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The predicting role of albumin to derived neutrophil-to-lymphocyte ratio for the prognosis of esophageal squamous cell carcinoma patients aged 60 years and above

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Abstract

Objective To explore the clinical significance of albumin(Alb) to the derive(d) neutrophil-to-lymphocyte ratio(NLR) in patients with esophageal squamous cell carcinoma (ESCC) aged 60 years and above.

Methods 328 patients with ESCC at Shanxi Province Cancer Hospital were enrolled in this study. The dNLR was calculated using the following formula: neutrophil count / (leukocyte count – neutrophil count). Alb to dNLR or the Alb/dNLR ratio was calculated by dividing the Alb level by the dNLR level.Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff values for Alb to dNLR.

Results ROC analysis displayed that the cut-off value of Alb to dNLR was defined to be 20.28 U/mL. The AlbtodNLR was not related to clinical features but to survival status (all $P > 0.05$). ESCC patients aged 60 years and above with a high AlbtodNLR had better survival than those with a low Alb-to-dNLR ($P = 0.005$). Similar results were observed in male patients with ESCC ($P = 0.001$), subgroups with upper and middle locations ($P = 0.013$ and 0.017), tobacco consumption ($P = 0.004$), non-drinkers ($P = 0.029$), well and moderate differentiation ($P = 0.014$), lymph node involvement ($P < 0.001$), advanced T stage ($P = 0.014$), and advanced TNM staging ($P = 0.001$). Univariate Cox regression analysis indicated that tumor grade, T staging, lymph node metastasis(LNM), TNM staging, and Alb to dNLR ratio were predictors of death from ESCC. In a multivariate Cox regression analysis, a lower AlbtodNLR levels, and advanced T stage were associated with an increased risk of ESCC-related death.

Conclusions Collectively, Alb to dNLR were inversely associated with outcome and were regarded as an independent influencing factor for ESCC subpopulation aged 60 years and above.

Keywords Esophageal squamous cell carcinoma, Albumin, Derived neutrophil-to-lymphocyte ratio, Prognosis

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Introduction

Esophageal squamous cell carcinoma (ESCC) is the most common subtype of esophageal cancer in China. Adversity in survival probability and aggressiveness are the traits that define ESCC. It continues to rank as the fourth most common cause of cancer-related deaths and sixth most common cause of cancer [1]. Despite the expanded efforts to combat ESCC and multidisciplinary treatment to improve survival in the past times, it has become increasingly important to investigate treatments suitable for older adult patients with esophageal cancer in the aging population. Regrettably, the limited indicator was adverse to early recognition and thus exacerbated the poor prognosis of ESCC, especially in the older population. Therefore, identifying a reliable clinically useful biomarker is essential for tracking the prognosis of this subset of ESCC patients aged ≥ 60 years.

Chronic inflammation and nutritional status have noticeable effects on the course and prognosis of cancer. Prior research has demonstrated a correlation between the prognosis of patients with ESCC and the dynamic biomarkers of inflammation and nutrition. Systemic inflammatory response biomarkers were used to assess the systemic inflammatory response and to predict the prognosis of esophageal cancer. These biomarkers include neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic inflammatory index (SII) [2–5]. Our previous study also found that a low LMR serves as an independent marker of poor prognosis in patients with ESCC undergoing surgery [6]. These inflammation-related markers combined with other indicators have excellent potential for predicting clinical outcomes in patients with ESCC. For instance, in patients with ESCC receiving sintilimab, NLR < 3 at six weeks after treatment and the combination of high high T-cell receptor（TCR） clonality with low molecular tumor burden index（mTBI） may be valuable markers for enlonged overall survival (OS) and progression-free survival (PFS) [7]. The lactate dehydrogenase (LDH) combined with PLR predicts the prognosis of patients with ESCC treated with camrelizumab [8]. Nutritional status has also been identified as a prognosis-related biomarker for esophageal cancer in addition to inflammatory markers. The C-reactive protein-to-albumin(Alb) ratio (CAR), controlling nutritional status (CONUT) score, modified Glasgow prognostic score (mGPS), prognostic nutritional index (PNI), and fibrinogen and Alb score (FA score) are additional indicators helpful in predicting cancer prognosis. All these measurements are used to aid in the diagnosis of malignancies, inflammatory diseases, and immune disorders. Furthermore, these indicators are believed to reflect inflammation, nutrition, and/or immunity and have been reportedly associated with the prognosis of patients with esophageal cancer.

According to previous reports, the derived(d) NLR (dNLR) is a straightforward prognostic predictor for several tumors based on the total leukocyte and neutrophil counts. The dNLR combined with serum LDH, termed the lung immune prognostic index (LIPI), was recently proposed to predict the prognosis of lung cancer. Feng et al. validated this index as a potential independent prognostic marker for patients with resected ESCC [9]. Similarly, in patients with locally advanced ESCC receiving definitive chemoradiotherapy (dCRT), a newly developed esophageal immune prognostic index (EIPI) comprising LDH and dNLR was an independent prognostic indicator [10]. Furthermore, a novel ADS score consisting of Alb to fibrinogen (Fib) ratio (AFR), Alb, and dNLR is a promising biomarker for the clinical efficacy of adjuvant radiochemotherapy and prognosis prediction in ESCC patients undergoing esophagectomy [11]. Alb-dNLR score was established to reflect the immune system and nutritional status. This score is a marker used to assess disease activity of rheumatoid arthritis. Two studies from Japan confirmed the value of Alb and dNLR for ESCC prognosis based on score and ratio, respectively [12, 13].

In the context of global population aging, integrated elderly care and medical services are indispensable old-age programs. Our previous study indicated increased tumor-specific growth factor (TSGF) predicted the adverse prognosis of ESCC, especially for male patients aged under 60 and with lymph node involvement, advanced disease stage, and smoking and drinking habits [14]. There is still some uncertainty about the clinical implications of Alb to dNLR in older Chinese ESCC patients. This study set out to evaluate how effective is the Alb to dNLR ratio to predict prognosis for ESCC.

Patients and methods

Patients

From January 2016 to July 2018, 328 resectable ESCC cases aged 60 years and above were collected from Shanxi Province Cancer Hospital. None of the patients received neoadjuvant chemotherapy or radiotherapy before surgery. Pathologists subsequently confirmed the diagnosis of ESCC after all the patients underwent surgery. The 8th edition of the TNM staging method for esophageal cancer, published by the American Joint Commission on Cancer and the Union for International Cancer Control, was used for clinical staging of esophageal cancer. The World Medical Association's Declaration of Helsinki was followed in executing the current investigation.

Hospitalization from January 2016 to July 2018; all patients having completed medical records; aged 60 years and above; not receiving neoadjuvant chemotherapy or radiotherapy before surgery; undergoing esophageal

resection; and pathologists' confirmation of the final diagnosis were among the included criteria. Patients who received neoadjuvant chemotherapy and radiation prior to surgery, did not have complete medical records, aged under 60 years, did not undergo esophageal resection, and did not have a pathological diagnosis of ESCC were excluded(Fig. 1).

Data collection

Clinical data, including basic details, lifestyle habits, such as alcohol and tobacco use, preoperative blood assays, and treatment approaches, were collected from the patients' medical records. The following formula was used to determine dNLR: neutrophil count/(leukocyte count – neutrophil count). Alb to dNLR or the Alb/dNLR ratio was calculated by dividing the serum Alb level by the dNLR level. Following the standards set forth by the National Comprehensive Cancer Network (NCCN), follow-up was conducted via telephone and routine outpatient consultation. The OS time was computed from the date of surgery to the date of the most recent follow-up or death. The follow-up period will end in December 2022.

Statistical analysis

SPSS software (version 22.0; IBS SPSS, Armonk, NY, USA) was used to process all the data. Using receiver operating characteristic (ROC) curve analysis, the optimal cutoff values for Alb to dNLR levels were established. The test variable was the Alb to dNLR, and the status variable was the survival of patients with ESCC. Using the chi-square test, its relationship with the clinicopathological characteristics of ESCC was examined. OS and stratified analyses were performed using the log-rank test and Kaplan-Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazard regression model. Statistical significance was defined as p values less than 0.05.

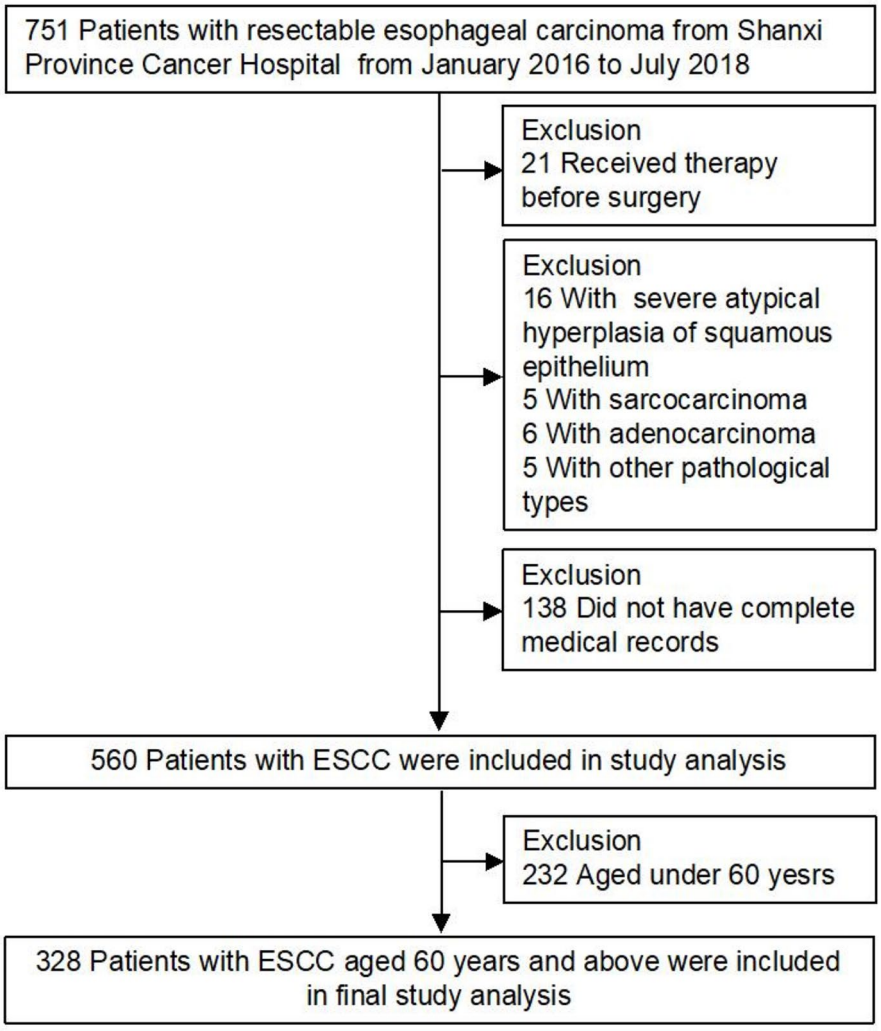

Fig. 1 Study population

Table 1 The clinical characteristics of ESCC patients aged 60 years and above

Characteristics	*n*
Gender	
Male/Female	214/114
Location	
upper/middle/lower	22/229/77
Smoking history	
No/Yes	165/163
Drinking history	
No/Yes	233/95
Grade	
G1/G2/G3	6/218/104
TNM staging	
I/II/III/IV	29/163/120/16
T stage	
T1/T2/T3/T4	33/77/216/2
Lymph node status	
Negative/Positive	187/141
Survival Status	
Live/Deceased	158/170

Results

The characteristics of ESCC patients aged 60 years and above

A total of 328 patients with ESCC (214 men and 114 women) were enrolled in this study (Table 1). Smoking and alcohol consumption are risk factors of ESCC. In our investigation, tobacco use was a factor in 163 ESCC cases, and alcohol consumption was a habit in 95 patients. The middle esophagus was the predominant location in 229 cases, followed by the lower segment in 77, and the upper esophagus in 22. Regarding tumor grade, the most common subtype was moderately differentiated ESCC, which accounted for 66.46% of all cases. Poorly differentiated ESCC was the second most common (31.71%), followed by well-differentiated ESCC (1.83%). Furthermore, 33.54% of patients with ESCC were diagnosed at an early T stage, whereas 66.46% of patients were diagnosed at an advanced T stage. Overall, 41.46% of patients with ESCC had advanced TNM stages when the primary diagnosis was made by clinicians, and 42.99% of all patients experienced lymph node involvement. Stage II patients accounted for the majority of cases (163/328), followed by stage III patients.

Alb/dNLR ratio is associated with features of ESCC aged 60 years and above

We defined the optimal critical value of Alb/dNLR ratio as 22.85 by a ROC analysis with an AUC of 0.591($P=0.005$), and then divided all included cases into two groups based on this threshold: high and low Alb/dNLR groups. There was no evidence that Alb/dNLR ratio was statistically correlated with sex, tumor location, smoking history, drinking history, tumor differentiation, pathological T stage, lymph node involvement, or TNM staging (Table 2) (all $P>0.05$). It was only correlated with survival status ($P=0.020$). What emerges from the results reported here indicate that Alb/dNLR ratio may be a helpful indicator of the unfavorable clinical outcome of ESCC, but is not directly related to the malignant properties of ESCC aged 60 years and above.

Table 2 The relationship between Alb/dNLR ratio and clinicopathological parameters in patients with ESCC aged 60 years and above

Clinicopathological features	Alb/dNLR		χ2	*P*
	low($n=99$)	high($n=229$)		
Gender				
Male	71(33.2)	143(66.8)	2.620	0.106
Female	28(24.6)	86(75.4)		
Location				
Upper	7(31.8)	15(68.2)	0.089	0.956
Middle	68(29.7)	161(70.3)		
Lower	24(31.2)	53(68.8)		
Smoking history				
No	45(27.3)	120(72.7)	1.334	0.248
Yes	54(33.1)	109(66.9)		
Drinking history				
No	64(27.5)	169(72.5)	2.814	0.093
Yes	35(36.8)	60(63.2)		
Grade				
G1 + G2	63(28.1)	161(71.9)	1.420	0.233
G3	36(34.6)	68(65.4)		
Pathological T stage				
T1 + T2	31(28.2)	79(71.8)	0.315	0.575
T3 + T4	68(31.2)	150(68.8)		
Lymph node involvement				
No	53(28.3)	134(71.7)	0.699	0.403
Yes	46(32.6)	95(67.4)		
TNM staging				
I+II	52(27.1)	140(72.9)	2.111	0.146
III+IV	47(34.6)	89(65.4)		
Survival status				
Live	38(24.1)	120(75.9)	5.444	0.020*
Deceased	61(35.9)	109(64.1)		

*: $P<0.05$

Alb/dNLR ratio predicted prognosis of ESCC patients who were age 60 and older

In the following survival analysis, we considered Alb/dNLR ratio as a predictive factor for cancer-related outcomes. We found that low levels predicted worse clinical outcomes in patients with ESCC than high levels ($P=0.005$) (Fig. 2). Alb/dNLR ratio may be a prognostic predictor of ESCC.

Further stratified analysis of the data revealed that decreased Alb/dNLR ratio was a superior marker for

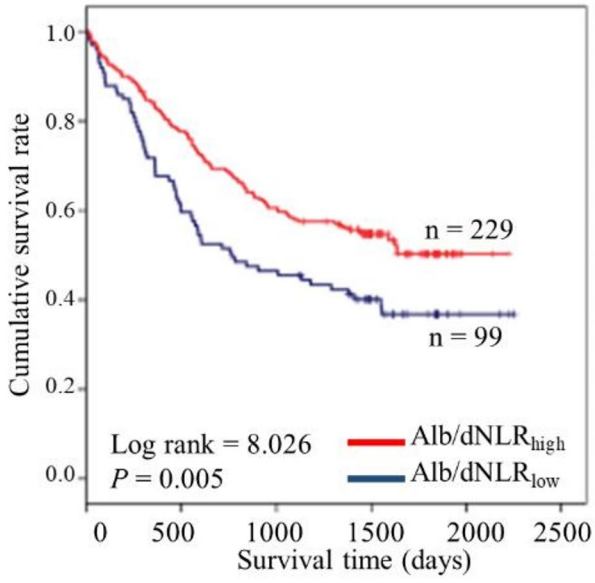

Fig. 2 The prognostic predictive role of preoperative Alb/dNLR ratio in patients with ESCC aged 60 years and above

unfavorable survival in male patients with ESCC aged 60 years and above ($P=0.001$) located in the upper and middle esophagus ($P=0.013$ and $P=0.017$, respectively), with habitual smoking history ($P=0.004$), no alcohol consumption ($P=0.029$), G1 + G2 ($P=0.014$), advanced T stage ($P=0.014$), lymph node involvement ($P<0.001$), and advanced TNM stage ($P=0.001$)(Table 3**and** Fig. 3).

Alb/dNLR is an independently essential predictor for the prognosis of ESCC aged 60 years and above

Our final section of the study focused on the role of Alb/dNLR ratio in survival prediction in patients with ESCC aged ≥ 60 years. Statistical tests indicated that poor differentiation ($P=0.035$), pathological T stage ($P<0.001$), lymph node metastasis(LNM) ($P<0.001$), advanced TNM staging ($P<0.001$), and decreased Alb/dNLR ratio ($P=0.005$) may induce adverse outcomes in this population of patients with ESCC (Fig. 4A). Multivariate Cox regression analysis revealed that higher Alb/dNLR ratio (*HR*: 0.593, *95%CI*: 0.428–0.820, $P=0.002$) and advanced pathologic T stage (*HR*: 1.752, *95%CI*: 1.2-2.556, $P=0.004$) were separate predictors of the survival of ESCC patients aged 60 years and older (Fig. 4B).

Table 3 The stratified analysis of the association between the preoperative Alb/dNLR ratio and the prognosis of ESCC patients aged 60 years and above

Clinicopathological features	Event(No.)/Total(No.)		Log-ank		Breslow	
	Alb/dNLR$_{low}$ ($n=99$)	Alb/dNLR$_{high}$ ($n=229$)	χ2	*P*	χ2	*P*
Gender						
Male	41/71	67/143	10.818	0.001**	12.174	< 0.001***
Female	14/28	42/86	0.016	0.900	0.008	0.929
Location						
Upper	6/7	6/15	6.133	0.013*	7.014	0.008**
Middle	42/68	76/161	5.705	0.017*	5.880	0.015*
Lower	13/24	27/53	0.189	0.663	0.316	0.574
Smoking history						
No	14/45	55/120	0.984	0.321	1.040	0.308
Yes	37/54	54/109	8.264	0.004**	9.187	0.002**
Drinking history						
No	38/64	77/169	4.759	0.029*	5.106	0.024*
Yes	23/35	32/60	2.882	0.090	3.619	0.057
Grade						
G1 + G2	37/63	70/161	6.056	0.014*	6.871	0.009**
G3	24/36	39/68	1.566	0.211	1.849	0.174
Pathological T stage						
T1 + T2	14/31	26/79	1.716	0.190	1.566	0.211
T3 + T4	47/68	83/150	5.994	0.014*	6.980	0.008**
Lymph node involvement						
No	22/53	49/134	0.319	0.572	0.290	0.590
Yes	39/46	60/95	15.348	< 0.001***	16.341	< 0.001***
TNM staging						
I+II	22/52	50/140	0.602	0.438	0.553	0.457
III+IV	39/47	59/89	10.589	0.001**	12.486	< 0.001***

Note: *: $P<0.05$; **: $P<0.01$; ***: $P<0.001$

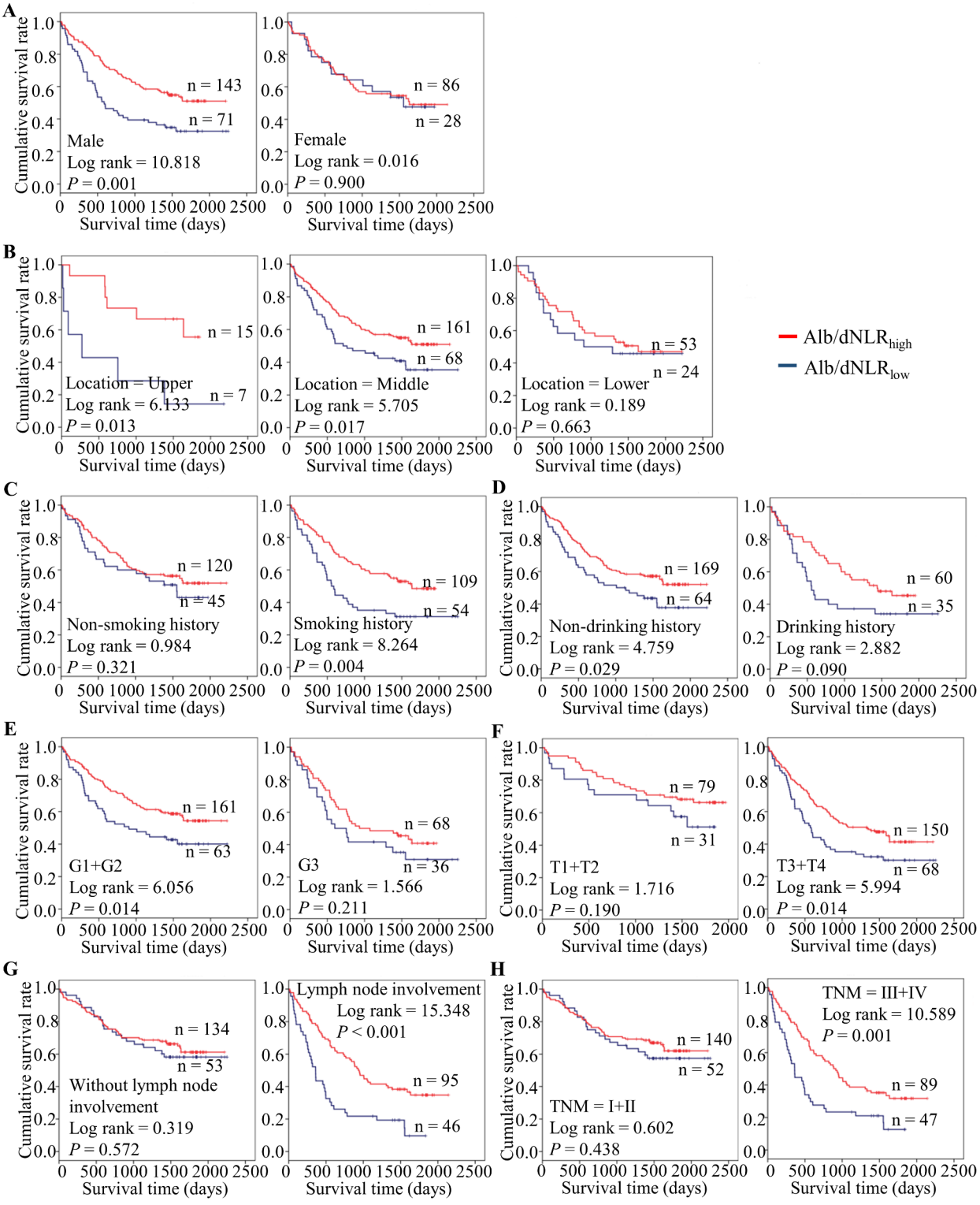

Fig. 3 The stratified analysis on predicating role of preoperative Alb/dNLR ratio for the OS of ESCC patients aged 60 years and above. A-I: Kaplan-Meier survival curves of ESCC patients with different Alb/dNLR ratio combined with diverse features such as sex (A), tumor location(B), smoking history(C), drinking history(D), tumor grade (E), T staging (F), lymph node involvement (G), and TNM staging (H).

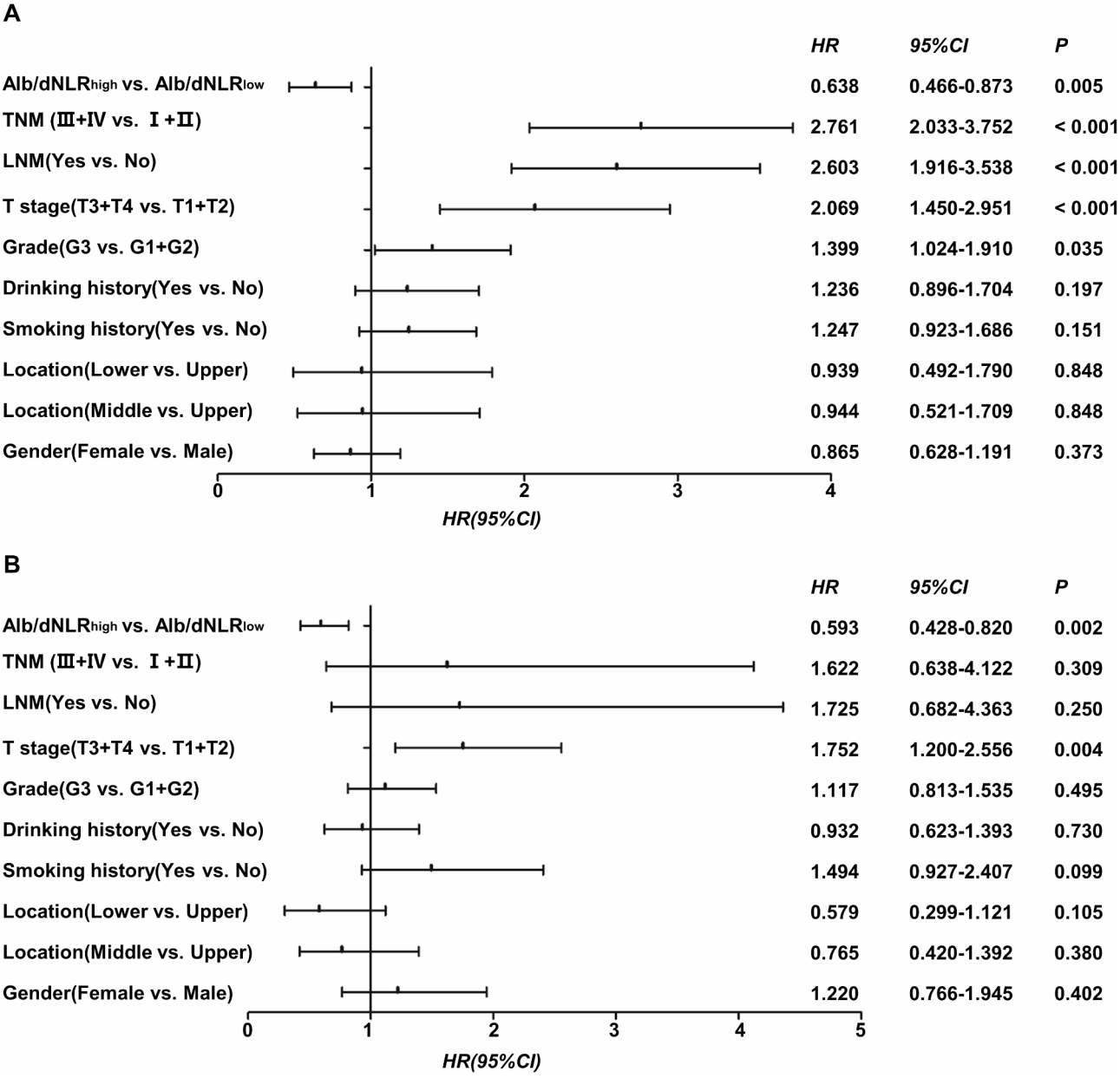

Fig. 4 Predicating role of preoperative Alb/dNLR ratio for risk of deaths of ESCC patients. (A) and (B) represent univariable and multivariable analysis by Cox proportional hazard regression model, respectively.

Discussion

In the present study, we examined the predictive ability of preoperative Alb level to dNLR and explored its clinical efficacy in predicting survival in patients with ESCC aged 60 years and above. We explored the plausible connection between Alb to dNLR and clinicopathological characteristics, including ESCC survival. Surprisingly, it was not correlated with various characteristics of elderly patients with ESCC who were ≥ 60 years of age, such as sex, tumor location, smoking and drinking history, TNM stage, and lymph node involvement. However, this biomarker is associated with survival status. This finding indicated that a lower Alb/dNLR ratio was significantly positively correlated with death in patients with ESCC aged 60 years and above.

It has been previously suggested that Alb/dNLR ratio is related to cancer-related death and treatment outcomes in some types of cancer. ΔAlb-dNLR is a beneficial prognostic factor for OS in patients with ESCC receiving neoadjuvant chemotherapy (nCT) [13]. Similarly, ΔAlb-dNLR shows significant potential as a usable and predictive biomarker for OS and DFS in locally advanced rectal cancer (LARC) patients undergoing neoadjuvant chemoradiotherapy (nCRT) [15]. The present investigation

confirmed that ESCC patients aged ≥ 60 years with diminished Alb/dNLR ratio presented worse clinical outcomes than those with higher Alb/dNLR. Moreover, further strata analysis yielded ideal prediction results for the survival of patients with ESCC. Previous studies have revealed that the survival and recurrence of esophageal carcinoma varies by sex regarding genetic/epigenetic alterations [16]; female sex potentially confers superior survival, a more negligible probability of tumor recurrence, and a better response to neoadjuvant chemotherapy [17]. Our analysis also showed a similar sex-related difference in survival. A lower Alb/dNLR ratio predicted poor survival in the male sex subgroup than in the corresponding female group. Evidence suggests a correlation between the primary location of esophageal cancers and distant metastases [18]. In contrast to lower esophageal cancer, which is more frequently linked to liver invasion, patients with upper esophageal cancer are more likely to develop lung metastasis. In the subgroups with upper and middle ESCC, we discovered that a lower Alb/dNLR ratio was more effective in predicting prognosis, indicating a relationship with tumor location. Considering the small number of upper ESCC cases, further research on location-related ESCC is required. Epidemiologically, alcohol consumption and smoking increase the risk of developing ESCC. According to previous studies, alcohol and tobacco use can have a favorable synergistic effect that increases the risk of ESCC by three times compared to the projected risk of any one item alone (20–30%) [19]. Smoking, alcohol consumption, and areca nut consumption may contribute to the onset of ESCC in men, as they have been shown to influence age at onset [20]. We found that lower Alb/dNLR ratio was associated with poor clinical outcomes of ESCC in the smoking and non-alcohol drinking groups.

Metastasis frequently results in adverse clinical outcomes in ESCC patients. Regarding ESCC, there is a noteworthy association between LNM and malignant characteristics. It could serve as a standalone prognostic factor for ESCC and predict worse outcome [21]. A slightly higher rate of LNM has been reported in the literature (36.8%), and 246 of 302 (43.77%) ESCC cases in our sample showed lymph node involvement. The tumor invasion depth may be related to varying LNM rates, as demonstrated by Min et al. [22]. Tumors infiltrating the SM1 layer, muscularis mucosa, and lamina propria had LNM rates of 40.7, 15.5, and 3.7%, respectively. Our study focused on the clinical utility of Alb/dNLR ratio in ESCC with or without lymphatic metastasis, and showed that decreased Alb/dNLR ratio accelerated the malignant outcome of ESCC patients ≥ 60 years with lymphatic metastasis. This finding implies that Alb/dNLR ratio may have a unique function in cancer development.

Generally, the TNM stage indicates the tumor load in patients with cancer. Poor survival is a consequence of advanced TNM stage in addition to an increased likelihood of metastasis, which includes greater lymph node involvement. Over the last few years, asymptomatic early illness and delayed diagnosis have hampered therapeutic benefits for patients with ESCC [1]. According to the results of the current investigation, 136 of 238 patients (41.47%) had advanced disease and 69.82% (229/328) were primarily at stage II. Additionally, poor prognosis and lymph node involvement were predicted by TNM stage [23]. This demonstrates its pro-tumor action in the progression of ESCC. In the subgroup with advanced TNM staging and pathological T stage, a lower Alb/dNLR ratio was associated with inferior survival. This inflammatory biomarker might play an essential role in advanced-stage ESCC. This indicated that Alb/dNLR ratio displayed powerful potential as a prognosis-related marker in advanced ESCC in patients aged ≥ 60 years. Based on these findings, clinicians may be able to determine the population at risk of further exposure to ESCC and where precise therapeutic intervention and clinical management can be tailored. Interestingly, we revealed that low Alb/dNLR represents a poor prognosis in well and moderately differentiated ESCC above 60 years of age. This study sheds light on the underlying mechanism of presurgical Alb/dNLR ratio during ESCC carcinogenesis.

Finally, we screened independent risk predictors for ESCC prognosis in population aged 60 years and above. Univariate analysis revealed that decreased Alb/dNLR ratio and regular invasive parameters such as advanced TNM stage, lymph node metastasis, advanced pathologic T stage, and poor tumor differentiation may cause adverse clinical outcomes in patients with ESCC who were ≥ 60 years of age. Nevertheless, further multivariate analysis revealed that only decreased Alb/dNLR ratio and advanced pathological T stage enhanced the risk of ESCC-related prognosis. Compared to the risk effect of advanced pathological T stage, ESCC patients aged ≥ 60 years with high preoperative Alb/dNLR ratio demonstrated improved postoperative survival outcomes. Our results suggest that Alb/dNLR ratio should be explored to determine their clinical implications.

The generalizability of these results is subject to certain limitations. Owing to tumor heterogeneity, personalized treatment has been employed to achieve satisfactory outcomes. Consequently, it is not unfavorable to perform a subgroup analysis based on distinct therapeutic methods and is also limited by the small number of patients receiving post-surgical treatment. The single-center sample size is the most significant limitation of this study. Inflammation plays a central role in age-related diseases including

cancer [24]. Hence, sample sizes from several centers are necessary to better evaluate Alb/dNLR ratio.

Conclusion

This study discussed the role and possible reasons for Alb/dNLR ratio in predicting survival outcomes in patients with resected ESCC aged ≥ 60 years. The relevance of Alb/dNLR ratio is supported by the current findings. This study has identified that increased Alb/dNLR ratio support a better prognosis of ESCC aged 60 years and above, especially in male patients, patients with lymph node involvement, and patients with advanced disease stage, as well as in patients who smoked and didn't drink alcohol. The insights gained from this study may assist our understanding of Alb/dNLR ratio, which was independently predictive of clinical outcomes according to multivariate analysis of ESCC patients.

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Author contributions
XX performed the analysis and wrote the manuscript; TS, XZ, WW, and YJ completed data collection; JJ supervised the analysis; JJ revised the manuscript. All authors have reviewed the final manuscript and agreed to its submission.

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Data availability
Data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
The present study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the Shanxi Province Cancer Hospital. The Medical Ethics Committee of Shanxi Province Cancer Hospital waived the requirement for written informed consent for participation. Due to the retrospective nature of the study design and the research data being sourced from the hospital's electronic medical record system, which does not involve any intervention or additional risks to patients' current treatment, and does not influence clinical decision-making, it is reasonable to exempt patient consent for this study. The study adhered to the principles of data confidentiality and ensured that all personal information was anonymized to protect patient privacy.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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