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RESEARCH

Clinical, immune cell, and genetic features predicting survival and long-term response to first-line chemo-immunotherapy treatment for non-small cell lung cancer

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Abstract

Introduction Chemo-immunotherapy has become a standard of care for the first-line treatment of non-small cell lung cancer (NSCLC), but currently still lacks reliable markers to predict therapeutic efficacy and long-term response (LTR).

Methods In this study, we retrospectively summarized the survival outcome of 319 patients with locally advanced or metastatic NSCLC who received anti-programmed cell death protein-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) based therapy from January 1st, 2018 to February 28th, 2022 at the Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. Then a comprehensive analysis of the association of LTR or survival outcomes with various characteristics including clinical parameters, peripheral blood lymphocyte subsets and common gene mutations in 167 NSCLC patients who received first-line anti-PD-1 plus chemotherapy treatment was conducted. LTR was defined as progression-free survival (PFS) exceeding 24 months, while non-responders had a PFS of less than 6 months.

Results With a median follow-up time of 32.1 months (95% confidence interval [CI] 29.2–38.0), the median overall survival (OS) was 29.9 months (95% CI 23.6–37.5) in locally advanced or metastatic NSCLC receiving anti-PD-1/PD-L1 based treatment. Among 167 patients who received the first-line chemo-immunotherapy, 25.1% (n = 42) achieved LTR. Independent baseline predictors of LTR included age < 65 years (odds ratio [OR] = 3.22, $p = 0.024$), overweight or obesity (body mass index [BMI] ≥ 24 kg/m^2, OR = 3.26, $p = 0.020$), and a C-reactive protein/albumin ratio (CAR) score < 0.07 (OR = 9.94, $p = 0.039$). In multivariate cox analysis, both patients with higher CAR scores of ≥ 0.07 (hazard ratio [HR] = 2.83, $p = 0.016$) and those who were underweight (BMI < 18.5 kg/m^2) (HR = 4.52, $p = 0.005$) were observed with significantly shorter OS. A peripheral B cell percentage ≥ 14.5% was more prevalent among LTR patients (OR = 9.23, $p = 0.045$) after adjusting for age, BMI and TNM stage. Additionally, the presence of *TP53* mutation (16/66) was associated with non-response to first-line chemo-immunotherapy ($p = 0.048$) and shorter PFS ($p = 0.028$) and OS ($p = 0.023$) outcomes in univariate analysis.

Conclusions This study provides some new insights into the features and predictors significantly associated with LTR and survival in NSCLC patient receiving first-line treatment of anti-PD-1 plus chemotherapy. Those whose age < 65 years, overweight or obesity, or has a baseline CAR score < 0.07 are more likely to achieve optimal benefit from the first-line treatment of chemo-immunotherapy.

Keywords NSCLC · Long-term response · First-line · PD-1 · Chemo-immunotherapy

Abbreviations

ADC	Adenocarcinoma
ACTH	Adrenocorticotropic hormone
ALBI	Albumin-bilirubin
BMI	Body mass index
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete response
CI	Confidence interval
CRP	C-reactive protein
CAR	C-reactive protein/albumin ratio
DCR	Disease control rate
ECOG	Eastern Cooperative Oncology Group
HR	Hazard ratio
irAE	Immune-related adverse events

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ICI	Immune checkpoint inhibitors
LDH	Lactate dehydrogenase
LTR	Long term response
LIPI	Lung immune prognostic index
LMR	Lymphocyte-monocyte ratio
SD	Standard deviation
NLR	Neutrophil–lymphocyte ratio
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death-ligand 1
TPS	Tumor proportion score
PFS	Progression-free survival
OS	Overall survival
NLR	Neutrophil-lymphocyte ratio
NGS	Next generation sequencing
NA	Not available
NSCLC	Non-small cell lung cancer
OR	Odds ratios
ORR	Overall response rate
PR	Partial response
PS	Performance status
PD	Progressive disease
PNI	Prognostic nutritional index
RECIST	Response Evaluation Criteria in Solid Tumors
RT-PCR	Reverse transcription-polymerase chain reaction
SCC	Squamous cell carcinoma
SD	Stable disease
TRAE	Treatment-related adverse event
TMB	Tumor mutational burden

Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all lung cancer cases [1, 2]. Immune checkpoint inhibitors (ICIs), especially targeting programmed cell death protein-1 (PD-1) and its ligand programmed cell death-ligand 1 (PD-L1), have revolutionized the therapeutic landscape of lung cancer, offering new hope for outcome improvement in this patient population due to its favorable safety profile, durable therapeutic responses driven by immunological memory generation [3].

However, not all patients benefit equally from immunotherapy, highlighting the need for searching for reliable and robust predictive biomarkers to predict immunotherapeutic efficacy and identify those most likely to respond. Among the various biomarkers investigated, tissue PD-L1 expression has been extensively studied and is currently used as a companion diagnostic test to guide ICI treatment [4, 5]. However, PD-L1 expression along does not fully capture the complexity of the tumor microenvironment and the host immune response, and fails to provide valid and optimal performance [6, 7]. Other factors, such as tumor mutational burden (TMB), some hematological indicators, the composition of lymphocyte subpopulations and the overall immune contexture, have been linked to efficacy of ICI treatment while with inconsistent evidence [8–11].

In this study, we aimed to comprehensively evaluate and summarize the treatment outcomes of anti-PD-1/PD-L1 based treatment in a real-world cohort of patients with locally advanced and metastatic NSCLC. Furthermore, we focused on patients who received first-line chemo-immunotherapy, to identify meaningful clinical, hematological, immunological, and genetic indicators to predict long term response (LTR) and better survival outcomes in this patient population, enhancing personalized treatment in the new era.

Methods

Inclusion and exclusion criteria

Inclusion Criteria: patients who were pathologically diagnosed with locally advanced or metastatic NSCLC and received treatment of PD-1/PD-L1 inhibitors as monotherapy or combined with other systemic treatments at the Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College between January 1st, 2018 and February 28th, 2022 (Cohort A) were included for survival outcomes analysis. Then we screened and extracted patients who received first-line chemo-immunotherapy as Cohort B to investigate markers to predict therapeutic efficacy and LTR in this patient population. Exclusion Criteria: patients without complete clinical information or subsequent follow-up data, or patients who received less than 2 cycles of anti-PD-1/PD-L1 inhibitor-based therapy would be ruled out from this study.

Patient clinical and pathological information collection

All data were collected from our hospital electronic medical records, including age, gender, TNM stage, histology, prior treatment history, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status (PS), organ metastasis status, lines of therapy, treatment modality, date of immunotherapy initiation, date of disease progression, date of last follow-up or death, pre-immunotherapy baseline write blood cell count, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, total bilirubin, albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH), peripheral lymphocyte subsets, tissue PD-L1 expression by tumor proportion score (TPS), common gene mutation information, best response,

immune-related adverse events (irAEs), and treatment outcomes.

According to the Chinese BMI classification, underweight was defined as < 18.5 kg/m^2, normal weight as 18.5 to < 24 kg/m^2, overweight as 24–28 kg/m^2, and obesity as ≥ 28 kg/m^2[12, 13]. The C-reactive protein/albumin ratio (CAR) score was calculated as dividing CRP (mg/dL) by albumin (mg/dL) [14]. The albumin-bilirubin (ALBI) score was calculated as $0.66 \times \log$ [bilirubin (μmol/L)] $- 0.085 \times$ albumin (mg/dL) [15]. The prognostic nutritional index (PNI) was calculated as $5 \times$ absolute lymphocyte count (10^9/L) + albumin (mg/dL) [16]. The neutrophil-lymphocyte ratio (NLR) was calculated as dividing absolute neutrophil count by absolute lymphocyte count [17]. The lymphocyte-monocyte ratio (LMR) was calculated as dividing absolute lymphocyte count by absolute lymphocyte count [18]. The lung immune prognostic index (LIPI) was based on derived neutrophil-lymphocyte ratio (dNLR) and LDH levels. dNLR > 3 or LDH > upper limit of normal (ULN) was deemed as one point, respectively[19]. PD-L1 expression was detected by using immunohistochemistry (IHC) with 22C3 antibody. The genetic features (*EGFR/KRAS/HER2/TP53* mutation) were detected via next generation sequencing (NGS) or reverse transcription-polymerase chain reaction (RT-PCR) performed at the department of pathology at Cancer Hospital, Chinese Academy of Medical Sciences.

Peripheral lymphocyte subset analysis

To perform peripheral lymphocyte subset, 3 mL whole blood per patient were collected if available and to conduct flow cytometry analysis. The monoclonal antibodies used in this staining panel included: CD3 FITC, CD4 PE, CD8 PE, CD19 APC, CD45RA FITC, and CD16 + CD56 PE (BD FACS Calibur). The percentage information of each lymphocyte subset of each individual including total T cells (CD3+), helper T cells (CD3+ CD4+), cytotoxic T cells (CD3+ CD8+), NK cells (CD3-CD16+ CD56+), B cells (CD3–CD19+) were collected.

Efficacy and adverse event evaluation

Imaging and hematological examinations were conducted at baseline and every 2 treatment cycles. Efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), and the best anti-tumor response was used as the objective response, classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Safety profile was assessed since the first dose of PD-1/PD-L1 inhibitors until the treatment discontinuation according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Follow-up and endpoints

Patients were regularly followed up through telephone or electronic medical record review to track patient disease progression status and survival status. For patients lost to follow-up, the last recorded follow-up date in their electronic medical record was used and censored in the subsequent survival analysis. The primary endpoints of this study were LTR. The second endpoints were progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from the start of PD-1/PD-L1 inhibitor therapy to disease progression or death from any cause or the last follow-up data. OS was defined as the time from the start of PD-1/PD-L1 inhibitor therapy to death from any cause or the last follow-up data. LTR was defined as patients with CR, PR, or SD lasting ≥ 24 months (i.e. PFS ≥ 24 months) [20, 21], non-responders were defined as patients with CR, PR, or SD lasting < 6 months (i.e. PFS < 6 months).

Statistical methods

Group comparisons for categorical data were performed using the χ^2 test or Fisher's exact test. Survival analyses were conducted using the Kaplan–Meier method. To assess the correlation between binary covariates with LTR, univariate and multivariate logistic regression were conducted to calculate odds ratios (OR). Prognostic factors for OS and PFS were evaluated using univariate and multivariate Cox proportional hazards models. Continuous variables were transformed into binary variables using their optimal cutoff values determined by the value for the maximal Yuden index (sensitivity + specificity-1) obtained by the "roc" function of the "pROC" R package or determined by the "surv_cutpoint" function of the "survminer" R package. Factors with p-values < 0.05 in univariate analysis were included in the multivariate regression for independent prognostic analysis, and p-values < 0.05 were considered statistically significant. All statistical analyses were performed using R version 4.2.2 and SPSS version 26.0.

Results

Treatment outcomes of all patients who received anti-PD-1/PD-L1 based treatment

From January 2018 to February 2022, a total of 319 patients with locally advanced or metastatic NSCLC who received anti-PD-1/PD-L1 based treatment at the Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union

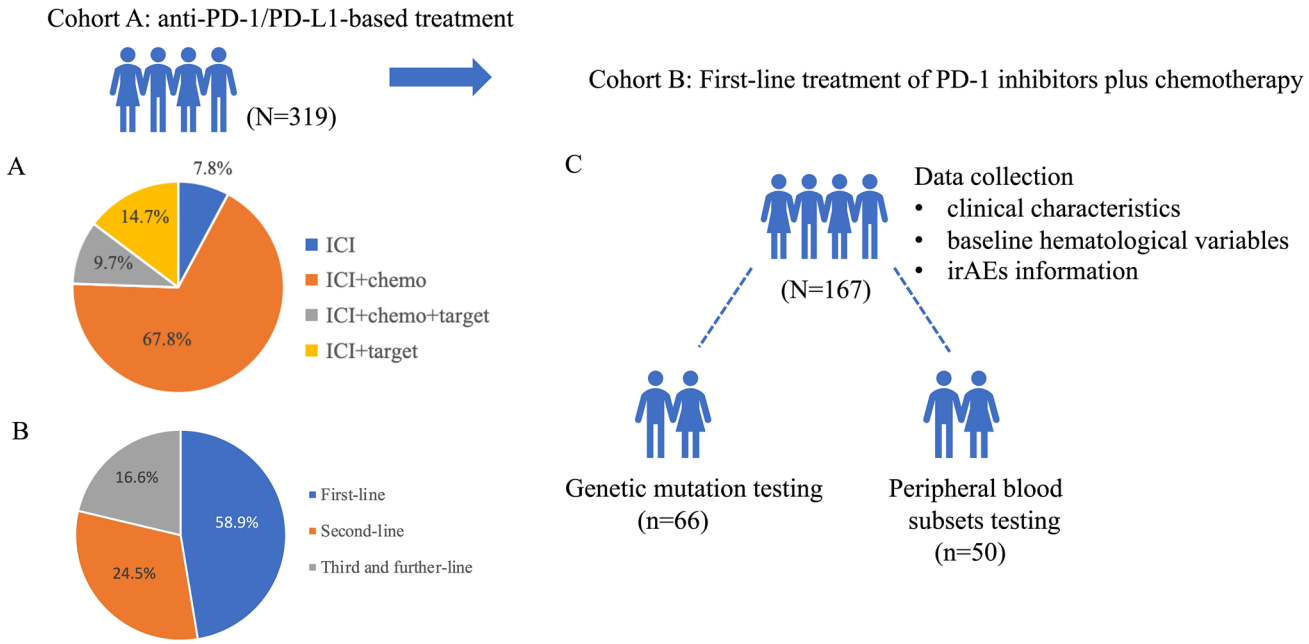

Fig. 1 The study cohort design. **A** a pie graph displaying the proportion of treatment strategy of all patients receiving anti-PD-1/PD-L1-based therapy (cohort A); **B** a pie graph displaying the proportion of lines of treatment in cohort A; **C** summarization of patients receiving first-line chemo-immunotherapy (cohort B). PD-1, programmed cell death protein-1; ICI, immune checkpoint inhibitors

Medical college and met the inclusion criteria were enrolled in the cohort A. In this cohort, 58.9% and 24.5% of patients received first-line (n = 188), and second-line (n = 78) anti-PD-1/PD-L1 based immunotherapy, respectively, while the rest 53 patients (16.6%) received third or further-lines of immunotherapy. Regarding treatment modalities, 25 patients (7.8%) received anti-PD-1/PD-L1 monotherapy, 216 patients (67.8%) received PD-1/PD-L1 inhibitors combined with chemotherapy, 47 patients (14.7%) received PD-1/PD-L1 inhibitors combined with anti-angiogenic therapy, and 31 patients (9.7%) received PD-1/PD-L1 inhibitors combined with both chemotherapy and anti-angiogenic therapy. With a median follow-up time of 32.1 months (95% CI 29.2–38.0), the median PFS was 7.7 months (95% CI 6.23–9.73), and the median OS was 29.9 months (95% CI 23.6–37.5). The 1-year, 3-year, and 5-year OS rates were 74.5% (95% CI 69.7–79.6), 45.1% (95% CI 39.1–52.0), and 35.6% (95% CI 29.2–43.4), respectively. The survival outcomes of different lines of anti-PD-1/PD-L1 based therapy in this study were summarized in Table S1.

Then patients who received first-line chemo-immunotherapy in cohort A were included in cohort B to conduct further analysis (i.e. investigating potent markers to predict LTR and survival outcomes). The study cohort design was presented in Fig. 1.

Baseline characteristics of patients who received first-line chemo-immunotherapy treatment

Cohort B contains 167 NSCLC patients who received first-line chemo-immunotherapy treatment. The median age was 63 (range 32–83), 86.2% of the patients were male, 75.4%, 22.8% and 1.8% of the patients had a ECOG PS of 0–1, 2 and 3, respectively. The cohort comprises 63 cases of lung adenocarcinoma (ADC) and 104 cases of squamous cell lung carcinoma (SCC). 70.7% of the patients are in stage IV. All patients received PD-1 inhibitors treatment. The specific PD-1 inhibitors and chemotherapy agents used in this population were summarized in Table S2. Among them, a total of 66 and 40 patients received genetic test and PD-L1 IHC examination, respectively, and 50 patients received peripheral lymphocyte subset test. The detailed patient baseline characteristics, genetic mutation features, PD-L1 expression, and peripheral lymphocyte subset profile in LTR group and non-LTR group were summarized in Tables 1 and 2.

Survival outcomes, and efficacy

With a median follow-up time of 32.1 months (95% CI 29.2–38.0), the median PFS was 14.4 months (95% CI 11.0–21.1), and the median OS was 42.0 months (95% CI 33.3-NA). The 1-year, 3-year, and 5-year OS rates were 81.5% (95% CI 75.7–87.7), 55.3% (95% CI 46.9–65.1), and 49.0% (95% CI 40.1–60.0), respectively. There were

Table 1 Patient baseline characteristics

	Non-LTR (N = 125)	LTR (N = 42)	Overall (N = 167)	*p* value
Age				
< 65	67 (53.6%)	30 (71.4%)	97 (58.1%)	0.128
≥ 65	58 (46.4%)	12 (28.6%)	70 (41.9%)	
Sex				
女	18 (14.4%)	5 (11.9%)	23 (13.8%)	0.921
男	107 (85.6%)	37 (88.1%)	144 (86.2%)	
BMI				
Underweight	10 (8.0%)	3 (7.1%)	13 (7.8%)	0.392
Normal	64 (51.2%)	15 (35.7%)	79 (47.3%)	
Overweight/obesity	41 (32.8%)	21 (50.0%)	62 (37.1%)	
Missing	10 (8.0%)	3 (7.1%)	13 (7.8%)	
ECOG PS				
0–1	85 (68.0%)	41 (97.6%)	126 (75.4%)	< 0.001
2–3	40 (32.0%)	1 (2.4%)	41 (24.6%)	
Histology				
ADC	46 (36.8%)	17 (40.5%)	63 (37.7%)	0.914
SCC	79 (63.2%)	25 (59.5%)	104 (62.3%)	
TNM stage				
III	30 (24.0%)	19 (45.2%)	49 (29.3%)	0.033
IV	95 (76.0%)	23 (54.8%)	118 (70.7%)	
ALBI				
< − 3.0	38 (30.4%)	21 (50.0%)	59 (35.3%)	0.049
≥ − 3.0	81 (64.8%)	18 (42.9%)	99 (59.3%)	
Missing	6 (4.8%)	3 (7.1%)	9 (5.4%)	
PNI				
< 50	64 (51.2%)	11 (26.2%)	75 (44.9%)	0.019
≥ 50	54 (43.2%)	28 (66.7%)	82 (49.1%)	
Missing	7 (5.6%)	3 (7.1%)	10 (6.0%)	
LIPI score				
0	59 (47.2%)	24 (57.1%)	83 (49.7%)	0.955
1	34 (27.2%)	11 (26.2%)	45 (26.9%)	
2	1 (0.8%)	0 (0%)	1 (0.6%)	
Missing	31 (24.8%)	7 (16.7%)	38 (22.8%)	
CAR				
< 0.07	66 (52.8%)	31 (73.8%)	97 (58.1%)	0.015
≥ 0.07	25 (20.0%)	1 (2.4%)	26 (15.6%)	
Missing	34 (27.2%)	10 (23.8%)	44 (26.3%)	
NLR				
< 3.0	63 (50.4%)	24 (57.1%)	87 (52.1%)	0.954
≥ 3.0	50 (40.0%)	17 (40.5%)	67 (40.1%)	
Missing	12 (9.6%)	1 (2.4%)	13 (7.8%)	
LMR				
< 3.0	33 (26.4%)	12 (28.6%)	45 (26.9%)	1
≥ 3.0	80 (64.0%)	29 (69.0%)	109 (65.3%)	
missing	12 (9.6%)	1 (2.4%)	13 (7.8%)	
Brain metastasis				
Yes	13 (10.4%)	2 (4.8%)	15 (9.0%)	0.543
No	112 (89.6%)	40 (95.2%)	152 (91.0%)	
Liver metastasis				
Yes	16 (12.8%)	1 (2.4%)	17 (10.2%)	0.155
No	109 (87.2%)	41 (97.6%)	150 (89.8%)	
Bone metastasis				
Yes	23 (18.4%)	2 (4.8%)	25 (15.0%)	0.101
No	102 (81.6%)	40 (95.2%)	142 (85.0%)	

LTR, long term response; BMI, body mass index; PFS, progression-free survival; OS, overall survival; SCC, squamous cell carcinoma; ADC: adenocarcinoma; ALBI, albumin-bilirubin; PNI, prognostic nutritional index; LIPI, lung immune prognostic index; CAR, C-reactive protein/albumin ratio; NLR, neutrophil–lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score

2 cases of CR (1.2%), 91 cases of PR (54.5%), 55 cases of SD (32.9%), and 19 cases of PD (11.4%), with an overall response rate (ORR) of 55.7% and a disease control rate (DCR) of 88.6%. Among all the patients, 25.1% of patients (n = 42) benefited tremendously from first-line anti-PD-1 plus chemotherapy and belonged to the LTR group, while 41 patients (24.6%) are non-responders. The median PFS was 38.6 months (95% CI 37.0- not available [NA]) in the LTR group, while the median OS was not reached. The 3-year PFS rate and 5-year OS rate of the LTR group were 84.3% (95% CI 72.2–98.3) and 79.9% (95% CI 66.2–96.4), respectively. While the median PFS and OS of the non-responder group were 2.9 months (95% CI 1.9–4.0) and 13.8 months (95% CI 8.9-NA) (Fig. 2 and Table 3).

Characteristics associated with long-term response

To investigate the factors contributing to LTR of NSCLC patients who received first-line chemo-immunotherapy, various baseline clinical, hematological and biological factors have been collected. In comparison to patients without LTR (Fig. 3), several clinical factors were significantly associated with LTR, including age < 65 years, TNM stage III, overweight or obesity (BMI ≥ 24), an ALBI score ≤ -3.0, PNI ≥ 50, and CAR < 0.07 in univariate analysis. Multivariable analysis identified age < 65 years (OR = 3.22, $p = 0.024$), BMI ≥ 24 kg/m^2 (OR = 3.26, $p = 0.020$), and a CAR score < 0.07 (OR = 9.94, $p = 0.039$) as independent predictors of LTR. Patients in LTR group tended to have lower CAR scores (Fig. 4A). In the comparison between LTR and non-responders (Figure S1), the CAR score was verified as the only independent factor related to LTR (OR = 11.8, $p = 0.036$). Meanwhile, the correlation between the CAR score and all peripheral blood subsets percentage

Table 2 Comparison of genetic mutation, PD-L1 expression, and peripheral immune cell subsets profile in LTR and non-LTR groups

	Non-LTR (N = 50)	LTR (N = 16)	Overall (N = 66)	*p* value
EGFR mutation				
No	46 (92.0%)	14 (87.5%)	60 (90.9%)	0.862
Yes	4 (8.0%)	2 (12.5%)	6 (9.1%)	
KRAS mutation				
No	43 (86.0%)	11 (68.8%)	54 (81.8%)	0.298
Yes	7 (14.0%)	5 (31.3%)	12 (18.2%)	
HER2 mutation				
No	48 (96.0%)	15 (93.8%)	63 (95.5%)	0.932
Yes	2 (4.0%)	1 (6.3%)	3 (4.5%)	
TP53 mutation				
No	36 (72.0%)	14 (87.5%)	50 (75.8%)	0.453
Yes	14 (28.0%)	2 (12.5%)	16 (24.2%)	
	Non-LTR (N = 34)	LTR (N = 16)	Overall (N = 50)	*p* value
CD3 + T cell (%)				
< 76%	26 (76.5%)	12 (75.0%)	38 (76.0%)	0.994
≥ 76%	8 (23.5%)	4 (25.0%)	12 (24.0%)	
CD4 + T cell (%)				
< 22%	4 (11.8%)	0 (0%)	4 (8.0%)	0.36
≥ 22%	30 (88.2%)	16 (100%)	46 (92.0%)	
CD8 + T cell (%)				
< 28%	13 (38.2%)	8 (50.0%)	21 (42.0%)	0.734
≥ 28%	21 (61.8%)	8 (50.0%)	29 (58.0%)	
B cell (%)				
< 14.5%	31 (91.2%)	9 (56.3%)	40 (80.0%)	0.016
≥ 14.5%	3 (8.8%)	7 (43.8%)	10 (20.0%)	
NK cell (%)				
< 25.6%	20 (58.8%)	12 (75.0%)	32 (64.0%)	0.539
≥ 25.6%	14 (41.2%)	4 (25.0%)	18 (36.0%)	
CD4 + /CD8 + T cell ratio				
< 1.25	19 (55.9%)	5 (31.3%)	24 (48.0%)	0.266
≥ 1.25	15 (44.1%)	11 (68.8%)	26 (52.0%)	
	Non-LTR (N = 30)	LTR (N = 10)	Overall (N = 40)	*p* value
PD-L1 TPS				
< 1%	9 (30.0%)	1 (10.0%)	10 (25.0%)	0.449
≥ 1%	21 (70.0%)	9 (90.0%)	30 (75.0%)	

LTR, long term response; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

were presented in Fig. 4G–K, no significant correlation was observed.

In the immune cell profile, a peripheral B cell percentage ≥ 14.5% was more prevalent in patients with LTR (OR = 8.04, $p = 0.008$) in the univariate analysis, while considering the limited data in this study, B cell percentage was not included in multivariable analysis as presented in Fig. 3. Additionally, after ruling out the interference of common clinical factors (age, BMI, and TNM stage), the peripheral B cell percentage still showed solid predictive value for LTR (OR = 9.23, $p = 0.045$) in patients who received first-line anti-PD-1 plus chemotherapy treatment (Fig. 5G).

In the mutation profile, when comparing the characteristics between LTR and non-LTR, none of *EGFR/KRAS/HER2/TP53* mutation or PD-L1 TPS expression was found to be significantly related to LTR in this population

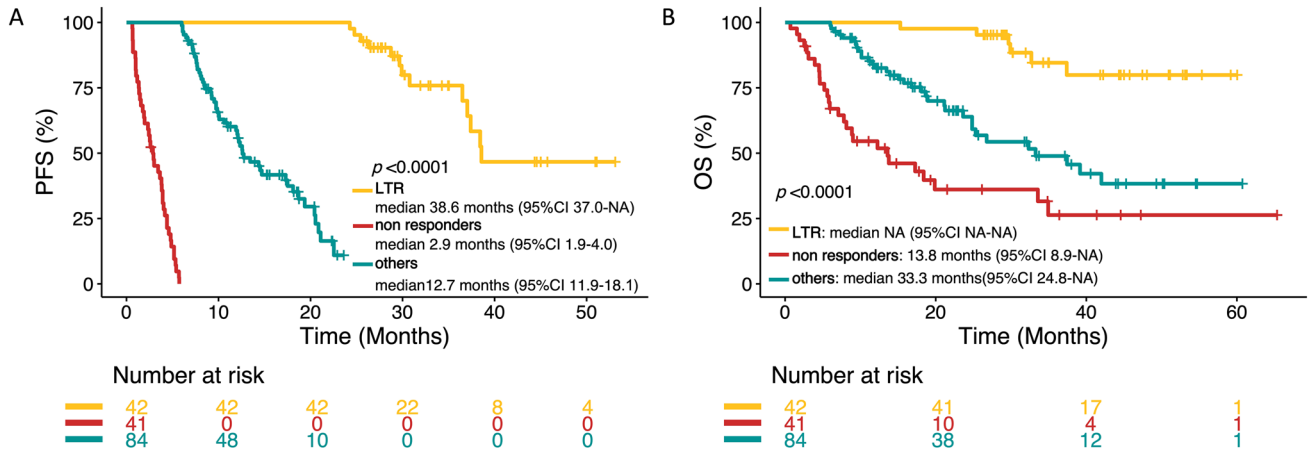

Fig. 2 Kaplan–Meier curves of PFS (**A**) and OS (**B**) among patients with LTR, non-responder, and others in patients receiving first-line chemo-immunotherapy. Abbreviation: LTR, long term response; PFS, progression-free survival; OS, overall survival; NA, not available

Table 3 The comparison of survival outcomes of first-line chemo-immunotherapy in NSCLC patients with different response

	LTR	Non-responders	Others	Overall
	(n = 42)	(N = 41)	(N = 84)	(N = 167)
Median PFS	38.6 (95% CI 37.0-NA)	2.9 months (95% CI 1.9–4.0)	12.7 months (95% CI 11.9–18.1)	14.4 months (95% CI 11.0–21.1)
Median OS	NA (95% CI NA-NA)	13.8 months (95% CI 8.9-NA)	33.3 months (95% CI 24.8-NA)	42.0 months (95% CI 33.3-NA)
1-year PFS rate	100% (95% CI 100–100)	0% (95% CI NA—NA)	63.9% (95% CI 53.7–76)	65.4% (95% CI 58.1–73.7)
2-year PFS rate	100% (95% CI 100–100)	0% (95% CI NA—NA)	44.2% (95% CI 31.3–62.6)	58.6% (95% CI 50.7–66.7)
3-year PFS rate	84.3% (95% CI 72.2–98.3)	0% (95% CI NA—NA)	NA	49.4% (95% CI 40.0–61.0)
1-year OS rate	97.6% (95% CI 93.1–100)	56.0% (95% CI 42.2–74.2)	82.5% (95% CI 74.6–91.3)	81.5% (95% CI 75.7–87.7)
3-year OS rate	79.9% (95% CI 66.2–96.4)	28.4% (95% CI 15.3–52.7)	48.9% (95% CI 36.8–65)	55.3% (95% CI 46.9–65.1)
5-year OS rate	79.9% (95% CI 66.2–96.4)	28.4% (95% CI 15.3–52.7)	38.3% (95% CI 25.7–57.0)	49.0% (95% CI 40.1–60.0)

LTR, long term response; PFS, progression-free survival; OS, overall survival; NA, not available; CI, confidence interval

(Fig. 3). While when comparing the characteristics between LTR and non-responders (Figure S1), *TP53* mutation was more observed in non-responders (OR = 6.12, $p = 0.048$), but it was not included in multivariate analysis considering its limited data.

Based on the available data, during the first-line anti-PD-1 plus chemotherapy treatment, the common irAEs included thyroid dysfunction (44.4%), abnormal ACTH (7.6%), immune-related pneumonitis (0.6%), and immune-related hepatitis (1.2%). 4.2% of patients (n = 7) suffered from grade ≥ 3 irAEs including immune-related pneumonitis (n = 3), immune-related hepatitis (n = 1), immune-related nephritis (n = 1), hypothyroidism (n = 1), and adrenal insufficiency (n = 1). However, the occurrence of irAEs including thyroid dysfunction and abnormal ACTH level failed to show meaningful predictive value in this cohort.

Characteristics associated with survival outcomes

We also explored the factors predicting PFS and OS in patients who received first-line chemo-immunotherapy, the results demonstrated that patients who are underweight (BMI < 18.5) (HR = 4.52, $p = 0.005$), an ALBI score > −3.0 (HR = 2.45, $p = 0.042$), LIPI score of 2 (HR = 27.5, $p = 0.015$), a CAR score ≥ 0.07 (HR = 2.83, $p = 0.016$), liver metastasis (HR = 3.51, $p = 0.02$) were identified as independent adverse factors related to poorer OS outcome. While stage IV (HR = 1.86, $p = 0.03$) and liver metastasis (HR = 2.80, $p = 0.01$) were related to shorter PFS. The prognostic factors predicting PFS and OS were also explored and summarized in Table 4. The K-M curves of the CAR score and BMI were presented in Fig. 4.

In the immune cell profile, patients in LTR group were observed with higher B cell percentage (Fig. 5A), but the B cell percentage failed to show significant association with PFS ($p = 0.052$) and OS ($p = 0.19$) (Fig. 5B, C). The

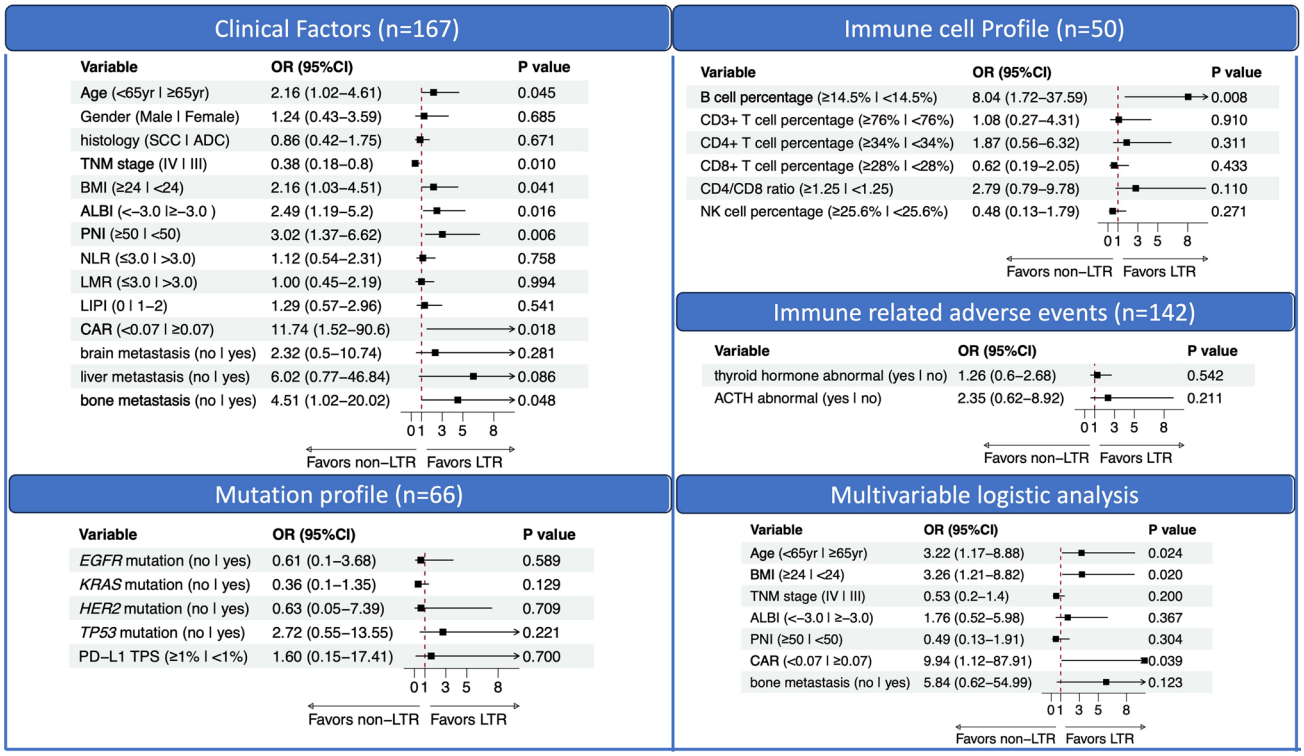

Fig. 3 Univariate and multivariable logistic analyses of association of clinical factors, immune cell and mutation profiles with LTR compared with non-LTR. BMI, body mass index; LTR, long term response; OR, odds ratio; SCC, squamous cell carcinoma; ADC: adenocarcinoma; ALBI, albumin-bilirubin; PNI, prognostic nutritional index; LIPI, lung immune prognostic index; CAR, C-reactive protein/albumin ratio; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score

CD4 + T cell percentage failed to show association with LTR (Fig. 5D), but presented meaningful value in predicting both PFS and OS outcomes (Fig. 5E, F). Other results of univariate Cox analysis for PFS and OS of peripheral lymphocyte subsets were presented in Fig. 5H-I. In the mutation profile, patients harboring *TP53* mutation were associated with shorter PFS ($p = 0.028$) and OS ($p = 0.023$) outcomes in the univariate analysis, while the prognostic value of either *EGFR* mutation or PD-L1 TPS expression was not observed in this cohort (Figure S2).The occurrence of irAEs also failed to show significance.

Discussion

The combination of chemo-immunotherapy in the first-line treatment in NSCLC patients without driver gene mutation has emerged as one of the standard of care. Though a subset of patients can achieve sustained benefits from immunotherapy, existing markers have been inadequate in identifying these individuals accurately [3]. This study aimed to address this significant gap in the field of lung cancer immunotherapy by focusing on markers predicting LTR. Our research provided a comprehensive analysis of a large, real-world cohort of locally advanced or metastatic NSCLC patients undergoing first-line PD-1 inhibitors plus chemotherapy combination therapy. By extensively evaluating various factors, including clinical characteristics, baseline laboratory variables, peripheral blood cell subsets, irAEs, and genetic mutation profile, we not only summarized the current treatment outcomes of NSCLC immunotherapy but also provided novel insights into the specific traits of patients who achieve long-term benefits in the first-line setting with the treatment of anti-PD-1 plus chemotherapy.

CAR, defined as the ratio of CRP to albumin, serves as an indicator of systemic inflammation. It was found to be associated with the survival of lung cancer and various other malignancies, demonstrating predictive value for survival outcomes, including those who received immunotherapy [14, 22–24]. Elevated CAR levels have been related to poor prognosis, however, no prior research has specifically explored the relationship between CAR and LTR to the combination of immunotherapy plus chemotherapy in the first-line setting of NSCLC patients. In our study, we identified CAR as an independent adverse prognostic factor for both LTR and OS in the population. High inflammatory

Table 4 The univariate and multivariate Cox analysis for PFS and OS outcomes

Variables	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (≥65 vs. <65)	0.99 (0.67–1.46)	0.96	–	–	0.95 (0.57–1.57)	0.828	–	–
Gender (Male vs. Female)	0.7 (0.42–1.17)	0.173	–	–	1.14 (0.56–2.32)	0.708	–	–
BMI (<18.5 vs. ≥18.5)	1.57 (0.81–3.03)	0.178	–	–	2.15 (1.02–4.53)	**0.045**	4.52 (1.59–12.86)	**0.005**
TNM stage (IV vs. III)	2.1 (1.32–3.34)	**0.002**	1.86 (1.05–3.3)	**0.033**	1.91 (1.04–3.51)	**0.038**	1.05 (0.44–2.5)	0.905
histology (SCC vs. ADC)	0.76 (0.52–1.11)	0.156	–	–	0.81 (0.49–1.32)	0.399	–	–
ALBI (>-3.0 vs. ≤-3.0)	2.03 (1.31–3.13)	**0.001**	1.11 (0.56–2.23)	0.761	2.27 (1.28–4.01)	**0.005**	2.45 (1.03–5.83)	**0.042**
PNI (<50 vs. ≥50)	2.29 (1.53–3.43)	**<0.001**	1.63 (0.82–3.23)	0.165	1.97 (1.17–3.32)	**0.011**	0.42 (0.17–1.02)	0.052
LIPI score (1 vs. 0)	1.23 (0.78–1.95)	0.372	0.93 (0.55–1.56)	0.778	1.5 (0.82–2.74)	0.187	0.69 (0.32–1.47)	0.336
LIPI score (2 vs. 0)	22.51 (2.69–188.48)	**0.004**	8.47 (0.88–81.2)	0.064	74.52 (6.65–834.44)	**<0.001**	27.5 (1.9–398.6)	**0.015**
CAR (≥0.07 vs. <0.07)	2.67 (1.56–4.58)	**<0.001**	1.7 (0.87–3.3)	0.119	3.08 (1.61–5.9)	**0.001**	2.83 (1.22–6.58)	**0.016**
NLR (>3.0 vs. ≤3.0)	1.27 (0.85–1.92)	0.243	–	–	1.36 (0.8–2.3)	0.258	–	–
LMR (>3.0 vs. ≤3.0)	1.03 (0.66–1.63)	0.883	–	–	0.92 (0.51–1.67)	0.785	–	–
brain metastasis (Yes vs. No)	1.67 (0.93–2.99)	0.086	–	–	1.54 (0.73–3.23)	0.253	–	–
liver metastasis (Yes vs. No)	2.66 (1.53–4.64)	**0.001**	2.80 (1.28–6.16)	**0.01**	3.31 (1.75–6.26)	**<0.001**	3.51 (1.21–10.13)	**0.02**
bone metastasis (Yes vs. No)	2.41 (1.48–3.92)	**<0.001**	1.17 (0.55–2.49)	0.686	3.98 (2.31–6.84)	**<0.001**	2.23 (0.89–5.63)	0.088
pleura metastasis (Yes vs. No)	1.21 (0.7–2.1)	0.49	–	–	0.83 (0.4–1.76)	0.634	–	–
adrenal metastasis (Yes vs. No)	1.9 (1.04–3.49)	**0.037**	0.75 (0.31–1.8)	0.518	2.46 (1.21–4.98)	**0.013**	1.26 (0.39–4.01)	0.701
PD-L1 TPS (<1% vs. ≥1%)	1.96 (0.87–4.41)	0.102	–	–	1.34 (0.46–3.86)	0.588	–	–
thyroid hormone abnormal (Yes vs. No)	0.74 (0.48–1.13)	0.16	–	–	0.95 (0.55–1.64)	0.863	–	–
ACTH abnormal (Yes vs. No)	0.64 (0.26–1.58)	0.328	–	–	0.22 (0.03–1.58)	0.132	–	–
immune-related pneumonia (Yes vs. No)	0.4 (0.06–2.89)	0.366	–	–	NA	–	–	–

LTR, long term response; BMI, body mass index; PFS, progression-free survival; OS, overall survival; NA, not available; HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC: adenocarcinoma; ALBI, albumin-bilirubin; PNI, prognostic nutritional index; LIPI, lung immune prognostic index; CAR, C-reactive protein/albumin ratio; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score

Those *p*-values less than 0.05 are shown in bold to indicate statistical significance

state may contribute to an immunosuppressive tumor microenvironment. Additionally, hypoalbuminemia, indicative of poor nutritional and the inflammatory state, has been associated with diminished immune competence [25]. This finding suggests that systemic inflammation and nutritional status may play a crucial role in determining long-term immunotherapeutic efficacy. Underlying mechanisms warrant further investigation. These findings highlight the importance of incorporating the assessments of CAR score into clinical practice to refine patient selection for immunotherapy and optimize treatment outcomes.

Another important finding of this study is the meaningful value of BMI in predicting both LTR and survival outcomes of this population. BMI is widely used to assess the degree of obesity and overall nutritional status [13]. In a large sample-based meta-analysis, obesity was a protective factor in patients with lung cancer, renal cell carcinoma, and melanoma, while it was an adverse factor in other cancer types [26]. A previous study suggested that overweight or obese individuals exhibited improved prognoses compared to those with normal weight [27]. While another study indicated that both underweight status and extreme obesity at diagnosis are linked to worse survival in patients with NSCLC and SCLC[28]. In our study, which focused on a Chinese NSCLC population receiving first-line immunotherapy combined with chemotherapy, we observed that patients

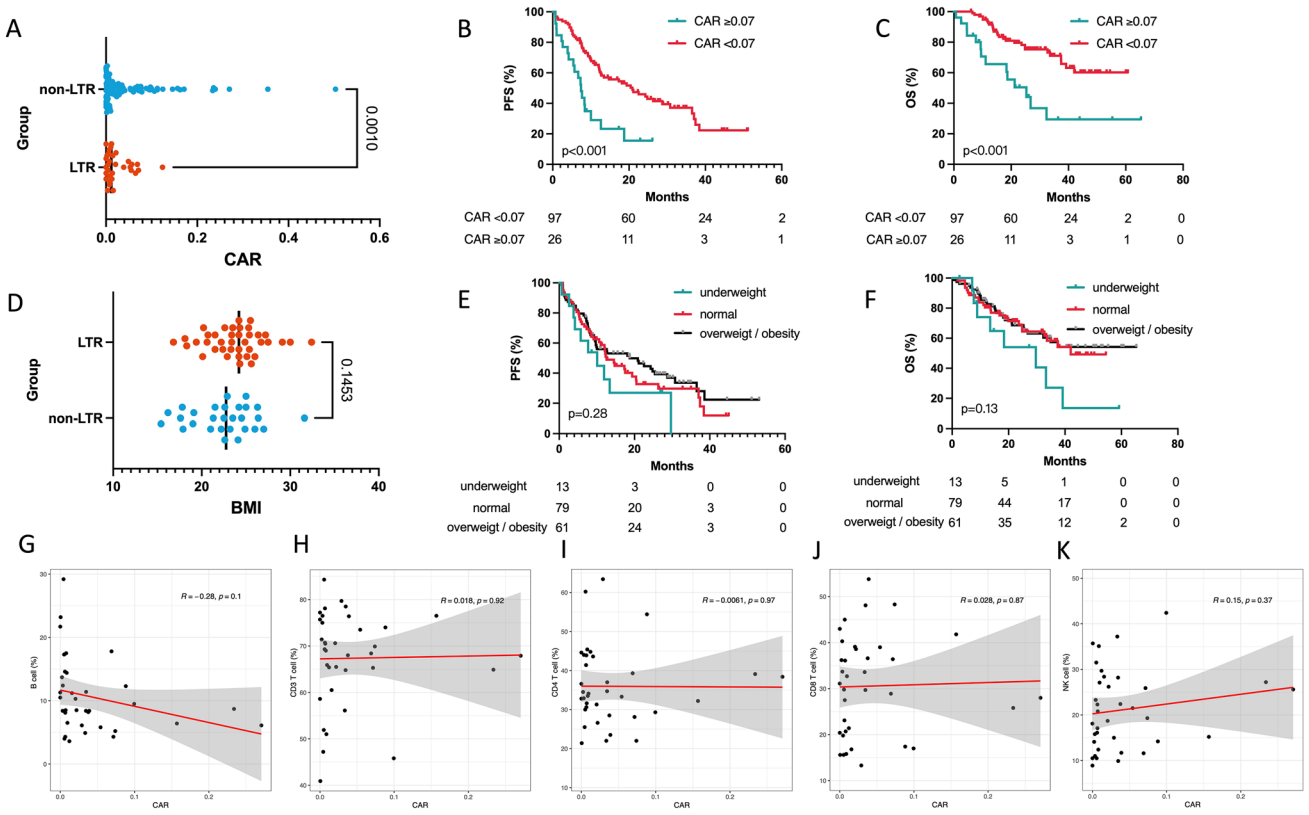

Fig. 4 The prognostic significance of CAR and BMI. **A** The distribution of CAR score in LTR group and non-LTR group. **B** and **C** The Kaplan–Meier curves of PFS and OS of CAR low and high groups. **D** The distribution of BMI in LTR group and non-LTR group. **E** and **F** The Kaplan–Meier curves of PFS and OS of different BMI groups. **G–K** Scatter plots of the correlation between the CAR score and B cell (**G**), CD3+T cell (**H**), CD4+T cell (**I**), CD8+T cell (**J**), and NK cell (**K**). LTR, long term response; CAR, C-reactive protein/albumin ratio; BMI, body mass index; PFS, progression-free survival; OS, overall survival

with BMI ≥ 24 (overweight or obesity) were more likely to achieve LTR, whereas underweight patients (BMI < 18.5) experienced significantly worse OS, which was consistent with previous findings. Another recent study by Ihara et al. proposed that conventional chemotherapy might be a better first-line therapy in patients with advanced NSCLC who are overweight or obesity than ICI treatment [29]. Unlike our study that focused on first-line immunotherapy combined with chemotherapy, Ihara's study included both ICI monotherapy and combination therapy, which may explain why their finding was different from ours.

The ALBI score is a validated metric used to assess liver function and liver reserve capacity based on serum albumin and bilirubin levels, higher score indicates poorer liver function [15]. It has demonstrated robust prognostic value in patients with hepatocellular carcinoma or liver-related diseases [30, 31]. In recent years, the prognostic significance of the ALBI score has been recognized in the context of lung cancer immunotherapy [32, 33]. Our study also reveals that ALBI is an independent adverse predictor of OS survival in NSCLC patients undergoing first-line chemo-immunotherapy, while its value in predicting LTR was not observed. In addition, the factor LIPI score was found to be related to OS but failed to show significance in predicting LTR, which might because only one patient in this study has a LIPI score of 2 (i.e. poor prognosis), others were belonged to good or intermittent prognosis according to LIPI score, which might diminish the predictive value of LIPI [19].

Previous studies have suggested that the proportion of peripheral CD8+T cells is positively correlated with the prognosis of immunotherapy [34, 35]. However, our study did not find prognostic value in CD8+T cells for NSCLC patients. Instead, we found that patients with a peripheral B cell percentage of ≥ 14.5% had a significantly higher likelihood of achieving LTR to immunotherapy. Elevated B cell levels may enhance anti-tumor immunity through antigen presentation, cytokine production, and the formation of tertiary lymphoid structures, which can potentiate the immune response against tumors [36, 37]. Besides, lower peripheral CD4+T cells percentage (< 22%) presented meaningful prognostic significance in predicting worse PFS and OS survival in our study. The result was consistent with the finding of another recent study, which showed high CD4+/total T cells ratio was associated with better response and prognosis

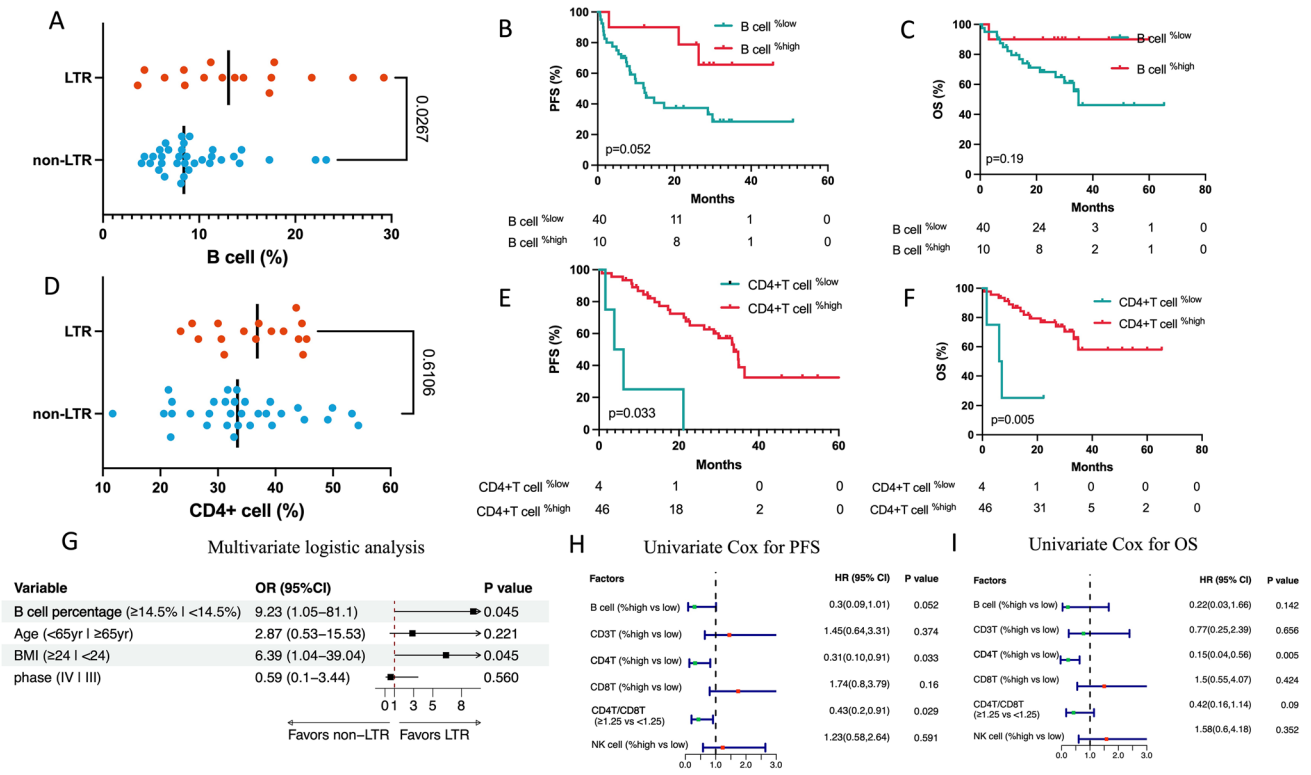

Fig. 5 The predictive value of peripheral lymphocyte subsets. **A** The distribution of B cell percentages in LTR group and non-LTR group. **B** and **C** The Kaplan–Meier curves of PFS and OS of B cell$^{\%high}$ and B cell$^{\%low}$ groups (cutoff: 14.5%). **D** The distribution of CD4+T cell percentages in LTR group and non-LTR group. **E** and **F** The Kaplan–Meier curves of PFS and OS of CD4+T cell$^{\%high}$ and CD4+T cell$^{\%low}$ groups (cutoff: 22%). **G** The association between B cell percentages and LTR after adjusting for age, BMI, and TNM stage. **H** and **I** the forest plot presenting univariate Cox result of peripheral lymphocyte subsets for PFS (**H**) and OS (**I**). LTR, long term response; OR, odds ratio; PFS, progression-free survival; OS, overall survival. Note: the cutoff values of all peripheral lymphocyte subsets here are consistent with those presented in Table 2

in advanced NSCLC receiving chemo-immunotherapy [38]. Unfortunately, in our study, only 4 people has a peripheral CD4+T cell percentage of $<22\%$ and all belonged to non-LTR, we cannot conduct LTR analysis about it. While the optimal cutoff value of 34% still failed to show significant association between CD4+T cell percentage and LTR. Further study should enlarge sample and investigate the association between peripheral CD4+T cell percentage and survival as well as LTR.

Our study also found that patients younger than 65 years were more likely to achieve LTR to immunotherapy. Older patients may benefit less due to immunosenescence, which diminishes the immune system's ability to mount effective responses to tumors [39]. Additionally, early administration of immunotherapy may lead to better survival outcomes. Alejandro et al.'s study also revealed that though any lines of immunotherapy can improve survival in advanced NSCLC, the administration of immunotherapy in the first-line setting was associated with increased survival and was crucial in achieving the greatest responses [40]. This highlights the importance of considering patient age and treatment timing to optimize immunotherapy strategies for NSCLC. On the other hand, our study added up the evidence that patients harboring *TP53* mutation showed poor response to anti-PD-1 plus chemotherapy, which was consistent with previous findings [41]. While the predictive value of *EGFR* mutation and PD-L1 expression failed to show in this study, which might because of the limited relevant data in this study. Besides, the possible reason why PD-L1 expression failed to show its significant value in predicting LTR in patients with NSCLC who received first-line chemo-immunotherapy may due to the heterogeneity of PD-L1 expression within tumors, the dynamic nature of its expression, and the influence of other immunological factors within the tumor microenvironment, as well as the fact that the presence of chemotherapy might interfere and diminish the predictive value of PD-L1 expression.

Additionally, some of previous research revealed the positive relationship between improved outcomes in cancer patients receiving immunotherapy and the occurrence of irAEs, especially the low-grade irAEs [42]. In this study, the tendency of the association between the occurrence of

abnormal ACTH during treatment and LTR was observed, but failed to show significance.

Several limitations existed in this study. Firstly, the total number of cases included and that of achieving LTR were limited, besides as a single-center study, the generalizability of our findings may be compromised. To obtain more reliable and broadly applicable conclusions, future research should involve larger cohorts across multiple centers in China. Additionally, the data on PD-L1 expression, genetic mutation profile, and peripheral blood lymphocyte subsets were relatively sparse. Expanding the sample size in future studies would allow for a more thorough exploration of the relationship between LTR and other characteristics, and may help identify other significant lymphocyte subsets and genetic markers.

Conclusions

In conclusion, this study provides some new insights into the features and predictors significantly associated with LTR and survival in NSCLC patient receiving first-line chemo-immunotherapy, facilitates early detection of patients who could receive LTR in the realm of immunotherapy and bring more benefit for those individuals.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-025-04022-2.

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Author contributions YKS: supervision, conceptualization, funding acquisition, project administration, patient medical decision making and medical care. LLH: data collection, visualization, writing—original draft, writing—review and editing. HHZ: data collection, writing—review and editing; LYD: data collection, writing—review and editing. YF: data collection; XRC, ZCX, LT and XHH: writing—review and editing; XSH, YTL, XZH, LL, HYW, SYZ: patient medical decision making and medical care; JRY: performing peripheral blood lymphocyte subset test and analysis. All authors contributed to manuscript revision and final approval.

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Data availability The cohort in this study can be available upon reasonable request to the corresponding author.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki, was approved by the institutional ethical committee of Cancer hospital, Chinese Academy of Medical Sciences & Peking Union Medical College and written informed consent was obtained from all patients.

Consent for publication Not applicable.

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