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Original Research

The novel pretreatment immune prognostic index discriminates survival outcomes in locally advanced non-operative esophageal squamous cell carcinoma patients treated with definitive chemoradiotherapy: a 6-year retrospective study

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ABSTRACT

Objective: We aimed to construct risk stratification to help set individualized treatment strategies and intensities for different subgroups of patients.

Methods: The Esophagus Immune Prognostic Index (EIPI) scores were constructed according to the levels of derived neutrophil-to-lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH) before treatment, and the patients were divided into low-, medium-, and high-risk groups. Finally, restricted cubic splines (RCS) were used to explore the relationship between dNLR, LDH, and survival outcomes.

Results: The median follow-up period of overall survival (OS) and progression-free survival (PFS) were 25.2 and 17.6 months, respectively. Multivariate Cox regression analysis showed dNLR were the independent prognostic factors that were associated with OS and PFS. The 3-year OS and PFS rates in the low-, medium-, and high-risk groups were 44.4% and 38.2%, 26.1% and 23.6%, and 10.5% and 5.3%, respectively. Patients who received chemotherapy had better OS and PFS than those who did not receive chemotherapy in low-risk and medium/high-risk groups (all $p < 0.05$). Besides, the results also revealed significant differences for patients with clinical T, N, and TNM stage groups of the OS and PFS in different risk groups. Finally, RCS analysis indicated a nonlinear relationship between the dNLR, LDH, and survival for esophageal squamous cell carcinoma (ESCC) patients. The death hazard ratios of dNLR and LDH sharply increased at 1.97 and 191, respectively.

Conclusions: In summary, the EIPI, a novel inflammatory-based and immune-related prognostic score, is an independent prognostic indicator in locally advanced ESCC patients undergoing definitive chemoradiotherapy (dCRT).

Introduction

Esophageal cancer (EC), one of the most common aggressive digestive tumors, is ranked as the sixth most deadly and the eighth-most frequently diagnosed malignancy all over the world [1,2]. Esophageal squamous cell carcinoma (ESCC) is the most predominant histologic type of EC in Asia [3,4]. For patients with early ESCC, surgery is the main treatment [5]. Nonetheless, most patients are always in the

Abbreviations: ESCC, esophageal squamous cell carcinoma; dCRT, definitive chemoradiotherapy; EIPI, esophagus immune prognostic index; OS, overall survival; PFS, progression-free survival; RCS, restricted cubic splines; EC, esophageal carcinoma; LDH, lactate dehydrogenase; dNLR, derived neutrophil-to-lymphocyte ratio; LIPI, lung immune prognostic index; NSCLC, non–small cell lung cancer; AJCC, American Joint Commission on Cancer; UICC, Union Cancer Control; RT, radiotherapy; 5-FU, 5-fluorouracil; 3D-CRT, three dimensional-conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CT, computed tomography; ULN, upper limit of normal; T, tumor; N, node; TNM, tumor-node-metastasis; HR, hazard ratio; CI, confidence interval; AUC, area under the curve; ROC, receiver-operating characteristic.

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advanced stage and lose the opportunity of operation at the time of their first diagnosis [6]. At this time, definitive chemoradiotherapy (dCRT) is identified as the standard treatment for inoperable patients [7,8]. Although dCRT improved overall survival and local control, the prognosis of EC remains poor, with a 5-year survival rate ranging from 15% to 25% [6]. Besides, the therapeutic effect of dCRT varies widely among different patients with the same TNM stage of ESCC. Therefore, it is necessary to better understand the impact of prognostic factors on survival, which is of great significance to assist physicians in identifying ESCC patients who are considered to be at risk of poor prognosis and to implement individualized treatment for these advanced patients.

Several recent studies have revealed that the inflammation process is an essential feature in cancer progression and disease development [9–11]. Numerous routinely tested blood parameters, such as blood cell count and lactate dehydrogenase (LDH) level, have been shown to be potential prognostic biomarkers in several cancer types [12–14]. Besides, it has been investigated whether derived neutrophil-to-lymphocyte ratio (dNLR), as a novel potential inflammatory biomarker, is associated with prognosis in some cancer [15–18]. The Lung Immune Prognostic Index (LIPI) is a marker combining serum LDH level and the dNLR. It has been reported to be a prognostic factor of non–small cell lung cancer (NSCLC), gastric cancer, and bladder cancer [19–21]. However, the predictive value of LIPI in the prognosis of ESCC patients who received dCRT remains unclear. Although both LDH and dNLR are accessible prognostic predictors of EC [15,22], it remains undefined whether these predictors can be combined to predict the outcome of ESCC patients who received dCRT. To the best of our knowledge, currently there is no reliable immune prognostic index for ESCC patients. Thus, the identity of more accurate prognostic indicators is meaningful to evaluate the prognosis of patients with ESCC. Therefore, we initially proposed a novel immune prognostic index, named EIPI (Esophagus Immune Prognostic Index, based on two variables of LDH and dNLR), to predict overall survival (OS) and progression-free survival (PFS) in locally advanced ESCC patients treated with dCRT.

Hence, in the present study, we aimed to evaluate the role of EIPI as a potential prognostic index focusing on OS and PFS in prognosticating clinical significance in patients with ESCC who received dCRT. A pretreatment prognostic risk score was established to estimate the prognosis of ESCC patients. Finally, we explored the association between pretreatment EIPI and survival outcomes for locally advanced ESCC patients treated with dCRT to help set individualized treatment intensities and strategies for different subgroups of patients.

Material and methods

Study population

We retrospectively analysed consecutive cases with ESCC and receiving dCRT in our cancer center between January 2011 and December 2016. Inclusion criteria were as follows. (1) patients with pathologically or cytologically confirmed stage II–IVA ESCC stage according to the 8th edition American Joint Commission on Cancer

Table 1
Patients' characteristics of 566 locally advanced ESCC patients and clinicopathological characteristics according to dNLR and LDH.

Clinicopathologic variable		N	dNLR≥1.97	dNLR<1.97	p	N	LDH≥191	LDH<191	p
Total(N)		566	174	392		566	57	509	
Age (years)					0.001				0.357
	≥70	202	44	158		202	24	178	
	<70	364	130	234		364	33	331	
Gender					0.044				0.010
	Male	405	135	270		405	32	373	
	Female	161	39	122		161	25	136	
Weight loss					0.895				0.230
	Yes	266	83	183		266	22	244	
	No	300	91	209		300	35	265	
Tumor location					0.460				0.417
	Cervical	69	19	50		69	5	64	
	Upper thoracic	145	40	105		145	11	134	
	Middle thoracic	300	95	205		300	36	264	
	Lower thoracic	52	20	32		52	5	47	
Chemotherapy					0.626				0.777
	Yes	450	141	309		450	44	406	
	No	116	33	83		116	13	103	
RT dose (Gy)					0.305				0.042
	<60	83	30	53		83	14	69	
	≥60	483	144	339		483	43	440	
Tumor thickness (cm)					0.208				0.924
	≥1.6	230	78	152		230	24	206	
	<1.6	336	96	240		336	33	303	
Tumor length (cm)					0.001				0.923
	≥7	137	58	79		137	13	124	
	<7	429	116	313		429	44	385	
T stage					0.439				0.545
	T2	35	11	24		35	2	33	
	T3	273	77	196		273	26	247	
	T4	258	86	172		258	29	229	
N stage					0.031				0.726
	N0	161	42	119		161	19	142	
	N1	247	69	178		247	25	222	
	N2	118	48	70		118	9	109	
	N3	40	15	25		40	4	36	
TNM stage					0.049				0.801
	Stage II	115	25	90		115	13	102	
	Stage III	168	52	116		168	15	153	
	Stage IV	283	97	186		283	29	254	

ESCC, esophageal squamous cell carcinoma; dNLR, derived neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; N, number; RT, radiotherapy; T, tumor; N, node; TNM, tumor-node-metastasis.

Table 2
Univariate and multivariate analyses of prognostic factors for OS in patients with ESCC.

Clinicopathologicparameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
≥70 vs. <70	1.200	0.989–1.457	0.065	-		
Gender						
Male vs. Female	1.106	0.892–1.370	0.359	-		
Weight loss						
Yes vs. No	1.062	0.879–1.284	0.531	-		
Tumor location						
Cervical/Upper vs. Middle/Lower	0.776	0.636–0.947	0.013	0.895	0.729–1.098	0.288
Chemotherapy						
No vs. Yes	1.415	1.130–1.772	0.002	1.523	1.204–1.926	< 0.001
RT dose (Gy)						
<60 vs. ≥60	1.456	1.131–1.875	0.004	1.168	0.901–1.513	0.241
Tumor thickness (cm)						
≥1.6 vs. <1.6	1.548	1.279–1.873	< 0.001	1.337	1.087–1.646	0.006
Tumor length (cm)						
≥7 vs. <7	1.282	1.032–1.591	0.025	1.086	0.859–1.373	0.491
T stage						
T4 vs. T2/T3	1.258	1.041–1.521	0.018	1.024	0.826–1.268	0.831
N stage						
N2/N3 vs. N0/N1	1.906	1.557–2.333	< 0.001	1.659	1.334–2.062	< 0.001
TNM stage						
Stage III/Stage IV vs. Stage II	1.740	1.346–2.249	< 0.001	1.494	1.097–2.034	0.011
dNLR						
≥ 1.97 vs. < 1.97	1.468	1.203–1.792	< 0.001	1.314	1.072–1.611	0.009
LDH						
≥ 191 vs. < 191	1.811	1.353–2.425	< 0.001	1.915	1.422–2.578	< 0.001

ESCC, esophageal squamous cell carcinoma; OS, overall survival; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; T, tumor; N, node; TNM, tumor-node-metastasis; dNLR, derived neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase.

(AJCC)/Union Cancer Control (UICC) TNM classification system; (2) patients treated with dCRT were conducted; (3) patients without any surgery treatment; (4) no distant metastasis; (5) blood routine and biochemical data were obtained before dCRT within one week.

Exclusion criteria were as follows. (1) patients who had a severe infection and other major diseases before dCRT (liver failure, renal failure, and severe cerebrovascular and cardiovascular diseases); (2) patients who were lost to follow-up. The present study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Fujian Province Cancer Hospital.

Data collections

The information of clinicopathologic data, including age, gender, weight loss, tumor location, chemotherapy, radiotherapy (RT) dose, tumor thickness, tumor length, TNM stage, pretreatment complete blood routine, and biochemical data were obtained from patients' electronic medical records.

Definitive chemoradiotherapy

Patients with chemotherapy received platinum-based chemotherapy as a first-line regimen. The chemotherapy regimens concurrent/sequential with RT included (A) paclitaxel + nedaplatin or cisplatin or lobaplatin or carboplatin; (B) 5-fluorouracil (5-FU) + cisplatin. Three dimensional-conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and computed tomography (CT)-based radiation planning were used in the patients.

Esophagus immune prognostic index

The EIPI was made up of the combination of the dNLR and the LDH (ref. 80-190U/L). The upper limit of normal (ULN) of LDH in our institute was 190U/L. According to the calculation method (dNLR = absolute neutrophil count / [white blood cell count-absolute neutrophil count]), we next calculated the dNLR value and EIPI score. The best cut-off value of dNLR was 1.97, and the cut-off value of LDH was defined according to the ULN of our hospital (The ULN value is also the optimal cut-off value calculated by X-tile software). In general, patients with both increased dNLR (≥ 1.97) and LDH (≥ 191 U/L) were assigned a score of 3. Patients with one or no increased dNLR (≥ 1.97) and LDH (≥ 191 U/L) were assigned to 2 or 1, respectively. Therefore, we classified the EIPI score into 3 groups (EIPI = 1, 2, and 3, respectively) EIPI = 1, 2, and 3 mean low-risk, medium-risk, and high-risk group.

Endpoints

OS was defined as the time from pathological diagnosis until death from any cause or up to the end of the follow-up. PFS was defined as the time from pathological diagnosis until disease progression, death, or the ending of the follow-up. The deadline for follow-up in the present study is April 2021.

Statistical analysis

The optimal cut-off values of radiotherapy dose, tumor thickness, tumor length, dNLR, and LDH are calculated by the X-tile software (https://medicine.yale.edu/ lab/rimm/research/software/). Comparisons between the categorical data were estimated by the chi-square test or Fisher's exact test. The OS and PFS analyses of all ESCC patients were performed using the Kaplan-Meier method. Significance tests for OS and PFS were compared using the log-rank test. OS and PFS were compared between the low-, medium-, and high-risk groups. Univariate and multivariate Cox proportional-hazard model analyses were carried out to identify independent prognostic factors. Factors with statistical significance in univariate analyses ($p < 0.05$) were then subjected to multivariate analysis to identify independent prognostic factors. According to the results of multivariate analysis, the nomogram was constructed by using Cox proportional hazard model. Finally, restricted cubic splines (RCS) were used to explore the relationship between dNLR, LDH, and survival outcomes. All analyses were two-sided, and all p-values < 0.05 were considered statistically significant. All statistical

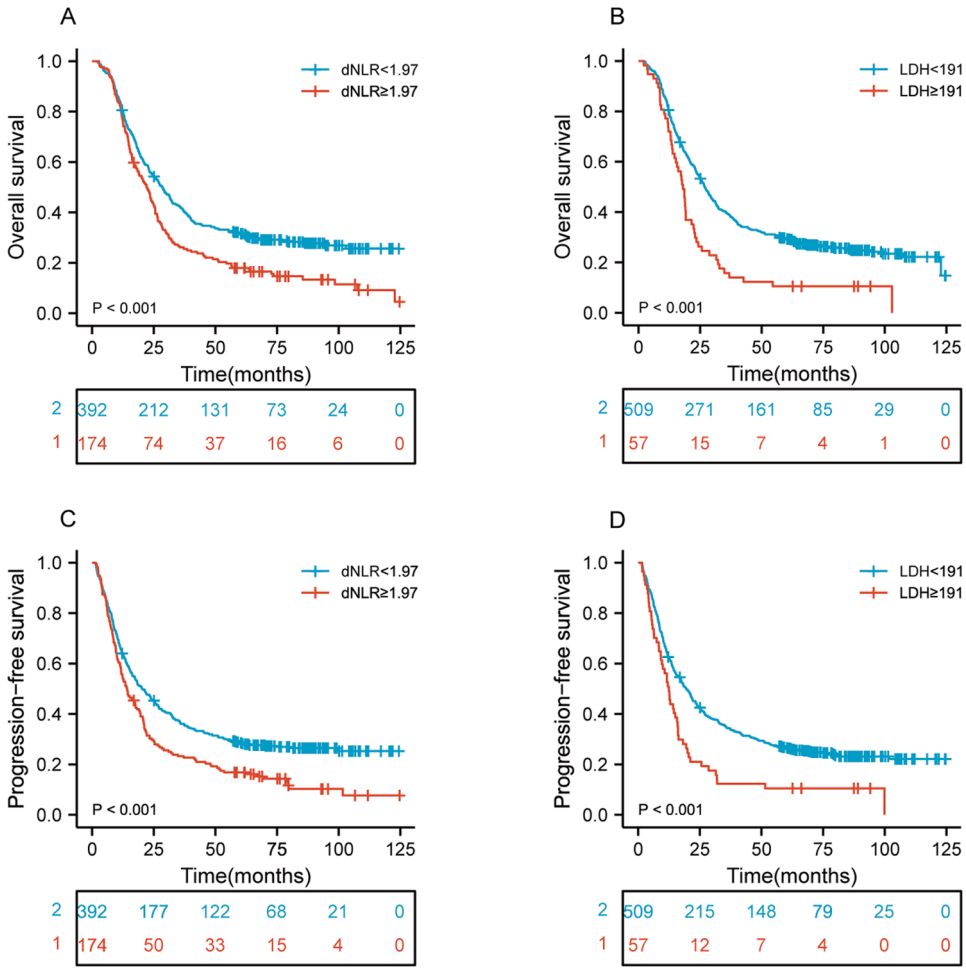

Fig. 1.. Kaplan-Meier curves of dNLR and LDH for the whole study population showing (A-B) Overall survival ($p < 0.001$, $p < 0.001$, respectively); (C-D) Progression-free survival ($p < 0.001$, $p < 0.001$, respectively).
dNLR, derived neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase.

analyses were conducted by IBM SPSS Statistics software (version 26) and R software (version 4.0.2).

Results

Patient characteristics according to dNLR and LDH

A total of 566 patients with ESCC were included in the current study (Table 1**)**. The patient cohort included 405 male patients (71.6%) and 161 female patients (28.4%). The TNM stage was stage II for 115 patients (20.3%), III for 168 patients (29.7%), and IV for 283 patients (50.0%). In the study, the median dNLR and LDH values were 1.65 (range, 0.15-13.88) and 149 (range, 69-291), respectively. There were 392 (69.3%) and 174 (30.7%) patients with low (< 1.97) and high (≥ 1.97) dNLR, respectively. A total of 509 (90.0%) and 57 (10.0%) patients with low (< 191) and high (≥ 191) LDH. Most patients received chemotherapy (79.5%). RT dose <60Gy were present only in a minority of patients (14.7%). The optimal cutoff values for RT dose, tumor thickness, tumor length, dNLR, and LDH were calculated to be 60 Gy, 1.6 cm, 7 cm, 1.97, and 191, respectively. Analysis of combined dNLR and LDH into EIPI showed 354 (62.5%) patients in the low-risk group (EIPI = 1), 193 (34.1%) patients in the medium-risk group (EIPI = 2), and 193 (3.4%) patients in the high-risk group (EIPI = 3).

Univariate and multivariate survival analysis of OS in ESCC

The median follow-up period of OS was 25.2 months (range, 2.1-124.7). Univariate and multivariate Cox analysis for predictors of OS are shown in Table 2. Univariate analyses showed that tumor location ($p = 0.013$), chemotherapy ($p = 0.002$), RT dose ($p = 0.004$), tumor thickness ($p < 0.001$), tumor length ($p = 0.025$), T stage ($p = 0.018$), N stage ($p < 0.001$), TNM stage ($p < 0.001$), dNLR ($p < 0.001$), and LDH ($p < 0.001$) were the significant risk factors for an inferior OS. On multivariate analysis, the chemotherapy ($p < 0.001$; hazard ratio [HR], 1.523; 95% confidence interval [CI], 1.204–1.926), tumor thickness ($p = 0.006$; HR, 1.337; 95% CI, 1.087–1.646), N stage ($p < 0.001$; HR, 1.659; 95% CI, 1.334–2.062), TNM stage ($p = 0.011$; HR, 1.494; 95% CI, 1.097–2.034), dNLR ($p = 0.009$; HR, 1.314; 95% CI, 1.072–1.611), and LDH ($p < 0.001$; HR, 1.915; 95% CI, 1.422–2.578) were found independently associated with an inferior OS. The results indicated that OS was significantly correlated with the dNLR and LDH in ESCC patients. The survival curves of dNLR and LDH for OS are shown in Fig. 1 A-B. Besides, the 3-year OS rates were 26.1% and 41.9% for dNLR ≥ 1.97 and dNLR < 1.97, respectively. Finally, the 3-year OS rates were 15.8% and 39.5% for LDH ≥ 191 and LDH < 191, respectively.

Univariate and multivariate survival analysis of PFS in ESCC

The median follow-up period of PFS was 17.6 months (range, 1.2-124.7). Univariate and multivariate analyses for predictors of PFS are

Table 3
Univariate and multivariate analyses of prognostic factors for PFS in patients with ESCC

Clinicopathologic parameters	Univariate analysis HR	95% CI	P	Multivariate analysis HR	95% CI	P
Age (years)						
≥70 vs. <70	1.200	0.990–1.456	0.063	-		
Gender						
Male vs. Female	1.153	0.931–1.428	0.191	-		
Weight loss						
Yes vs. No	1.062	0.880–1.281	0.532	-		
Tumor location						
Cervical/Upper vs. Middle/Lower	0.793	0.650–0.966	0.021	0.912	0.745–1.117	0.375
Chemotherapy						
No vs. Yes	1.453	1.162–1.816	0.001	1.627	1.288–2.054	<0.001
RT dose (Gy)						
<60 vs. ≥60	1.408	1.096–1.809	0.007	1.084	0.837–1.404	0.541
Tumor thickness (cm)						
≥1.6 vs. <1.6	1.576	1.305–1.905	<0.001	1.399	1.140–1.717	0.001
Tumor length (cm)						
≥7 vs. <7	1.259	1.015–1.561	0.036	1.063	0.843–1.341	0.604
T stage						
T4 vs. T2/T3	1.262	1.046–1.523	0.015	1.044	0.844–1.291	0.693
N stage						
N2/N3 vs. N0/N1	1.873	1.533–2.290	<0.001	1.667	1.343–2.069	<0.001
TNM stage						
Stage III/Stage IV vs. Stage II	1.728	1.341–2.226	<0.001	1.471	1.084–1.996	0.013
dNLR						
≥1.97 vs. <1.97	1.463	1.200–1.783	<0.001	1.337	1.092–1.637	0.005
LDH						
≥191 vs. <191	1.726	1.290–2.310	<0.001	1.769	1.314–2.382	<0.001

ESCC, esophageal squamous cell carcinoma; OS, overall survival; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; T, tumor; N, node; TNM, tumor-node-metastasis; dNLR, derived neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase.

shown in Table 3. Univariate analyses showed that tumor location ($p = 0.021$), chemotherapy ($p = 0.001$), RT dose ($p = 0.007$), tumor thickness ($p < 0.001$), tumor length ($p = 0.036$), T stage ($p = 0.015$), N stage ($p < 0.001$), TNM stage ($p < 0.001$), dNLR ($p < 0.001$), and LDH ($p < 0.001$) were the significant risk factors for an inferior PFS. On multivariate analysis, the chemotherapy ($p < 0.001$; hazard ratio [HR], 1.627; 95% confidence interval [CI], 1.288–2.054), tumor thickness ($p = 0.001$; HR, 1.399; 95% CI, 1.140–1.717), N stage ($p < 0.001$; HR, 1.667; 95% CI, 1.343–2.069), TNM stage ($p = 0.013$; HR, 1.471; 95% CI, 1.084–1.996), dNLR ($p = 0.005$; HR, 1.337; 95% CI, 1.092–1.637), and LDH ($p < 0.001$; HR, 1.769; 95% CI, 1.314–2.382) were independently associated with an inferior PFS. Our results indicate that PFS was significantly correlated with the dNLR and LDH in ESCC patients. The survival curves of dNLR and LDH for PFS are shown in Fig. 1 C-D. Besides, the 3-year PFS rates were 23.3% and 36.1% for dNLR ≥1.97 and dNLR <1.97, respectively. Finally, the 3-year PFS rates were 12.3% and 34.4% for LDH ≥ 191 and LDH < 191, respectively.

Establishment of prognostic models for ESCC

The abovementioned results demonstrated that chemotherapy, tumor thickness, N stage, TNM stage, dNLR, and LDH were the independent prognostic factors for ESCC. Therefore, we established prediction models for OS and PFS by fitting these variables. A higher nomogram score represented a worse prognostic factor. The calibration curve was performed to evaluate the performance of the nomogram. The prediction nomogram models had a C-index for OS and PFS of 0.65 and 0.64 (Fig. 2A,B). The calibration curves for predicting the probability of 1-, 3-, and 5-year OS and PFS of the models were shown in Fig. 2C–H.

Subgroup analyses of the relationship between EIPI, chemotherapy, and outcome

We next investigated the association between the EIPI category and survival. The median OS was 29.4 months (range, 2.2–124.4), 22.0 months (range, 2.1–124.7), and 15.7 months (range, 6.0–54.5) for the low-risk, medium-risk, and high-risk groups, respectively. The 2- and 3-year OS rates in the low-risk, medium-risk, and high-risk groups were 58.4% and 44.4%, 43.4% and 26.1%, and were 26.3% and 10.5%, respectively. The median PFS was 22.1 months (range, 1.2–124.4), 14.4 months (range, 1.5–124.7), and 9.6 months (range, 2.5–51.5) for the low-, medium-, and high-risk groups, respectively. The 2- and 3-year PFS rates in the low-risk, medium-risk, and high-risk groups were 47.7% and 38.2%, 31.4% and 23.6%, and 10.5% and 5.3%, respectively. In stratified analysis, as shown in Fig. 3**A,B**, the higher risk group was significantly associated with shorter OS and PFS in ESCC patients (both $p < 0.001$ for all). We further analysed the effects of chemotherapy on OS and PFS in different risk groups. As shown in Fig. 3**C–F**, patients who received chemotherapy had better OS and PFS than those who did not receive chemotherapy in low-risk and medium/high-risk groups (all $p < 0.05$). Besides, the time-dependent area under the curve (AUC) values of the receiver-operating characteristic (ROC) curves for the prediction of OS and PFS according to EIPI are shown in Fig. 3**G,H**. The time-dependent AUC values of OS for the prediction of 1- year, 3- year, and 5-year were 0.539, 0.601, 0.601, respectively, and were 0.550, 0.592, 0.592 for 1-,3-, and 5- year PFS, respectively.

Kaplan-Meier curves of different risk groups according to the clinical T stage and N stage

A comparison of the OS rates in different risk groups showed no statistically significant differences for ESCC patients with clinical T2-4 and N0-1 stage groups (all $p < 0.05$). However, there was no statistical significance in the clinical N2-3 stage group ($p > 0.05$). Similarly, significant differences were observed in PFS for ESCC patients with clinical T2-4 and N0-1 stage groups (all $p < 0.05$). The clinical N2-3 stage group was not statistically significant ($p > 0.05$) (Fig. 4**A–H**).

Kaplan-Meier curves of different risk groups according to the clinical TNM stage

We also analysed different risk groups according to the clinical TNM

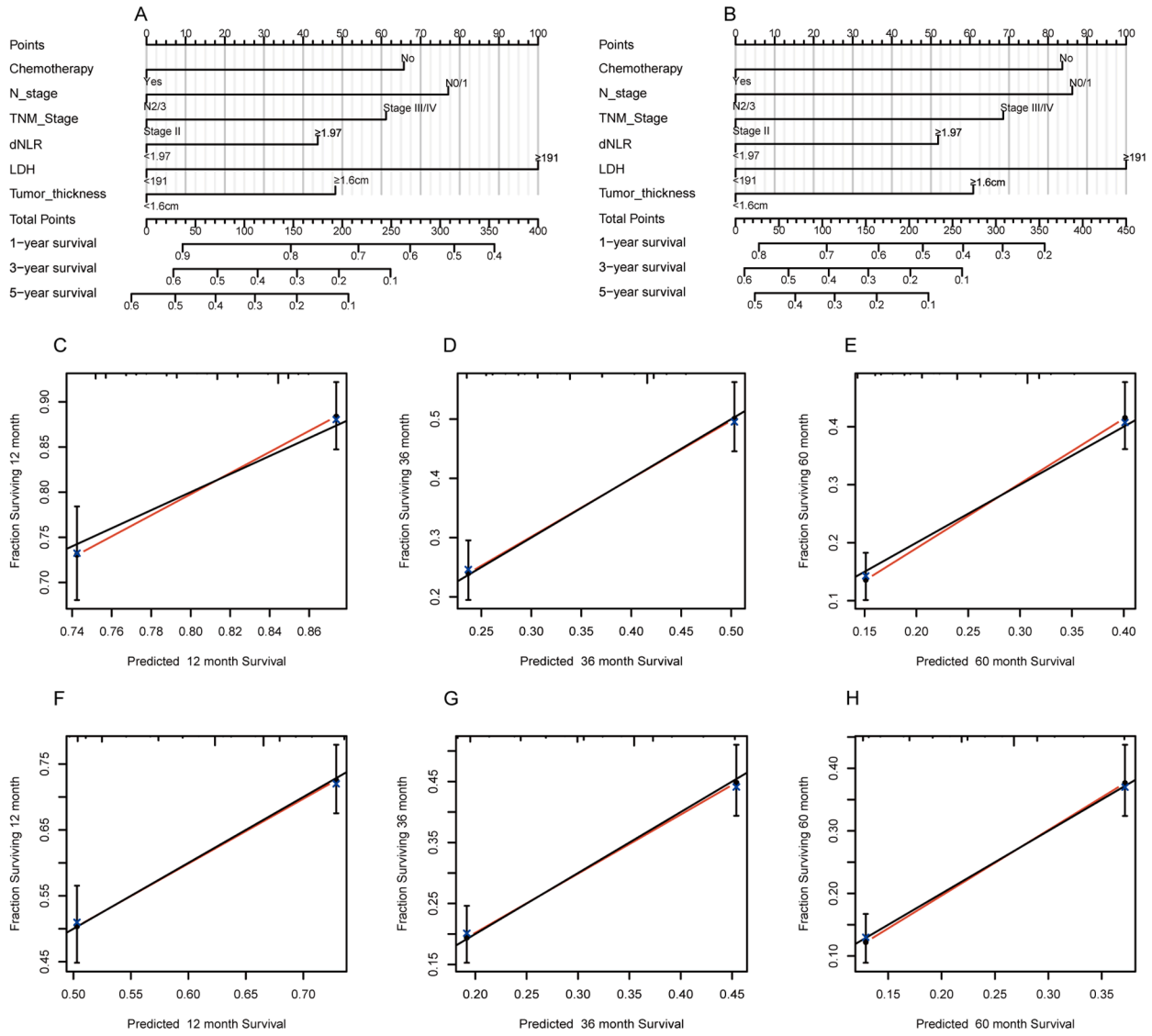

Fig. 2.. Nomogram and calibration curve for predicting the probability of OS and PFS showing (A,B) A nomogram that integrates chemotherapy, N stage, TNM stage, dNLR, LDH, and tumor thickness in ESCC patients; (C-H) The calibration curve of the nomogram.
OS, overall survival; PFS, progression-free survival; N, node; TNM, tumor-node-metastasis; dNLR, derived neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; ESCC, esophageal squamous cell carcinoma.

stage. The results revealed that there were statistically significant differences for ESCC patients with clinical III-IVA stage groups of the OS rates in different risk groups (all $p < 0.05$). But there was no statistically significant in the clinical II stage group ($p > 0.05$). Furthermore, there were significant differences in PFS for ESCC patients with clinical II-IVA stage groups (all $p < 0.05$) (Fig. 5**A–F**).

The relationship between the dNLR, LDH, and survival

RCS analysis was carried out to classify the association between the dNLR, LDH, and survival. The results indicated a nonlinear relationship between the dNLR and OS as well as PFS for ESCC patients. The death hazard of dNLR sharply increased at 1.97 ($p < 0.05$ for non-linearity, Fig. 6**A,B**). Likewise, the results also indicated a nonlinear relationship between the LDH and survival. The death hazard of LDH sharply increased at 191 ($p < 0.05$ for non-linearity, Fig. 6**C,D**).

Discussion

Esophageal cancer remains a challenging and progressive disease with poor outcomes and high morbidity and mortality worldwide [23]. Despite significant improvements in early diagnosis and multidisciplinary therapy recently, the prognosis of ESCC patients remains unsatisfactory due to the insufficient understanding of the potential mechanism of ESCC[5]. Currently, the TNM staging system acts as the most important prognostic factor for evaluating the outcome of ESCC patients. Nevertheless, the TNM staging system does not seem to provide reliable prognostic information for patients who receive dCRT or who do not have surgery [24]. For patients receiving dCRT, other factors may affect the prognosis. Hence, we need to identify other new prognostic factors in order to better predict treatment outcomes. We carried out this study to further investigate the potential prognostic factors for identifying patients with different prognoses.

Previous studies have revealed that dCRT can provide similar outcomes compared with surgery for patients with locally advanced ESCC [7,8]. Nonetheless, the outcome may vary differently among ESCC patients with the same TNM stage, as survival is affected by individual differences. Recently, increasing evidence revealed that the development of the tumor is related to the tumor microenvironment, and the changes in the tumor microenvironment can be reflected by the changes

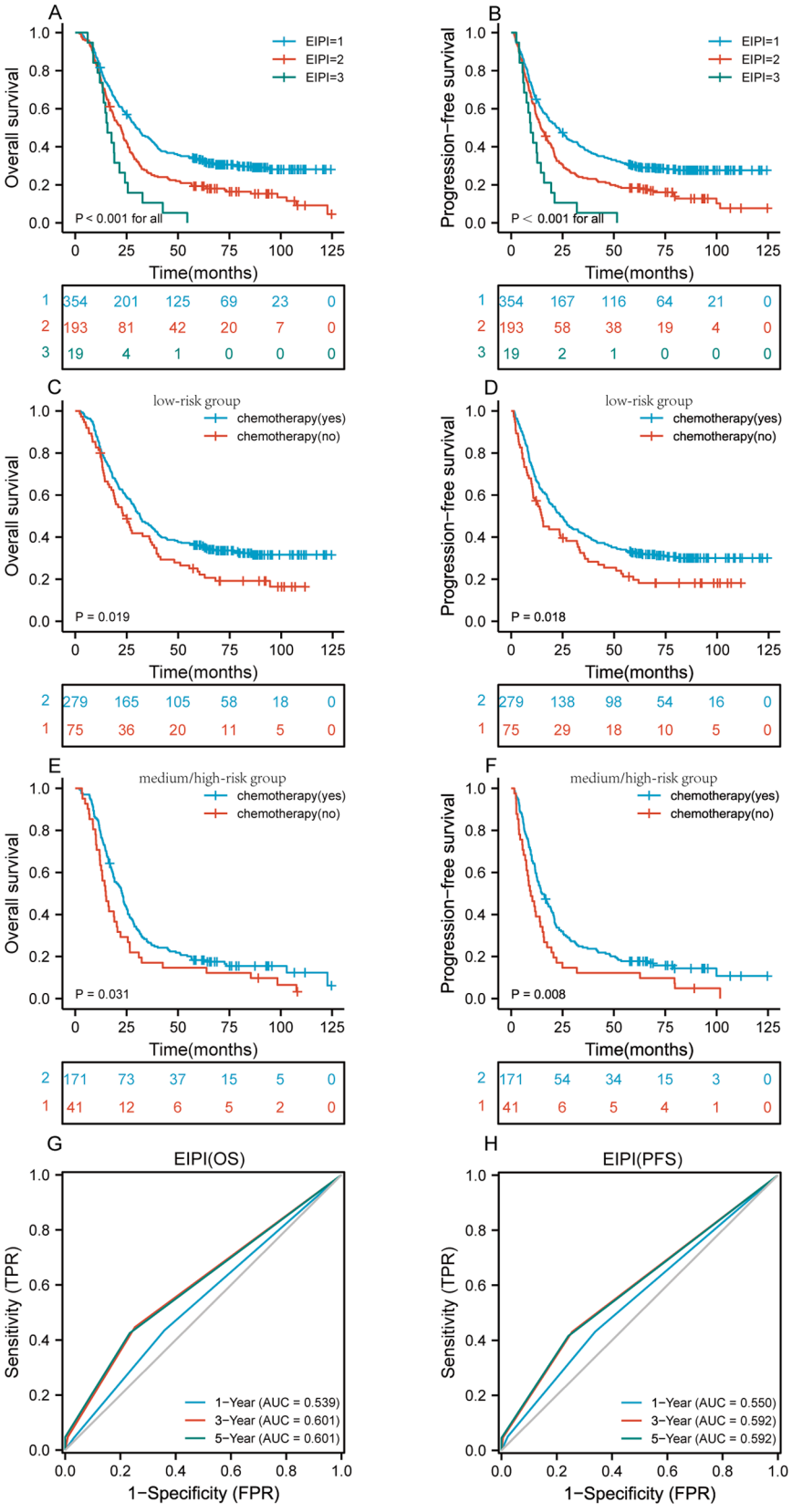

Fig. 3.. Risk stratification for EIPI on OS and PFS according to risk groups. (A) Risk stratification for EIPI on OS ($p < 0.001$ for all); (B) Risk stratification for RIPI on PFS ($p < 0.001$ for all); (C,D) OS ($p = 0.019$) and PFS ($p = 0.018$) for patients receive and did not receive chemotherapy in low-risk group; (E–F) OS ($p = 0.031$) and PFS ($p = 0.008$) for patients receive and did not receive chemotherapy in median/high-risk group; (G–H)The time dependent AUC values of OS and PFS for the prediction of 1- year, 3- year, and 5-year.
EIPI, esophagus immune prognostic index; OS, overall survival; PFS, progression-free survival; AUC, area under the curve.

of serum inflammatory cells [25,26]. In previous studies, the dNLR and LDH have been shown to be useful prognostic factors [15–18,22,27–29]. In 2018, Mezquita et al. demonstrated that LIPI (combined with dNLR and LDH) had a significant relationship with prognosis in NSCLC patients [30]. The LIPI was then verified in other cancers [19–21]. The results also indicated that LIPI might be a useful factor to predict the outcome of tumors. Therefore, we proposed a novel immune prognostic index to predict the outcomes in ESCC patients. To the best of our

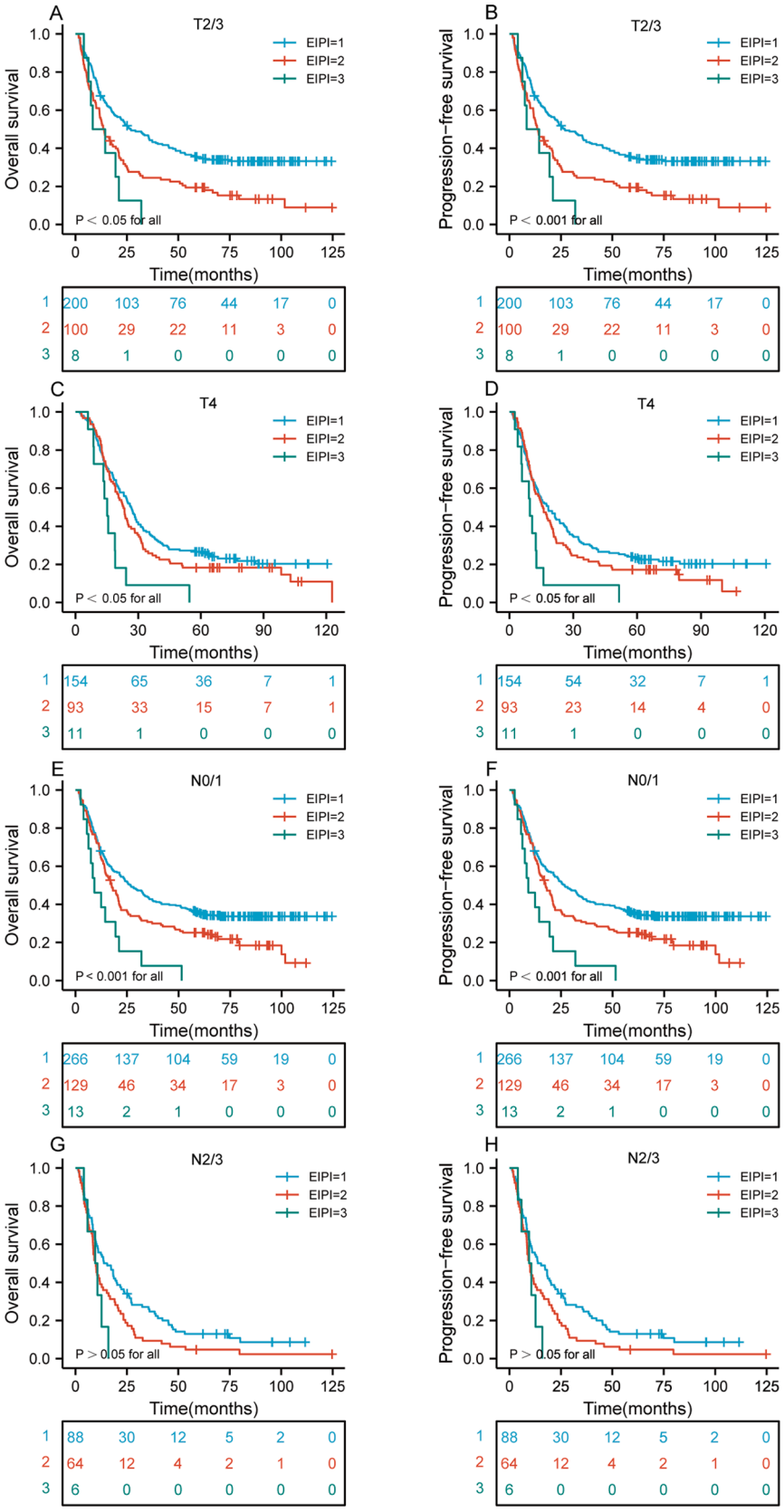

Fig. 4.. Kaplan-Meier curves according to T and N stage categories for the whole study population showing (A-B) OS and PFS ($p < 0.05$ for all, $p < 0.001$ for all, respectively) of patients with T2/3; (C-D) OS and PFS ($p < 0.05$ for all, $p < 0.05$ for all, respectively) of patients with T4; (E-F) OS and PFS ($p < 0.001$ for all, $p < 0.001$ for all, respectively) of patients with N0/1; (G-H) OS and PFS ($p > 0.05$ for all, $p > 0.05$ for all, respectively) of patients with N2/3.

T, tumor; N, node; OS, overall survival; PFS, progression-free survival.

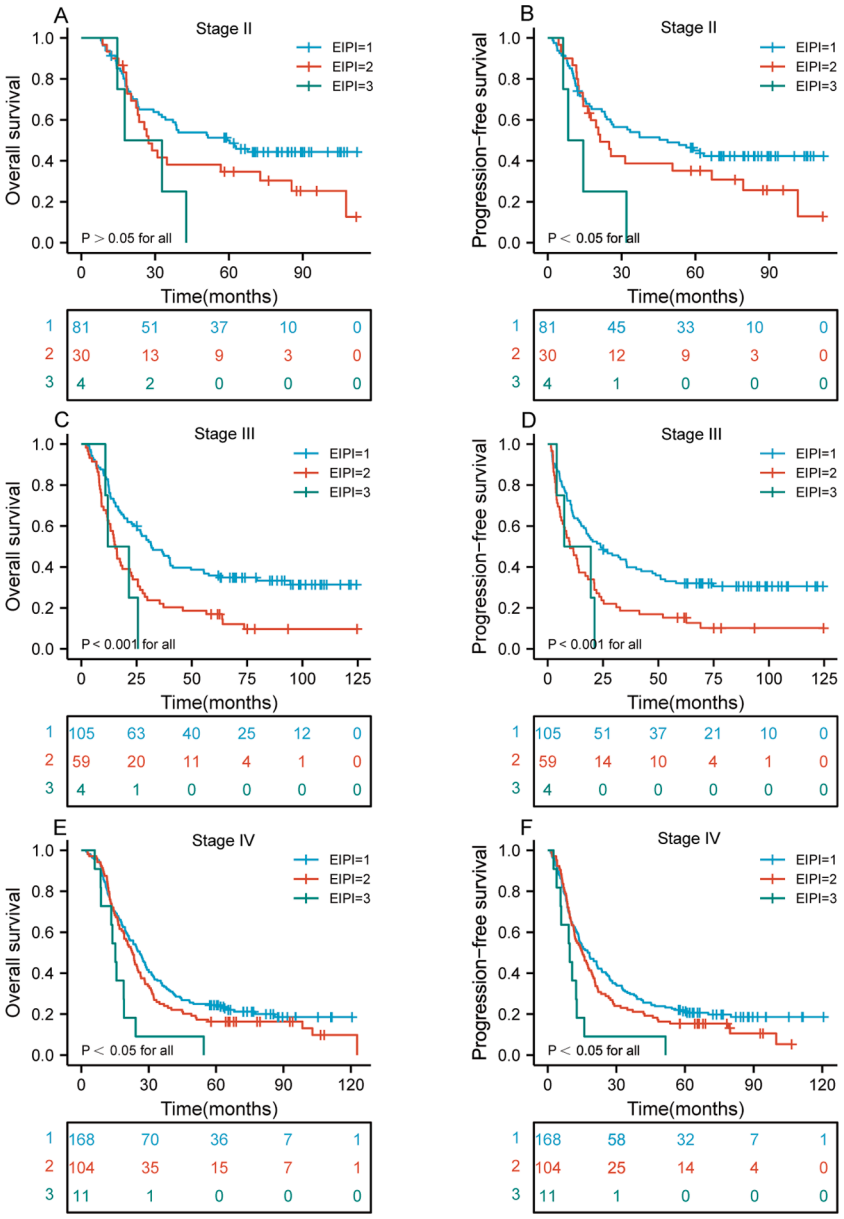

Fig. 5.. Kaplan-Meier curves according to TNM stage categories for the whole study population showing (A-B) OS and PFS ($p > 0.05$ for all, $p < 0.05$ for all, respectively) of patients with stage II; (C-D) OS and PFS ($p < 0.001$ for all, $p < 0.001$ for all, respectively) of patients with stage III; (E,F) OS and PFS ($p < 0.05$ for all, $p < 0.05$ for all, respectively) of patients with stage IVA.
TNM, tumor-node-metastasis; OS, overall survival; PFS, progression-free survival.

knowledge, the current study is the first study to explore and identify the underlying prognostic value of EIPI (combined with dNLR and LDH) in locally advanced ESCC patients who received dCRT.

In this retrospective study, we first explored the influence of EIPI on the prognosis of ESCC patients. Based on EIPI scores, the patients were divided into three groups, low-risk (1 score), medium-risk (2 scores), and high-risk (3 scores). The results indicated that both dNLR and LDH are independent prognostic factors for OS and PFS in ESCC. Therefore, we built a nomogram to predict the prognosis of patients, which would help clinicians to assess the patient's prognosis after dCRT. In addition, we found that the higher risk group was associated with an elevated risk of cancer-related death and cancer progression. In stratified analysis, patients who received chemotherapy had better OS and PFS than those who did not receive chemotherapy in low-risk and medium/high-risk groups. The results also revealed statistically significant differences for ESCC patients with clinical T, N, and TNM stage groups of the OS and PFS in different risk groups. Finally, RCS analysis indicated a nonlinear relationship between the dNLR, LDH, and survival for ESCC patients. The death hazard ratio of dNLR and LDH sharply increased at 1.97 and 191. This study indicated that EIPI serves as a useful independent prognostic factor. According to the outcomes above, ESCC patients with high dNLR and high LDH tend to undergo inferior prognosis, and the higher-risk group may need more in-depth follow-up care. We can improve survival outcomes by setting individual treatment intensities and strategies for different risk groups. Therefore, early evaluation of tumor progression and prognosis before therapy may be beneficial to heterogeneous patients.

Recently, the relationship between the immune system and the occurrence and development of cancer has been further clarified, and inflammation is regarded as a marker of cancer [9]. Therefore, the prognostic value of multiple blood markers has been broadly investigated. So far, many new inflammatory markers have been identified as predictors of tumor treatment. They can predict the prognosis of some cancers [31]. It is also essential that these biomarkers may be easily obtained in all centers and are affordable. Among these biomarkers, dNLR is a popular and novel biomarker that measures the immunity or inflammation ratio in cancers. Increasing evidence has shown that high dNLR is significantly associated with poor prognosis in several types of cancers, including ESCC, NSCLC, non-colorectal gastrointestinal cancer, prostate cancer, melanoma, testicular cancer, and ampullary cancer

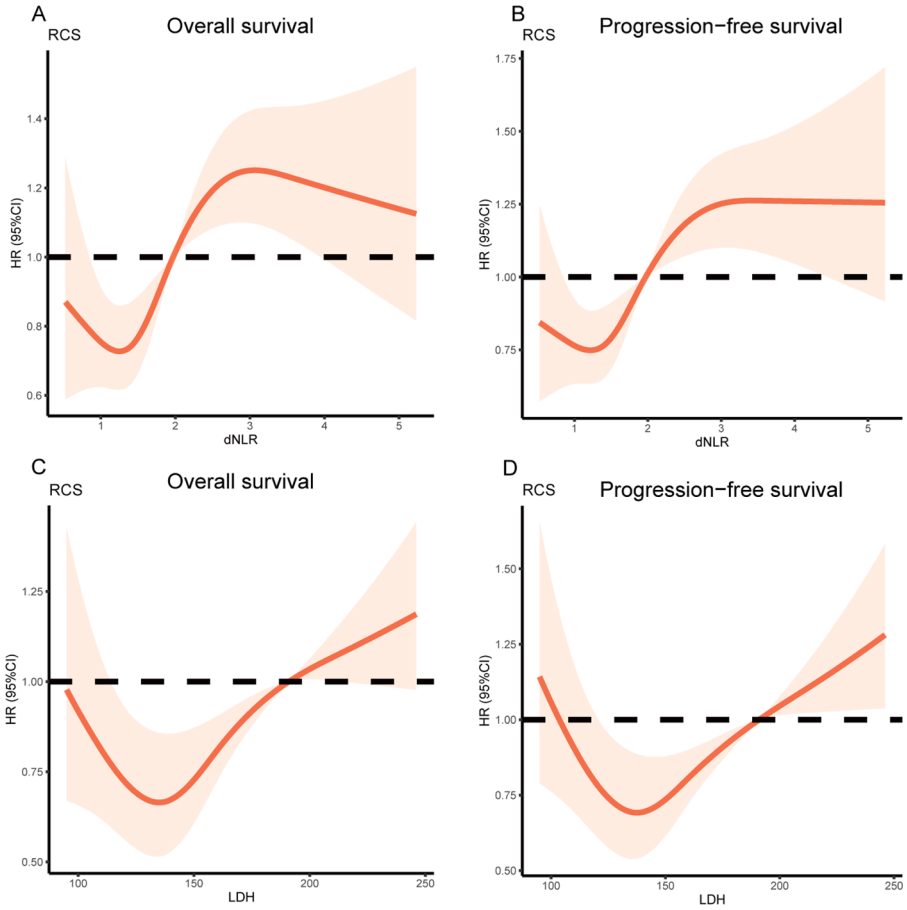

Fig. 6.. Restricted Cubic Spline analysis was used to classify the association between dNLR, LDH, and survival in ESCC patients. The hazard ratio derived from a Multivariate Cox model is shown on the y-axis. The 95% CI of the adjusted hazard ratio is represented by the shaded area. 1.97 and 191 are the reference of dNLR and LDH (HR=1). (A,B) A nonlinear relationship between the dNLR and survival for patients with ESCC. The death hazard of dNLR sharply increased at 1.97 ($p < 0.05$ for non-linearity); (C,D) A nonlinear relationship between the LDH and survival for patients with ESCC. The death hazard of LDH sharply increased at 191 ($p < 0.05$ for non-linearity).
dNLR, derived neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval.

[15–18,32–34]. It is encouraging that these studies were consistent with our results. The increase of dNLR is related to lymphocytopenia and neutrophilia. Neutrophils are the main substances in promoting inflammation and play a crucial role in the tumor microenvironment [10,35]. Neutrophils can be manipulated to produce anti-tumor or pro-tumor effects in the tumor microenvironment [36]. Previous research has indicated that tumor-associated neutrophils can inhibit the immune system in the tumor microenvironment, thus promoting the development of cancer [37]. Similarly, the decrease of lymphocyte count leads to the inhibition of the immune system and the promotion of tumor migration and proliferation [10]. The relation between poor outcome and high level of dNLR is supported by the strong evidence suggesting that cancer-related inflammatory response affects tumor development and disease progression.

LDH is an important enzyme in the conversion of lactic acid to pyruvic acid [38]. It is associated with cell death, cell damage, inflammation, neoplasms, and hemolysis [39]. Based on previous research, elevated LDH level is more common in cancer cells than normal cells [40]. A large number of LDH can be produced by fast-growing tumors, which further reflects the condition of tumor burden. The hypoxic microenvironment in cancer cells is associated with a high level of LDH. The association between cancer progression and the level of serum LDH has been considered. For a long time, elevated LDH has been considered to be a poor prognostic factor for various malignant tumors [27–29]. Besides, the prognostic value of LDH has also been explored in ESCC, but unanimity eludes the definition of the cut-off value [22,41]. In our research results, we define the cut-off value of the study as the upper limit of LDH, which is consistent with most studies. Our results revealed that ESCC patients with a high LDH level (LDH $\geq$191μ/L) had worse OS and PFS. LDH can promote tumor development by regulating the tumor microenvironment and metabolism [40,42]. Previous studies have demonstrated that LDH could be used to effectively predict and assess the treatment response [43]. As a result of the above analyses, growing evidence has indicated that upregulation of LDH was observed in various cancers and could be a predictive indicator of treatment response.

Although LIPI is proposed for NSCLC patients, its elements (i.e., LDH and dNLR) are not the only indicators for NSCLC. Therefore, LIPI has great potential as a present inexpensive marker and readily obtained from routine tests, which can be applied to other tumors at the same time [19–21]. Therefore, we combined dNLR and LDH to form a new immune prognostic index (e.g., EIPI) and applied it to locally advanced ESCC patients received dCRT. EIPI can comprehensively reflect the systemic inflammation state of the body. Our study demonstrated the momentous influence of EIPI on tumor prognosis and progression. Our data are the first to highlight the potential value for EIPI to be integrated into the clinical field in ESCC. Furthermore, given that EIPI reflects cancer-related inflammation, it is expected to be a target of immunotherapy and a useful prognostic indicator. Taken together, the dynamic changes of EIPI may help to choose the best treatment plan for patients in clinical practice. Nevertheless, the potential mechanism still needs future prospective validation. Finally, the question of particular interest is that since we include patients who received dCRT, whether EIPI can be used in patients who receive immunotherapy is an issue that we need to explore in the future.

To our knowledge, it is the first study to explore the potential role of EIPI in evaluating cancer progression and prognosis in ESCC patients who underwent dCRT. However, there are still some limitations in our study. First, the present study is a retrospective study with a single center, which may lead to a selection bias and potential confounding biases. Nonetheless, the sample size of our study was relatively sufficient, and multivariate Cox regression was performed to eliminate the

bias caused by patient heterogeneity. Second, a small number of patients who cannot tolerate chemotherapy only receive radiotherapy, which leads to the bias of treatment selection. Third, peripheral blood indicators may be influenced by a variety of other factors, which may lead to biased results. Furthermore, we need to note that using X-tile analysis to determine the optimal cut-off value of continuous variables may not provide the most accurate results. Finally, because of the lack of prospective studies, the verification of our findings should be carried out with a larger sample and multicenter randomized prospective trials in the future.

Conclusion

In summary, the EIPI, a novel inflammatory-based and immune-related prognostic score, was an independent prognostic indicator in locally advanced ESCC patients undergoing dCRT. The decreased EIPI score was associated with a worse outcome of OS and PFS. EIPI may have vital clinical value in identifying high-risk patients and guiding individualized treatment. Further randomized prospective research with larger populations is required to provide optimal treatment strategies and intensity for ESCC patients who receive dCRT and test its clinical utility.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Ethics approval and consent to participate

The current study was approved by the ethics committee of Fujian Medical University Cancer Hospital, Fuzhou, China and was conducted in accordance with the principles of the Declaration of Helsinki and its amendment. All patients provided written informed consent prior to treatment, and all the information was anonymized prior to analysis.

CRediT authorship contribution statement

Yilin Yu: Visualization, Data curation, Supervision, Writing – original draft, Writing – review & editing. **Haishan Wu:** Visualization, Supervision, Writing – original draft, Writing – review & editing. **Jianjian Qiu:** Data curation, Writing – original draft, Writing – review & editing. **Dongmei Ke:** Data curation, Writing – review & editing. **Yahua Wu:** Data curation, Formal analysis, Writing – review & editing. **Mingqiang Lin:** Data curation, Writing – review & editing. **Qunhao Zheng:** Formal analysis, Writing – review & editing. **Hongying Zheng:** Formal analysis, Writing – original draft, Writing – review & editing. **Zhiping Wang:** Formal analysis, Writing – review & editing. **Hui Li:** Formal analysis, Writing – review & editing. **Lingyun Liu:** Writing – original draft, Writing – review & editing. **Jiancheng Li:** Visualization, Formal analysis, Writing – review & editing. **Qiwei Yao:** Visualization, Formal analysis, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors have read and understood the journal's policy on the declaration of interest and declare that there is no conflict of interest pertaining to this work.

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References

[1] F. Bray, et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424, https://doi.org/10.3322/caac.21492.
[2] L.A. Torre, et al., Global cancer statistics, 2012, CA Cancer J. Clin. 65 (2015) 87–108, https://doi.org/10.3322/caac.21262.
[3] Y. Lin, et al., Esophageal cancer in high-risk areas of China: research progress and challenges, Ann. Epidemiol. 27 (2017) 215–221, https://doi.org/10.1016/j.annepidem.2016.11.004.
[4] Y. Lin, et al., Epidemiology of esophageal cancer in Japan and China, J. Epidemiol. 23 (2013) 233–242, https://doi.org/10.2188/jea.je20120162.
[5] J.A. Ajani, et al., Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Cancer Netw. 17 (2019) 855–883, https://doi.org/10.6004/jnccn.2019.0033.
[6] A.K. Rustgi, H.B. El-Serag, Esophageal carcinoma, N. Engl. J. Med. 371 (2014) 2499–2509, https://doi.org/10.1056/NEJMra1314530.
[7] J.S. Cooper, et al., Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation therapy oncology group, JAMA 281 (1999) 1623–1627, https://doi.org/10.1001/jama.281.17.1623.
[8] J. Lagergren, E. Smyth, D. Cunningham, P. Lagergren, Oesophageal cancer, Lancet 390 (2017) 2383–2396, https://doi.org/10.1016/S0140-6736(17)31462-9.
[9] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674, https://doi.org/10.1016/j.cell.2011.02.013.
[10] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (2010) 883–899, https://doi.org/10.1016/j.cell.2010.01.025.
[11] D.C. McMillan, The systemic inflammation-based glasgow prognostic score: a decade of experience in patients with cancer, Cancer Treat. Rev. 39 (2013) 534–540, https://doi.org/10.1016/j.ctrv.2012.08.003.
[12] B.J. Laird, et al., Quality of life in patients with advanced cancer: differential association with performance status and systemic inflammatory response, J. Clin. Oncol. 34 (2016) 2769–2775, https://doi.org/10.1200/JCO.2015.65.7742.
[13] S. Valpione, et al., Personalised medicine: development and external validation of a prognostic model for metastatic melanoma patients treated with ipilimumab, Eur. J. Cancer 51 (2015) 2086–2094, https://doi.org/10.1016/j.ejca.2015.06.130.
[14] T. Namikawa, et al., Prognostic significance of serum alkaline phosphatase and lactate dehydrogenase levels in patients with unresectable advanced gastric cancer, Gastric Cancer 22 (2019) 684–691, https://doi.org/10.1007/s10120-018-0897-8.
[15] T. Abe, et al., Albumin-derived NLR score is a novel prognostic marker for esophageal squamous cell carcinoma, Ann. Surg. Oncol. (2021), https://doi.org/10.1245/s10434-021-11012-y.
[16] J.V. Alessi, et al., Low peripheral blood derived neutrophil-to-lymphocyte ratio (dNLR) is associated with increased tumor T-cell infiltration and favorable outcomes to first-line pembrolizumab in non-small cell lung cancer, J. Immunother. Cancer 9 (2021), https://doi.org/10.1136/jitc-2021-003536.
[17] S. Li, et al., Baseline derived neutrophil-to-lymphocyte ratio as a prognostic biomarker for non-colorectal gastrointestinal cancer patients treated with immune checkpoint blockade, Clin. Immunol. 212 (2020), 108345, https://doi.org/10.1016/j.clim.2020.108345.
[18] Y. Yamada, et al., Prognostic value of an inflammatory index for patients with metastatic castration-resistant prostate cancer, Prostate 80 (2020) 559–569, https://doi.org/10.1002/pros.23969.
[19] T. Zhang, et al., A validation study on the lung immune prognostic index for prognostic value in patients with locally advanced non-small cell lung cancer, Radiother. Oncol. 156 (2021) 244–250, https://doi.org/10.1016/j.radonc.2020.12.039.
[20] B. Hou, et al., Association of the pretreatment lung immune prognostic index with survival outcomes in advanced gastric cancer patients treated with immune checkpoint inhibitors, Clin. Res. Hepatol. Gastroenterol. 45 (2021), 101748, https://doi.org/10.1016/j.clinre.2021.101748.
[21] K. Obayashi, et al., The prognostic value of the preoperative lung immune prognostic index in patients with urothelial bladder cancer undergoing radical cystectomy, Int. J. Clin. Oncol. (2021), https://doi.org/10.1007/s10147-021-02059-8.
[22] H.S. Luo, et al., Prognostic significance of baseline neutrophil count and lactate dehydrogenase level in patients with esophageal squamous cell cancer treated with radiotherapy, Front. Oncol. 10 (2020) 430, https://doi.org/10.3389/fonc.2020.00430.
[23] W. Chen, et al., Cancer statistics in China, 2015, CA Cancer J. Clin. 66 (2016) 115–132, https://doi.org/10.3322/caac.21338.
[24] M. Chen, et al., Proposed revision of the 8th edition AJCC clinical staging system for esophageal squamous cell cancer treated with definitive chemo-IMRT based on

CT imaging, Radiat. Oncol. 14 (2019) 54, https://doi.org/10.1186/s13014-019-1258-4.
[25] W. Huang, S. Wang, H. Zhang, B. Zhang, C. Wang, Prognostic significance of combined fibrinogen concentration and neutrophil-to-lymphocyte ratio in patients with resectable non-small cell lung cancer, Cancer Biol. Med. 15 (2018) 88–96, https://doi.org/10.20892/j.issn.2095-3941.2017.0124.
[26] T.H. Silva, A.O.C. Schilithz, W.A.F. Peres, L.B. Murad, Neutrophil-lymphocyte ratio and nutritional status are clinically useful in predicting prognosis in colorectal cancer patients, Nutr. Cancer 72 (2020) 1345–1354, https://doi.org/10.1080/01635581.2019.1679198.
[27] L. Peng, et al., Peripheral blood markers predictive of outcome and immune-related adverse events in advanced non-small cell lung cancer treated with PD-1 inhibitors, Cancer Immunol. Immunother. 69 (2020) 1813–1822, https://doi.org/10.1007/s00262-020-02585-w.
[28] X. Liu, et al., Prognostic significance of pretreatment serum levels of albumin, LDH and total bilirubin in patients with non-metastatic breast cancer, Carcinogenesis 36 (2015) 243–248, https://doi.org/10.1093/carcin/bgu247.
[29] H. Wang, M.S. Wang, Y.H. Zhou, J.P. Shi, W.J. Wang, Prognostic values of LDH and CRP in cervical cancer, OncoTargets Ther. 13 (2020) 1255–1263, https://doi.org/10.2147/OTT.S235027.
[30] L. Mezquita, et al., Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer, JAMA Oncol. 4 (2018) 351–357, https://doi.org/10.1001/jamaoncol.2017.4771.
[31] R.Z. Sharaiha, et al., Elevated preoperative neutrophil:lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer, Ann. Surg. Oncol. 18 (2011) 3362–3369, https://doi.org/10.1245/s10434-011-1754-8.
[32] A. Hernando-Calvo, et al., Dynamics of clinical biomarkers as predictors of immunotherapy benefit in metastatic melanoma patients, Clin. Transl. Oncol. 23 (2021) 311–317, https://doi.org/10.1007/s12094-020-02420-9.
[33] D. Ribnikar, et al., The prognostic value of neutrophil-to-lymphocyte ratio in metastatic testicular cancer, Curr. Oncol. 28 (2020) 107–114, https://doi.org/10.3390/curroncol28010014.
[34] S. Sun, et al., The prognostic significance of inflammation-based scores in patients with ampullary carcinoma after pancreaticoduodenectomy, BMC Cancer 20 (2020) 981, https://doi.org/10.1186/s12885-020-07482-0.
[35] E. Pylaeva, S. Lang, J. Jablonska, The essential role of type I interferons in differentiation and activation of tumor-associated neutrophils, Front. Immunol. 7 (2016) 629, https://doi.org/10.3389/fimmu.2016.00629.
[36] R.V. Sionov, Z.G. Fridlender, Z. Granot, The multifaceted roles neutrophils play in the tumor microenvironment, Cancer Microenviron. 8 (2015) 125–158, https://doi.org/10.1007/s12307-014-0147-5.
[37] K. Moses, S. Brandau, Human neutrophils: their role in cancer and relation to myeloid-derived suppressor cells, Semin. Immunol. 28 (2016) 187–196, https://doi.org/10.1016/j.smim.2016.03.018.
[38] M. Adeva-Andany, et al., Comprehensive review on lactate metabolism in human health, Mitochondrion 17 (2014) 76–100, https://doi.org/10.1016/j.mito.2014.05.007.
[39] M. Drent, N.A. Cobben, R.F. Henderson, E.F. Wouters, M. van Dieijen-Visser, Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation, Eur. Respir. J. 9 (1996) 1736–1742, https://doi.org/10.1183/09031936.96.09081736.
[40] K. Urbanska, A. Orzechowski, Unappreciated role of LDHA and LDHB to control apoptosis and autophagy in tumor cells, Int. J. Mol. Sci. 20 (2019), https://doi.org/10.3390/ijms20092085.
[41] X.L. Wei, et al., The predictive value of alkaline phosphatase and lactate dehydrogenase for overall survival in patients with esophageal squamous cell carcinoma, Tumour. Biol. 37 (2016) 1879–1887, https://doi.org/10.1007/s13277-015-3851-y.
[42] J.R. Doherty, J.L. Cleveland, Targeting lactate metabolism for cancer therapeutics, J. Clin. Invest. 123 (2013) 3685–3692, https://doi.org/10.1172/JCI69741.
[43] J. Li, et al., Pretreatment serum lactate dehydrogenase is an independent prognostic factor for patients receiving neoadjuvant chemotherapy for locally advanced cervical cancer, Cancer Med. 5 (2016) 1863–1872, https://doi.org/10.1002/cam4.779.