcomes. The older patients usually had worse body condition with poor pulmonary

function, cardiac function, or renal function before surgery, which may impact prognosis. The patients who accepted pre-operative therapy usually had poor TNM stages, and it was necessary to shrink the tumor by pro-operative therapy before esophagectomy. In addition, the side effect of pre-operative therapy may impact patients' organ function causing unfavorable outcomes.

Our study had important limitations. It was a single center, retrospective study. The bias of patient number among the 3 cohorts was unsatisfactory, with more cases in the NLR-Alb 2 cohort (n=220) compared to other 2 cohorts (n=70, n=76).

Conclusions

In summary, pre-operative NLR-Alb is a favorable and cost-effective index to predict prognosis of patients with ESCC individually, which can stratify patients into different risk categories. In addition, the calculation and obtaining of NLR-Alb is simple, so that NLR-Alb can be easily applied in daily practice.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-333/rc>

Data Sharing Statement: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-333/dss>

Peer Review File: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-333/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-333/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent. The study was approved by the Ethics Committee of Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital (No. K2023-025-01).

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