Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

A Novel Inflammation-Marker-Based Prognostic Model for Advanced Pulmonary Lymphoepithelioma-Like Carcinoma

Xueyuan Chen[1,*], Tingting Liu[1,*], Silang Mo[1,*], Yuwen Yang[1], Xiang Chen[1], Shaodong Hong[1], Ting Zhou[1], Gang Chen[1], Yaxiong Zhang[1], Yuxiang Ma[2], Yuanzheng Ma[1], Li Zhang[1], Yuanyuan Zhao[1]

[1]Medical Oncology Department, 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; [2]Department of Clinical Research, 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: Li Zhang; Yuanyuan Zhao, Sun Yat-sen University Cancer Center, 651 Dong Feng Road East, Guangzhou, 510060, People's Republic of China, Email zhangli@sysucc.org.cn; zhaoyy@sysucc.org.cn

Purpose: This study aimed to investigate the prognostic value of inflammation markers for advanced pulmonary lymphoepithelioma-like carcinoma (PLELC) and develop an effective prognostic model based on inflammation markers to predict the overall survival (OS) of this population.

Methods: Cox regression analysis was performed on 18 clinical and inflammation features, and a nomogram was created to predict overall survival (OS). The nomogram was evaluated by the concordance index (C-index), the time-dependent area under the receiver operating (ROC) curves (AUCs), calibration curves, and Decision Curve Analysis (DCA).

Results: This study included a training cohort (n = 177) and a validation cohort (n = 77). The following variables were found to be independent prognostic factors for OS and used in the nomogram: Hepatitis B virus surface antigen status, gender, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein-to-albumin ratio (CAR). The C-indexes of the nomogram in the training and validation cohort were 0.740 (95% CI: 0.706–0.747) and 0.733 (95% CI: 0.678–0.788), respectively. Furthermore, time-dependent AUCs and well-fitted calibration curves showed good discriminative ability in both cohorts. Additionally, among the subset of EBV DNA data (n = 111), both ROC curve and DCA curve analysis demonstrated that the nomogram plus EBV DNA provided superior predictive performance compared to EBV DNA or the nomogram alone. Patients who received chemoimmunotherapy as the first-line treatment had better OS (not reached vs 44.4 months, P = 0.015) than those with chemotherapy alone and those who received immunotherapy at any line had better OS than those who never received it (not reached vs 31.0 months, P < 0.001).

Conclusion: This study established and validated a prognostic nomogram model for patients with advanced PLELC. Combining the nomogram with EBV DNA more effectively predicted the prognosis of patients than the nomogram alone. Immunotherapy was found to be a critical treatment option for PLELC.

Keywords: pulmonary lymphoepithelioma-like carcinoma, overall survival, inflammation markers, nomogram

Introduction

Pulmonary lymphoepithelioma-like carcinoma (PLELC) is an extremely rare subtype of non-small cell lung cancer (NSCLC) with an incidence of less than 1% that was first reported in 1987,[1] and the incidence of PLELC is higher in the Asian population than in the Western population.[2] In 2021, the World Health Organization (WHO) updated the criteria for lung tumor classification and reclassified PLELC as a special type of lung squamous cell carcinoma excluding lung metastasis from nasopharyngeal carcinoma.[3,4] Histologically, the tumor is composed of large or poorly or

Received: 4 November 2024
Accepted: 6 February 2025
Published: 20 February 2025

undifferentiated cells with vesicular nuclei and prominent nucleoli. In situ hybridization results have shown that almost all patients are positive for Epstein–Barr virus-encoded small nuclear RNA (EBER) as well.[5,6] Marked infiltration of lymphocytes and other inflammatory cells such as macrophages and neutrophils has been found, in the tumor cell nests and the surrounding stroma of PLELC.[7] In terms of gene mutations,[8] the median tumor mutation burden is low at 2.5 mutations/Mb, and sensitive driver gene mutations such as epidermal growth factor receptor gene (EGFR), Kirsten rat sarcoma viral oncogene homolog gene (KRAS), and b-Raf proto-oncogene, serine/threonine kinase gene (BRAF) mutations are infrequent, with programmed death ligand-1 (PD-L1) and TP53 being highly expressed.[9,10]

Plasma Epstein–Barr virus (EBV) deoxyribonucleic acid (DNA) copy number has been found to be an independent risk factor for poor prognosis in PLELC patients. In previous studies, high baseline EBV DNA copy number has been shown to be associated with shorter disease-free survival (DFS),[11] progression-free survival (PFS),[12,13] and overall survival (OS).[12,14] However, there are limited prognostic tools for PLELC. Inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR) and monocyte–lymphocyte ratio (MLR), are considered related to the prognosis of nasopharyngeal carcinoma,[15–18] and as mentioned above, the tumor microenvironment in PLELC is similar to nasopharyngeal carcinoma with infiltration of inflammatory cells around the tumor cells such as lymphocytes and macrophages.[19] Inflammatory markers thus might be closely related to PLELC.

We therefore sought to construct an effective prognostic nomogram model based on inflammatory markers and clinical factors that could be used to predict the OS of PLELC patients. This work could help to predict the survival of patients and formulate individual diagnosis and treatment plans for each patient.

Methods

Study Population

An electronic medical record search was performed for data from September, 2009, to February, 2023, at the Sun Yat-sen University Cancer Center (SYSUCC), China. Study inclusion criteria were as follows: (1) histologically confirmed PLELC, (2) age 18–75 years, (3) presence of local progression or distant metastasis, (4) presence of measurable target lesions, (5) absence of other primary tumors, and (6) complete medical records. The exclusion criteria were (1) lung metastasis originating from nasopharyngeal cancer and lymphoepithelioma-like carcinoma of other primary sites, (2) nonadvanced PLELC, (3) lack of measurable target lesions, (4) other active tumors, and (5) incomplete medical history. The need to obtain written informed consent from each participant was waived due to the retrospective nature of the study, and the data were anonymous. The study was approved by the Institutional Review Board of SYSUCC (ID: B2020-402-Y02).

Follow-up and Endpoints

Telephone follow-up is conducted every 6 to 12 months until death or loss to follow-up. Clinical efficacy of the treatment was evaluated every 2 cycles of chemotherapy or every 3 months intervals after radical surgery using CT or 18F-FDG PET imaging, according to Response Evaluation Criteria In Solid Tumors (RECIST1.1).[20] The overall response rate (ORR) was defined as the proportion of patients with partial or complete response (PR/CR), and the disease control rate (DCR) was defined as the proportion of PR/CR plus stable disease (SD) cases. Progression-free survival (PFS) was defined as the time from the initiation of first-line therapy to progressive disease (PD) or death from any cause, whichever occurred first. Overall survival (OS), calculated from the date of first-line therapy to the date of death from any cause or the date of last follow-up, served as the main outcome measure.

Baseline Biomarkers

Information obtained at baseline included clinical staging, body mass index (BMI), age, sex, smoking history, metastasis sites, performance status (PS), treatment, and serum markers, including albumin, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), total cholesterol (TC), lactate dehydrogenase (LDH), serum amyloid A (SAA), C-reactive protein (CRP), neutrophil count, monocyte count, lymphocyte count, and platelet count. The formulas used to calculate for the inflammatory markers and nutritional indices (PLR, MLR, NLR, CAR, PNI) are given below.

Prognostic nutritional index (PNI), serum albumin (g/L)+5×lymphocyte count ($\times10^9$/L); C-reactive protein-to-albumin ratio (CAR), C-reactive protein (mg/L)/albumin (g/L); neutrophil-to-lymphocyte ratio (NLR), neutrophil count ($\times10^9$/L)/lymphocyte count ($\times10^9$/L); monocyte-to-lymphocyte ratio (MLR), monocyte count ($\times10^9$/L)/lymphocyte count ($\times10^9$/L); and platelet-to-lymphocyte ratio (PLR), platelet count ($\times10^9$/L)/lymphocyte count ($\times10^9$/L).

Continuous and raw variables were dichotomized based on their clinical normal ranges. For converted continuous variables such as PLR, MLR, NLR, CAR, and PNI, the patients were classified into two subtypes by a cutpoint using the "surv_cutpoint" function implemented in the R package "survminer" (version 0.4.9). The optimal cut-off values were then calculated based on OS as follows: neutrophil-to-lymphocyte ratio (NLR): 5.57, platelet-to-lymphocyte ratio (PLR): 300.7, monocyte-to-lymphocyte ratio (MLR): 0.57, C-reactive protein albumin ratio (CAR): 0.85 and prognostic nutritional index (PNI): 41.6.

Statistical Analysis

Differences in baseline clinical features between patients in the training and validation cohort were analyzed using the chi-squared test, and the Cox proportional risk model was used for univariate and multivariate survival analysis. Any statistically significant ($P < 0.05$) variable from the univariate Cox regression was included in the multivariate Cox regression analysis. Nomograms were then constructed, and the nomogram score was calculated using the R packages "rms" and "nomogram Formula". The training group was used for the development of the nomogram, and the generalizability of the model was evaluated using the validation cohort. To measure the predictive accuracy and discriminative ability of the nomogram, we calculated the consistency index (C-index) and the area under the curve (AUC) of the Receiver Operating Characteristic (ROC), constructed calibration plots and carried out decision curve analysis. Using the survival ROC method, sensitivity and specificity were calculated at 1, 2, and 3 years to generate time-dependent survival ROC curves for nomogram model indicators by "timeROC" package in R 4.2.3 referred to previous studies.[21,22] PFS and OS were assessed by the Kaplan–Meier method with the Log rank test. All statistical analysis was conducted using R software, version 4.2.3, and all statistical tests were two-sided, with $P < 0.05$ assumed to indicate statistical significance.

Results

Patient Characteristics and Survival

A total of 451 patients were screened with histologically diagnosed PLELC at Sun Yat-sen University Cancer Center from May, 2009, to June, 2023. Of those, 185 patients were excluded due to being stage I–IIIA, 2 patients were excluded for receiving radical surgery or radiotherapy, and 10 patients were excluded for being lost to follow-up. Finally, 254 patients diagnosed with recurrent or metastatic PLELC were selected according to the inclusion and exclusion criteria and randomly assigned to a training cohort (177 cases) and validation cohort (77 cases) at a 7:3 ratio (Figure 1).

The median age was 53 years (interquartile range (IQR), 47–59 years). One hundred and thirty-six (53.5%) patients were younger than 55 years, 250 (98.3%) patients had PS scores between 0 and 1 and the ratio of men to women was similar. Because most of the patients had PS scores between 0 and 1, the PS score was not included in the subsequent analysis. Additionally, 59 (23.2%) patients were positive for hepatitis B virus antigen. In the first-line treatment, 102 (40.2%) patients received platinum-based doublet chemoimmunotherapy, and 88 received (34.6%) platinum-based doublet chemotherapy. One hundred and eleven cases (43.8%) had EBV DNA copy number data at baseline, and the median EBV copy number was 13,800 copies/mL. Except for total cholesterol and low-density lipoprotein cholesterol, other characteristics were balanced between the training and the validation cohort (Table 1).

The PFS and OS were 8.9 months and 50.0 months for the whole population, 8.6 months and 51.8 months in the training cohort, and 11.0 months and 41.5 months in the validation cohort, respectively (Figure S1).

Constructing a Nomogram

Univariate Cox regression analysis in the training cohort revealed that BMI, hepatitis B virus surface antigen status, gender, hemoglobin, PNI, PLR, MLR, NLR, and CAR were significantly associated with overall survival ($P < 0.05$) (Table S1). In the multivariate Cox regression analysis, the following variables were identified as independent prognostic factors: hepatitis B virus surface antigen status ($P = 0.023$, 95% confidence interval (CI): 1.102–3.731,

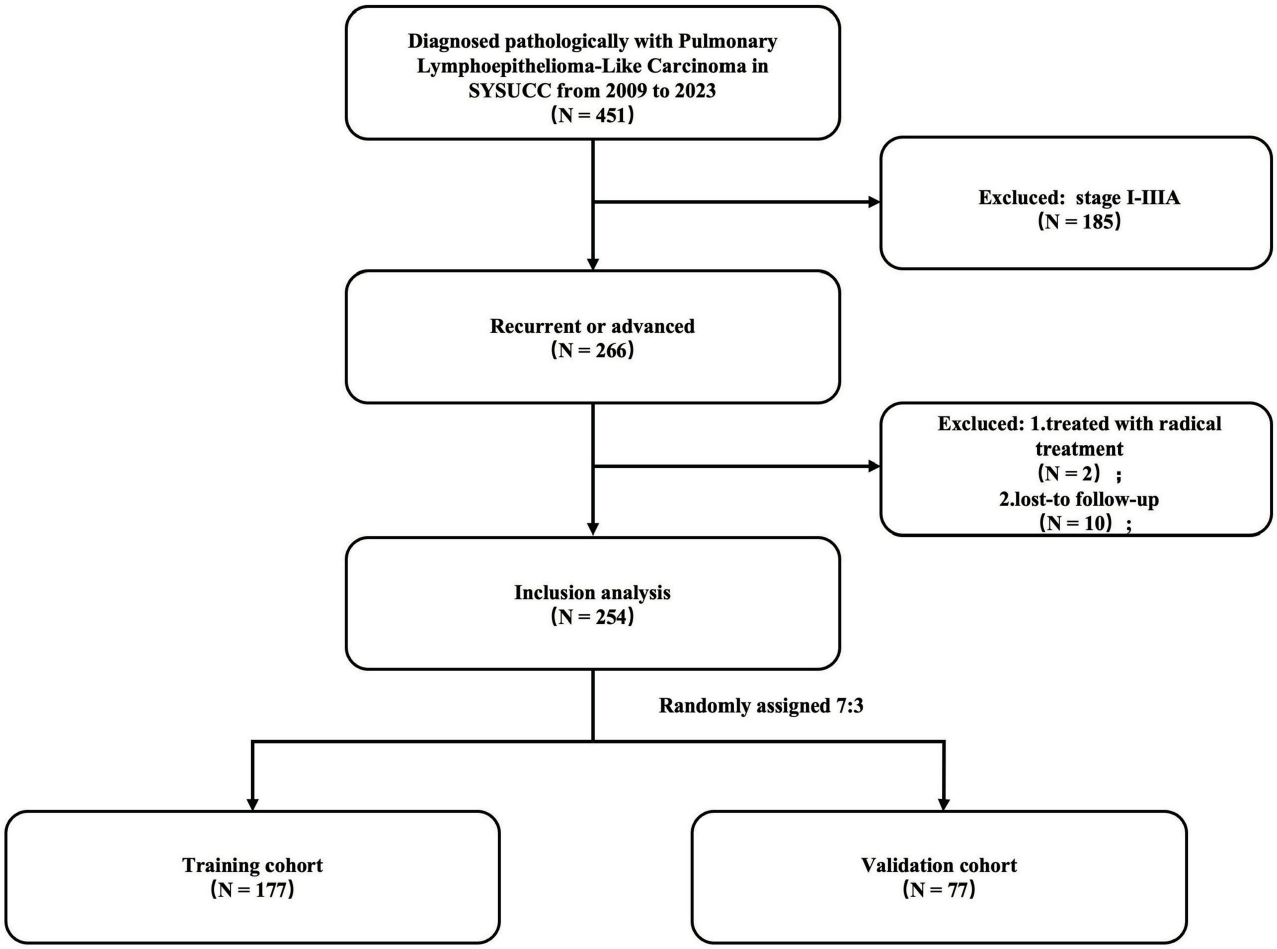

Figure 1 The patient enrollment procedure.

Hazard Ratio (HR): 2.028), Gender (P = 0.021, 95% CI: 0.258–0.895, HR: 0.481), NLR (P = 0.027, 95% CI: 1.121–6.282, HR: 2.653), and CAR (P = 0.013, 95% CI: 1.205–4.983, HR: 2.451) (Table 2). These four independent risk factors were used to draw a tumor-specific survival prognosis nomogram model (Figure 2). To facilitate clinical application, free online software for the implementation of this nomogram was provided in our study (https://nomogramcxy.shinyapps.io/DynNomapp/).

Table 1 Baseline Characteristics of Patients in the Training and Validation Cohorts

Characteristics	All Patients n=254	Training Cohort n=177	Validation Cohort n=77	P
Age (years)				0.149
≤55	136 (53.5%)	89 (50.3%)	47 (61.0%)	
>55	118(46.5%)	88 (49.7%)	30 (39.0%)	
BMI (kg/m^2)				0.533
≤21	58 (22.8%)	38 (21.5%)	20 (26.0%)	
>21	196 (77.2%)	139 (78.5%)	57 (74.0%)	
Hepatitis B virus surface antigen status				0.901
Negative	195 (76.8%)	135 (76.3%)	60 (77.9%)	
Positive	59 (23.2%)	42 (23.7%)	17 (22.1%)	

(*Continued*)

Table 1 (Continued).

Characteristics	All Patients n=254	Training Cohort n=177	Validation Cohort n=77	P
Sex				1.000
Male	128 (50.4%)	89 (50.3%)	39 (50.6%)	
Female	126 (49.6%)	88 (49.7%)	38 (49.4%)	
Smoking history				0.994
No	183 (72.0%)	127 (71.8%)	56 (72.7%)	
Yes	71 (28.0%)	50 (28.2%)	21 (27.3%)	
Bone metastasis				0.823
No	164 (64.6%)	113 (63.8%)	51 (66.2%)	
Yes	90 (35.4%)	64 (36.2%)	26 (33.8%)	
Liver metastasis				0.574
No	189 (74.4%)	134 (75.7%)	55 (71.4%)	
Yes	65 (25.6%)	43 (24.3%)	22 (28.6%)	
Site				0.409
0–1	150 (59.1%)	108 (61.0%)	42 (54.5%)	
>1	104 (40.9%)	69 (39.0%)	35 (45.5%)	
Total cholesterol (mmol/L)				**0.041**
≤5.7	199 (78.3%)	132 (74.6%)	67 (87.0%)	
>5.7	55 (21.7%)	45 (25.4%)	10 (13.0%)	
LDL-L (mmol/L)				**0.029**
≤3.4	168 (66.1%)	109 (61.6%)	59 (76.6%)	
>3.4	86 (33.9%)	68 (38.4%)	18 (23.4%)	
TG (mmol/L)				0.965
≤1.92	200 (78.7%)	140 (79.1%)	60 (77.9%)	
>1.92	54 (21.3%)	37 (20.9%)	17 (22.1%)	
Hb (mg/L)				0.619
>110	37 (14.6%)	24 (13.6%)	13 (16.9%)	
≤110	217 (85.4%)	153 (86.4%)	64 (83.1%)	
SAA (mg/L)				0.319
≤10	89 (35.0%)	66 (37.3%)	23 (29.9%)	
>10	165 (65.0%)	111 (62.7%)	54 (70.1%)	
LDH (U /L)				0.853
≤250	149 (58.7%)	105 (59.3%)	44 (57.1%)	
>250	105 (41.3%)	72 (40.7%)	33 (42.9%)	
PNI				0.704
≤41.6	125 (49.2%)	89 (50.3%)	36 (46.8%)	
>41.6	129 (50.8%)	88 (49.7%)	41 (53.2%)	
CAR				0.487
≤0.85	203 (79.9%)	144 (81.4%)	59 (76.6%)	
>0.85	51 (20.1%)	33 (18.6%)	18 (23.4%)	
MLR				0.255
≤0.57	213 (83.9%)	152 (85.9%)	61 (79.2%)	
>0.57	41 (16.1%)	25 (14.1%)	16 (20.8%)	
NLR				0.448
≤5.57	216 (85.0%)	153 (86.4%)	63 (81.8%)	
>5.57	38 (15.0%)	24 (13.6%)	14 (18.2%)	
PLR				0.309
≤300.7	212 (83.5%)	151 (85.3%)	61 (79.2%)	
>300.7	42 (16.5%)	26 (14.7%)	16 (20.8%)	

(*Continued*)

https://doi.org/10.2147/JIR.S502286

Table 1 (Continued).

Characteristics	All Patients n=254	Training Cohort n=177	Validation Cohort n=77	P
EBV viral load data				0.947
Gained	143 (56.2%)	100 (56.5%)	43 (55.8%)	
None	111 (43.8%)	77 (43.5%)	34 (44.2%)	
EBV Viral load (copy/mL)	13,800.00	12,400	19,000	0.274
(median [IQR])	[2210.00,67,750.00]	[1630;62,500]	[3548;165,250]	
First-line treatment				0.073
Platinum-based dual chemoimmunotherapy	102 (40.2%)	63 (35.6%)	39 (50.6%)	
Platinum-based dual chemotherapy	88 (34.6%)	66 (37.3%)	22 (28.6%)	
Others	64 (25.2%)	48 (27.1%)	16 (20.8%)	
Immunotherapy used				
No	75 (29.5%)	121 (68.4%)	58 (75.3%)	0.333
Yes	179 (70.5%)	56 (31.6%)	19 (24.7%)	
TNM				
III	41 (16.1%)	12 (15.6%)	29 (16.4%)	1.000
IV	203 (79.9%)	62 (80.5%)	141 (79.7%)	
Relapse	10 (4.0%)	3 (3.90%)	7 (3.95%)	

Notes: Values in bold are significant (P < 0.05). Others: 22 patients received non-platinum-based chemotherapy alone or combined with immunotherapy, and 33 patients received chemotherapy combined with anti-angiogenic therapy. 4 patients received immunotherapy only, 2 patients received targeted therapies only, and 3 patients received immunotherapy plus anti-angiogenic therapy.

Abbreviations: BMI, height/weight/weight, body mass index; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol SAA, serum amyloid A; LDH, lactate dehydrogenase; PNI, prognostic nutritional index; CAR, C-reactive protein-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; IQR, interquartile range.

Table 2 Multivariate Cox Regression Analysis for OS in the Training Cohort

Characteristics	Multivariate Analysis	
	HR (95% CI)	P
BMI	0.667 (0.320–1.389)	0.279
Hepatitis B surface antigen status	2.028 (1.102–3.731)	**0.023***
Sex	0.481 (0.258–0.895)	**0.021***
Hb	0.936 (0.307–2.852)	0.910
PNI	0.507 (0.249–1.032)	0.061
PLR	1.001 (0.453–2.214)	1.000
MLR	0.948 (0.394–2.280)	0.900
NLR	2.653 (1.121–6.282)	**0.027***
CAR	2.451 (1.205–4.983)	**0.013***

Notes: *P < 0.05; Values in bold are significant (P < 0.05). *P < 0.05.

Abbreviations: HR, Hazard Ratio; CI, confidence interval; BMI, height/weight/weight, body mass index; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; SAA, serum amyloid A; LDH, lactate dehydrogenase; PNI, prognostic nutritional index; CAR, C-reactive protein-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio, PLR, platelet-to-lymphocyte ratio.

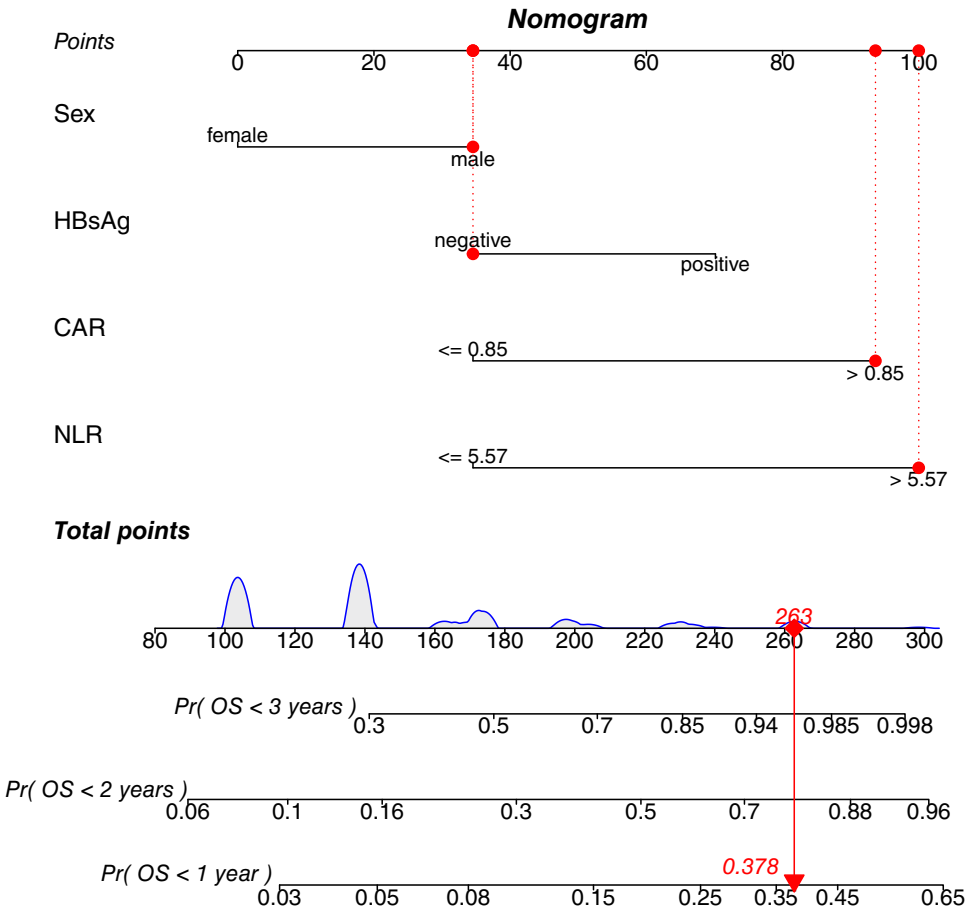

Figure 2 The Nomogram model for 1-, 2-, and 3-year OS in the training cohort.
Abbreviation: OS, overall survival.

Evaluation and Validation of the Nomogram Model

The nomogram model was evaluated and validated using several methods. First, the C-index in the training cohort was 0.740 (95% CI: 0.706–0.747), and the C-index of the validation cohort was 0.733 (95% CI: 0.678–0.788), which was very similar to the actual OS. The AUCs for the training cohort were 0.846 (95% CI: 0.759–0.933), 0.730 (95% CI: 0.623–0.836), and 0.763 (95% CI: 0.665–0.860) at 1, 2, and 3 years, respectively (Figure 3A), and the AUCs for the validation cohort were 0.702 (95% CI: 0.485–0.920), 0.884 (95% CI: 0.780–0.988), and 0.682 (95% CI: 0.506–0.858) at 1, 2, and 3 years, respectively (Figure 3C). Calibration plots of OS probabilities at 1, 2, and 3 years for patients with advanced PLELC showed a high degree of agreement between the actual survival predictions of the training and validation cohorts as well (Figure 3B and D). The model had good prediction accuracy, high discrimination ability, and excellent reliability in the training and validation cohort.

Comparison of the Nomogram Model with EBV DNA

One hundred eleven out of the 254 patients with EBV-DNA copy-number data in the baseline were included in this study. The baseline characteristics of these patients were similar to the overall population (Table S2). PFS was 11.2 months, and OS was 61.4 months in this population, and the level of EBV DNA predicted the OS of PLELC. Importantly, the population with low-level EBV DNA had a better OS (P = 0.025) (Figure S2A). When comparing the predictive power of EBV DNA, the nomogram model, and the nomogram model plus EBV DNA, the C-index values were 0.617 (95% CI:

https://doi.org/10.2147/JIR.S502286

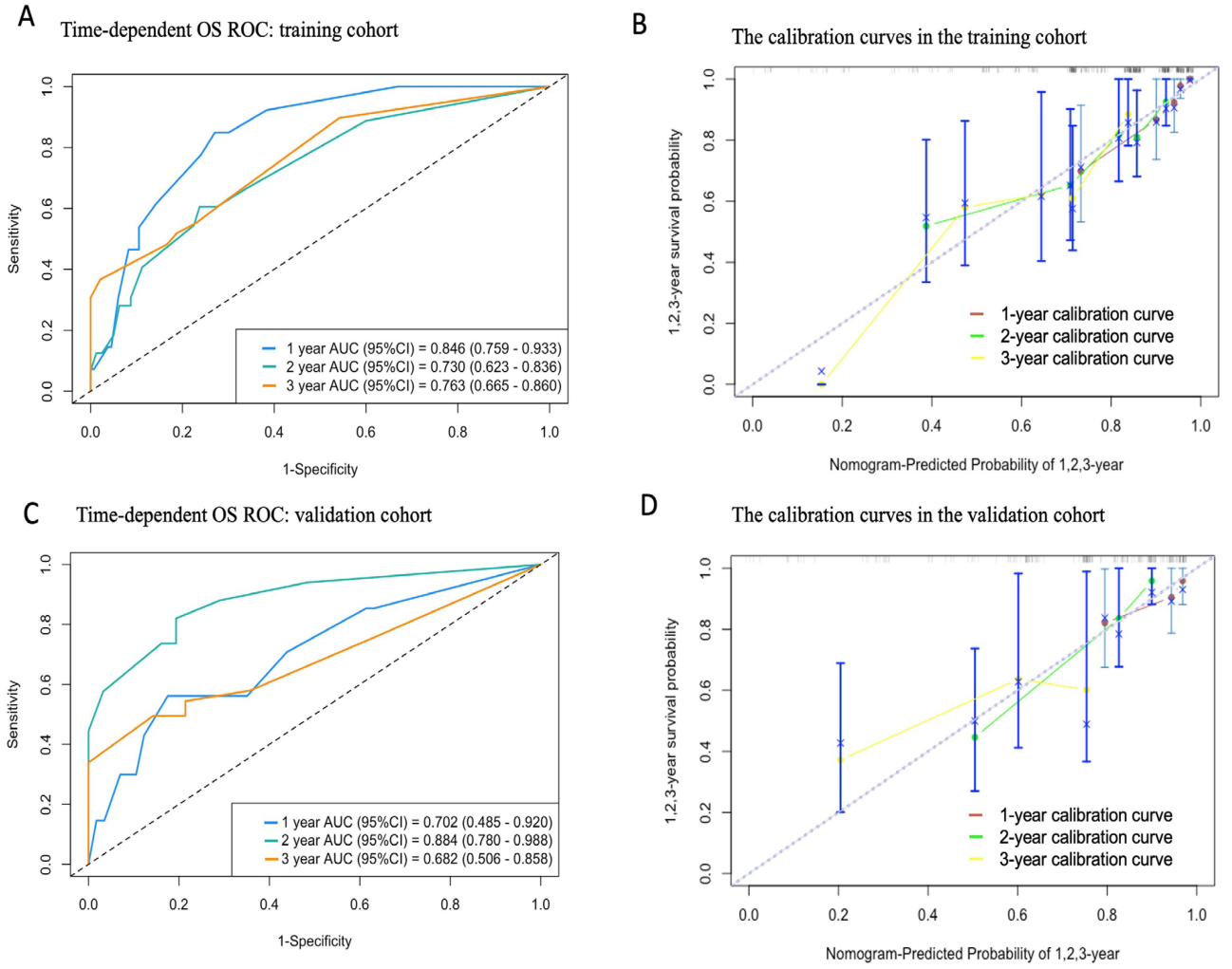

Figure 3 ROC curves and calibration curves to predict OS at 1, 2, and 3 years in the training cohort (**A** and **B**) and in the validation cohort (**C** and **D**).
Abbreviation: OS, overall survival.

0.572–0.662), 0.744 (95% CI: 0.696–0.791), and 0.769 (95% CI: 0.718 −0.820), respectively. In addition, the AUCs were 0.619 (95% CI: 0.519–0.719), 0.695 (95% CI: 0.586–0.804), and 0.715 (95% CI: 0.604–0.826), respectively (Figure 4A). In Decision Curve Analysis (DCA), the 1-year and 2-year decision curves showed that the nomogram model had better clinical application ability compared to the EBV copy number, but the nomogram plus EBV copy number model was the best (Figure 4B and C).

Efficacy of Immunotherapy in PLELC Patients

A total of 190 patients in our study received platinum-based doubled chemotherapy (88 cases) or chemoimmunotherapy (102 cases) in first-line treatment. The median OS and PFS of the 190 patients were 51.8 and 9.4 months, and the baseline clinical characteristics of the patients were well balanced except for hepatitis B virus surface antigen status and age (Table S3). Furthermore, the ORR for those receiving chemoimmunotherapy was higher than the chemotherapy group (71.1% vs 42.2%), as was DCR (97.8% vs 86.7%) (Table S4). Kaplan–Meier survival analysis showed that the median PFS of chemoimmunotherapy as the first-line treatment was longer than that of chemotherapy alone (16.5 vs 7.2

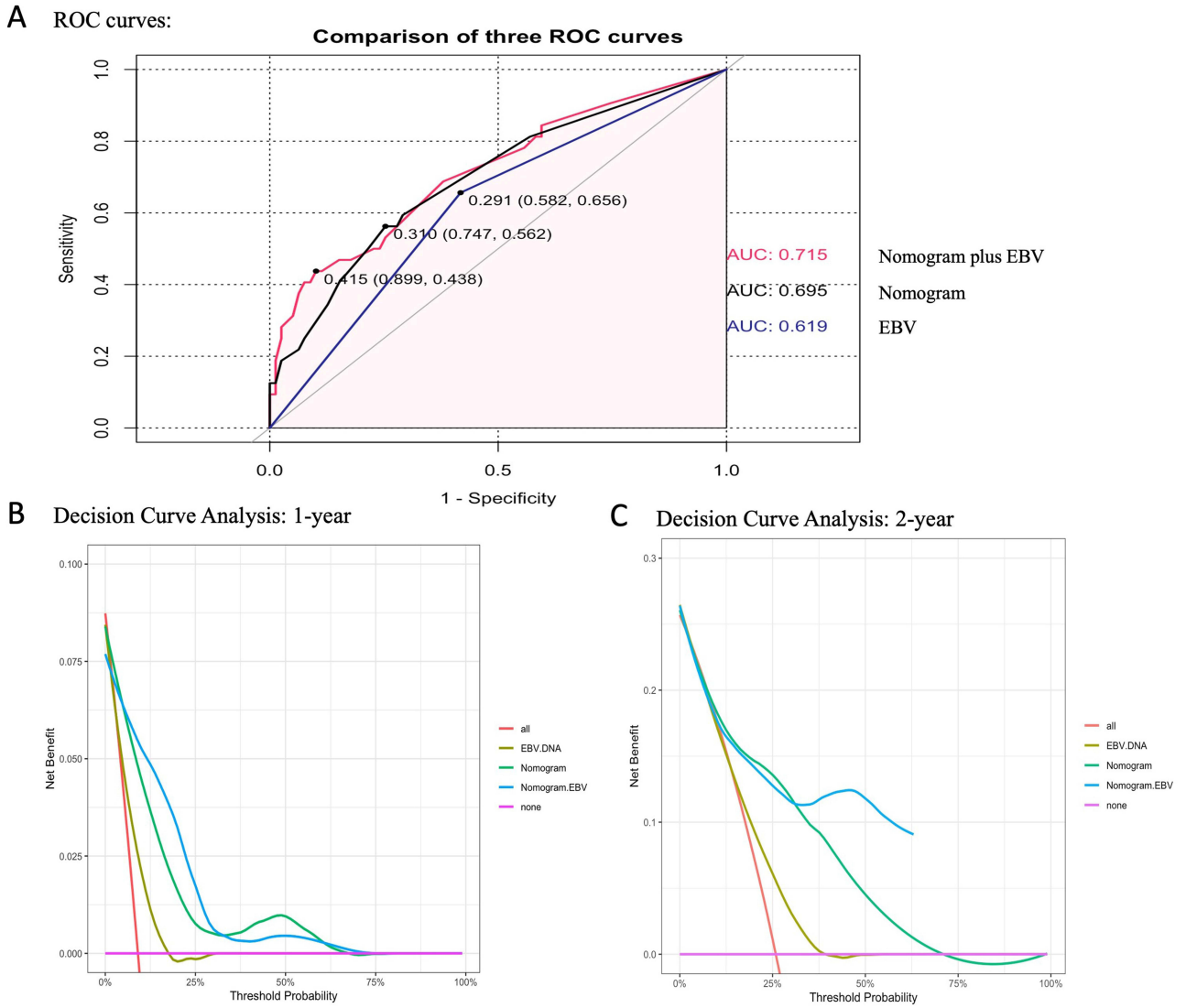

Figure 4 ROC curves (**A**) and decision curves for 1-year (**B**) and 2-year (**C**) overall survival for different models in patients with available EBV DNA data.

months, P < 0.001) (Figure 5A). Similarly, Kaplan–Meier survival analysis also showed that the OS of chemoimmunotherapy was longer (not reached vs 44.4 months, P = 0.015) (Figure 5B). We further verified that the first-line chemoimmunotherapy (P = 0.036, 95% CI: 0.26–0.96, HR: 0.50), hepatitis B virus status (P = 0.001, 95% CI: 1.44–4.24, HR: 2.47), sex (P = 0.041, 95% CI: 0.32–0.98, HR: 0.56), NLR (P < 0.001, 95% CI: 1.72–7.60, HR: 3.62), and CAR (P = 0.026, 95% CI: 1.09–4.18, HR: 2.14) were independent prognostic factors in multivariate cox regression analysis (Figure S3).

Moreover, we compared OS between patients who had previously used immunotherapy (179 cases) and those who had not received immunotherapy (75 cases). Most baseline clinical characteristics of the patients were well balanced (Table S5). Kaplan–Meier survival curve analysis also showed that OS was significantly prolonged in patients who received immunotherapy in the first line or later, compared to those who had never received immunotherapy (not reached vs 31.0 months, P < 0.001) (Figure S2B).

https://doi.org/10.2147/JIR.S502286

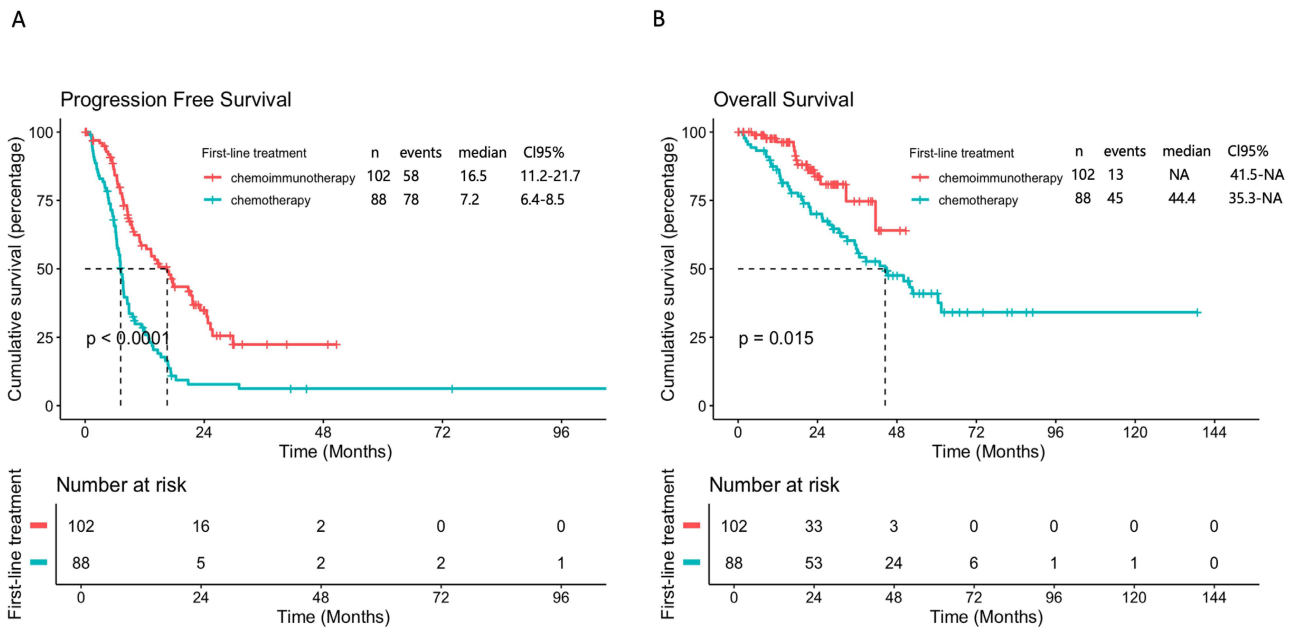

Figure 5 Kaplan–Meier survival analysis of PFS (**A**) and OS (**B**) in patients who received first-line chemoimmunotherapy and chemotherapy.
Abbreviations: m, months; OS, overall survival; PFS, progression-free survival.

Discussion

This study successfully established a nomogram model composed of inflammatory markers and clinical characteristics that predict the survival of patients with advanced PLELC. The nomogram model plus baseline plasma EBV-DNA copy shows an even better predictive effect. This study was the largest real-world study of advanced PLELC patients ever to be reported to our knowledge, as it included 254 patients with advanced PLELC. Finally, four factors, gender, hepatitis B virus surface antigen status, NLR, and CAR, were identified as independent prognostic factors and used to construct a prognostic nomogram model.

The dynamics of immune cell subsets in peripheral blood is correlated with the systemic inflammatory response and intratumorally inflammatory state, which might be a relevant factor in metastatic and active tumors.[23–27] PLELC is an immunologically "hot" tumor that displays highly immunologically activated cells and a highly inflammatory environment. Therefore, it is of great significance to establish an inflammation-related prediction model in PLELC which is closely related to inflammation. Due to the low incidence of PLELC, there is a lack of effective predictive models for advanced PLELC. We included 11 systemic inflammation-related factors and 7 clinical factors in univariate Cox regression analysis. To our knowledge, this is the first study to evaluate the prognostic abilities of immune inflammatory indicators and clinical factors in PLELC.

Some previous studies had reported the relationship between hematological factors and prognosis in PLELC. Mao et al[28] developed a model including 14 hematological and 3 clinical indicators, while our study established a 4-factor model based on hematological and clinical indicators, which comprehensively reflected the characteristics of tumors and was more convenient in clinical practice. In addition, the online tool makes it easier to apply. Due to the low incidence and long survival of PLELC, Mao et al[28] only explored a model of PFS. Our model further explored the model based on OS, which could more directly reflect the survival of patients and have higher clinical reference value. EBV-DNA was a classical prognostic biomarker for PLELC.[11,14] However, in the Mao's study,[28] the prognostic role of EBV-DNA in PLELC was not considered. Our study's results align with and extend these previous findings, demonstrating that the model plus EBV-DNA has better predictive power in the context of PLELC. The model is a powerful complementary tool to EBV-DNA. Previous studies have shown that EBV promotes cancer cell growth and metastasis by inducing ATR pathway activation through affecting the inflammatory microenvironment in nasopharyngeal carcinoma, such as M2

tumor-associated macrophages.[29] Therefore, EBV may be associated with the inflammatory phenotype of PLELC tumors, but the exact mechanism needs to be further studied.

Recent studies have shown that inflammatory markers are closely related to the poor clinical prognosis of various cancers.[30–34] Neutrophils release MMP-9 and other substances, promote angiogenesis, and provide more escape routes for tumor cells.[35] Tumor-associated neutrophils induce genetic instability and the occurrence of tumors.[36] Tumor lymphocytes promote antitumor activity through their unique pattern of antigen presentation.[37] To some extent, these support the conclusion that NLR is a poor prognostic factor in our study. Previous studies have shown an inverse association between albumin and CRP levels.[38] C-reactive protein inhibits tumor immunity and promotes tumor lung metastasis by activating FcγR2B in pulmonary macrophages.[39] Albumin is the most abundant carrier protein in plasma with a tendency to be enriched in tumors, which plays an important role in the efficacy of drugs.[40] In addition, the low albumin level is one of the manifestations of cachexia, which might also be related to the poor prognosis.[41] CAR, the ratio of CRP to albumin, may be associated with survival outcomes,[42] which is consistent with our findings that CAR was a poor prognostic factor for PLELC.

Hepatitis B virus infection is associated with poor prognosis in a variety of cancers besides liver cancer, including nasopharyngeal carcinoma, cervical cancer, NSCLC, and others.[43–45] The reasons for worse prognoses in patients with hepatitis B virus infection are possibly due to hepatitis flare-up after chemotherapy or poor liver function reserve. The findings of Li[46] suggest that the coordinated action of the hepatitis B virus and EBV might promote the invasion and migration of cancer cells through epithelial–mesenchymal transition. Our present results suggest that hepatitis B virus positivity may be predictive of poor prognoses for the EBV-associated tumors in addition to nasopharyngeal carcinoma. However, the specific mechanism for interaction between HBV and EBV in PLELC remains to be further explored in the future. Gender is also recognized as an independent prognostic factor for NSCLC,[47] a result that we also found in this study. Males had worse prognoses, which may be due to men's tendencies to make riskier lifestyle choices (especially smoking) than women, as well as the different genetic, epigenetic and metabolic mechanisms inherent in tumors.[48,49]

We confirmed that platinum-based immune-chemotherapy in first-line treatment had a longer PFS than chemotherapy for advanced PLELC patients.[50,51] Moreover, we also demonstrated the overall survival benefit from first-line immunotherapy using real-world data. In addition, patients who used immunotherapy in any line during the treatment had a longer survival time than those who never used it. Therefore, our research shows that immunotherapy is an important treatment for advanced PLELC patients. The high expression of PD-L1 may also be the reason for the good efficacy of immunotherapy in PLELC.[8,9]

The main limitations of this study are that it is a single-center and retrospective study with a predominantly Asian population, which may introduce selection biases. Second, the research about biomarkers and different combination regimens of immunotherapy remain to be explored in PLELC. Lastly, different doses of drugs have an effect on the prognosis, and the retrospective study has limited information on the detailed doses. However, our prognostic model still showed good discrimination, reliability, and reproducibility. Multi-center, large-sample, and prospective studies are needed to validate our results.

Conclusion

In conclusion, this study established a nomogram prognostic model for patients with advanced pulmonary lymphoepithelioma-like carcinoma, and the model was even more effective at predicting prognosis when combined with EBV copy number. Immunotherapy was also found to be an important treatment option for PLELC. However, prospective, large-sample studies are needed to validate the prognostic ability of our model and the role of immunotherapy in PLELC.

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary Material, and further inquiries can be directed to the corresponding authors.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (ID: B2020-402-Y02).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Qin Y, Gao G, Xie X. et al. Clinical Features and Prognosis of Pulmonary Lymphoepithelioma-like Carcinoma: summary of Eighty-five Cases. *Clin Lung Cancer*. 2019;20(3):e329–e337. doi:10.1016/j.cllc.2018.12.014
2. Fan Y, Li C, Qin J, Lu H. Primary pulmonary lymphoepithelioma-like carcinoma. *Med Oncol*. 2020;37(3):20. doi:10.1007/s12032-020-1344-3
3. Sathirareuangchai S, Hirata K. Pulmonary Lymphoepithelioma-like Carcinoma. *Arch Pathol Lab Med*. 2019;143(8):1027–1030. doi:10.5858/arpa.2018-0149-RS
4. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO Classification of Lung Tumors: impact of Advances Since 2015. *J Thorac Oncol*. 2022;17(3):362–387. doi:10.1016/j.jtho.2021.11.003
5. Chang YL, Yang CY, Lin MW, Wu CT, Yang PC. Eber- and LMP-1-expressing pulmonary lymphoepithelioma-like carcinoma in a Caucasian patient 10.1016/s0046-8177(03)00081-9. *Lung Cancer*. 2015;88(3):254–259. doi:10.1016/j.lungcan.2015.03.017
6. Sasaki A, Kato T, Ujiie H, Cho Y, Sato M, Kaji M. Primary pulmonary lymphoepithelioma-like carcinoma with positive expression of Epstein-Barr virus and PD-L1: a case report. *Int J Surg Case Rep*. 2021;79:431–435. doi:10.1016/j.ijscr.2021.01.066
7. Han S, Tay JK, Loh CJL, et al. Epstein-Barr Virus Epithelial Cancers-A Comprehensive Understanding to Drive Novel Therapies. *Front Immunol*. 2021;12:734293. doi:10.3389/fimmu.2021.734293
8. Chen B, Zhang Y, Dai S, et al. Molecular characteristics of primary pulmonary lymphoepithelioma-like carcinoma based on integrated genomic analyses. *Signal Transduct Target Ther*. 2021;6(1):6. doi:10.1038/s41392-020-00382-6
9. Xie Z, Liu L, Lin X, et al. A multicenter analysis of genomic profiles and PD-L1 expression of primary lymphoepithelioma-like carcinoma of the lung. *Mod Pathol*. 2020;33(4):626–638. doi:10.1038/s41379-019-0391-9
10. Fan Y, Shan Q, Gong J, Qin J, Lu H. Molecular and Clinical Characteristics of Primary Pulmonary Lymphoepithelioma-Like Carcinoma. *Front Mol Biosci*. 2021;8:736940. doi:10.3389/fmolb.2021.736940
11. Xie M, Wu X, Wang F, et al. Clinical Significance of Plasma Epstein-Barr Virus DNA in Pulmonary Lymphoepithelioma-like Carcinoma (LELC) Patients. *J Thorac Oncol*. 2018;13(2):218–227. doi:10.1016/j.jtho.2017.10.031
12. Zou Q, Luo K, Kang L, et al. Clinical significance of baseline Epstein-Barr virus DNA for recurrent or metastatic primary pulmonary lymphoepithelioma-like carcinoma. *Future Oncol Lond Engl*. 2023;19(37):2481–2492. doi:10.2217/fon-2023-0722
13. Chen B, Chen X, Zhou P, et al. Primary pulmonary lymphoepithelioma-like carcinoma: a rare type of lung cancer with a favorable outcome in comparison to squamous carcinoma. *Respir Res*. 2019;20(1):262. doi:10.1186/s12931-019-1236-2
14. Wei X, Wei Z, Zheng G, et al. Prognostic significance of circulating Epstein-Barr virus DNA in pulmonary lymphoepithelioma-like carcinoma: a meta-analysis and validation study. *J Med Virol*. 2023;95(1):e28349. doi:10.1002/jmv.28349
15. Chua MLK, Tan SH, Kusumawidjaja G, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in locally advanced nasopharyngeal carcinoma: a pooled analysis of two randomised controlled trials. *Eur J Cancer*. 2016;67:119–129. doi:10.1016/j.ejca.2016.08.006
16. Mao JR, Lan KQ, Liu SL, et al. Can the prognosis of individual patients with nasopharyngeal carcinoma be predicted using a routine blood test at admission? *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2023;179:109445. doi:10.1016/j.radonc.2022.109445
17. Zeng X, Liu G, Pan Y, Li Y. Development and validation of immune inflammation-based index for predicting the clinical outcome in patients with nasopharyngeal carcinoma. *J Cell Mol Med*. 2020;24(15):8326–8349. doi:10.1111/jcmm.15097
18. Zhao R, Liang Z, Chen K, Zhu X. Nomogram Based on Inflammatory Biomarkers and Nutritional Indicators for Predicting Overall Survival in Locoregionally Advanced Nasopharyngeal Carcinoma. *J Inflamm Res*. 2022;15:2971–2981. doi:10.2147/JIR.S366299
19. Chen YP, Yin JH, Li WF, et al. Single-cell transcriptomics reveals regulators underlying immune cell diversity and immune subtypes associated with prognosis in nasopharyngeal carcinoma. *Cell Res*. 2020;30(11):1024–1042. doi:10.1038/s41422-020-0374-x
20. Schwartz LH, Litière S, De Vries E, et al. RECIST 1.1-Update and clarification: from the RECIST committee. *Eur J Cancer*. 2016;62:132–137. doi:10.1016/j.ejca.2016.03.081
21. Cao K, Zhu J, Lu M, et al. Analysis of multiple programmed cell death-related prognostic genes and functional validations of necroptosis-associated genes in oesophageal squamous cell carcinoma. *EBioMedicine*. 2024;99:104920. doi:10.1016/j.ebiom.2023.104920
22. Liu Y, Ma J, Wang X, et al. Lipophagy-related gene RAB7A is involved in immune regulation and malignant progression in hepatocellular carcinoma. *Comput Biol Med*. 2023;158:106862. doi:10.1016/j.compbiomed.2023.106862
23. Hu W, Zhang L, Dong Y, Tian Z, Chen Y, Dong S. Tumour dormancy in inflammatory microenvironment: a promising therapeutic strategy for cancer-related bone metastasis. *Cell mol Life Sci*. 2020;77(24):5149–5169. doi:10.1007/s00018-020-03572-1
24. Jjx L, Syb N, Tsang JYS, et al. Neutrophil-lymphocyte ratio reflects tumour-infiltrating lymphocytes and tumour-associated macrophages and independently predicts poor outcome in breast cancers with neoadjuvant chemotherapy. *Histopathology*. 2024;84(5):810–821. doi:10.1111/his.15125
25. Ohashi K, Nishito Y, Fukuda H, et al. Neutrophil-to-lymphocyte ratio is a prognostic factor reflecting immune condition of tumor microenvironment in squamous cell lung cancer. *Sci Rep*. 2024;14(1):429. doi:10.1038/s41598-023-50378-9
26. Hwang M, Canzoniero JV, Rosner S, et al. Peripheral blood immune cell dynamics reflect antitumor immune responses and predict clinical response to immunotherapy. *J Immunother Cancer*. 2022;10(6):e004688. doi:10.1136/jitc-2022-004688
27. Dominguez C, David JM, Palena C. Epithelial-mesenchymal transition and inflammation at the site of the primary tumor. *Semin Cancer Biol*. 2017;47:177–184. doi:10.1016/j.semcancer.2017.08.002

28. Sheng H, He X, Chen Z, et al. Development of a haematological indices-based nomogram for prognostic prediction and immunotherapy response assessment in primary pulmonary lymphoepithelioma-like carcinoma patients. *Transl Lung Cancer Res*. 2024;13(3):453–464. doi:10.21037/tlcr-23-813
29. Zhang B, Miao T, Shen X, et al. EB virus-induced ATR activation accelerates nasopharyngeal carcinoma growth via M2-type macrophages polarization. *Cell Death Dis*. 2020;11(9):742. doi:10.1038/s41419-020-02925-9
30. Barbon CE, Velasco R, Sacdalan DBL, Angeles RR. Prognostic value of C-reactive protein, albumin and C-reactive protein to albumin ratio in small cell lung cancer: a meta-analysis. *Ann Oncol*. 2019;30:ix178. doi:10.1093/annonc/mdz437.055
31. Li J, Lai C, Peng S, et al. The prognostic value of integration of pretreatment serum amyloid A (SAA)-EBV DNA (S-D) grade in patients with nasopharyngeal carcinoma. *Clin Transl Med*. 2020;9(1):2. doi:10.1186/s40169-019-0252-7
32. Han QY, Zhang X, Zhang JG, et al. Pre-operative neutrophil-to-lymphocyte ratio is an independent prognostic factor in patients with gastric cancer. *Int Immunopharmacol*. 2022;113(Pt A):109371. doi:10.1016/j.intimp.2022.109371
33. Lee JH, Hyung S, Lee J, Choi SH. Visceral adiposity and systemic inflammation in the obesity paradox in patients with unresectable or metastatic melanoma undergoing immune checkpoint inhibitor therapy: a retrospective cohort study. *J Immunother Cancer*. 2022;10(8):e005226. doi:10.1136/jitc-2022-005226
34. Zhao X, Wu X, Yu H, et al. Prognostic value of hematologic parameters in advanced non-small cell lung cancer patients receiving anti-PD-1 inhibitors. *Front Immunol*. 2022;13:1003581. doi:10.3389/fimmu.2022.1003581
35. Xiong S, Dong L, Cheng L. Neutrophils in cancer carcinogenesis and metastasis. *J Hematol Oncol*. 2021;14(1):173. doi:10.1186/s13045-021-01187-y
36. Que H, Fu Q, Lan T, Tian X, Wei X. Tumor-associated neutrophils and neutrophil-targeted cancer therapies. *Biochim Biophys Acta Rev Cancer*. 2022;1877(5):188762. doi:10.1016/j.bbcan.2022.188762
37. Laumont CM, Banville AC, Gilardi M, Hollern DP, Nelson BH. Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities. *Nat Rev Cancer*. 2022;22(7):414–430. doi:10.1038/s41568-022-00466-1
38. Sheinenzon A, Shehadeh M, Michelis R, Shaoul E, Ronen O. Serum albumin levels and inflammation. *Int J Biol Macromol*. 2021;184:857–862. doi:10.1016/j.ijbiomac.2021.06.140
39. Feng JR, Li X, Han C, et al. C-Reactive Protein Induces Immunosuppression by Activating FcγR2B in Pulmonary Macrophages to Promote Lung Metastasis. *Cancer Res*. 2024;84(24):4184–4198. doi:10.1158/0008-5472.CAN-24-0253
40. Park CR, Jo JH, Song MG, et al. Secreted protein acidic and rich in cysteine mediates active targeting of human serum albumin in U87MG xenograft mouse models. *Theranostics*. 2019;9(24):7447–7457. doi:10.7150/thno.34883
41. Zhang FM, Zhuang CL, Dong QT, et al. Characteristics and prognostic impact of cancer cachexia defined by the Asian Working Group for Cachexia consensus in patients with curable gastric cancer. *Clin Nutr Edinb Scotl*. 2024;43(6):1524–1531. doi:10.1016/j.clnu.2024.05.018
42. Uchimoto T, Matsuda T, Komura K, et al. C-Reactive Protein-Albumin Ratio Predicts Objective Response to Enfortumab Vedotin in Metastatic Urothelial Carcinoma. *Target Oncol*. 2024;19(4):635–644. doi:10.1007/s11523-024-01068-7
43. Peng JW, Liu DY, Lin GN, jun XJ, Xia ZJ. Hepatitis B Virus Infection Is Associated with Poor Prognosis in Patients with Advanced Non Small Cell Lung Cancer. *Asian Pac J Cancer Prev APJCP*. 2015;16(13):5285–5288. doi:10.7314/apjcp.2015.16.13.5285
44. Feng X, Lu H, Wei Y, et al. Prognostic impact of hepatitis B virus infection in patients with primary cervical cancer. *Cancer Med*. 2021;10(23):8310–8319. doi:10.1002/cam4.4358
45. Weng J, Wei J, Li M, et al. Effects of hepatitis B virus infection and antiviral therapy on the clinical prognosis of nasopharyngeal carcinoma. *Cancer Med*. 2020;9(2):541–551. doi:10.1002/cam4.2715
46. Li H, Cao D, Li S, et al. Synergistic Association of Hepatitis B Surface Antigen and Plasma Epstein-Barr Virus DNA Load on Distant Metastasis in Patients With Nasopharyngeal Carcinoma. *JAMA Netw Open*. 2023;6(2):e2253832. doi:10.1001/jamanetworkopen.2022.53832
47. Shin JY, Yoon JK, Marwaha G. Progress in the Treatment and Outcomes for Early-Stage Non-Small Cell Lung Cancer. *Lung*. 2018;196(3):351–358. doi:10.1007/s00408-018-0110-1
48. Haupt S, Caramia F, Klein SL, Rubin JB, Haupt Y. Sex disparities matter in cancer development and therapy. *Nat Rev Cancer*. 2021;21(6):393–407. doi:10.1038/s41568-021-00348-y
49. Xiao T, Lee J, Gauntner TD, Velegraki M, Lathia JD, Li Z. Hallmarks of sex bias in immuno-oncology: mechanisms and therapeutic implications. *Nat Rev Cancer*. 2024;24(5):338–355. doi:10.1038/s41568-024-00680-z
50. Zhang X, Zhou Y, Chen H, et al. PD-1 inhibition plus platinum-based chemotherapy (PBC) or PBC alone in the first-line treatment of locally advanced or metastatic pulmonary lymphoepithelioma-like carcinoma. *Front Immunol*. 2022;13:1015444. doi:10.3389/fimmu.2022.1015444
51. Pang L, Liao J, Huang Y, et al. Exploration of immunotherapy in advanced pulmonary lymphoepithelioma-like carcinoma. *Int, J, Cancer*. 2023;152(11):2338–2350. doi:10.1002/ijc.34426