European Review for Medical and Pharmacological Sciences 2022; 26: 9416-9425

Analysis of clinical features, treatment, and prognosis of primary XIymphoepithelioma-like carcinoma of the lung

H.-Y. HU[1,2], L. LONG[3], S.-A. DAI[1], G.-Q. YAN[4], Y. HUANG[1], J. HE[5]

[1]State Key Laboratory of Biotherapy, Lung Cancer Center, West China Hospital of Sichuan University, Chengdu, Sichuan, China
[2]Department of Medical Oncology, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, Medicine School of University of Electronic Science and Technology, Chengdu, China
[3]Department of Pediatric Respiratory and Neurology, The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, Hubei Enshi, China
[4]Department of Rheumatology and Immunology, Minda Hospital of Hubei Minzu University, Hubei Enshi, China
[5]Department of Oncology, The Third Hospital of Mianyang (Sichuan Mental Health Center), Mianyang, Sichuan, China

Haoyue Hu, Lang Long and Shuang Dai contributed equally to this work

Abstract. – OBJECTIVE: Primary pulmonary lymphoepithelioma-like carcinoma (PPLELC) is a rare lung malignancy occurring most frequently in young non-smokers from Southeast Asia. Given its low incidence, PPLELC clinical features, treatment methods, and the factors affecting its prognosis remain elusive. To date, PPLELC data are mainly derived from clinical case reports, and no cohort studies are available. Therefore, we retrospectively analyzed a group of PPLELC cases and summarized the clinical features of patients, treatment responses, and the factors affecting patient prognosis.

PATIENTS AND METHODS: A total of 91 patients having primary pulmonary lymphoepithelioma-like carcinoma were recruited in this study. These included sex, age, place of birth, smoking history, pre-treatment symptoms, tumor location, tumor markers, maximum tumor diameter, treatment regimen, lymph node presence metastasis after an operation, pathological picture, immunohistochemistry, genetic findings, and tumor stage grading. We determined the overall survival (OS), progression-free survival (PFS), basic clinical characteristics, treatment option, treatment response, and recurrence pattern among the patients. In addition, we understood the influence of sex, age, tumor, nodes, and metastases (TNM) stage, tumor size, and surgery over patient prognosis.

RESULTS: Primary pulmonary lymphoepithelioma-like carcinoma is more common among young non-smokers, with a slightly higher incidence in women than in men. The expression of Epstein-Barr virus-encoded small RNA (EBER), pancytokeratin (PCK), Cytokeratin 5/6 (CK5/6), and tumor protein 63 (P63) was positive in immunohistochemistry. Serum cytokeratin 19 fragment antigen (CYFRA21-1) and Epstein-Barr DNA (EB-DNA) could be used as markers to diagnose primary pulmonary lymphoepithelioma-like carcinoma. TNM stage and surgery were independent prognostic factors.

CONCLUSIONS: Primary pulmonary lymphoepithelioma-like carcinoma is rare, showing a good prognosis.

Key Words:
Primary pulmonary lymphoepithelioma-like carcinoma, Clinical features, Immunohistochemistry, Tumor markers, Therapy, Prognostic factors.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, according to the World Health Organization (WHO). In the Chinese population, lung cancer-associated morbidities have been increasing over the years, posing a severe threat to human health[1-3]. Lung cancer cases are divided into two categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), according to the WHO classification of tumors of the lung from 2015[4]. Primary pulmonary lymphoepithelioma-like carcinoma (PPLELC) is a rare subtype of NSCLC, most frequently detected in

Corresponding Author: Jun He, MD; e-mail: he-001jun@163.com

young son-smoking patients[5]. PPLELC incidence might be somewhat linked to geographical factors, as it has been mainly detected in Southeast Asia[6,7]. Like other NSCLC subtypes, most patients with PPLELC do not present early clinical symptoms. Common clinical features mainly include cough, sputum, chest tightness and pain, hemoptysis, and fever[7,8]. Previous research[9] has reviewed the clinical characteristics of 107 cases of PPLELC and found that these included coughs (47%) and hemoptysis (30%), with asymptomatic patients in 22% of cases. Additional clinical manifestations mainly included chest pain and dyspnea.

Currently, most reported cases come from Guangdong, Hong Kong, Taiwan, and other places[10]. The studies in other areas are rare and only have a few sporadic cases. Recent progress in precision medicine has significantly improved the treatment of NSCLC patients. Especially, new gene detection techniques have generated vast knowledge in terms of lung cancer whole genome[11]. Moreover, patient prognosis has been favored with new chemotherapeutic drugs and immune- and radiotherapy techniques[12]. However, due to the low incidence of PPLELC, the clinicopathological features, optimal treatment approaches, and predictive prognostic factors remain to be clarified. Nevertheless, evidence shows that patients with PPLELC have a better prognosis than other NSCLC patients, achieving longer survival under multimodal treatment regimens[13-15]. This study analyzed a cohort of 91 patients and summarized their clinicopathological findings. We further reviewed the applied therapeutic approaches and discussed the factors affecting the prognosis of patients, aiming at widening the understanding of the disease.

Patients and Methods

Patients

The clinical data of patients with PPLELC treated in West China Hospital of Sichuan University from July 2009 to April 2019 were collected. These included: sex, age, place of birth, smoking history, pre-treatment symptoms, tumor location, tumor markers, maximum tumor diameter, treatment regimen, presence of lymph node metastasis after the operation, pathological picture, immunohistochemistry, genetic findings, and tumor stage. We gathered information about treatment strategies and patient prognosis to establish a clinical case database, including outpatient and inpatient data. The patient follow-up period ended in April 2019. We calculated the overall survival (OS), progression-free survival (PFS), basic clinical characteristics, treatment options, treatment response, and recurrence pattern of the patients. In addition, we discussed the influence of sex, age, tumor, nodes, and metastases (TNM) stage, tumor size, and surgery on patient prognosis.

Statistical Analysis

The continuous variable was transformed into the classified variable using X-tile to select the best truncation value. Survival data were analyzed by the Kaplan Meier method and log-rank test with SPSS (IBM, Armonk, NY, USA). Taking OS as the end point of the study, univariate Cox regression analysis was used to screen the prognostic factors, and the statistically significant variables were further incorporated into multivariate Cox regression analysis, which was used to estimate the hazard ratio (HR) and the corresponding 95% confidence interval (CI) of prognostic factors. $p<0.05$ was considered to be statistically significant. All statistical tests were performed in the bilateral mode.

Results

Clinicopathological Characteristics of 91 PLELC Patients

Ninety-one patients with primary pulmonary lymphoepithelioma-like carcinoma were included in this study (Table I). The median age of the patients was 53 years old, ranging from 35 to 80 years old. Among them, 23 patients were 60 years old or above (25.3%). There were 39 male (42.9%) and 52 female patients (57.1%; male to female ratio of 1.33). The percentage of patients reporting having ever smoked was about 26.4%. Regarding geographic incidence, most patients originated from Sichuan (84/91). Other patients came from Yunnan (2/91), Hunan (2/91), Xinjiang (1/91), Shanghai (1/91), and Guizhou (1/91). 68 patients (74.7%) underwent surgical resection, whereas the other 23 cases (25.3%) presented advanced inoperable disease. Early clinical manifestations included cough in 33 patients (36.3%), hemoptysis in 10 patients (10.9%), chest pain, chest tightness, shortness of breath, and neck mass in 16 patients (17.6%). 32 (35.2%) patients remained asymptomatic.

Table I. Clinicopathological characteristics of 91 PPLELC patients.

Clinical features	Number of cases [n (%)]
Gender	
Male	40 (44.0%)
Female	51 (56.0%)
Age (years)	
< 60	68 (74.7%)
≥ 60	23 (25.3%)
Smoking history	
Yes	24 (26.4%)
No	67 (73.6%)
TNM stage	
I	22 (24.2%)
II	18 (19.8%)
III	31 (34.1%)
IV	20 (21.9%)
T stage	
T1	26 (28.5%)
T2	28 (30.7%)
T3	14 (15.3%)
T4	23 (25.5%)
N stage	
N0/N1	45 (49.5%)
N2/N3	46 (50.5%)
M stage	
M0	71 (78.0%)
M1	20 (22.0%)
Location	
Upper lobe of left lung	16 (17.6%)
Left lower lobe of lung	21 (23.1%)
Upper lobe of right lung	12 (13.1%)
Middle lobe of right lung	26 (28.6%)
Lower lobe of right lung	16 (17.6%)
Therapy	
Surgery	22 (24.2%)
Surgery+chemotherapy	30 (32.9%)
Surgery+chemoradiation	16 (17.6%)
Chemotherapy	11 (12.1%)
Chemotherapy+radiotherapy/ Immunotherapy	12 (13.2)

Diagnostic Methods

The following diagnostic procedures were reported in this patient cohort: CT-guided percutaneous lung biopsy in nine patients (9.9%); bronchoscopic biopsy in 13 patients (14.3%); surgical biopsy in 68 patients (74.7%); lymph node biopsy in one patient (1.1%). 48 patients presented with tumors above 4 cm (52.7%), with the rest presenting tumors of inferior size (47.3%). Anatomically, patients exhibited tumors in the following locations: left lung upper lobe (17.6%), left lung lower lobe (23.1%), right lung upper lobe (13.1%), right lung middle lobe (28.6%), and right lung lower lobe (17.6%). According to TNM staging, patients were divided in T1 (28.5%), T2 (30.7%), T3 (15.3%), and T4 (25.5%) stages. There were 35 (38.5%), 10 (10.9%), 35 (38.5%) and 11 (12.1%) patients in N0, N1, N2 and N3 respectively, and 71 (78.0%) and 20 (22.0%) patients in M0 and M1, respectively. The numbers of patients in stages I, II, III, and IV were 22 (24.2%), 18 (19.8%), 31 (34.1%), and 20 (21.9%), respectively.

Pathological Features

Morphologically, tumor cells exhibited syncytium-like cells with large cell sizes, different shapes, abundant cytoplasm, and light staining. The nuclei were lightly stained, showing vacuoles, nucleoli, and visible interstitial disease. We further observed lymphocyte infiltrates. Immunohistochemistry showed high expression of anti-pan cytokeratin antibody/Phosphoenolpyruvate carboxykinase (PCK), cytokeratin 5/6 antibody (CK5/6), tumor protein 63 (P63), P40, and negative expressions of thyroid transcription factor-1 (TTF-1), chromogranin A (CgA), and synaptophysin (Syn) (Table II); Ki-67 expression was determined in the tumor samples of 33 patients.

Table II. Immunohistochemical markers of patients.

Immunohistochemical staining	Negative	Positive	% (positive/total)
PCK	0	50	100.0%
P63	5	79	94.0%
CK5/6	4	78	95.1%
P40	0	69	100.0%
TTF-1	71	0	0.0%
CD56	38	5	11.6%
CK19	0	7	100.0%
EMA	0	10	100.0%
CgA	41	0	0.0%
Syn	38	0	0.0%
Ki-67	0	33	100.0%
EBER	6	79	92.9%

11 cases showed less than 30% of Ki-67$^+$ cells, 19 showed between 30%-70% Ki-67$^+$ cells, and 3 presented more than 70% Ki-67$^+$ cells. We performed *in situ* hybridization in 85 tumor samples to detect Epstein-Barr virus-encoded small RNA (EBER). Here, 79 patients were positive, and the remaining six cases were negative. Epidermal growth factor receptor (EGFR) was detected in 20 patients, all presenting the wild-type gene. Anaplastic lymphoma kinase (ALK) was detected in 50 patients, and the results were all negative; proto-oncogene receptor tyrosine kinase (ROS-1) was detected in 48 patients, and the effects were all negative; programmed death-ligand 1 (PD-L1) was detected in 34 patients, and the results were negative in three patients, 31 patients had positive test results, of which six patients had PD-L1 expression between 1% and 49%, 25 patients had PD-L1 expression ≥50%.

Tumor Markers

Serum neuron-specific enolase (NSE) expression was evaluated in 74 patients before treatment. Of these, 28 (37.8%) patients showed elevated NSE. In 79 patients, serum carcinoembryonic antigen (CEA) was detected before treatment, and of these, 4 (5.1%) patients showed elevated CEA, the highest of which was 6.17 ng/mL. 77 patients were tested for serum cytokeratin 19 fragment antigen (CYFRA21-1) before treatment, and 49 (63.6%) CYFRA21-1 was elevated in all patients. Plasma EBV-DNA was not detected before treatment in patients submitted to surgery. After the operation, 11 patients underwent plasma EBV-DNA copy number detection, and five patients showed positive plasma EBV-DNA copy number amplification. Three patients with postoperative recurrence had significantly increased plasma EB-DNA (>103 copies/mL). 5 patients with advanced inoperable tumors showed plasma EB-DNA amplification.

Treatment

Twenty-three patients with advanced primary pulmonary lymphoepithelioma-like cancer were treated with palliative care, 11 with chemotherapy alone, and 12 with chemotherapy combined with radiotherapy and/or immunotherapy. Chemotherapy was platinum-based, combined with paclitaxel, gemcitabine, pemetrexed, and fluorouracil in 14, 6, 2, and 1 patient, respectively. 9 patients received radiotherapy at a dose between 5,000 cGy-6,000 cGy, and four received immunotherapy, including three with nivolumab and one with pembrolizumab. Two patients with stage IV pulmonary lymphoepithelioma-like carcinoma received nivolumab as third-line therapy, one patient had a PFS for nine months, and the other had a PFS of 10 months, and the disease remained stable.

68 patients with primary lung lymphoepithelioma-like carcinoma underwent surgery. Of these, 22 received radical surgery without adjuvant therapy, 30 received postoperative adjuvant or neoadjuvant chemotherapy, and 16 underwent surgery combined with radiotherapy and chemotherapy. The adjuvant chemotherapy regimen was platinum-based, along with paclitaxel, gemcitabine, pemetrexed, docetaxel, and fluorouracil in 21, 13, 4, 7, and 1 patient, respectively. After surgery, one patient was given adjuvant therapy with pemetrexed combined with cisplatin, and the disease progressed during the treatment. The EGFR-tyrosine kinase inhibitor (EGFR-TKI) was utilized as rescue therapy. However, the disease progressed rapidly within three months.

Survival Data

91 patients with lung lymphoepithelioma-like carcinoma were followed up to December 2019. The median follow-up time for all patients was 40 months (8 months to 111 months). 48 patients were still alive. The median survival period was 64 months [95% confidence interval (CI) 55.7-77.2]. The 1-year cumulative survival rate was 97.8%. The 3-year cumulative survival rate was 73.0%. The 5-year cumulative survival rate was 51.3%. Progressive survival was 83.4%; 3-year progression-free survival was 45.7%; and 5-year progression-free survival was 26.7% (Figure 1).

Prognostic Factors

Kaplan-Meier univariate analysis showed that T (p<0.001), N (p<0.001), and M stages (p<0.001), as well as TNM (p<0.001) (Figure 2), surgery performance (p<0.001) and chemotherapy (p=0.049) were significantly associated with patient prognosis, and there is also a trend improved OS in patients with PD-L1 expression ≥50% (p=0.869) (Figure 3). These were included in the multivariate Cox regression model analysis (Table III). Only TNM stage (HR=4.131, 95% CI 1.265-13.448; p=0.019) and surgery performance (HR=3.930, 95% CI 1.037-14.894; p=0.044) were found to be independent factors affecting patient prognosis.

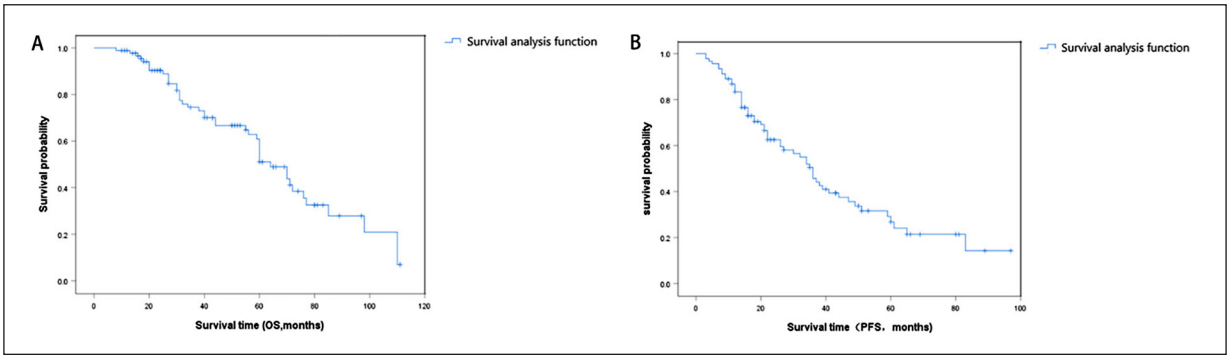

Figure 1. Kaplan-Meier survival curves for the 91 patients of primary pulmonary lymphoepithelioma-like carcinoma depicted an OS (**A**) (p<0.001) and PFS (**B**) (p<0.001).

In our study, PPLELC was more frequently found in young non-smokers. Moreover, PPLELC incidence in female patients was slightly higher than in males, with a male-to-female ratio of 1:1.33. To date, no standard clinical presentation has been established for PPLELC patients. In this cohort, common clinical manifestations included cough, hemoptysis, chest tightness, chest pain, and shortness of breath.

Immunohistochemical findings showed high expression of EBER, PCK, CK5/6, and P63, and no expression of TTF-1, CgA, Syn. common driv-

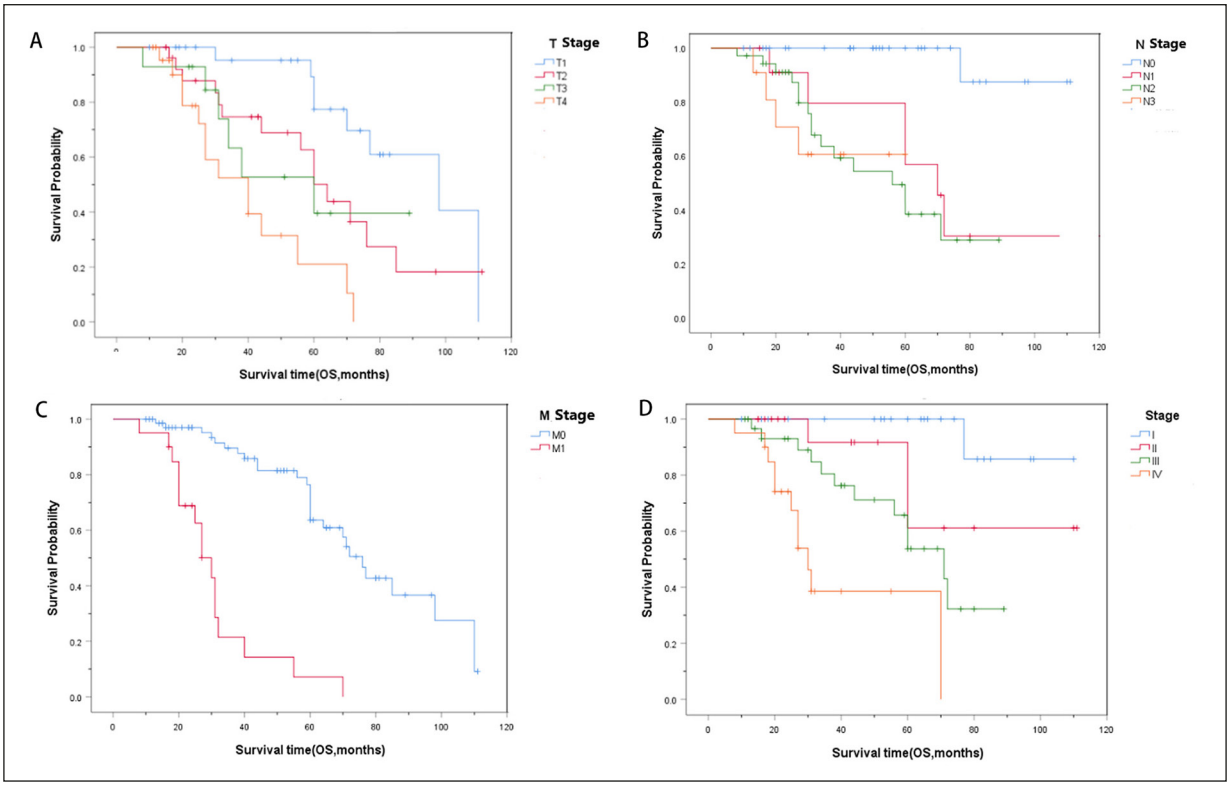

Figure 2. The effect of T stage on OS of primary pulmonary lymphoepithelioma-like carcinoma (**A**) (p<0.001). The effect of N stage on OS in primary pulmonary lymphoepithelioma-like carcinoma (**B**) (p<0.001). The effect of M stage on OS in primary pulmonary lymphoepithelioma-like carcinoma (**C**) (p<0.001). The effect of tumor stage on OS of primary pulmonary lymphoepithelioma-like carcinoma (**D**) (p<0.001).

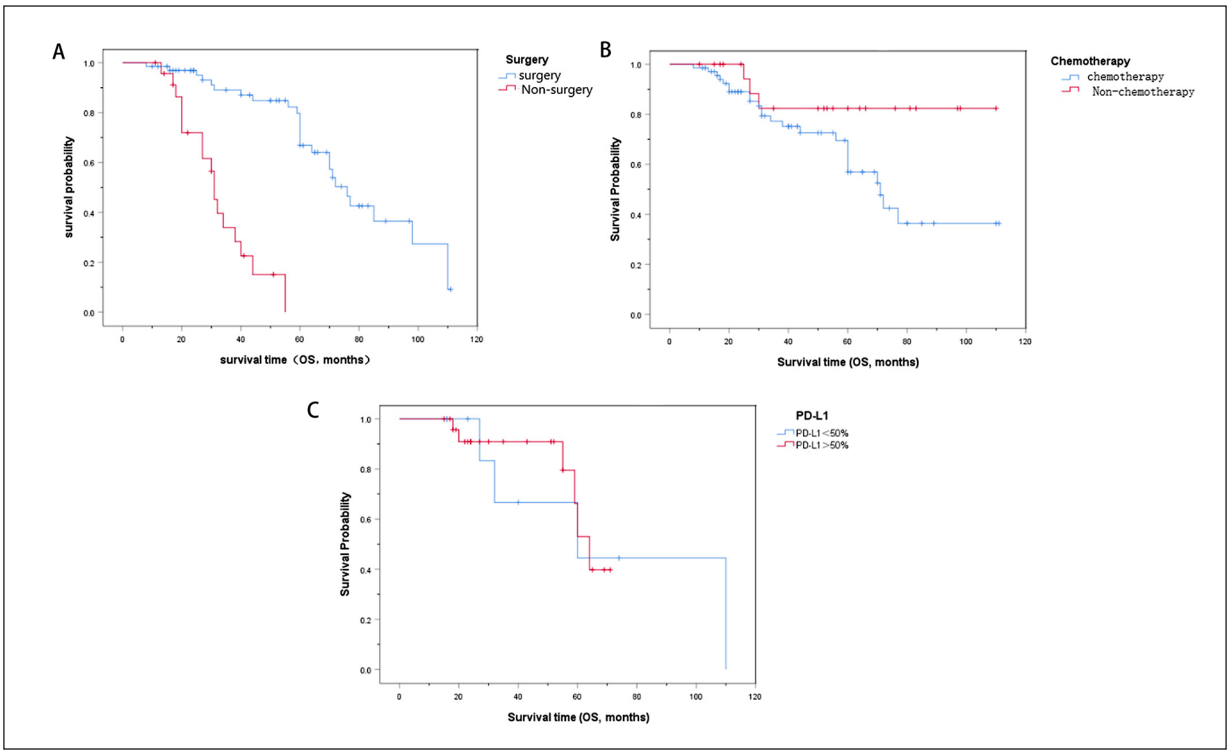

Figure 3. The effect of surgery on OS of primary pulmonary lymphoepithelioma-like carcinoma (**A**) (p<0.001). The effect of chemotherapy on OS of primary pulmonary lymphoepithelioma-like carcinoma (**B**) (p=0.049). The effect of PD-L1 expression on OS of primary pulmonary lymphoepithelioma-like carcinoma (**C**) (p=0.869).

er genes in NSCLC such as EGFR, ALK, ROS-1 in PPLELC. CYFRA21-1 and EB-DNA can be used as PPLELC diagnosis markers.

Discussion

Primary pulmonary lymphoepithelioma-like carcinoma is a rare and specific subtype of NSCLC, more frequently detected in Southeast Asia. PPLELC etiology might be linked to Epstein-Barr virus infection[16,17]. PPLELC histology resembles undifferentiated nasopharyngeal carcinoma[16,18]. Given its low incidence, PPLELC data is mainly derived from clinical case reports. Therefore, no standard treatment guidelines have been established, and patient management is still based on empirical findings. The National Comprehensive Cancer Network (NCCN) guidelines implement the guidelines for the treatment of non-small cell lung cancer. Nevertheless, PPLELC patient prognosis is better than other types of NSCLC[19,20].

Table III. Multivariate OS analysis for primary pulmonary lymphoepithelioma-like carcinoma by the COX proportional hazards.

Parameters	Multifactor analysis		
	HR	(95% CI)	*p*-value
T Stage	1.072	0.704-1.631	0.746
N Stage	0.788	0.379-1.639	0.524
M Stage	0.478	0.094-2.433	0.374
TNM Stage	4.131	1.265-13.448	0.019*
Chemotherapy	1.755	0.434-7.103	0.430
Surgery	3.930	1.037-14.894	0.044*

Surgery is the primary treatment for early diagnosed patients. Conversely, comprehensive treatments, such as conventional surgical resection, radio-, chemo-, and immune therapy, are applied in late diagnosed and metastatic patients.

This study collected clinical data from PPLELC patients, summarized the clinical features and treatment methods of the disease, and explored the factors influencing the prognosis among patients. In our study, patients with primary pulmonary lymphoepithelioma always lack specific clinical symptoms. Through analysis of case data, we found that 33 patients (36.3%) had a cough as the first symptom, 10 (12%) had hemoptysis, 10 had chest pain and tightness (9.9%), six (6.6%) were short of breath, and 32 (35.2%) were asymptomatic. This result is consistent with previous reports[9,15,21]. Yu et al[15] showed that the most common symptom of 32.1% of patients was a chronic cough, and other first symptoms or signs included hemoptysis (3.6%), chest pain (3.6%), weight loss (3.6%) and skin rash (3.6%)[15]. Among the 107 patients enrolled by Qin et al[9], the main first clinical symptom was cough (47%), and the remaining first symptoms or signs included hemoptysis (30%), chest pain (13%), dyspnea (5%), and body weight relief (5%), night sweats (3%), joint pain (3%) and fever (2%), etc. The above data suggest that the main clinical manifestation of patients with primary pulmonary lymphoepithelioma-like carcinoma is cough, and some patients present with hemoptysis. In contrast, others, such as dyspnea, weight loss, pain, and cachexia, are relatively rare[21].

Monitoring serum tumor markers is highly relevant in lung cancer diagnosis, treatment, and prognosis. In malignant lung tumors, blood CEA, NSE, and CYFRA21-1 are routinely monitored[22,23]. NSE is highly expressed in neuroendocrine carcinomas and predicts small cell lung cancer[24,25]. CEA is elevated in lung adenocarcinoma, whereas CYFRA21-1 is frequently elevated in lung squamous cell carcinoma[26,27]. However, the association between such serum tumor markers and PPLELC is still unclear. A previous study[28] showed that serum NSE and CYFRA21-1 levels might be associated with disease activity, suggesting that regular monitoring of these must be performed during treatment. In this study as well, 79 patients underwent CEA test before treatment, 75 patients were in the normal range, four patients had elevated CEA, the highest was 6.17 ng/mL; serum neuron-specific enolase (NSE) was tested in 74 patients before treatment,

46 patients were in the normal range, 28 patients had elevated NSE; 77 patients were tested for CYFRA21-1 before treatment, 28 patients were in the normal range, and CYFRA21-1 was elevated in 49 patients. Therefore, our research suggests that CYFRA21-1 might be a potential tumor marker in PPLELC. However, further research is necessary to establish protein expression and disease progression. Previous studies[29] showed that EB virus infection might be associated with PPLELC onset. In our study, 11 patients submitted to surgery underwent plasma EBV DNA copy number detection, of which 5 showed positive amplification, and 3 patients had postoperative plasma EBV DNA amplification. In patients with relapsed PPLELC, we observed significant EBV DNA amplification. However, given that this is not a standard tumor marker in the context of lung cancer, not all patients submitted EBV DNA testing before surgery. Conversely, we found EBV DNA amplification in 5 advanced non-operated patients. Two patients were continuously monitored, and plasma EBV DNA copy number increased with tumor progression. Strikingly, we observed a reduction in EBV DNA copy number in remission tumors, suggesting that circulating serum EBV DNA copy number might be used as a PPLELC tumor marker. Further attention should be paid to the value of plasma EBV DNA in tumor diagnosis, treatment, and prognosis judgment. Its relationship with tumor recurrence and patient survival should be explored. Pathological diagnosis is the gold standard in PPLELC diagnosis. Our immunohistochemical results show positive expression of PCK, CK5/6, P63, and P40, suggesting that PPLELC might be linked to the squamous epithelium. In contrast, the absence of TTF-1, CgA, and Syn expression suggest that PPLELC does not present neither neuroendocrine nor glandular epithelial characteristics, which is consistent with the results of Chang et al[30]. Ki-67 is a nuclear protein highly expressed in actively proliferating cells. The ki-67 index is closely related to the degree of differentiation, invasion, metastasis, and prognosis of many tumors[31,32]. In our cohort, 33 patients were tested for Ki-67, all positive. However, the positive rate was different, which suggested that the tumor may have a high risk of recurrence and metastasis, and the results were not found in previous research reports. To the best of our knowledge, this is the first study evaluating the potential association between the Ki-67 index and PPLELC patient prognosis.

In the era of precision medicine, pathology-based therapeutic approaches no longer meet the modern tumor treatment model. With the rapid development of medical technology, individualized treatments based on the expression of driving target genes have opened new opportunities in the context of lung cancer therapy[33,34]. Literature has shown that the fusion gene of the EGFR pathway and acanthoid microtubule-associated protein 4 anaplastic lymphoma kinase (EML4-ALK) plays a vital role in the pathogenesis of lung cancer. Still, the development of targeted therapies for PPLELC management remains largely unexplored. Recently, Liang et al[28] reported the follow-up of 52 PPLELC patients, 11 of whom presented no mutations in EGFR[28]. Liu et al[35] followed up on 85 PPLELC patients, 49 of whom were tested for EGFR. Of these, one patient presented mutated EGFR and was treated with EGFR-TKI. The condition of the patient progressed in 30 days[35]. Our study did not detect EGFR mutations in any of the tested patients. Moreover, immunohistochemical findings showed no alterations of ALK nor ROS-1. This suggests that the changes in EGFR, ALK, and ROS-1 in PLELC are not frequent and thus might not be suitable therapeutic targets in the context of this tumor. Tumor immunotherapy is a research hotspot, having shown efficient results in treating advanced lung tumors. Studies have shown that in PPLELC patients, the expression of PD-L1 is generally higher. Jiang et al[36] demonstrated that PPLELC patients with positive expression of PDL-1 had higher progression-free and overall survival than those with negative PDL-1[36]. Fang et al[37] analyzed the expression of PD-L1 in tumor tissues of 113 patients with primary PPLELC and found that 74.3% (84/113) of the tumor tissues expressed PD-L1, while patients with negative PD-L1 expression got longer PFS and OS[37]. Among our patients, 34 were tested for PD-L1, three were negative, and 31 were positive. Among them, 6 had PD-L1 expression between 1% and 49%, and 25 had PD-L1 expression ≥50%. Our study did not observe any significant difference in the overall survival between PD-L1 positive and PD-L1 negative patients (p=0.704). However, we found that patients with PD-L1 expression ≥50% showed a higher survival rate. Still, we acknowledge that future large-scale clinical studies support the exact association between PDL-1 expression and patient prognosis.

To date, PPLELC treatment is primarily based on the National Comprehensive Cancer Network (NCCN) standard guidelines for NSCLC treatment. Radical surgery is recommended for early diagnosed patients, and a multidisciplinary comprehensive treatment model is recommended for advanced patients. Finally, multivariate Cox retrospective analysis showed that TNM staging and surgery execution are the only factors, among those tested, that independently influence patient prognosis. In addition, based on the pathological characteristics of pulmonary lymphoepithelioma-like carcinoma, we believed that the biological behavior of PPLELC may be closer to lung squamous cells. At the same time, pemetrexed has a better effect on non-squamous NSCLC. While choosing chemotherapy regimens, we recommended using GP (gemcitabine + cisplatin) or TP (paclitaxel + cisplatin) as the first-line chemotherapy regimen against PPLELC. From our clinical cases, 68 patients underwent surgical treatment, 23 advanced patients received platinum-based dual-drug with palliative care, and 2 of these advanced patients chose immunotherapy after first-line treatment progressed and got well controlled. One patient developed disease progression after surgery and was treated with an EGFR-tyrosine kinase inhibitor (EGFR-TKI). The disease progressed rapidly within three months, and the patient finally died, suggesting that it was difficult for PPLELC to benefit from the targeted therapy. Our study shows that immunotherapy-based regimens significantly improve the prognosis of patients with pulmonary lymphoepithelioma-like carcinoma and that PDL-1 may be a potential therapeutic target in the context of this tumor.

Conclusions

Thus, we analyzed the clinical characteristics of a rare subtype of malignant lung tumor in this retrospective study and provided new insights into factors affecting patient survival and prognosis. However, further research on the geographical incidence of cases, with larger sample size, and long-term follow-up, is necessary to optimize the therapeutic approaches to pulmonary lymphoepithelioma-like carcinoma.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements
We thank the patients for participating in this study. We are grateful to the contributors from the following centers: West China Hospital, Sichuan University, China.

Informed Consent
The patients' written informed consent was waived since all the data in this retrospective study were anonymous.

Ethics Statement
This study was approved by the Ethics Committee of West China Hospital, Sichuan University & The Research Units of West China.

Funding
Not applicable.

Authors' Contribution
Jun He contributed to the study conception and design. All the authors performed data collection and analysis. The first manuscript draft was written by Haoyue Hu, Lang Long, and Shuang Dai. Guoqing Yan and Yan Huang discussed the previous versions of the manuscript. All the authors approved the final submitted version.

References

1) Sase K, Fujisaka Y, Shoji M, Mukai M. Cardiovascular Complications Associated with Contemporary Lung Cancer Treatments. Curr Treat Option On 2021; 22: 71.
2) Shi JF, Liu CC, Ren JS, Parascandola M, Zheng R, Tang W, Huang HY, Li F, Wang L, Su K, Li N, Zhang K, Chen WQ, Wu N, Zou XN, Liu GX, Dai M. Economic burden of lung cancer attributable to smoking in China in 2015. Tob Control 2020; 29: 191-199.
3) Hong QY, Wu GM, Qian GS, Hu CP, Zhou JY, Chen LA, Li WM, Li SY, Wang K, Wang Q, Zhang XJ, Li J, Gong X, Bai CX. Prevention and management of lung cancer in China. Cancer 2015, 17: 3080-3088.
4) Karlsson A, Brunnström H, Micke P, Veerla S, Mattsson J, La Fleur L, Botling J, Jönsson M, Reuterswärd C, Planck M, Staaf J. Gene Expression Profiling of Large Cell Lung Cancer Links Transcriptional Phenotypes to the New Histological WHO 2015 Classification. J Thorac Oncol 2017; 12: 1257-1267.
5) Wu Z, Xian X, Wang K, Cheng D, Li W, Chen B. Immune Checkpoint Blockade Therapy May Be a Feasible Option for Primary Pulmonary Lymphoepithelioma-like Carcinoma. Front Oncol 2021, 11: 626566.
6) Zhang L, Hao T, Wei Y, Dong M, Xiong Y. Primary pulmonary lymphoepithelioma-like carcinoma: A case report of pathological complete response (pCR) by neoadjuvant treatment. Medicine 2021; 100: 24987.
7) Tay CK, Chua YC, Takano A, Min Chee MY, Lim WT, Lim C, Koh MS. Primary pulmonary lymphoepithelioma-like carcinoma in Singapore. Ann Thorac Med 2018; 13: 30-35.
8) Fan Y, Li C, Qin J, Lu H. Primary pulmonary lymphoepithelioma-like carcinoma. Med Oncol 2020; 37: 20.
9) Qin Y, Gao G, Xie X, Zhu Z, Guan W, Lin X, Xie Z, Ming O, Chen R, Zhong N, Li S, Zhou C. Clinical Features and Prognosis of Pulmonary Lymphoepithelioma-like Carcinoma: Summary of Eighty-five Cases. Clin Lung Cancer 2019; 20: 329-337.
10) Zhou N, Lin Y, Peng X, Wang Y, Wang Y. Thorough survey and analysis of pulmonary lymphoepithelioma-like carcinoma in Macau and multimodality treatment for advanced disease. Lung Cancer 2019, 138: 116-123.
11) Cao L, Hong W, Cai P, Xu C, Bai X, Zhao Z, Huang M, Jin J. Cryptotanshinone strengthens the effect of gefitinib against non-small cell lung cancer through inhibiting transketolase. Eur J Pharmacol 2021, 890: 173647.
12) Téglási V, Pipek O, Lózsa R, Berta K, Szüts D, Harkó T, Vadász P, Rojkó L, Döme B, Bagó AG, Tímár J, Moldvay J, Szállási Z, Reiniger L. PD-L1 Expression of Lung Cancer Cells, Unlike Infiltrating Immune Cells, Is Stable and Unaffected by Therapy During Brain Metastasis. Clin Lung Cancer 2019; 20: 363-369.
13) Huang C, Feng A, Fang Y, Ku W, Chu N, Yu C, Liu C, Lee M, Hsu L, Tsai S, Shih C, Wang C. Multimodality treatment and long-term follow-up of the primary pulmonary lymphoepithelioma-like carcinoma. Clin Lung Cancer 2012; 13: 359-362.
14) Chen B, Chen X, Zhou P, Yang L, Ren J, Yang X, Li W. Primary pulmonary lymphoepithelioma-like carcinoma: a rare type of lung cancer with a favorable outcome in comparison to squamous carcinoma. Resp Res 2019; 20: 262.
15) Yu X, Wen Y, Qin R, Lin Y, Zhang X, Wang W, Chen Y, Zhang L. Prognosis and distribution of lymph nodes metastases in resectable primary pulmonary lymphoepithelioma-like carcinoma: A large cohort from a single center. Thorac Cancer 2018; 9: 360-367.
16) Yeh Y, Kao H, Lee K, Wu M, Ho H, Chou T. Epstein-Barr Virus-Associated Pulmonary Carcinoma: Proposing an Alternative Term and Expanding the Histologic Spectrum of Lymphoepithelioma-like Carcinoma of the Lung. Am J Surg Pathol 2019; 43: 211-219.
17) Li Y, Zhang W, Zhang H, Hu J, Zhou C, Zhang X, Fan W. Prognostic Significance of Regional/Systemic Metabolic Parameters on F-FDG PET in Pulmonary Lymphoepithelioma-Like Carcinoma. Front Oncol 2021, 11: 675961.

18) Ma H, Wu Y, Lin Y, Cai Q, Ma G, Liang Y. Computed tomography characteristics of primary pulmonary lymphoepithelioma-like carcinoma in 41 patients. Eup J Radiol 2013; 82: 1343-1346.

19) Osmani L, Askin F, Gabrielson E, Li QK. Current WHO guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC): Moving from targeted therapy to immunotherapy. Semin Cancer Biol 2018; 52: 103-109.

20) Lin Z, Fu S, Zhou Y, Zhang X, Chen C, He L, Li H, Wang Y, Chen T, Zhang L, Hong S. First-line platinum-based chemotherapy and survival outcomes in locally advanced or metastatic pulmonary lymphoepithelioma-like carcinoma. Lung Cancer 2019, 137: 100-107.

21) Zhu N, Lin S, Xu N, Chen L, Piao Z, Cao C. Primary pulmonary lymphoepithelioma-like carcinoma accompanied by hypertrophic pulmonary osteoarthropathy in a non-epidemic region: a case report and literature review. J Int Med Res 2020; 48: 300060520965816.

22) Jiang ZF, Wang M, Xu JL. Thymidine kinase 1 combined with CEA, CYFRA21-1 and NSE improved its diagnostic value for lung cancer. Life Sci 2018, 194: 1-6.

23) Qiu Z, Zhou P, Wang K. Primary Pulmonary Lymphoepithelioma-Like Carcinoma Response Favorably To Nivolumab: A Case Report. Onco Targets Ther 2019, 12: 8595-8600.

24) Tian Z, Liang C, Zhang Z, Wen H, Feng H, Ma Q, Liu D, Qiang G. Prognostic value of neuron-specific enolase for small cell lung cancer: a systematic review and meta-analysis. World J Surg Oncol 2020; 18: 116.

25) Du J, Li Y, Wang L, Zhou Y, Shen Y, Xu F, Chen Y. Selective application of neuroendocrine markers in the diagnosis and treatment of small cell lung cancer. Clin Chim Acta 2020, 509: 295-303.

26) Mei X, Zhu X, Zuo L, Wu H, Guo M, Liu C. Predictive significance of CYFRA21-1, squamous cell carcinoma antigen and carcinoembryonic antigen for lymph node metastasis in patients with esophageal squamous cancer. Int J Biol Markers 2019; 34: 200-204.

27) Yang Y, Huang X, Zhou L, Deng T, Ning T, Liu R, Zhang L, Bai M, Zhang H, Li H, Ba Y. Clinical use of tumor biomarkers in prediction for prognosis and chemotherapeutic effect in esophageal squamous cell carcinoma. BMC Cancer 2019; 19: 526.

28) Liang Y, Wang L, Zhu Y, Lin Y, Liu H, Rao H, Xu G, Rong T. Primary pulmonary lymphoepithelioma-like carcinoma: fifty-two patients with long-term follow-up. Cancer 2012; 118: 4748-4758.

29) Sathirareuangchai S, Hirata K. Pulmonary Lymphoepithelioma-like Carcinoma. Arch Pathol Lab Med 2019; 143: 1027-1030.

30) Chang YL, Wu C, Shih J, Lee Y. Unique p53 and epidermal growth factor receptor gene mutation status in 46 pulmonary lymphoepithelioma-like carcinomas. Cancer Sci 2011; 102: 282-287.

31) Shao X, Zheng Y, Cao W, Shen X, Li G, Chen J, Huang Y, Huang P, Shi L, Ye W, Zou W, Lou C, Lei L, Huang J, Chen Z, Wang X. Ki67 and progesterone receptor status predicts sensitivity to palbociclib: a real-world study. Ann Transl Med 2021; 9: 707.

32) Hasanov R, Aydoğan B, Kiremitçi S, Erden E, Güllü S. The Prognostic Roles of the Ki-67 Proliferation Index, P53 Expression, Mitotic Index, and Radiological Tumor Invasion in Pituitary Adenomas. Endocr Pathol 2019; 30: 49-55.

33) Zheng R, Shen Q, Mardekian S, Solomides C, Wang Z, Evans N. Molecular profiling of key driver genes improves staging accuracy in multifocal non-small cell lung cancer. J Thorac Cardiov Sur 2020; 160: 71-79.

34) Ono A, Isaka M, Serizawa M, Omae K, Kojima H, Nakashima K, Omori S, Wakuda K, Kenmotsu H, Naito T, Murakami H, Urakami K, Nagashima T, Sugino T, Kusuhara M, Takahashi T, Yamaguchi K, Ohde Y. Genetic alterations of driver genes as independent prognostic factors for disease-free survival in patients with resected non-small cell lung cancer. Lung Cancer 2019, 128: 152-157.

35) Liu Q, Ma G, Yang H, Wen J, Li M, Yang H, Luo K, Hu Y, Fu J. Lack of epidermal growth factor receptor gene mutations in exons 19 and 21 in primary lymphoepithelioma-like carcinoma of the lung. Thorac Cancer 2014; 5: 63-67.

36) Jiang L, Wang L, Li P, Zhang X, Chen J, Qiu H, Wu X, Zhang B. Positive expression of programmed death ligand-1 correlates with superior outcomes and might be a therapeutic target in primary pulmonary lymphoepithelioma-like carcinoma. Onco Targets Ther 2015, 8: 1451-1457.

37) Fang W, Hong S, Chen N, He X, Zhan J, Qin T, Zhou T, Hu Z, Ma Y, Zhao Y, Tian Y, Yang Y, Xue C, Tang Y, Huang Y, Zhao H, Zhang L. PD-L1 is remarkably over-expressed in EBV-associated pulmonary lymphoepithelioma-like carcinoma and related to poor disease-free survival. Oncotarget 2015; 6: 33019-33032.