Original Article

A new risk score model based on lactate dehydrogenase for predicting prognosis in esophageal squamous cell carcinoma treated with chemoradiotherapy

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Background: The prognostic role of lactate dehydrogenase (LDH) has been confirmed in many malignant tumors, but it has not been widely discussed in esophageal squamous cell cancer (ESCC). This study aimed to assess the prognostic value of LDH in patients with ESCC and to generate a risk score model to predict prognosis in patients who were treated with chemoradiotherapy.

Methods: A total of 614 patients with ESCC who received chemoradiotherapy from 2012 to 2016 were examined in this single-center retrospective study. The optimal cutoff points for age, cytokeratin 19 fragment antigen 21-1 (Cyfra21-1), carcinoembryonic antigen (CEA), tumor length, total dose, and LDH were calculated by the X-tile software. We analyzed the association between the level of LDH and clinicopathological characteristics, and a 1:3 propensity score matching analysis was used to compensate for differences in baseline characteristics. Kaplan-Meier and Cox regression models were used to determine the prognostic factors for overall survival (OS) and progression-free survival (PFS). Based on the results, we developed a corresponding risk score model and established a nomogram to assess its predictive capacity.

Results: The optimal cutoff point of LDH was 134 U/L. Patients in the high-LDH group had significantly shorter PFS and worse OS than did those in the low-LDH group (all P values <0.05). Multivariate survival analysis indicated that pretreatment serum LDH level (P=0.039), Cyfra21-1 level (P=0.003), tumor length (P=0.013), clinical N stage (P=0.047), and clinical M stage (P=0.011) were independent predictors for OS in patients with ESCC who underwent chemoradiotherapy. Furthermore, a risk score model based on these 5 prognostic factors was established to divide patients into 3 prognostic groups to identify those patients with ESCC who were most likely to benefit from chemoradiotherapy (χ^2=20.53; P<0.0001). However, the prediction nomogram that integrated the significant independent factors for OS is not performed very well in predicting survival (C-index =0.599).

Conclusions: Pretreatment serum LDH level may be a reliable factor in predicting the therapeutic effect of chemoradiotherapy in ESCC. Further validation is needed before this model can be widely used in clinical practice.

Keywords: Lactate dehydrogenase; esophageal squamous cell carcinoma; chemoradiotherapy; prognosis

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Introduction

Esophageal cancer (EC) is a common malignancy with an increasing incidence, ranking sixth as a leading cause of cancer-related death worldwide (1,2). More than 85% of all EC cases are diagnosed with esophageal squamous cell carcinoma (ESCC) (3). Despite advancement in therapeutic strategies having improved the prognosis of patients with ESCC, the long-term survival of these patients remains dismal (4). It is widely acknowledged that TNM staging system is correlated with survival in predicting prognosis for ESCC (5). However, clinical outcomes can vary greatly among patients, even at those at the same stage of disease. Therefore, identifying potential indicators and establishing an accurate and dependable prediction model for evaluating the prognosis of patients with ESCC before treatment is critically important to clinical practice.

Lactate dehydrogenase (LDH) is a key enzyme involved in anaerobic glycolysis, mainly catalyzing the conversion between pyruvate and lactate, and the expression of serum LDH levels in tumor tissue is higher than that in normal tissue due to the fact that tumor cells are mainly powered by anaerobic fermentation (6) Patients may experience elevated serum LDH levels due to active cell proliferation, enhanced metabolism, and increased normal tissue infiltration prior to progression, leading to low survival rates in patients with tumor metastasis in various cancer types (7). A growing number of studies are providing insight into the relationship between LDH and overall survival (OS) in different malignancies, such melanoma (8), lymphoma (9), nasopharyngeal carcinoma (10), lung cancer (11,12), and pancreatic carcinoma (13). Several investigators also scrutinized the prognostic value of LDH in ESCC, such as ESCC patients receiving surgical treatment (14-16) or immunotherapy (17,18), or chemoradiotherapy but reached inconsistent conclusions (19,20), serum LDH thereby remains a controversial prognostic biomarker concerning its value in ESCC prognosis and needs to be further investigated. Furthermore, studies regarding the influence of LDH on the prognosis have rarely examined those patients with ESCC who have undergone chemoradiotherapy. A prognostic classification model for predicting the outcome of ESCC patients based on genetic information obtained from ESCC samples has also been reported by Lian *et al.* (21). Considering the significant differences in prognosis among ESCC patients, it is crucial to develop a reliable and convenient prognostic tool to guide prognosis. Besides, serum LDH levels, which is easily available in routine clinical practice. Thus, we conducted a sing-center retrospective analysis aimed at investigating the prognostic value of LDH level in patients with ESCC who received chemoradiotherapy. We further performed univariate and multivariate analyses to identify the prognostic factors in patients with ESCC. Based on the results of the multivariate analysis, we designed a risk score model for determining the prognosis of patients with ESCC who have undergone chemoradiotherapy in order to guide personalized management. And then a nomogram is established to stratify patients at different risk of clinical outcomes. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-388/rc).

Highlight box

Key findings

- Pretreatment serum LDH levels may be a reliable factor in predicting the therapeutic effect of chemoradiotherapy in ESCC.

What is known and what is new?

- TNM staging system has been correlated with survival in predicting prognosis for ESCC, and the prognostic value of LDH has been confirmed in many malignant tumors.
- LDH may be a powerful independent predictor for OS in patients with ESCC treated with chemoradiotherapy.

What is the implication, and what should change now?

- An accurate and dependable prediction model that incorporated LDH level was established for evaluating the prognosis of patients with ESCC. Studies with greater homogeneity are needed to confirm the results.

Methods

Patient characteristics and study design

The data of 614 patients were retrieved from the database of Shandong Cancer Hospital from January 1, 2012, to December 31, 2016. All patients had either rejected surgery or were unable to undergo surgery. The criteria for study inclusion were the following: (I) pathologically or cytologically proved ESCC; (II) undergone chemoradiotherapy before recurrence or progression; (III) no acute or chronic inflammatory diseases or infections, such as acute myocardial infarction, acute hepatitis B virus infection, acute cholecystitis, and bone diseases; and (IV) no evidence of prior malignant carcinoma with the previous 5 years. The following clinical data were collected from

the medical records: gender, age, performance status (PS), clinical T stage (cT), clinical N stage (cN), clinical M stage (cM), tumor length, baseline LDH levels, date of diagnosis, and recurrence date. All the pathological diagnoses were confirmed by pathologists in our department. The TNM stage in this study was determined according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system (seventh edition) (22). The PS was defined according to the criteria of Eastern Clinical Oncology Group (ECOG) (23). Our study also included several previously identified prognostic factors to adjust the prognostic effect of LDH, such as cytokeratin 19 fragment antigen 21-1 (Cyfra21-1) and carcinoembryonic antigen (CEA). The LDH, Cyfra21-1 and CEA levels were tested by the reagents used to in our hospital. Those patients with incomplete medical records were further excluded. All registered patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Shandong Cancer Hospital (No. SDTHEC2023004014).

Treatment protocol and follow-up

The therapeutic strategies were based on the National Comprehensive Cancer Network (NCCN) clinical practice guidelines. All participants underwent 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). They underwent radiotherapy for 4–7 weeks, receiving a total dose of 45–70 Gy. Each patient with ESCC received concurrent chemoradiotherapy (CCRT) or sequential chemoradiotherapy (SCRT) based on the individualized treatment strategy. The chemotherapy regimens mainly included cisplatin plus 5-fluorouracil or cisplatin plus paclitaxel. The patients were followed up every 3–6 months, and the overall follow-up time was at least 2 years. Overall survival (OS) was defined as the date of pathological diagnosis to the date of death or last follow-up. Progression-free survival (PFS) interval was defined as the date of pathological diagnosis to the date of disease progression or the date of death or last contact.

Statistical analyses

Statistical analyses were performed using SPSS version 24.0 (IBM Corp.). The continuous variables were stratified into 2 groups by the optimal cutoff points using the X-tile program (24). Chi-squared tests were used to compare categorical data between 2 groups. The OS and PFS were analyzed with the Kaplan-Meier method using GraphPad Prism 7.0. A 1:3 optimal propensity score-matched method was used to control confounding (25). The propensity scores were estimated using a multivariable logistic regression model (25). The covariates used to calculate propensity scores included 15 variables, which were listed in *Table 1*. Univariable and multivariable Cox proportional hazards regression methods were used to the identify independent risk factors of ESCC. A nomogram was developed based on the results of multivariate analysis and by using the rms package in R software version 4.0.5 (http://www.r-project.cog/). The performance of the nomogram was assessed by concordance index (C-index) and calibration curve. Statistical significance was indicated by a P value ≤0.05.

Results

Patient characteristics

The study examined the data from 614 patients with ESCC. There were 478 (77.9%) males and 136 (22.1%) females, with a median age of 63 years (range 35–85). According to the X-tile program, the optimal cutoff points for age, CEA, Cyfra21-1, tumor length, total dose, and LDH were respectively 69 years, 2.4 ng/mL, 6.4 ng/mL, 6.5 cm, 58.8 Gy and 134 U/L. The X-tile analyses for LDH are shown in *Figure 1*. The patients then were stratified into low and high groups based on LDH for further analyses (LDH ≤134 and LDH >134). A total of 546 (88.9%) patients were placed in the high-LDH group, whereas 68 (11.1%) patients were placed in the low-LDH group.

We found that patients with a high-LDH level were associated with more advanced cM stage (P=0.005) and larger tumor length (P=0.026). No statistically significant association was observed between LDH level and other clinical features. To balance differences in the clinical features among groups, all patients were randomly selected and matched in a 1:3 ratio to another group with similar characteristics. A total of 256 patients were matched successfully, with 68 patients in the low-LDH group and 188 in the high-LDH group. Patients' clinical features were balanced between the low-LDH group and the high-LDH group after matching. The correlation between patient characteristics with LDH level is summarized in *Table 1*.

Prognostic value of pretreatment serum LDH levels

In the whole cohort, the median PFS was 31.5 and

Table 1 Clinical features of patients with ESCC based on LDH before and after propensity score matching

Variable	Before matching			After matching		
	Low-LDH (n=68)	High-LDH (n=546)	P value	Low-LDH (n=68)	High-LDH (n=188)	P value
Gender			0.208			0.653
Male	57	421		57	153	
Female	11	125		11	35	
Age (years)			0.176			0.859
≤69	58	427		58	162	
>69	10	119		10	26	
ECOG PS			0.288			0.707
0	34	236		34	99	
1–2	34	310		34	89	
cT stage			0.816			0.856
T1-2	6	53		6	18	
T3-4	62	493		62	170	
cN stage			0.568			0.602
N0	10	67		10	23	
N+	58	479		58	165	
cM stage			0.005			0.937
M0	62	417		62	172	
M1	6	129		6	16	
Differentiation			0.077			0.659
High	61	442		61	172	
Moderate or poor	7	104		7	16	
Length (cm)			0.026			0.655
≤6.5	48	447		48	138	
>6.5	20	99		20	50	
Tumor location			0.308			0.523
Cervical	6	59		6	23	
Upper	24	156		24	59	
Medium	22	232		22	73	
Lower	16	99		16	33	
Radiotherapy technology			0.296			0.635
3DCRT	21	204		21	64	
IMRT	47	342		47	124	
Treatment options						
CCRT	24	255		24	77	

Table 1 *(continued)*

Table 1 *(continued)*

Variable	Before matching			After matching		
	Low-LDH (n=68)	High-LDH (n=546)	P value	Low-LDH (n=68)	High-LDH (n=188)	P value
SCRT	44	291	0.075	44	111	0.413
Total dose (Gy)			0.167			0.669
≤58.8	12	138		12	29	
>58.8	56	408		56	159	
CEA (ng/mL)			0.651			0.552
≤2.4	25	190		25	62	
>2.4	21	199		21	72	
NA	22	157		22	54	
Cyfra21-1 (ng/mL)			0.150			0.665
≤6.4	35	311		35	103	
>6.4	2	41		2	9	
NA	31	194		31	76	

ESCC, esophageal squamous cell carcinoma; LDH, lactate dehydrogenase; ECOG, Eastern Clinical Oncology Group; PS, performance status; Cyfra21-1, cytokeratin 19 fragment antigen 21-1; CEA, carcinoembryonic antigen; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy; cT stage, clinical T stage; cN stage, clinical N stage; cM stage, clinical M stage; NA, not applicable.

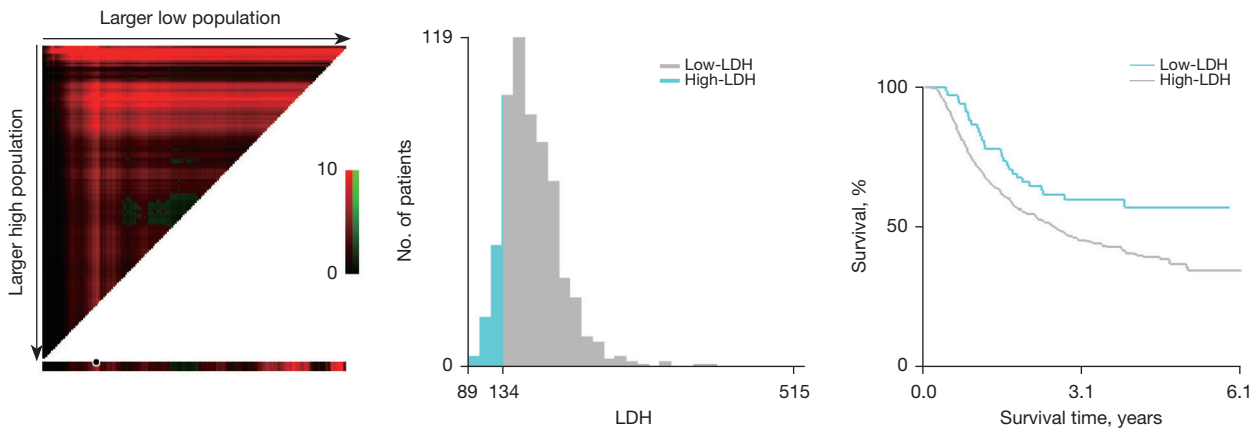

Figure 1 X-tile analyses. The optimum cutoff point for LDH was 134 U/L according to the X-tile program. LDH, lactate dehydrogenase.

17.5 months for the low-LDH group and the high-LDH group, respectively, while the median OS was 32.4 and 25.5 months for the low-LDH group and the high-LDH group, respectively. Notably, more than half of the patients in the low-LDH group survived to the last follow-up. Before matching, the patients in the high-LDH group had significantly shorter PFS and worse OS than did those in the low-LDH group according to Kaplan-Meier analysis (all log-rank P values <0.05, Figure S1).

For the matched cohort, Kaplan-Meier analysis showed that the PFS and OS in the high-LDH group were significantly shorter than those in the low-LDH group (*Figure 2*). The survival curves on OS for Cyfra21-1 level (P=0.0004), tumor length (P=0.0162), cN stage (P=0.0098), and cM stage (P=0.0198) are shown in *Figure 3A-3D*, respectively.

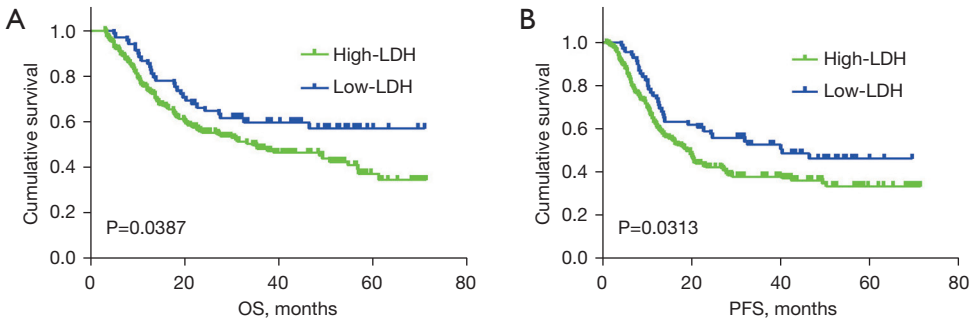

Figure 2 Kaplan-Meier survival curves of OS and PFS grouped by LDH for 256 patients in the matched cohort. (A) The OS curve of patients with ESCC who underwent chemoradiotherapy classified by LDH. (B) The PFS curve of patients with ESCC who underwent chemoradiotherapy classified by LDH. OS, overall survival; PFS, progression-free survival; LDH, lactate dehydrogenase.

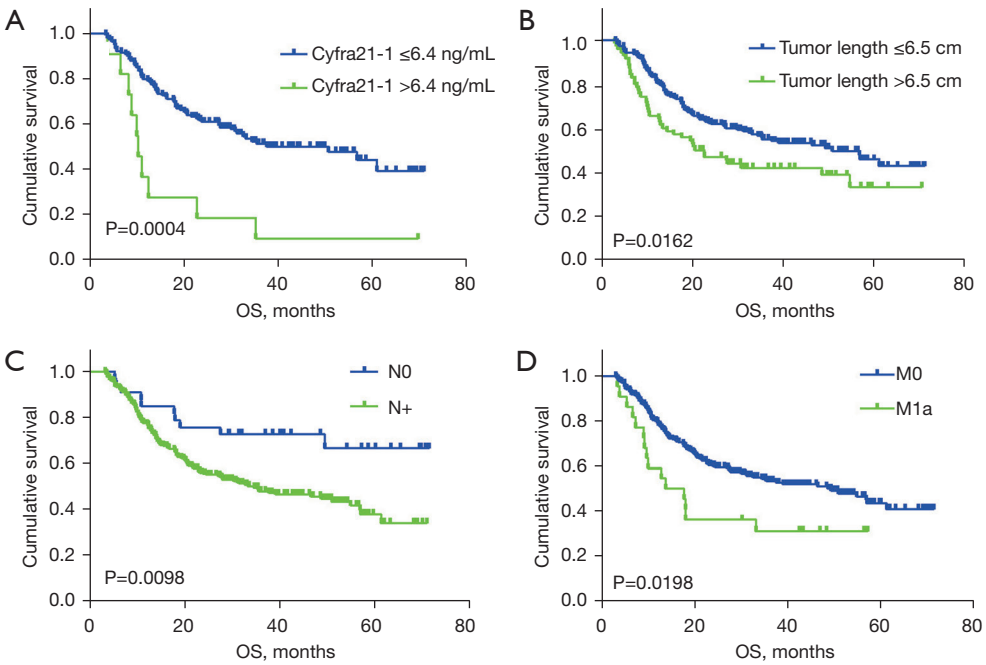

Figure 3 Kaplan-Meier survival curves of OS for patients with ESCC who underwent chemoradiotherapy classified according to the different prognostic factors. (A) Patients classified by Cyfra21-1 (Cyfra21-1 ≤6.4 ng/mL *vs*. Cyfra21-1 >6.4 ng/mL). (B) Patients classified by tumor length (tumor length ≤6.5 cm *vs*. tumor length >6.5 cm). (C) Patients classified by cN stage (N0 *vs*. N+ stage). (D) Patients classified by cM stage (M0 *vs*. M1a stage). OS, overall survival; ESCC, esophageal squamous cell carcinoma; Cyfra21-1, cytokeratin 19 fragment antigen 21-1. cN, clinical N stage; cM, clinical M stage.

Survival risk according to univariate and multivariate Cox regression analysis

The results of univariate and multivariate Cox regression analyses of PFS and OS after chemoradiotherapy of patients with ESCC before matching are presented in Tables S1,S2. After matching, according to the univariate Cox regression analysis of PFS, Cyfra21-1 level, LDH level, and tumor length were significantly associated with tumor recurrence (all P values <0.05). We additionally found there to be a significant correlation between the following characteristics and OS in the univariate analysis: Cyfra21-1 level, tumor length, cN stage, cM stage, and LDH level (all P values <0.05). The significant factors were then subjected to the

Table 2 Univariate and multivariate analysis of PFS in patients with ESCC (N=256) after propensity score matching

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (female *vs.* male)	0.99 (0.66, 1.49)	0.960	–	–
Age (>69 *vs.* ≤69 years)	1.16 (0.75, 1.81)	0.501	–	–
ECOG PS (1–2 *vs.* 0)	1.17 (0.86, 1.61)	0.324	–	–
cT stage (T3–4 *vs.* T1–2)	1.06 (0.61, 1.83)	0.843	–	–
cN stage (N+ *vs.* N0)	1.54 (0.92, 2.58)	0.104	–	–
cM stage (M1 *vs.* M0)	1.40 (0.82, 2.39)	0.213	–	–
Differentiation (moderate/poor *vs.* high)	1.40 (0.83, 2.35)	0.204	–	–
Tumor length (>6.5 *vs.* ≤6.5 cm)	1.58 (1.12, 2.21)	0.009	1.62 (1.15, 2.28)	0.005
Tumor location		0.108		
Upper *vs.* cervical	0.60 (0.36, 1.03)	0.062	–	–
Medium *vs.* cervical	0.82 (0.49, 1.36)	0.437	–	–
Lower *vs.* cervical	1.00 (0.58, 1.74)	0.991	–	–
Radiotherapy technology (IMRT *vs.* 3DCRT)	0.83 (0.60, 1.15)	0.263	–	–
Treatment options (CCRT *vs.* SCRT)	1.29 (0.93, 1.79)	0.126	–	–
Dose (>58.8 *vs.* ≤58.8 Gy)	0.78 (0.52, 1.17)	0.234	–	–
CEA (ng/mL)				
>5.5 *vs.* ≤5.5	1.09 (0.74, 1.59)	0.668	–	–
NA *vs.* ≤5.5	1.04 (0.70, 1.54)	0.855	–	–
Cyfra21-1 (ng/mL)				
>6.4 *vs.* ≤6.4	2.49 (1.29, 4.83)	0.007	2.37 (1.22, 4.60)	0.011
NA *vs.* ≤6.4	0.80 (0.58, 1.12)	0.194	0.80 (0.58, 1.12)	0.196
LDH (>134 *vs.* ≤134 U/L)	1.51 (1.03, 2.20)	0.033	1.50 (1.03, 2.19)	0.035

HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; ECOG, Eastern Clinical Oncology Group; PS, performance status; Cyfra21-1, cytokeratin 19 fragment antigen 21-1; CEA, carcinoembryonic antigen; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy; cT stage, clinical T stage; cN stage, clinical N stage; cM stage, clinical M stage; ESCC, esophageal squamous cell carcinoma; PFS, progression-free survival; NA, not applicable.

multivariate analysis to identify the independent prognostic factors. Multivariate analysis revealed that Cyfra21-1 level [hazard ratio (HR) =2.37, 95% CI: 1.22–4.60; P=0.011], LDH level (HR =1.50; 95% CI: 1.03–2.19; P=0.035), and tumor length (HR =1.62; 95% CI: 1.15–2.28; P=0.005) were independent factors associated with PFS in patients with ESCC; meanwhile, Cyfra21-1 level (HR =2.81; 95% CI: 1.43–5.50; P=0.003), tumor length (HR =1.61; 95% CI: 1.11–2.34; P=0.013), cN stage (HR =1.94; 95% CI: 1.01–3.72; P=0.047), cM stage (HR =2.04; 95% CI: 1.18–3.53; P=0.011), and LDH level (HR: 1.56; 95% CI: 1.02–2.39; P=0.039) were independent factors associated with OS in patients with ESCC (*Tables 2*,*3*).

A new risk score model and a prediction nomogram for OS based on LDH level

A new risk score model for OS among ESCC patients underwent chemoradiotherapy was constructed incorporating the 5 adverse factors (LDH level, tumor length, cN stage, cM stage, and Cyfra21-1 level) identified in the multivariate analysis, According to this prediction

Table 3 Univariate and multivariate analysis of OS in patients with ESCC (N=256) after propensity score matching

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (female *vs.* male)	0.89 (0.56, 1.41)	0.625	–	–
Age (>69 *vs.* ≤69 years)	1.04 (0.63, 1.70)	0.891	–	–
ECOG PS (1–2 *vs.* 0)	1.17 (0.83, 1.65)	0.368	–	–
cT stage (T3–4 *vs.* T1–2)	0.87 (0.49, 1.54)	0.628	–	–
cN stage (N+ *vs.* N0)	2.29 (1.20, 4.38)	0.012	1.94 (1.01, 3.72)	0.047
cM stage (M1 *vs.* M0)	1.88 (1.10, 3.22)	0.022	2.04 (1.18, 3.53)	0.011
Differentiation (moderate/poor *vs.* high)	1.40 (0.80, 2.44)	0.236	–	–
Tumor length (>6.5 *vs.* ≤6.5 cm)	1.56 (1.08, 2.26)	0.017	1.61 (1.11, 2.34)	0.013
Tumor location				
Upper *vs.* cervical	0.68 (0.39, 1.20)	0.134	–	–
Medium *vs.* cervical	0.68 (0.39, 1.20)	0.134	–	–
Lower *vs.* cervical	1.04 (0.57, 1.88)	0.904	–	–
Radiotherapy technology (IMRT *vs.* 3DCRT)	0.80 (0.56, 1.14)	0.220	–	–
Treatment options (CCRT *vs.* SCRT)	1.43 (0.99, 1.79)	0.054	–	–
Dose (>58.8 *vs.* ≤58.8 Gy)	0.75 (0.48, 1.17)	0.206	–	–
CEA (ng/mL)				
>5.5 *vs.* ≤5.5	1.08 (0.71, 1.63)	0.733	–	–
NA *vs.* ≤5.5	1.13 (0.74, 1.73)	0.584	–	–
Cyfra21-1 (ng/mL)				
>6.4 *vs.* ≤6.4	3.17 (1.63, 6.18)	0.001	2.81 (1.43, 5.50)	0.003
NA *vs.* ≤6.4	0.98 (0.68, 1.40)	0.895	1.00 (0.70, 1.44)	0.983
LDH (>134 *vs.* ≤134 U/L)	1.55 (1.02, 2.35)	0.040	1.56 (1.02, 2.39)	0.039

HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; ECOG, Eastern Clinical Oncology Group; PS, performance status; Cyfra21-1, cytokeratin 19 fragment antigen 21-1; CEA, carcinoembryonic antigen; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy (SCRT); cT stage, clinical T stage; cN stage, clinical N stage; cM stage, clinical M stage; ESCC, esophageal squamous cell carcinoma; NA, not applicable.

model, patients were stratified into 3 risk groups with distinct prognoses: low-risk group (0–1 adverse factors), intermediate-risk group (2 adverse factors) and high-risk group (3–5 adverse factors), as shown in *Figure 4* (P<0.0001).

The prediction nomogram that integrated the significant independent factors for OS is shown in *Figure 5*. The C-index for OS prediction was 0.599 (95% CI: 0.569–0.629). It could be observed that lower total points correspond to worse prognosis. The calibration curve for the probability of survival demonstrated good agreement between the prediction and actual observation in the probability of 1-year survival, but a relatively poor agreement for 3-year survival probability (see *Figure 6A*,*6B*).

Discussion

This study demonstrated that lower LDH levels were associated with a better prognosis compared with higher LDH levels, as shown in both multivariable analysis based on the whole cohort of 614 patients and the propensity score-matched cohort of 256 patients. More importantly, it is among the few to establish a new risk prognostic scoring

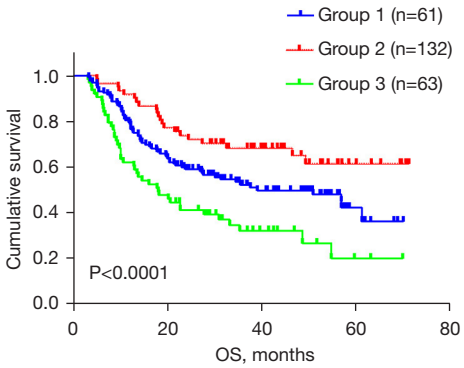

Figure 4 Kaplan-Maier survival curves of overall survival for patients with ESCC who underwent chemoradiotherapy stratified according to the new risk score model. ESCC, esophageal squamous cell carcinoma.

model based on the baseline LDH levels, and it stratified patients into 3 groups with different prognoses. Moreover, our study found that elevated LDH was linked to distant metastasis and larger tumor length, suggesting that a high level LDH is likely to reflect a heavier tumor burden and may represent a more aggressive disease in ESCC.

Studies on whether increased LDH is related to tumor survival have been reported for several solid tumors (9-13). The underlying mechanism between LDH and poor survival remains unknown. It has been hypothesized that elevated serum LDH levels were considered as a marker of tumor hypoxia or immunosuppression in cancer patients (26,27). Alderuccio *et al.* confirmed that the prognosis of patients with lymphoma with high LDH level was poor (9) whereas Ali *et al.* reported pretreatment LDH level to be an independent predictor of OS in nasopharyngeal carcinoma (10). Additionally, de Jong *et al.* reviewed 593 patients with advanced non-small cell lung cancer (NSCLC) and found that a high pretreatment LDH level was related to lower OS (11). Wang *et al.* also reported that high LDH levels indicated poor prognosis for patients with NSCLC and brain metastases (12). Additionally, in a study by Xiao *et al.*, baseline LDH levels were proven to have significant prognostic value in patients with pancreatic cancer (13). Several other studies have evaluated the prognostic value of LDH in ESCC (14-20). The study on the prognostic value of LDH in ESCC published by Wei *et al.* is the largest study of its kind, including 906 patients with ESCC, which showed that the survival time of patients with a high level of LDH is shorter than those with a lower level (14). Li *et al.* identified LDH to be a powerful independent factor for OS in patients with advanced ESCC treated with anti-programmed cell death protein 1 (PD-1) therapy, which is in line with the findings of Wang *et al.*'s research, but both these studies included fewer than 50 patients (17,18). Additionally, an investigation that recruited 567 patients with ESCC conducted by Luo *et al.* also demonstrated an elevated LDH level to be an independent indicator for poor prognosis (19). Similarly, our results in patients with ESCC who had undergone chemoradiotherapy showed that those with high LDH at baseline had shorter OS than did those with low LDH at baseline. However, this conflicted with the results of another retrospective study on 212 patients with ESCC undergoing chemoradiotherapy by Zhang *et al.*, which indicated LDH to not be associated with OS or PFS (20). Another 2 studies also reported that LDH was not a prognostic factor regarding the OS of patients with ESCC (15,16). It is worth mentioning that the cutoff LDH values in these articles were inconsistent, and the cutoff value of LDH in our study was significantly lower than that of the others. Another possible explanation for the discrepancy is that the patients included in our study might have been in the earlier stages, implying a relatively lower tumor burden than that in previous studies. Furthermore, there may be a difference in the method for determining the optimal cutoff value of LDH. Moreover, only 68 patients were enrolled in our study according to the calculation of X-tile software in the low-LDH group. In summary, there was no standard point for optimal cutoff value of LDH, which might be affected by various conditions in clinical practice. Thus, more prospective studies are urgently need to solve the problem of inconsistent optimal LDH cutoff values. Overall, although definitive conclusions exist regarding pretreatment serum LDH levels as a predictor for prognosis in ESCC, our results suggest it may be a reliable factor in predicting the therapeutic effect of chemoradiotherapy in patients with ESCC. However, given the small sample sizes and the different disease stage distributions within each sample, additional research is warranted to further validate the prognostic value of LDH before it can be widely used in clinical settings.

This is the first report identifying LDH, ECOG-PS, Cyfra-21, tumor-length, cN stage and cM stage as the dependent parameters to construct a new risk score model with P<0.0001 and a nomogram for predicting the survival rate with a C-index of 0.599. To note, the significance of the risk score model is guiding the individual treatment. But the nomogram were not performed very well in predicting survival. However, we still recommend a comprehensive

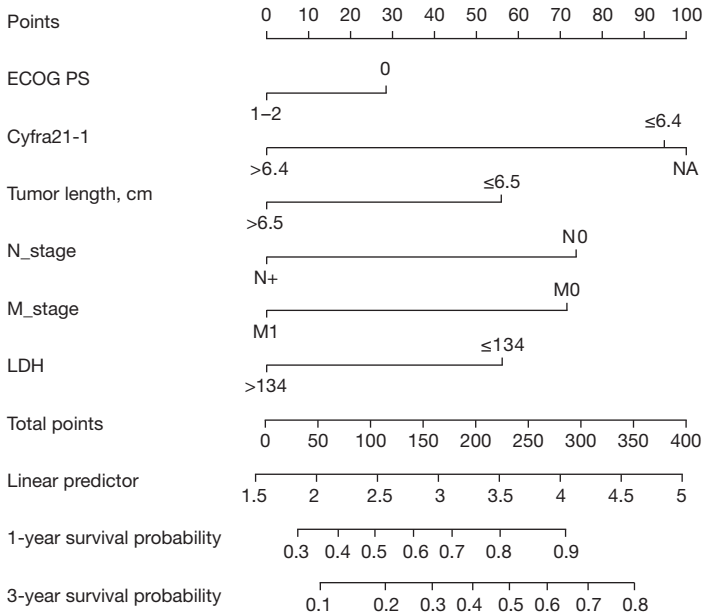

Figure 5 Prediction nomogram for OS. OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase.

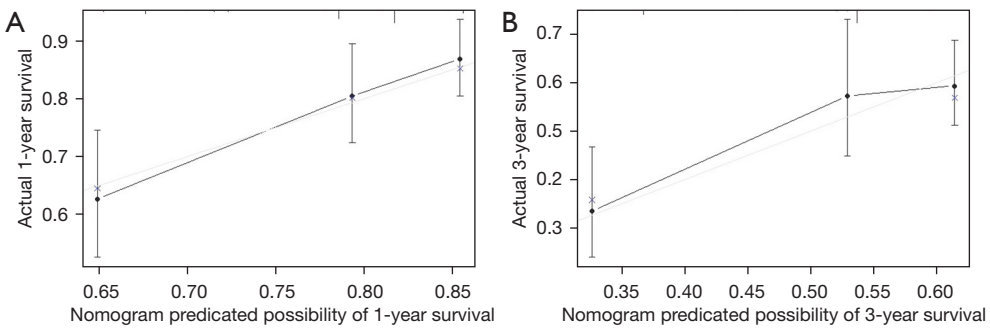

Figure 6 The calibration plot for the probability of survival. (A) The calibration plot for the probability of 1-year survival. (B) The calibration plot for the probability of 3-year survival.

treatment for ESCC patients with high serum LDH levels. If no distant metastasis was found during pre-treatment examinations but with high serum LDH value, attention should be paid to the presence of small distant metastases that were not clinically detected, or the tendency for distant metastasis. It may provide a practical, economical, and reliable detection indicator for the selection of treatment plans for ESCC patients. Further large-scaled prospective trials are warranted to verify our results.

Moreover, according to the result of Cox multivariate analysis, we found that, in addition to LDH, tumor length was another independent prognostic factor for OS, while advanced cN stage and advanced cM stage were shown to be associated with worse OS. This was consistent with the findings of a previous study by Yu *et al.*, with the difference being that our findings indicated OS to be related to cM stage, while Yu *et al.*'s results indicated OS was related to T stage (28). This can be explained by the fact that the patient selection in our study included patients with ESCC who underwent chemoradiotherapy, while in the retrospective study mentioned above, more than 80% of the patients underwent curative esophagectomy. Although the cT stage and cN stage in our study were determined using endoscopic ultrasound (EUS), enhanced-scanning

computed tomography (CT), positron emission tomography (PET)-CT, or pathological biopsy, it was not completely equivalent to postoperative pathological staging. With regard to the Cyfra21-1 level in our study, multivariate analysis indicated that a high level of Cyfra21-1 was an adverse prognostic factor and was better than CEA level as a predictor for prognosis in ESCC. Our study results support the prognostic value of Cyfra21-1 in predicting OS and PFS. The finding was in accordance with 2 earlier studies (29,30). However, Yang *et al.* reported a conflicting result, with CEA being superior to other tumor biomarkers as prognostic indicators in ESCC (31). The prognostic value of tumor marker index (TMI) based on Cyfra21-1 and squamous cell carcinoma antigen (SCC-Ag) has been reported in recent years (32,33). Unfortunately, SCC-Ag was not assessed in our study. Overall, studies with greater homogeneity are needed to identify the prognostic factors for ESCC patients in the context of inconsistent results.

Recently, Alderuccio *et al.* proposed a new prognostic index based on LDH to better predict the survival of recognize patients (9). Moreover, Luo *et al.* developed a prognostic risk scoring model that included the levels and neutrophil count to help verify the prognosis of patients with ESCC (19). However, no studies thus far have examined the combination of LDH levels with tumor markers for the prognosis of patients with ESCC treated with chemoradiotherapy. Using the findings derived in our analysis, we established a model based on serum LDH levels, tumor biomarkers, and the TNM staging system to identify those patients with ESCC who were most likely to benefit from chemoradiotherapy. No widely used predictive model for prognosis has been constructed for patients with ESCC receiving chemoradiotherapy until now, and developing a more effective and reliable prediction model for estimating the prognosis will be our main focus in the subsequent studies.

Our study also has some limitations that should be noted. First, we used a single-center retrospective design, which likely introduced some degree of selection bias. Second, it was difficult to obtain the complete pathological data for the patients in this study who underwent chemoradiotherapy but not surgery. Third, the role of LDH in predicting prognosis was limited due to there being some other factors influencing the LDH levels but not tumors. Third, the most sensitive cutoff points of serum LDH need to be determined through large-scale clinical trials.

Conclusions

In summary, serum LDH level was found to be a predictive factor for poor survival in ESCC patients undergone chemoradiotherapy. LDH should be considered a relevant clinical variable and included in the prognostic classification of patients with ESCC, with the aim to better determine the most appropriate treatment strategies and to better stratify patients included in clinical trials. Therefore, a multicenter, large-sample prospective study is needed to further verify the conclusions before this method can be applied to routine clinical studies.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-388/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). The study was approved by the Institutional Review Board of Shandong Cancer Hospital (No. SDTHEC2023004014). All registered patients provided written informed consent.

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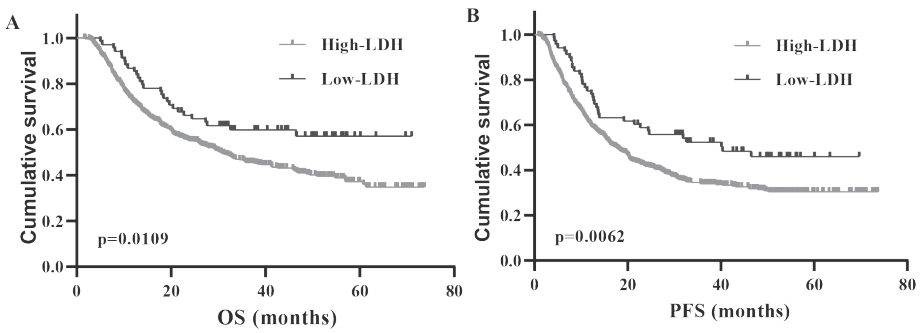

Figure S1 Kaplan-Meier survival curves of OS and PFS grouped by LDH for 614 patients in the whole cohort. (A) The OS curve of ESCC patients underwent chemoradiotherapy classfied by LDH before matching; (B) The PFS curve of ESCC patients underwent chemoradiotherapy classfied by LDH before matching; OS, overall survival; PFS, progression-free survival; LDH, lactate dehydrogenase.

Table S1 Univariate and multivariate analysis of PFS in patients with ESCC before propensity score matching

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (female *vs.* male)	0.74 (0.58, 0.95)	0.019	0.77 (0.60, 0.99)	0.048
Age (>69 *vs.* ≤69 years)	1.27 (1.00, 1.61)	0.047	1.09 (0.84, 1.42)	0.515
ECOG PS (1–2 *vs.* 0)	1.34 (1.10, 1.64)	0.004	1.22 (0.97, 1.54)	0.086
cT stage (T3-4 *vs.* T1-2)	1.30 (0.90, 1.86)	0.159	–	–
cN stage (N+ *vs.* N0)	1.70 (1.22, 2.38)	0.002	1.54 (1.09, 2.16)	0.014
cM stage (M1 *vs.* M0)	1.70 (1.36, 2.12)	<0.001	1.49 (1.18, 1.89)	0.001
Differentiation (moderate/poor *vs.* high)	1.09 (0.85, 1.41)	0.496	–	–
Tumor length (>6.5 *vs.* ≤6.5 cm)	1.44 (1.13, 1.83)	0.003	1.40 (1.09, 1.79)	0.008
Tumor location				
Upper *vs.* cervical	0.89 (0.62, 1.29)	0.541	0.84 (0.58, 1.26)	0.348
Medium *vs.* cervical	1.22 (0.87, 1.72)	0.162	1.01 (0.70, 1.44)	0.964
Lower *vs.* cervical	1.49 (1.02, 2.17)	0.022	1.27 (085, 1.90)	0.240
Radiotherapy technology (IMRT *vs.* 3DCRT)	0.77 (0.63, 0.95)	0.013	0.84 (0.68, 1.03)	0.092
Treatment options (CCRT *vs.* SCRT)	1.21 (0.98, 1.47)	0.067	–	–
Dose (>58.8 *vs.* ≤58.8 Gy)	0.74 (0.59, 0.93)	0.008	0.87 (0.69, 1.90)	0.247
CEA (ng/mL)				
>5.5 *vs.* ≤5.5	1.28 (1.01, 1.62)	0.041	1.09 (0.86, 1.39)	0.482
NA *vs.* ≤5.5	1.13 (0.88, 1.44)	0.355	1.16 (0.88, 1.53)	0.307
Cyfra21-1 (ng/mL)				
>6.4 *vs.* ≤6.4	2.45 (1.73, 3.45)	<0.001	1.90 (1.33, 2.72)	<0.001
NA *vs.* ≤6.4	1.02 (0.82, 1.26)	0.864	0.98 (0.77, 1.25)	0.870
LDH (>134 *vs.* ≤134 U/L)	1, 62 (1.14, 2.29)	0.007	1.61 (1.13, 2.30)	0.009

HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; ECOG, Eastern Clinical Oncology Group; PS, performance status; Cyfra21-1, cytokeratin 19 fragment antigen 21-1; CEA, carcinoembryonic antigen; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy; cT stage, clinical T stage; cN stage, clinical N stag; cM stage, clinical M stage; ESCC, esophageal squamous cell carcinoma; PFS, progression-free survival.

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Table S2 Univariate and multivariate analysis of OS in patients with ESCC before propensity score matching

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (female *vs.* male)	0.71 (0.54, 0.94)	0.016	0.74 (0.56, 0.99)	0.043
Age (>69 *vs.* ≤69 years)	1.37 (1.06, 1.77)	0.015	1.16 (0.88, 1.55)	0.296
ECOG PS (1–2 *vs.* 0)	1.47 (1.18, 1.83)	0.001	1.37 (1.06, 1.76)	0.014
cT stage (T3-4 *vs.* T1-2)	1.13 (0.77, 1.66)	0.522		
cN stage (N+ *vs.* N0)	2.34 (1.55, 3.55)	<0.001	2.14 (1.40, 3.27)	<0.001
cM stage (M1 *vs.* M0)	1.67 (1.31, 2.13)	<0.001	1.52 (1.18, 1.97)	0.001
Differentiation (moderate/poor *vs.* high)	1.00 (0.76, 1.32)	0.999	–	–
Tumor length (>6.5 *vs.* ≤6.5 cm)	1.45 (1.12, 1.88)	0.005	1.45 (1.11, 1.89)	0.007
Tumor location				
Upper *vs.* cervical	0.95 (0.63, 1.42)	0.783	0.89 (0.60, 1.34)	0.585
Medium *vs.* cervical	1.21 (0.83, 1.77)	0.328	0.95 (0.64, 1.41)	0.795
Lower *vs.* cervical	1.58 (1.04, 2.40)	0.031	1.24 (0.80, 1.91)	0.334
Radiotherapy technology (IMRT *vs.* 3DCRT)	0.79 (0.64, 0.99)	0.037	0.86 (0.68, 1.08)	0.196
Treatment options (CCRT *vs.* SCRT)	1.21 (0.98, 1.51)	0.081	–	–
Dose (>58.8 *vs.* ≤58.8 Gy)	0.72 (0.57, 0.92)	0.008	0.87 (0.67, 1.12)	0.278
CEA (ng/mL)				
>5.5 *vs.* ≤5.5	1.26 (0.97, 1.63)	0.080	1.06 (0.81, 1.38)	0.693
NA *vs.* ≤5.5	1.09 (0.83, 1.44)	0.515	1.01 (0.75, 1.38)	0.919
Cyfra21-1 (ng/mL)				
>6.4 *vs.* ≤6.4	2.45 (1.73, 3.45)	0.000	1.90 (1.33, 2.72)	0.000
NA *vs.* ≤6.4	1.02 (0.82, 1.26)	0.864	0.98 (0.77, 1.25)	0.870
LDH (>134 *vs.* ≤134 U/L)	1.64 (1.12, 2.42)	0.012	1.64 (1.10, 2.43)	0.015

HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; ECOG, Eastern Clinical Oncology Group; PS, performance status; Cyfra21-1, cytokeratin 19 fragment antigen 21-1; CEA, carcinoembryonic antigen; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy; cT stage, clinical T stage; cN stage, clinical N stag; cM stage, clinical M stage; ESCC, esophageal squamous cell carcinoma.

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