

# Platelet Indices and ApoA1 as Predictive Markers in Neoadjuvant Immunochemotherapy for Locally Advanced Esophageal Squamous Cell Carcinoma: A Retrospective Study

Tao Zeng<sup>1,2,\*</sup>, Yue-chang Liu<sup>1,2,\*</sup>, Xiang-hui Wang<sup>1,2,\*</sup>, Jun Yan<sup>3</sup>, Shi-bing Li<sup>1,2</sup>, Danning Deng<sup>1,2</sup>, Shan Xing<sup>4</sup>

<sup>1</sup>Department of Clinical Laboratory, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, 510655, People's Republic of China; <sup>2</sup>Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510655, People's Republic of China; <sup>3</sup>Department of Clinical Laboratory, Guangdong Medical University, Zhanjiang, 524023, People's Republic of China; <sup>4</sup>Department of Clinical Laboratory, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, 510060, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Danning Deng, Department of Clinical Laboratory, the Sixth Affiliated Hospital, Sun Yat-sen University, No. 26 Erheng Road of Yuancun, Tianhe District, Guangzhou, 510655, People's Republic of China, Email dengdn@mail.sysu.edu.cn; Shan Xing, Department of Clinical Laboratory, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, 651 Dongfeng East Road, Guangzhou, 510060, People's Republic of China, Email Xingshan@sysucc.org.cn

**Purpose:** To evaluate the predictive value of baseline and preoperative blood parameters for treatment efficacy and prognosis in patients with locally advanced esophageal squamous cell carcinoma (LA-ESCC) undergoing neoadjuvant chemoimmunotherapy (nCIT) followed by radical surgery.

**Patients and Methods:** This retrospective study analyzed clinical data from patients with LA-ESCC patients treated with nCIT followed by surgery (October 2019–November 2024). Patients were categorized based on pathological response (pathological complete response [pCR] and major pathological response [MPR]). Univariate and multivariate analyses identified factors associated with pCR and MPR. Cox regression and Kaplan-Meier methods were used to evaluate overall survival (OS) and disease-free survival (DFS). Nomograms and Receiver Operating Characteristic (ROC) curves were created for prognostic prediction.

**Results:** Among 236 patients, the pCR rate was 31.8%, and the MPR rate was 51.7%. pCR was associated with improved DFS (Hazard Ratio [HR] = 0.27, 95% CI: 0.16–0.43,  $p < 0.0001$ ) but not OS ( $p = 0.058$ ). MPR was significantly correlated with both DFS (HR=0.27, 95% CI: 0.17–0.44,  $p < 0.0001$ ) and OS (HR=0.38, 95% CI: 0.21–0.71,  $p = 0.0023$ ). Identified predictors of treatment response included baseline and preoperative platelet indices (mean platelet volume [MPV], platelet distribution width [PDW], platelet-large cell ratio [P-LCR]) for both pCR and MPR, along with preoperative Apolipoprotein A1 (ApoA1) specifically for MPR (all identified as independent predictors on univariate and multivariate analysis,  $p < 0.05$ ), reflecting their role in modulating the inflammatory response. A predictive model combining MPV (HR = 0.86, 95% CI: 0.61–1.22) and ApoA1 (HR = 0.24, 95% CI: 0.07–0.81) demonstrated good accuracy in forecasting DFS (30 months: AUC = 0.71, 95% CI: 0.60–0.81).

**Conclusion:** Baseline and preoperative blood parameters (MPV, PDW, P-LCR) and preoperative ApoA1 are valuable predictors of treatment response and prognosis in LA-ESCC. Nomograms incorporating these markers offer reliable prognostic insights for DFS.

**Keywords:** esophageal squamous cell carcinoma, neoadjuvant therapy, pathological complete response, prognosis, inflammation, biomarkers

## Introduction

Esophageal cancer is a prevalent and aggressive malignancy of the upper gastrointestinal tract.<sup>1</sup> Globally, it ranks as the 11th most prevalent cancer and the seventh leading cause of cancer-related death, with an estimated 510,716 new cases and approximately 445,129 deaths in 2022.<sup>2</sup> In China, esophageal cancer ranks seventh in incidence and fifth in mortality among all malignant tumors.<sup>3</sup> Histologically, esophageal squamous cell carcinoma (ESCC) is the most common subtype, accounting for over 90% of cases.<sup>4,5</sup> Neoadjuvant chemoradiotherapy combined with surgery has been established as the standard treatment for locally advanced esophageal cancer, based on landmark studies such as CROSS and NEOCRTEC5010.<sup>6–8</sup>

In recent years, clinical trials including KEYNOTE-181, KEYNOTE-590, and ESCORT-1st have confirmed that immunotherapy combined with chemotherapy serves as a first-line treatment for metastatic esophageal cancer, significantly improving overall survival (OS) and progression-free survival (PFS).<sup>9,10</sup> More recently, the ESCORT-NEO trial in 2024 evaluated the efficacy of neoadjuvant immunotherapy (nICT) combined with chemotherapy in resectable locally advanced esophageal squamous cell carcinoma (LA-ESCC). This trial demonstrated a substantial increase in the pathological complete response (pCR) rate (28%) and major pathological response (MPR) rate (59.1%), indicating promising potential for improving patient outcomes.<sup>11</sup>

However, not all patients with esophageal cancer benefit from immunotherapy. Clinically validated biomarkers for ESCC include programmed death-ligand 1 (PD-L1) expression, tumor mutational burden (TMB), microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR), and nutritional status.<sup>12</sup> In addition, emerging biomarkers such as gene mutation profiles, gut microbiota composition, and peripheral blood markers have shown potential predictive value.<sup>13,14</sup> As nearly one-third of LA-ESCC patients exhibit limited radiologic response to nICT, radiologic staging alone is insufficient to predict pCR.<sup>15</sup> Even among biomarker-selected patients, the predictive accuracy of existing clinicopathologic factors remains limited. For example, in the ESCORT-1st study, more than 27% of PD-L1 positive (CPS  $\geq 10$ ) patients showed no objective response to immunochemotherapy, while in the KEYNOTE-181 trial, up to 65% of TMB-high patients failed to respond to immunotherapy.<sup>9,10</sup> Additionally, MSI-H/dMMR and TMB-H are rarely present in esophageal cancer.<sup>12,16</sup> These findings underscore the current accuracy limits of clinicopathologic predictors and highlight the unmet need for reliable pretreatment biomarkers.<sup>12–15</sup> Previous studies have demonstrated that platelets express PD-L1 and can upregulate PD-L1 expression on tumor cells, thereby inducing exhaustion of cytotoxic CD8+ T cells.<sup>17</sup> In addition, platelet-derived proteins such as ADAM10, ADAM17, and TGF- $\beta$  suppress natural killer (NK) cell activity, suggesting that platelet-related parameters may serve as accessible and biologically relevant biomarkers of immunotherapy response.<sup>18</sup> Furthermore, lipid accumulation within the tumor microenvironment drives metabolic reprogramming of myeloid-derived suppressor cells (MDSCs) from glycolysis to fatty acid oxidation (FAO), enhancing their immunosuppressive function.<sup>19</sup> Given these mechanisms, circulating markers such as platelet indices and lipid indicators may reflect the host's immune and metabolic status. By using conventional blood indicators, which are easily accessible and low-cost, rapid assessment can be conducted before surgery.<sup>20</sup>

This study integrates data from the entire hospital focusing on patients with LA-ESCC who underwent surgical resection following nICT. The aim is to evaluate the predictive value of baseline and preoperative blood-based biomarkers for treatment response and survival in patients with LA-ESCC receiving nICT.

## Materials and Methods

### Patients

All patients were consecutively enrolled from the Department of Thoracic Surgery at Sun Yat-sen University Cancer Center (Guangzhou, China). This was a single-center, retrospective study. Between October 2019 and November 2024, a total of 305 patient records were initially reviewed. After applying predefined inclusion and exclusion criteria, data from 236 patients with locally advanced esophageal squamous cell carcinoma (LA-ESCC) who underwent neoadjuvant chemoimmunotherapy (nCIT) followed by radical surgery were analyzed. Clinical characteristics, preoperative blood parameters, and follow-up data (with follow-up completed on July 31, 2025) were retrospectively extracted from patient records (CONSORT flowchart, see [Figure S1](#)).

## Inclusion Criteria

1. Patients with pre-treatment clinical staging according to the 8th edition of the AJCC/UICC staging system, specifically T1b-4aN1-3M0 or T2-4aN0M0 resectable ESCC, with pathological diagnosis as the gold standard.<sup>21</sup>
2. Patients who had not received any prior anti-tumor treatment.
3. Age  $\geq 18$  years, regardless of gender.
4. Performance Status (PS) score of 0–1.<sup>22</sup>

## Exclusion Criteria

1. Patients who had previously received anti-tumor treatment (including chemotherapy, radiotherapy, surgery, immunotherapy, etc).
2. Patients who received radiotherapy combined with immunotherapy.
3. Patients with distant organ metastases.
4. Patients who did not undergo surgery or lacked surgical pathological results.
5. Patients with a history of malignant tumors other than esophageal cancer.
6. Patients with incomplete clinical data or follow-up information.

## Immunotherapy Drugs

The following immunotherapy drugs were used: camrelizumab, sintilimab, toripalimab, tislelizumab, and pembrolizumab.

## Immunotherapy Efficacy Assessment

The pathological outcomes of nCIT were evaluated by two experienced pathologists, using resected tissue specimens. Pathological complete response (pCR) was defined as the absence of residual cancer cells in the tumor specimen and lymph nodes. Major pathological response (MPR) was defined as  $\leq 10\%$  viable tumor cells remaining in the surgically resected specimen. Tumor regression grade (TRG) was used as follows: Grade 0: No residual cancer cells (pCR); Grade 1:  $\leq 10\%$  viable tumor cells; Grade 2: 10–50% viable tumor cells; Grade 3:  $> 50\%$  viable tumor cells. TRG 0–1 was considered achieving MPR, while TRG 2–3 was considered not achieving MPR.<sup>23</sup>

## Follow-Up

The follow-up cutoff date was July 31, 2025. The median follow-up duration was 25.5 months. Disease-free survival (DFS) was defined as the time from the initiation of immunotherapy to confirmed progressive disease or cancer-related death. Overall survival (OS) was defined as the time from the initiation of treatment to death from any cause.<sup>24</sup>

## Methods

### General Clinical Information

The following clinical parameters were collected: gender, age, body mass index (BMI), smoking history, alcohol consumption history, and family history of cancer.

### Tumor Information

Data collected included tumor location, degree of differentiation, T stage, N stage, clinical TNM stage, and information on the treatment drugs used.

### Hematological Indicators

A total of 114 hematological indicators were collected at baseline and prior to surgery following nCIT. These included data from blood cell analysis, biochemical and tumor marker tests, coagulation parameters, inflammation-related markers (eg, C-reactive protein [CRP], serum amyloid A [SAA]), and derived metrics (eg, neutrophil-to-lymphocyte ratio [NLR], derived NLR [dNLR], systemic immune-inflammation index [SII], etc). Peripheral venous blood samples were collected

at baseline (within 1 week prior to neoadjuvant therapy) and preoperatively (1–3 days before surgery). The interval between the last neoadjuvant cycle and surgery followed current Chinese clinical practice (4–6 weeks).<sup>11</sup> Complete blood count parameters were measured using Sysmex XN-9000 analyzers; serum biochemical parameters were measured using the Roche cobas 8000 series (module c702); and tumor markers were measured using the Roche cobas 8000 series (module e801).

## Statistical Analysis

Data analysis was performed using R software (version 4.5.0) and Python (version 3.11.4). Univariate analyses were conducted using the Chi-square test or Fisher's exact test for qualitative data. Normally distributed continuous data were compared using the *t*-test, while non-normally distributed data were analyzed with non-parametric tests. Multivariate analysis was conducted using logistic regression. OS and DFS were assessed using univariate and multivariate Cox regression models. Kaplan-Meier curves were generated, and survival differences between groups were compared using the log-rank test. A *p*-value of less than 0.05 was considered statistically significant. Optimal cut-off values for continuous hematologic parameters were defined using ROC curves based on the Youden index for pCR prediction ("pROC" package), and were determined with the "survival" and "survminer" packages for survival outcomes. Multicollinearity was evaluated by Spearman correlation with Bonferroni correction and VIF calculation ("corrplot" and "car" packages).

## Results

### Patient Characteristics

A total of 236 patients with LA-ESCC who received nICT were included in this study. The baseline characteristics of the patients are summarized in Table 1. The median age of the participants was 60 years (interquartile range [IQR], 39–76 years); 198 patients (83.9%) were male, and 38 patients (16.1%) were female. Clinical staging was as follows: stage II in 37 cases (15.7%), stage III in 172 cases (72.9%), stage IVA in 25 cases (10.6%), and 2 cases (0.8%) with indeterminate staging between stage II and III. Tumor location was classified as upper esophagus in 13 cases (5.5%), middle esophagus in 123 cases (52.1%), and lower esophagus in 100 cases (42.4%).

Postoperative pathology revealed that 75 patients (31.8%) achieved pCR and 161 patients (68.2%) were non-pCR, while 122 patients (51.7%) achieved MPR and 114 patients (48.3%) were non-MPR. Tumor differentiation was categorized as low in 89 cases (37.7%), moderate in 106 cases (44.9%), high in 5 cases (2.1%), and unknown in 36 cases (15.3%).

Clinical follow-up data showed a median follow-up duration of 25.5 months (95% confidence interval [CI], 23.2–27.2 months), with a maximum follow-up time of 68.9 months. The median OS and DFS had not yet been reached. The 1-year and 2-year OS rates were 95.6% (95% CI: 93.0–98.3) and 86.7% (95% CI: 82.1–91.6), respectively (Figure 1A). The 1-year and 2-year DFS rates were 86.5% (95% CI: 82.2–91.1) and 71.7% (95% CI: 65.8–78.1), respectively (Figure 1B).

### Univariate and Multivariate Analysis of Predictors for pCR

A significant association was observed between tumor differentiation and pCR rate (Table 2). When using the low differentiated group as a reference, the moderately differentiation group showed a significantly reduced odds of pCR (Odds Ratio [OR] = 0.49, 95% CI: 0.26–0.93, *p* < 0.05). As shown in Figure 1C, patients with moderately differentiated tumors were less likely to achieve pCR compared to those with high or low differentiation (20.8% vs 35.1%,  $\chi^2=4.45$ , *p* < 0.05). We observed significant differences in three baseline platelet parameters (*n*=236, Univariate analysis). These are mean platelet volume (MPV, OR = 1.65, 95% CI: 1.21–2.25, *p* = 0.002), platelet distribution width (PDW, OR = 1.27, 95% CI: 1.10–1.46, *p* = 0.001), and platelet-large cell ratio (P-LCR, OR = 1.07, 95% CI: 1.03–1.11, *p* = 0.001). Notably, similar significant differences in MPV (OR = 1.84, 95% CI: 1.29–2.63, *p* = 0.001), PDW (OR = 1.36, 95% CI: 1.14–1.62, *p* = 0.001), and P-LCR (OR = 1.08, 95% CI: 1.04–1.13, *p* < 0.001) were found when comparing preoperative data following nICT, with these differences being even more pronounced (higher ORs and smaller *p*-values, *n*=235). However, no significant differences were observed in platelet count (PLT) or platelet hematocrit (P-HCT) (Figure 1D).

**Table 1** Baseline Demographics and Clinical Information

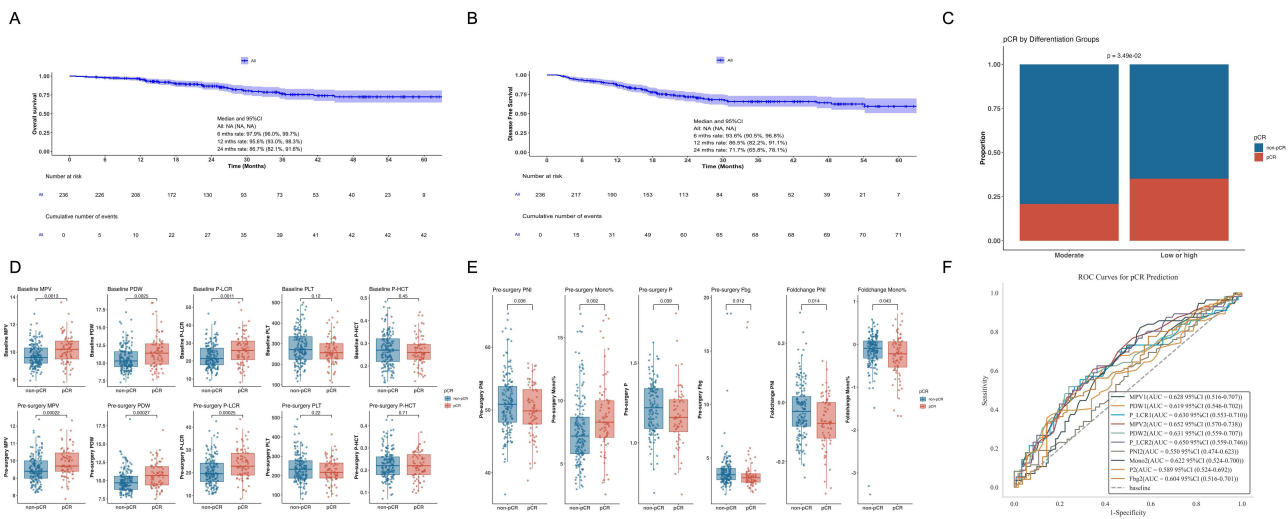
Characteristics	No.=236 (%)	pCR Group (n=75)	Non-pCR Group (n=161)	$\chi^2$	p value
Age, years					
≥60	127(53.8)	47(37.0)	80(63.0)	2.964	0.085
<60	109(46.2)	28(25.7)	81(74.3)		
Gender					
Male	198(83.9)	64(32.3)	134(67.7)	0.048	0.827
Female	38(16.1)	11(28.9)	27(71.1)		
BMI, kg/m <sup>2</sup>					
≥18.5	213(90.3)	68(31.9)	145(68.1)	1.49e-29	1
<18.5	23(9.7)	7(30.4)	16(69.6)		
Tumor location					
Upper	13(5.5)	3(23.1)	10(76.9)	NA	0.476
Middle	123(52.1)	36(29.3)	87(70.7)		
Lower	100(42.4)	36(36.0)	64(64.0)		
Clinical T stage					
T1b	4(1.7)	3(0.75)	1(0.25)	NA	0.133
T2-3	225(95.3)	69(30.7)	156(69.3)		
T4a	7(3.0)	3(42.9)	4(57.1)		
Clinical N stage					
N0	14(5.9)	3(21.4)	11(78.6)	NA	0.156
N1	57(24.2)	21(36.8)	36(63.2)		
N2	65(27.5)	25(38.5)	40(61.5)		
N3	20(8.5)	8(40.0)	12(60.0)		
Nx	80(33.9)	18(22.5)	62(77.5)		
Clinical TNM stage					
II	37(15.7)	10(27.0)	27(73.0)	NA	0.384
III	172(72.9)	53(30.8)	119(69.2)		
IVA	25(10.6)	11(44.0)	14(56.0)		
Unknown	2(0.8)	1(50.0)	1(50.0)		
Tumor differentiation					
Low	89(37.7)	31(34.8)	58(65.2)	NA	0.020
Moderate	106(44.9)	22(20.8)	84(79.2)		
High	5(2.1)	2(40.0)	3(60.0)		
Unknown	36(15.3)	16(44.4)	20(55.6)		
pCR, n (%)	75(31.8)				
MPR, n (%)	122(51.7)				
DFS, n (%)	165(69.9)				

**Notes:**  $\chi^2$ -test was used for comparison of categorical variables; Fisher's exact test was applied when the expected frequency was <5.

**Abbreviations:** BMI, body mass index; pCR, Pathological complete response, TRG=0; MPR, Major pathological response; DFS, Disease-free survival.

Analysis of all hematological indicators showed that preoperative prognostic nutritional index (PNI,  $p = 0.036$ ), monocyte percentage (Mono%,  $p = 0.002$ ), phosphorus (P,  $p = 0.039$ ), and fibrinogen (Fbg,  $p = 0.012$ ) differed significantly between groups (Figure 1E), although the differences were less marked than those observed for platelet-related parameters. When analyzing the change in values between preoperative and baseline data, only PNI ( $p = 0.014$ ) and Mono% ( $p = 0.043$ ) showed significant differences.

Multivariate logistic regression analysis including age, sex demonstrated that both baseline and preoperative MPV, PDW, and P-LCR were independent predictors of pCR and MPR (all  $p < 0.05$ ). The baseline values of MPV (OR = 1.64, 95% CI: 1.20–2.24,  $p = 0.002$ ), PDW (OR = 1.27, 95% CI: 1.10–1.47,  $p = 0.001$ ), and P-LCR (OR = 1.07, 95% CI: 1.03–1.11,  $p = 0.001$ ) were independent predictors of pCR. Similarly, the preoperative values of these platelet parameters also showed significant independent associations with pCR, with further strengthened effect sizes after nICT (MPV: OR



**Figure 1** Survival curves and comparison of pCR across different indicators. **(A)** Kaplan-Meier curves of OS for patients who received immunochemotherapy followed by surgery (n=236). **(B)** Kaplan-Meier curves of DFS for patients who received immunochemotherapy followed by surgery (n=236). **(C)** Stacked bar chart of pCR rates according to different tumor differentiation levels (n=200). **(D)** Box plots of platelet counts and related parameters among different pCR groups (n=236). **(E)** Box plots of other significantly different indicators among different pCR groups (n=154). **(F)** ROC curves for predictors of pCR identified in univariate analysis (n=154), 1 indicates baseline levels, and 2 indicates preoperative levels.

= 1.84, 95% CI: 1.29–2.63; PDW: OR = 1.35, 95% CI: 1.14–1.61; P-LCR: OR = 1.08, 95% CI: 1.03–1.13; all  $p < 0.001$ ). ROC curve analysis revealed that preoperative MPV, PDW, and P-LCR showed higher AUC values for predicting pCR (AUC of MPV = 0.65, 95% CI: 0.57–0.74, cutoff = 9.70, Figure 1F). These three platelet-related variables were highly correlated, with preoperative MPV showing a strong correlation with P-LCR and PDW (all Spearman’s  $r > 0.9$ ,  $p < 0.001$ ), preventing the construction of a combined multivariate prediction model.

### Survival Outcomes and Impact of pCR

Kaplan-Meier (KM) curves, log-rank tests, and Cox regression analyses were employed to evaluate survival outcomes. Although the median OS and DFS have not yet been reached due to the excellent efficacy of nICT, we explored whether achieving pCR influences short-term and long-term survival (n=236). The KM curves demonstrated a significant difference in DFS between the pCR and non-pCR groups (Hazard Ratio [HR] = 0.27, 95% CI: 0.16–0.43, log-rank  $p < 0.0001$ ), as shown in Figure 2A. However, the difference in OS was not statistically significant (HR=0.50, 95% CI: 0.26–0.94, log-rank  $p = 0.058$ ) (Figure 2B). These results suggest that achieving pCR after nICT is primarily associated with improved short-term survival, with a more limited impact on long-term survival.

### Stratified Survival Analysis and Multivariate Cox Regression

Stratified survival analysis and multivariate Cox regression were performed to evaluate the influence of various predictors on OS and DFS. Univariate Cox regression analyses revealed that indicators such as MPV, PDW, and P-LCR did not significantly impact OS or DFS (all  $p > 0.05$ ). Consequently, subgroup survival comparisons based on these factors were not feasible. Similarly, other variables previously associated with pCR, including PNI, Mono%, P, and Fbg, also showed no significant association with OS or DFS (all  $p > 0.05$ ).

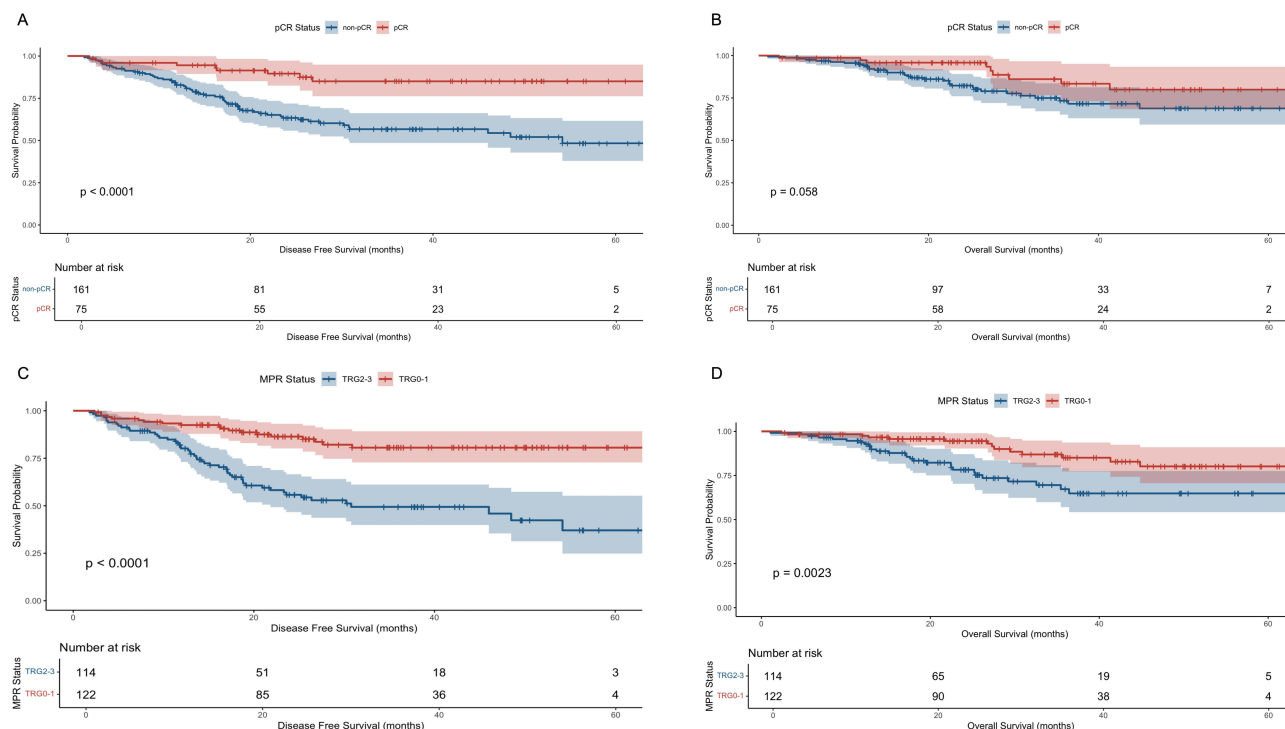
### Impact of MPR on Survival Outcomes

We further evaluated whether achieving MPR could improve both short-term and long-term survival outcomes (n=236). Kaplan-Meier curve analysis revealed a significant difference in DFS between patients with TRG 0–1 and TRG 2–3 (HR=0.27, 95% CI: 0.17–0.44, log-rank  $p < 0.0001$ ). Notably, OS was also significantly improved in the TRG 0–1 group compared to the TRG 2–3 group (HR=0.38, 95% CI: 0.21–0.71, log-rank  $p = 0.0023$ ), as shown in Figure 2C and D. These findings suggest that achieving MPR is associated with favorable short- and long-term survival outcomes. In

**Table 2** Dynamic Changes in Blood Test Results: From Baseline to Pre-Surgery

	Baseline Data				After Immunotherapy and Pre-Surgery				foldchange p.value
	[ALL] N=236	Non-pCR N=161	pCR N=75	p.value	[ALL] N=236	Non-pCR N=161	pCR N=75	p.value	
PLT,median	265	271	256	0.125	227	233	217	0.221	0.825
[Q1-Q3]	[224,323]	[224,334]	[224,301]		[187,275]	[187,277]	[186,266]		
MPV,median	9.80	9.60	10.20	0.001	9.60	9.40	9.700	<0.001	0.714
[Q1-Q3]	[9.20,10.50]	[9.20,10.30]	[9.40,10.80]		[9.10,10.10]	[9,10]	[9.400,10.500]		
PDW,median	10.60	10.30	11.40	0.002	9.90	9.700	10.700	<0.001	0.864
[Q1-Q3]	[9.60,12.10]	[9.50,11.60]	[9.80,12.70]		[9,11.10]	[8.800,10.600]	[9.400,11.900]		
P_HCT,median	0.260	0.270	0.260	0.445	0.220	0.220	0.220	0.709	0.922
[Q1-Q3]	[0.220,0.312]	[0.220,0.320]	[0.230,0.295]		[0.180,0.260]	[0.180,0.260]	[0.180,0.270]		
P_LCR,median	22.70	21.40	25.90	0.001	20.60	19.60	22.900	<0.001	0.535
[Q1-Q3]	[18.40,29]	[17.90,27.20]	[20,31.60]		[17.20,25.40]	[16.20,24.20]	[19,28.600]		
P_LCC,median	6190.40	6050.70	6705.60	0.073	4781.60	4586.40	5148	0.092	0.527
[Q1-Q3]	[5062.90,7682]	[4972.50,7454.30]	[5217.30,7939.40]		[3656.20,6026.40]	[3501.10,5851.50]	[3757.20,6650]		
PNl,mean (±SD)	53.169±4.532	52.930±4.613	53.682±4.307	0.237	50.779±4.585	51.194±4.699	49.885±4.185	0.036	0.014
NLR,median	2.43	2.43	2.35	0.522	2.42	2.53	2.35	0.555	0.804
[Q1-Q3]	[1.81,3.31]	[1.85,3.25]	[1.60,3.48]		[1.69,3.57]	[1.70,3.61]	[1.60,3.53]		
Mono,median	6.70	6.600	6.900	0.197	7.600	7.200	8.300	0.002	0.043
[Q1-Q3]	[5.50,8.10]	[5.200,8.10]	[6.8.10]		[6,9.40]	[5.800,8.700]	[7.100,10]		
P <sub>r</sub> ,median	1.130	1.130	1.110	0.168	1.200	1.220	1.160	0.039	0.978
[Q1-Q3]	[1.040,1.230]	[1.050,1.250]	[1,1.200]		[1.082,1.320]	[1.090,1.340]	[1.070,1.270]		
Fbg,median	3.850	3.820	3.870	0.935	3.320	3.430	3.150	0.012	0.132
[Q1-Q3]	[3.220,4.600]	[3.320,4.510]	[3.110,4.670]		[2.855,3.915]	[2.960,4.022]	[2.735,3.525]		
Differentiation, N (%):									
Low	89 (37.712%)	58 (36.025%)	31 (41.333%)	ref					
Moderate	106 (44.915%)	84 (52.174%)	22 (29.333%)	0.029					
High	5 (2.119%)	3 (1.863%)	2 (2.667%)	0.814					

**Notes:** foldchange = (Pre-surgery value - Baseline value) / Baseline value; Q1-Q3, Q1, the 25th percentile; Q3, the 75th percentile; SD, Standard Deviation; ref, reference. For normally distributed data, results are presented as mean ± standard deviation. For non-normally distributed data, results are reported as median and interquartile range.



**Figure 2** Kaplan-Meier survival curves of DFS and OS stratified by pCR and MPR status. **(A)** Kaplan-Meier curves for DFS in patients stratified by pCR status (n=236). **(B)** Kaplan-Meier curves for OS in patients stratified by pCR status (n=236). **(C)** Kaplan-Meier curves for DFS in patients stratified by MPR status (n=236). **(D)** Kaplan-Meier curves for OS in patients stratified by MPR status (n=236).

contrast to pCR, MPR appears to be a more suitable predictor of nICT efficacy and survival benefit. In other words, a TRG score of 1 indicates a survival benefit from immunotherapy, even in the absence of complete tumor eradication.

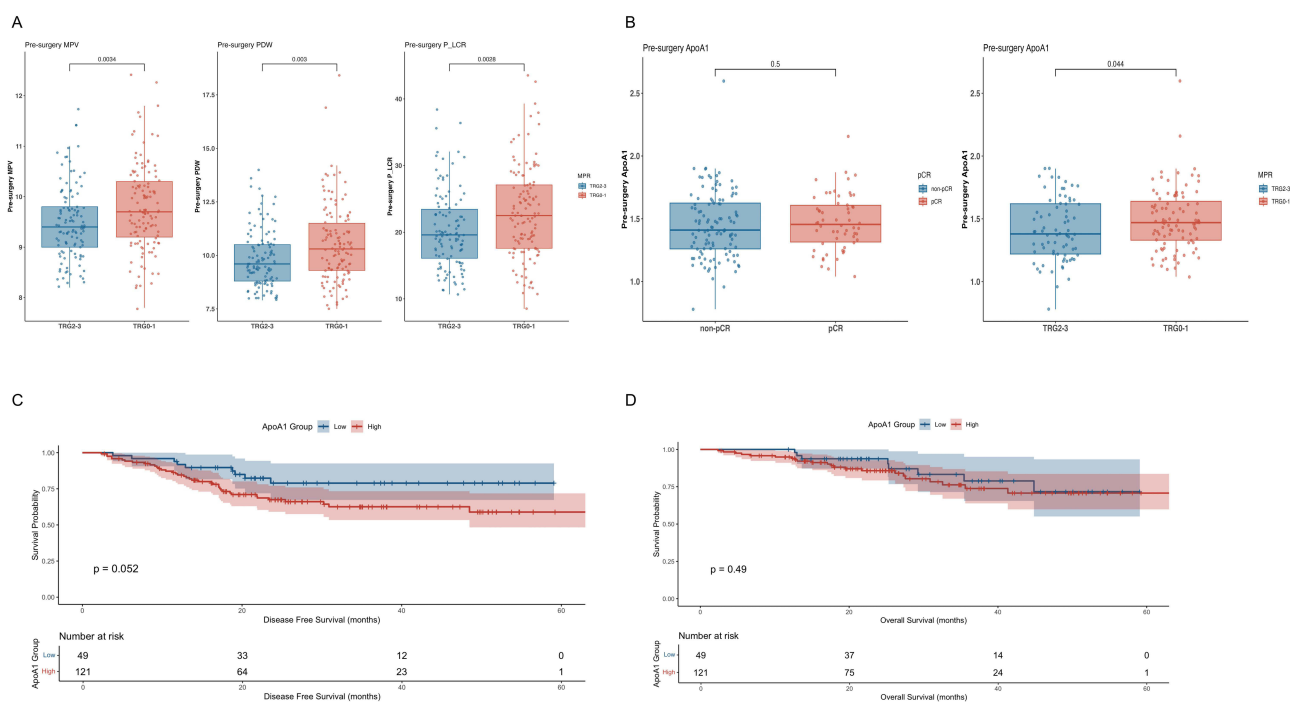
Univariate logistic regression analysis demonstrated that preoperative MPV (OR = 1.62, 95% CI: 1.15–2.26,  $p = 0.005$ ), PDW (OR = 1.31, 95% CI: 1.10–1.55,  $p = 0.003$ ), and P-LCR (OR = 1.07, 95% CI: 1.02–1.11,  $p = 0.003$ ) differed significantly between MPR groups (n=235). Additionally, preoperative apolipoprotein A1 (ApoA1, OR = 4.19, 95% CI: 1.14–15.39,  $p = 0.031$ ) levels were significantly different between MPR groups (n = 169). Multivariate logistic regression analyses demonstrated that preoperative MPV (OR = 1.71, 95% CI: 1.14–2.57,  $p = 0.01$ ), PDW (OR = 1.35, 95% CI: 1.09–1.68,  $p = 0.006$ ), and P-LCR (OR = 1.07, 95% CI: 1.02–1.13,  $p = 0.007$ ) were independent predictors of MPR. Univariate Cox regression analysis for DFS showed that preoperative ApoA1 was significantly associated with DFS (HR=0.23, 95% CI: 0.07–0.78, log-rank  $p = 0.018$ ), whereas baseline ApoA1 levels were not ( $p > 0.05$ , Figure 3A and B).

Although the median survival for OS and DFS was not reached, survival analysis for MPV, PDW, and P-LCR revealed no statistically significant differences (all  $p > 0.05$ ). While the log-rank test for DFS and ApoA1 approached significance (ApoA1 cutoff = 1.4 mmol/L, log-rank  $p = 0.052$ ), KM analyses for OS did not show a significant association for ApoA1 ( $p > 0.05$ , Figure 3C and D).

## Cox Regression and Predictive Model for DFS

We employed a Cox proportional hazards model with the “all” method for multivariable adjustment to assess the impact of preoperative MPV combined with ApoA1 on DFS (n=169). The results indicated that ApoA1 remained a significant predictor of DFS (HR = 0.24, 95% CI: 0.07–0.81,  $p=0.021$ ), whereas MPV did not show significance (HR = 0.86, 95% CI: 0.61–1.22,  $p = 0.4$ , Figure 4A). Our model demonstrated a moderate predictive performance with a C-index of 0.622 (95% CI: 0.548–0.697).

The model’s Wald test, log-rank test, and likelihood ratio test all yielded  $p$ -values  $< 0.05$ , confirming the model’s robustness. The predictive performance for DFS at 12, 18, 24, and 30 months demonstrated AUC values of 0.643 (95%



**Figure 3** Comparative analysis among MPR subgroups and survival curves by ApoA1 levels. **(A)** Boxplots of platelet-related parameters across different MPR subgroups (n=235). **(B)** Boxplots of ApoA1 levels in patients stratified by pCR and MPR status (n=169). **(C)** Kaplan-Meier curves for DFS in patients stratified by ApoA1 levels (cutoff = 1.4, n=169). **(D)** Kaplan-Meier curves for OS in patients stratified by ApoA1 levels (cutoff = 1.4, n=169).

CI: 0.53–0.756), 0.649 (95% CI: 0.552–0.747), 0.662 (95% CI: 0.56–0.765), and 0.706 (95% CI: 0.604–0.809), respectively (Figure 4B and 4C). Additionally, we constructed nomograms to predict 12-, 24-, and 30-month DFS, which may facilitate clinical prediction of DFS in patients with LA-ESCC (Figure 4D). Calibration curves and decision curve analyses are shown in Figure S2 and Figure S3, respectively.

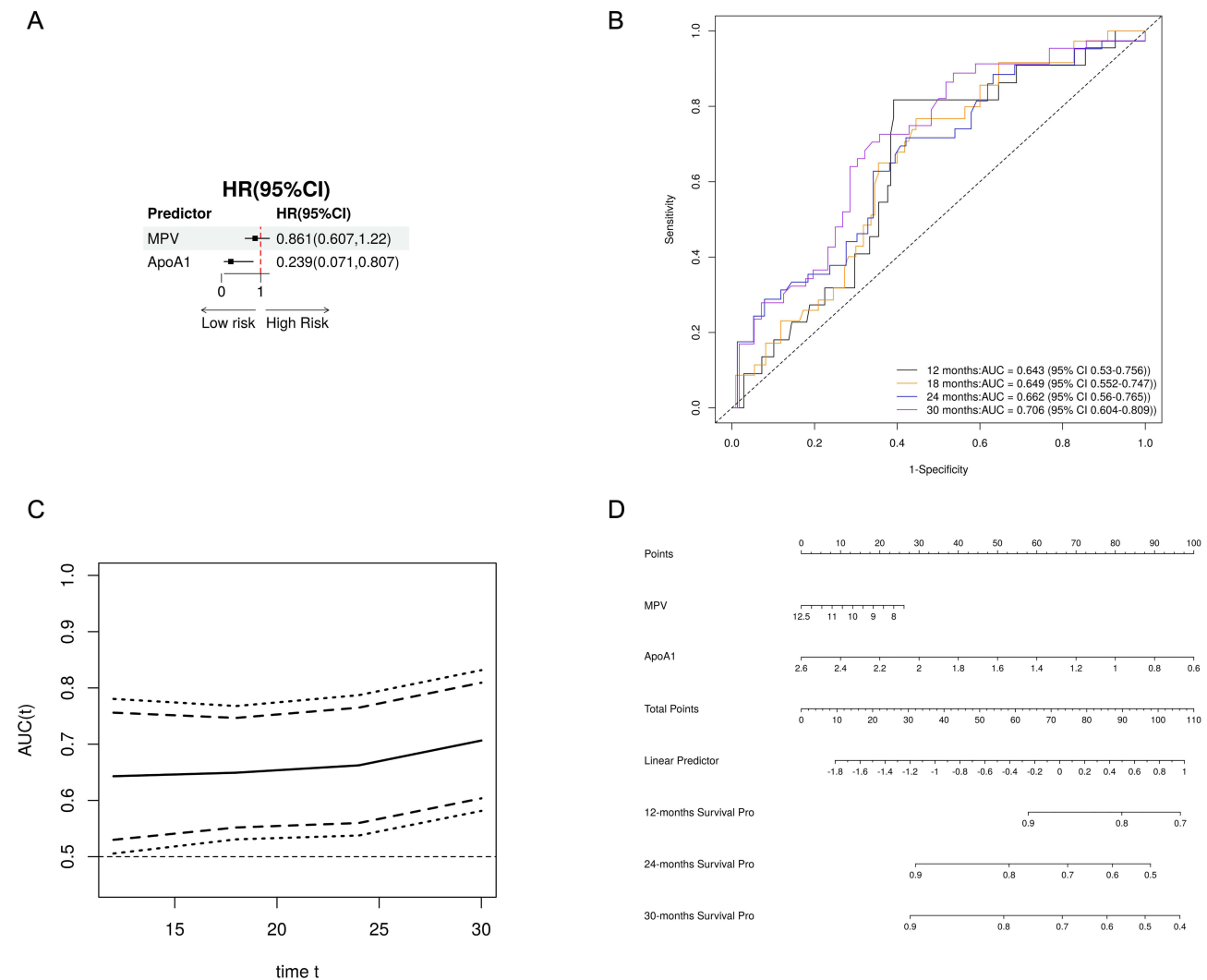
## Discussion

This study aimed to investigate the blood parameters that influence the therapeutic efficacy and prognosis of nCIT in LA-ESCC. Through a retrospective analysis of routinely assessed hematological indices, clinical data, pathological findings, and prognostic outcomes from stage II/III ESCC patients treated at our institution, we identified important predictive biomarkers.

Our multivariate analyses revealed that both baseline and preoperative MPV, PDW, and P-LCR were independent predictors of pCR, with preoperative values showing even more pronounced differences (all  $p < 0.001$ ). These findings suggest that platelet-related parameters may serve as useful indicators of treatment response in LA-ESCC patients undergoing nCIT. Furthermore, preoperative MPV, PDW, P-LCR, and ApoA1 exhibited significant differences across MPR groups (all  $p < 0.05$ ). Notably, preoperative ApoA1 was independently associated with DFS in both univariate and multivariate Cox regression analyses (all  $p < 0.05$ ).

A predictive model combining preoperative MPV and ApoA1 demonstrated promising performance in predicting DFS, with AUC values for 12, 18, 24, and 30 months of 0.643 (95% CI: 0.53–0.756), 0.649 (95% CI: 0.552–0.747), 0.662 (95% CI: 0.56–0.765), and 0.706 (95% CI: 0.604–0.809), respectively. These results underscore the potential clinical utility of combining these readily available hematological markers to predict patient outcomes and personalize treatment strategies for LA-ESCC.

In our cohort, pCR was associated with improved DFS ( $p < 0.0001$ ) but showed no significant impact on OS ( $p = 0.058$ ). In comparison, MPR was significantly associated with both better DFS ( $p < 0.0001$ ) and OS ( $p = 0.0023$ ). This discrepancy may be attributed to the fact that the median OS and DFS have not yet been reached, coupled with a relatively short median follow-up of 25.5 months. Although OS remains the gold standard endpoint for assessing



**Figure 4** Prognostic value of preoperative MPV combined with ApoA1 for DFS. **(A)** Forest plot illustrating the prognostic value of preoperative MPV combined with ApoA1 for DFS (n=169). **(B)** Time-dependent ROC curves for DFS prediction using preoperative MPV combined with ApoA1 (n=169). **(C)** Continuous time-dependent ROC curves for DFS prediction using preoperative MPV combined with ApoA1 (n=169). **(D)** Nomogram for predicting DFS based on preoperative MPV combined with ApoA1 (n=169).

clinical benefit in cancer therapeutics, recent evidence from nCIT in lung cancer has shown superior 5-year survival rates for patients achieving pCR compared to those without (95.3% vs 55.7%) with a median follow-up of 68.4 months.<sup>25</sup> The median OS and DFS were not reached, limiting the analysis of long-term survival outcomes. The conclusion regarding the impact of pCR on OS may therefore be premature. However, long-term OS data for nCIT in ESCC remain unavailable.

One study cautioned against using pCR as a surrogate for OS in resectable ESCC, while another suggested recurrence-free survival (RFS) could serve as a more appropriate surrogate for OS to expedite clinical trial timelines in ESCC.<sup>26,27</sup> The Keystone-001 trial evaluated preoperative nCIT for LA-ESCC, The trial chose MPR as the primary endpoint instead of pCR. This choice was based on evidence that MPR in resected specimens may better predict long-term survival.<sup>24,28</sup>

Our observed pCR and MPR rates were 31.8% and 51.7%, respectively, slightly lower than those reported in the Keystone-001 trial (41% and 72%).<sup>24</sup> In comparison, our 1-year OS rate was modestly higher (95.6% vs 91.3%), while the 2-year OS rate was lower (86.7% vs 91.3%). These differences may be attributed to variations in sample size (n = 236

vs  $n = 46$ ) or treatment regimens (multi-drug versus pembrolizumab). Given these discrepancies, determining the optimal surrogate endpoint for long-term survival in nCIT-treated ESCC will require extended follow-up in larger patient cohorts.

Our findings further suggest that elevated levels of MPV, PDW, and P-LCR are associated with a higher likelihood of achieving pCR and MPR following nCIT. Specifically, an increase in MPV reflects larger platelet volumes in peripheral blood, which likely indicates the presence of freshly released, immature, or activated platelets.<sup>29–32</sup> Similarly, an elevated PDW signifies increased heterogeneity in platelet size, indicative of a higher proportion of activated platelets. An increase in P-LCR means more platelets are larger than the normal volume threshold, which is usually greater than 12 fL. This increase is also a marker for freshly activated or reactive platelets. The platelet indices MPV, PDW, and P-LCR together show systemic platelet activation. Platelet activation is commonly seen in inflammation, thrombosis, tumor growth, and cardiovascular diseases. Although MPV, PDW, and P-LCR were associated with treatment response (pCR/MPR), their direct correlation with OS or DFS was not significant. This may be because pathological response serves as a stronger surrogate endpoint for long-term survival, overshadowing the effect of baseline hematologic parameters. These markers may therefore influence survival indirectly through their impact on treatment response. In addition, the short follow-up and limited survival events might have reduced the statistical power to detect their prognostic value.

ApoA1, the principal protein component of high-density lipoprotein (HDL), is crucial in lipid metabolism, modulation of inflammation, and immune response regulation.<sup>33</sup> Previous studies have shown that serum ApoA1 levels are significantly reduced in ESCC patients compared to healthy controls, with low levels of ApoA1 correlating strongly with poor prognosis and serving as an independent predictor of adverse OS.<sup>34–36</sup> In our study, preoperative ApoA1 levels had a significant effect on DFS. Lower preoperative ApoA1 levels were linked to better DFS outcomes. However, this counterintuitive result may be explained by metabolic and immune interactions. Hypercholesterolemia, often accompanied by reduced ApoA1 levels, has been associated with better outcomes in patients receiving immunotherapy.<sup>37</sup> It may reflect a pro-inflammatory state that enhances tumor immunogenicity and responsiveness to immunotherapy. Moreover, cholesterol and mature HDL particles can modulate the tumor immune microenvironment by promoting M1-like macrophages and activated CD8<sup>+</sup> T cells, thereby improving antitumor immunity.<sup>35,38</sup>

Despite the valuable insights provided by our study, several limitations warrant consideration. Firstly, this was a retrospective, single-center study with a relatively modest sample size, which may limit the generalizability of the results. The follow-up duration was not yet sufficient to reach the median OS or DFS, restricting the interpretation of long-term outcomes. Additionally, treatment regimens were not fully homogeneous, introducing potential confounding effects. Commonly utilized biomarkers, such as PD-L1 expression, were not included in the current analysis, and external validation cohorts were unavailable, which may reduce the robustness of the findings.

Nevertheless, our study retains several strengths, including consecutive patient enrollment and the systematic, protocol-driven approach to extracting laboratory data from the clinical database, which support the consistency and reliability of the results. In future studies, we aim to include larger cohorts of patients with LA-ESCC, integrate a wider range of biomarkers (eg, PD-L1, cytokines), and conduct multicenter validation with longer follow-up periods to further confirm and broaden the applicability of our conclusions.<sup>39</sup> Furthermore, mechanistic investigations will be essential to explore the role of platelets in modulating the tumor microenvironment in ESCC, specifically their interactions with tumor cells, T lymphocytes, and other immune effector cells.

## Conclusion

Baseline and preoperative MPV, PDW, and P-LCR serve as valuable predictors of response and prognosis to nCIT in LA-ESCC. Nomograms integrating these with preoperative ApoA1 show promising performance in prognosticating DFS, offering clinical utility.

## Data Sharing Statement

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

## Ethics Statement

The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and received ethical approval from the Ethics Committee of Sun Yat-sen University Cancer Center of Sun Yat-sen University (Approval Number: B2025-394-01). Given the retrospective design, the Ethics Committee granted a waiver of informed consent after thoroughly reviewing the study protocol and confirming that the criteria for exemption were met. Patient privacy was strictly protected, and data confidentiality was fully maintained.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Tao Zeng, Yue-chang Liu, Xiang-hui Wang: Conceptualization, Data curation, Formal analysis, Project administration, Visualization, Writing – original draft. Jun Yan: Data curation, Formal analysis, Project administration, Writing – review and editing; Shi-bing Li: Conceptualization, Formal analysis, Project administration, Funding acquisition, Writing – review and editing; Danning Deng, Shan Xing: Conceptualization, Formal analysis, Project administration, Visualization, Funding acquisition, Writing – review and editing.

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## Disclosure

The authors declare that they have no competing interests in this work.

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