



# High programmed death-ligand 1 expression is a poor prognostic indicator for esophageal squamous cell carcinoma and is correlated with two-field lymph node metastasis

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**Background:** This study detected programmed death-ligand 1 (PD-L1) expression in esophageal squamous cell carcinoma (ESCC) samples and investigated the association between the clinicopathological features of ESCC and PD-L1 expression. Furthermore, this study evaluated whether lymph node metastasis (LNM) status affected the prognosis of ESCC patients with diverse PD-L1 expression.

**Methods:** A total of 108 ESCC paraffin-embedded specimens were collected and further used to detect the expression of PD-L1 by immunohistochemistry. The correlation between PD-L1 expression and clinicopathological characteristics and its prognostic significance were evaluated. Finally, the clinical outcomes were investigated in the subgroup of patients with simultaneous high PD-L1 expression and LNM.

**Results:** PD-L1 expression was observed in 85.2% of ESCC cases, 43.5% of which showed high expression. Only N stage (P=0.038) was associated with high PD-L1 expression. Univariate and multivariate Cox regression analyses showed that T stage (P=0.012), N stage (P=0.029), and PD-L1 expression (P=0.044) were independent prognostic factors in ESCC patients. Moreover, further analysis of the N stage subgroup showed that skip LNM (P=0.286) or laryngeal nerve LNM (P=0.387) showed no prognostic significance, while two-field LNM was highly correlated with a worse 5-year overall survival (P=0.037).

**Conclusions:** High PD-L1 expression was significantly correlated with N stage and can be used as an independent prognostic biomarker in ESCC. Its expression level can also be used to guide appropriate lymph node dissection in ESCC.

**Keywords:** Esophageal squamous cell carcinoma (ESCC); programmed death-ligand 1 (PD-L1); prognosis; lymph node metastasis (LNM)

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## Introduction

Esophageal cancer is the seventh most malignant tumors; with high mortality, it also ranks sixth in cancer-related deaths worldwide (1). The two major histological types are esophageal adenocarcinoma (EC) and esophageal squamous

cell carcinoma (ESCC). The former frequently occurs in western countries, while the latter is more predominant in Asian countries, particularly China, accounting for more than 90% of the total cases (2). Despite advances in therapy such as surgery, radiation therapy, chemotherapy, and

biological therapy, the prognosis of ESCC patients remains poor, with a 5-year overall survival rate of 20–30% (3). Among related factors, lymph node metastasis (LNM) is central to unfavorable prognosis. Therefore, there is a need to identify effective prognostic biomarkers, to develop innovative therapeutics, and to improve ESCC patient survival.

The programmed cell death 1/programmed death-ligand 1 (PD-1/PD-L1) signaling pathway plays a vital role in tumor immune escape (4), leading to the poor prognosis of cancer patients (5). Several studies have demonstrated the association of PD-L1 expression with adverse outcomes of patients with various types of malignant tumors, including non-small cell lung cancer, gastric cancer, renal cell carcinoma, colorectal cancer, and breast cancer (6–9). Immunological checkpoint inhibitors targeting the PD-1/PD-L1 pathway in a variety of human tumor therapies are promising therapeutics (10). However, as only a minority of patients can benefit from immunotherapy, the identification of predictive indicators to guide treatment decisions is of widespread concern in clinical practice. Although the prognostic value of PD-L1 expression in ESCC patients has been partly investigated, the conclusions remain controversial. Therefore, the present study further assessed PD-L1 expression in ESCC to determine its correlation with clinicopathological features and prognosis and explore the association between PD-L1 expression and LNM status in ESCC to provide a reference for the clinical treatment of esophageal cancer.

## Methods

### *Patients and samples*

The present study enrolled 108 patients with ESCC who underwent minimally invasive esophagectomy in the Thoracic Department of Fujian Medical University Union Hospital between January 2012 and March 2014. No patients received preoperative neoadjuvant therapy. The clinicopathologic features of each patient are summarized in *Table 1*. The clinical stages of the tumors were determined according to the 8th American Joint Commission on Cancer TNM staging system. Complete follow-up data from the postoperative period were available for these patients. This study was approved by the ethics committee of Fujian Medical University Union Hospital, Fuzhou, China (No. 2016KY012).

### *Immunohistochemistry*

Formalin-fixed and paraffin-embedded tissue samples were serially cut into 4- $\mu$ m-thick sections for immunohistochemical (IHC) analysis. In brief, sections were deparaffinized and hydrated, followed by antigen retrieval (95 °C, 20 min). After blocking endogenous peroxidase activity, the sections were incubated with anti-PD-L1 rabbit monoclonal primary antibody (dilution 1:50; ab213524; Abcam, Cambridge, MA, USA) for 2 hours at room temperature or overnight at 4 °C. Following three rinses in phosphate-buffered saline (PBS), the sections were incubated with an anti-rabbit polymer (Envision Plus; Fuzhou Maixin Biotechnology Company, Fuzhou, China) for 15 min at room temperature. Thereafter, staining was performed with a 3,3-diaminobenzidine (DAB) solution. The sections were visualized with DAB and lightly counterstained with hematoxylin for histological observation on a light microscope (11).

### *Evaluation of immunostaining*

All slides were evaluated independently by two senior pathologists who were blinded to patients' clinicopathological characteristics. The proportion of stained tumor cells was semi-quantitatively scored as 0% (n=0), 1–30% (n=1), 30–60% (n=2), and 60–100% (n=3), while the predominant PD-L1 staining intensity was scored as negative (n=0), weak (n=1), moderate (n=2), or strong (n=3) (12). PD-L1 expression on the normal tonsil tissues was used as a positive control. The final score of each patient was calculated by multiplying the score for the proportion of stained tumor cells by the intensity score (ranging from 0 to 9). Samples with scores  $\geq 4$  were classified as high expression, while the remaining samples were considered low expression.

### *Statistical analysis*

The statistical analyses were conducted using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). The clinicopathological factors were compared between groups by Pearson's chi-square or Fisher's exact tests. The Kaplan-Meier method and log-rank tests were used for survival curve analysis and to determine statistical differences in GraphPad Prism 7.0 (GraphPad Software Inc., San Diego, CA, USA). Univariate and multivariate

**Table 1** The clinicopathologic characteristics of 108 ESCC patients

Index	Cases (n)	Percent (%)
Age (year)		
<60	61	56.5
≥60	47	43.5
Gender		
Female	29	26.9
Male	79	73.1
Nerve invasion		
No	88	81.5
Yes	20	18.5
Vascular invasion		
No	91	84.3
Yes	17	15.7
Tumor size (cm)		
<4	91	84.3
≥4	17	15.7
Tumor grading		
G1	36	33.3
G2	61	56.5
G3	11	10.2
Tumor location		
Upper	7	6.5
Middle	68	62.9
Low	33	30.6
T stage		
T1a	21	19.4
T1b	15	13.9
T2	56	51.9
T3	16	14.8
N stage		
N0	62	57.4
N1	31	28.7
N2	11	10.2
N3	4	3.7
TNM stage		
I	18	16.7
II	40	37
III	43	39.8
IV	7	6.5

survival analysis adopted a Cox proportional hazards regression model. P values <0.05 in all statistical tests were statistically significant.

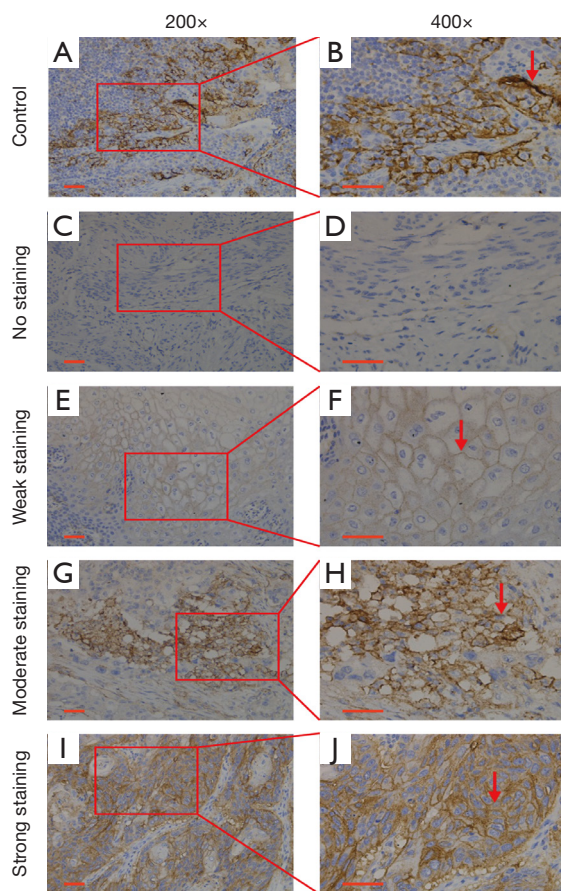
## Results

### *Patient characteristics*

As shown in *Table 1*, the cohort comprised 29 (26.9%) female and 79 (73.1%) male patients with a median age of 60 years (range, 31–71 years). Seventeen (15.7%) and 20 (18.5%) patients had vascular and nerve invasion, respectively. Seven (6.5%), 68 (62.9%), and 33 (30.6%) tumors were in the upper, middle, and lower locations, respectively. Most patients (84.3%) had tumors <4 cm in diameter. The tumor grades included low (36 patients, 33.3%), intermediate (61, 56.5%) and high (11, 10.2%). By staging, 21 (19.4%), 15 (13.9%), 56 (51.9%), and 16 (14.8%) tumor were T1a, T1b, T2, and T3, respectively. Regarding LNM, 46 (42.6%) patients were node-positive (28.7% in N1, 10.2% in N2 and 3.7% in N3). Among all patients, 18 (16.7%), 40 (37.0%), 43 (39.8%), and 7 (6.5%) were classified as stage I, II, III, and IV, respectively according to TNM staging.

### *Association of PD-L1 expression with clinicopathological characteristics of patients with ESCC*

PD-L1 protein expression was examined by IHC in 108 ESCC tissue samples. Representative images of negative expression and weak, moderate, and strong PD-L1 staining are shown in *Figure 1*. PD-L1 IHC staining was predominantly present on the cell membrane of ESCC tissues. Stained tonsil tissue was used as a positive control. PD-L1 expression in the ESCC specimens in the present study was categorized as low (<4) and high (≥4) for further analysis according to the evaluation scores defined above. In this study, 43.5% of cases showed high PD-L1 expression, while 56.5% showed low expression. Analysis of the associations between clinicopathological characteristics and PD-L1 expression showed that only N stage was significantly correlated with high expression (P=0.038), while age (P=0.859), sex (P=0.113), nerve invasion (P=0.882), vascular invasion (P=0.832), tumor size (P=0.788), tumor grade (P=0.071), tumor location (P=0.816), T stage (P=0.991), and TNM stage (P=0.070) were not (*Table 2*).



**Figure 1** IHC for PD-L1 in ESCC. Tonsil tissue was stained with an anti-PD-L1 antibody as a positive control (A:  $\times 200$ ; B:  $\times 400$ ). Negative staining in ESCC tissue (C:  $\times 200$ ; D:  $\times 400$ ). Weak staining in ESCC tissue (E:  $\times 200$ ; F:  $\times 400$ ). Moderate staining in ESCC tissue (G:  $\times 200$ ; H:  $\times 400$ ). Strong staining in ESCC tissue (I:  $\times 200$ ; J:  $\times 400$ ). The red arrow indicates positive PD-L1 staining on the cell membrane. ESCC, esophageal squamous cell carcinoma; IHC, immunohistochemistry; PD-L1, programmed cell death ligand 1.

### Overall survival (OS) in ESCC

The median follow-up duration was 54.1 months (range, 2.3–84.1 months). Univariate and multivariate analyses were conducted to identify clinicopathological features affecting the prognosis of ESCC patients. As shown in *Table 3*, univariate Cox regression showed that T stage ( $P < 0.001$ ), N stage ( $P < 0.001$ ), TNM stage ( $P = 0.004$ ), and high PD-L1 expression ( $P = 0.032$ ) were prognostic factors contributing to poor 5-year OS (*Table 3*). Moreover, multivariate analysis revealed that T stage ( $P = 0.001$ ), N stage ( $P = 0.031$ ) and

PD-L1 expression ( $P = 0.049$ ) were independent prognostic factors. In this study, Kaplan-Meier analyses demonstrated unfavorable OS in patients with high PD-L1 expression compared to that in patients with low PD-L1 expression (*Figure 2A*). Furthermore, T, N, and TNM stage were also significantly related to patient OS (*Figure 2B,C,D*).

### PD-L1 high expression correlated with LNM

The subgroup analysis stratified patients with both high PD-L1 expression and LNM into three LNM statuses: skip- or skip+ LNM, the LNM around recurrent laryngeal nerve (RLN+ or RLN- LNM), and the different operative fields of LNM (two-field or one-field LNM). The results revealed that skip ( $P = 0.730$ ) and RLN ( $P = 0.441$ ) LNM status were not associated with a worse prognosis (*Figure 3A,B*), whereas the OS of two-field LNM (0%) was significantly lower than that of one-field LNM (49.0%) ( $P = 0.040$ ) (*Figure 3C*). In this study, skip LNM was defined as LNM out of the adjacent lymph node areas. For example, the adjacent lymph nodes for the middle thoracic ESCC were the upper, middle, and lower thoracic lymph nodes, while cervical and abdomen lymph nodes metastasis were considered skip LNM.

### Discussion

Recent advances in cancer immunology have emphasized the importance of the PD-1 signaling pathway (13). PD-1 is a negative costimulatory receptor expressed mainly on activated T cells. The interaction of PD-1 with its ligands, PD-L1 or PD-L2, plays an important role in antigen-specific T-cell response, mediating PD-1-dependent immune suppression, which facilitates tumor cell escape from immune surveillance and promotes tumor progression (4,14,15). PD-L1 can be expressed in both tumor and immune cells (16). In this study, the PD-L1 was widely expressed in ESCC tissue samples, with high expression observed in 43.5% of samples. This result was consistent with those previously reported by Ohigashi *et al.* (43.9%) (17) and Chen *et al.* (41.4%) (18).

The relationship between PD-L1 expression and prognosis in esophageal cancer is controversial and difficult to clarify (19–22). A recent meta-analysis of 18 published studies and 3,306 patients with esophageal cancer reported summary statistics indicating that PD-L1 overexpression had an unfavorable impact on OS, with a pooled hazard ratio (HR) of 1.42 (95% CI: 1.09–1.86) (23). In the

**Table 2** The correlation between PD-L1 expression and the clinicopathological features

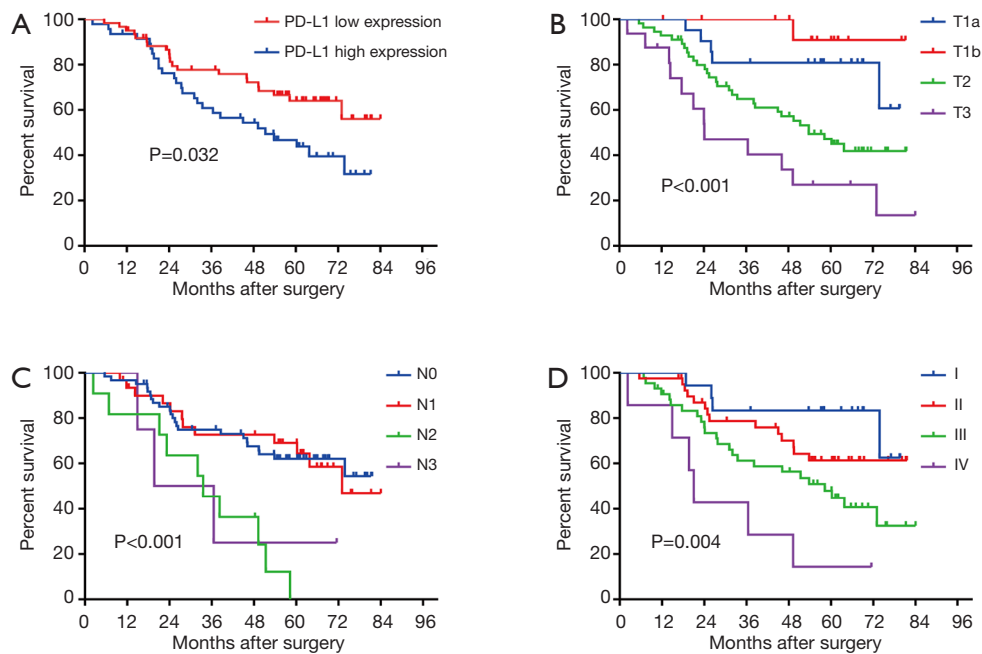
Variable	Cases	PD-L1 expression		$\chi^2$ score	P value
		Low (n=61)	High (n=47)		
Age (year)				0.032	0.859
<60	61	34	27		
≥60	47	27	20		
Gender				2.514	0.113
Female	29	20	9		
Male	79	41	38		
Nerve invasion				0.022	0.882
No	88	50	38		
Yes	20	11	9		
Vascular invasion				0.045	0.832
No	91	51	40		
Yes	17	10	7		
Tumor size (cm)				0.072	0.788
<4	75	43	32		
≥4	33	18	15		
Tumor grading				5.19	0.071
G1	36	24	12		
G2	61	34	27		
G3	11	3	8		
Tumor Location				0.637	0.816
Upper	7	3	4		
Middle	68	39	29		
Low	33	19	14		
T stage				0.184	0.991
T1a	21	12	9		
T1b	15	9	6		
T2	56	31	25		
T3	16	9	7		
N stage				7.881	0.038*
N0	62	41	21		
N1	31	16	15		
N2	11	3	8		
N3	4	1	3		
TNM stage				7.002	0.07
I	18	10	8		
II	40	27	13		
III	43	23	20		
IV	7	1	6		

\*, indicates as statistical significance ( $P \leq 0.05$ ).

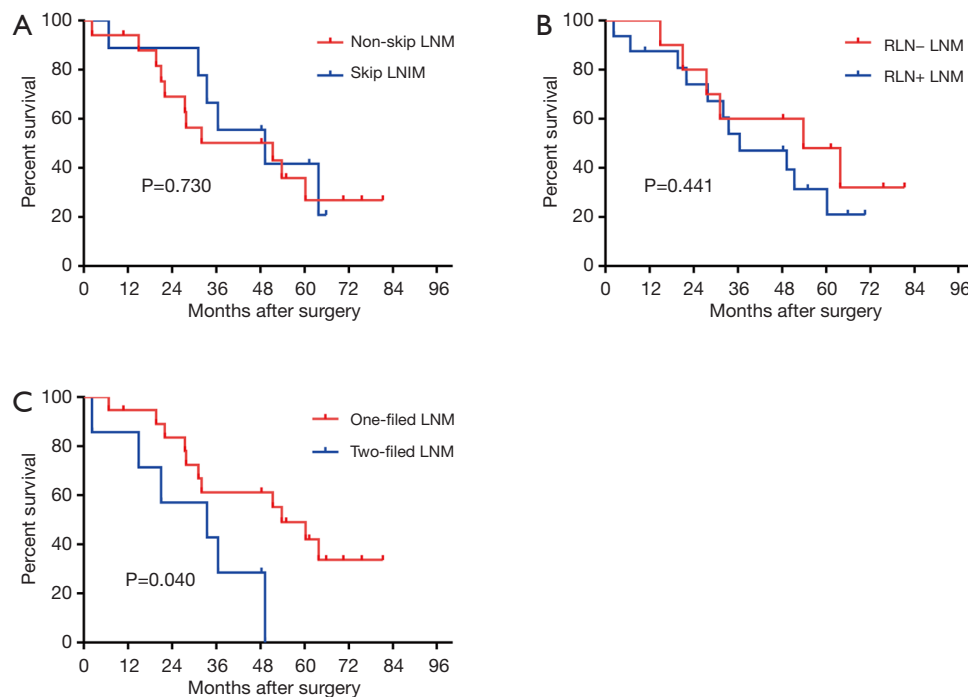
**Table 3** The univariate and multivariate Cox regression analysis of ESCC patients

Variable	Cases	univariate analysis			multivariate analysis		
		HR	95% CI	P	HR	95% CI	P
Age(year)							
<60	61	1					
≥60	47	1.661	0.942–2.929	0.080			
Gender							
Female	29	1					
Male	79	0.803	0.429–1.502	0.492			
Nerve invasion							
No	88	1					
Yes	20	1.773	0.936–3.358	0.079			
Vascular invasion							
No	91	1					
Yes	17	1.821	0.927–3.574	0.082			
Tumor size, cm							
<4	65	1					
≥4	33	1.354	0.748–2.449	0.317			
Tumor grading							
G1	36	1					
G2/3	72	1.201	0.652–2.215	0.557			
Tumor location							
Upper/middle	75	1					
Low	33	0.630	0.327–1.214	0.167			
T stage							
T1	36	1			1		
T2–3	72	4.657	1.978–10.968	<0.001*	4.168	1.727–10.060	0.001*
N stage							
N0-1	93	1			1		
N2–3	15	3.565	1.857–6.843	<0.001*	2.129	1.073–4.224	0.031*
TNM stage							
I-II	58	1			1		
III-IV	50	2.385	1.328–4.282	0.004*	0.904	0.426–1.920	0.794
PD-L1 expression							
Low	61	1			1		
High	47	1.869	1.056–3.310	0.032*	1.81	1.001–3.277	0.049*

\*, indicates as statistical significance ( $P \leq 0.05$ ). HR, hazard ratio; CI, confidence interval.



**Figure 2** Kaplan-Meier plot of overall survival in all ESCC patients according to tumor PD-L1 expression, T stage, N stage, and TNM stage. Tumor expression of PD-L1 (A,  $P=0.032$ ), T stage (B,  $P<0.001$ ), N stage (C,  $P<0.001$ ), and TNM stage (D,  $P=0.004$ ). P values were calculated by log-rank analysis.



**Figure 3** Kaplan-Meier plot of overall survival in 26 esophageal squamous cell carcinoma patients with high PD-L1 expression and LNM according to skip LNM, recurrent laryngeal nerve (RLN) LNM, and different fields of LNM. Skip LNM (A,  $P=0.730$ ), RLN LNM (B,  $P=0.441$ ), different fields of LNM (C,  $P=0.040$ ). The P values were calculated by Log-rank analysis.

present study, both univariable and multivariable survival analyses demonstrated that high PD-L1 expression was an independent prognostic factor (HR: 1.810, 95% CI: 1.001–3.277,  $P=0.049$ ), a finding consistent with previous reports. In addition, Kaplan-Meier survival analyses showed that ESCC patients with high PD-L1 expression had more unfavorable clinical outcomes compared to those in patients with low PD-L1 expression. Our results provided new evidence and reconfirmed that high PD-L1 expression predicts adverse clinical outcomes in patients with ESCC.

Increasing numbers of studies have semi-quantitatively detected PD-L1 expression in tumor tissues by IHC. PD-L1 expression is heterogeneous, which may be related to the accuracy of IHC detection in different studies. The main factors are as follows: first, the antibody sensitivities and concentrations may not be the same. Secondly, the evaluation criteria for high PD-L1 expression varied in different studies (18). Finally, PD-L1 heterogeneity in tumors and different sampling times and sampled areas can also affect PD-L1 staining results (24).

The patients in the present study were classified into high and low PD-L1 expression groups. We observed a significant correlation between high PD-L1 expression and N stage, similar to a previous finding (17). LNM is widely regarded as the key factor affecting 5-year OS in ESCC patients; however, skip LNM, RLN LNM, and the operative fields LNM remain fiercely contested by scholars at home and abroad (25–27). The results of this study showed that PD-L1 expression and N stage were both independent prognostic factors in ESCC patients. Subgroup analyses were conducted to determine the effects of LNM status on prognosis in patients with high PD-L1 expression. The high PD-L1 expression group was further divided into three groups according to LNM status. We observed a lower 5-year OS rate in patients with two-field LNM than that in patients with one-field LNM, while skip and RLN LNM showed no prognostic significance.

The present study first explored the correlation between prognosis and skip LNM in ESCC patients. However, we observed no difference in 5-year OS between these two groups (52.0% in the skip+ and 36.9% in the skip–LNM groups,  $P=0.286$ ). Moreover, lymph node dissection around the recurrent laryngeal nerve is the focus of esophagectomy (26). The harvested number and quality of lymph node dissection in this site directly affect the recurrence and long-term survival of ESCC patients (28). Therefore, this study analyzed the impact of RLN LNM on the prognosis of ESCC patients. We observed no significant

difference in 5-year OS between RLN+ (54.2%) and RLN– (43.6%) LNM ( $P=0.387$ ).

Did esophagectomy accompany two-field or three-field lymphadenectomy? Western scholars have suggested that LNM is a systemic disease, especially cervical LNM, which is not an option for radical dissection through surgery. However, eastern scholars, including those in China and Japan, consider cervical LNM to be regional metastasis; thus, they are a local disease and should undergo radical resection. These different views partially stem from the different esophageal pathology types between Western and Eastern countries (27,29,30). In this study, the 5-year OS of two-field LNM was only 12.1%, significantly lower than that of one-field LNM (58.6%,  $P=0.037$ ). This finding has important implications for the development of individualized treatment strategies, suggesting the need for moderated expanded lymphadenectomy for ESCC patients with high PD-L1 expression. Expanded lymphadenectomy cannot only enhance the detection rate of LNM and facilitate accurate pathological staging but can also guide the comprehensive treatment and improve the OS of ESCC patients. Unfortunately, the present study did not include any patients with simultaneous three-field LNM, possibly due to the limited number of cases of this study and the fact that surgery was ruled out for patients with preoperative concurrent three-field LNM.

This study has several limitations. Firstly, the results might be influenced by selection bias due to the retrospective assessment of data from a single institution. Further validation is required in large-scale, multi-center prospective studies. Secondly, PD-L1 expression was evaluated from a partial tumor sample; thus, we could not differentiate tumor heterogeneity. Hence, the reproducibility of our results requires further validation. Finally, IHC was used to evaluate the clinical significance of PD-L1 but could not address mechanistic questions.

## Conclusions

The results of this study demonstrated widespread PD-L1 expression in ESCC patients and that high PD-L1 expression was closely associated with N stage. High PD-L1 expression was also significantly related to poor 5-year OS and can serve as an independent prognostic biomarker for ESCC. In addition, our findings suggested that patients with simultaneous high PD-L1 expression and two-field LNM had a worse prognosis, providing further evidence of the significance of moderated expanded lymphadenectomy.



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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.03.22>). 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. This study was approved by the ethics committee of Fujian Medical University Union Hospital, Fuzhou, China (No. 2016KY012) and written informed consent was obtained from all patients.

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