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Research Article

Effectiveness and Safety of PD-1 Inhibitors' Treatment for Patients with Non-Small-Cell Lung Cancer in China: A Real-World Study

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Background. In this research, programmed cell death protein 1 (PD-1) inhibitors, including toripalimab, sintilimab, and camrelizumab, were evaluated for the treatment of non-small-cell lung cancer (NSCLC). *Methods*. This retrospective research was conducted on patients with locally advanced and advanced NSCLC receiving various PD-1 inhibitors including toripalimab, sintilimab, and camrelizumab, between April 2019 and March 2023. *Results*. In total, the ORR and DCR of 167 patients included in this research were 40.72% (68/167) and 92.81% (155/167), respectively, while the statistical median PFS was 13.90 months (95% CI, 10.657–17.143), and the median OS was 30.10 months (95% CI, 22.142–38.058). Multifactorial analysis showed that two factors, line of treatment and history of smoking, had a statistically significant benefit on the patients' PFS benefit ($P < 0.05$), while the factor that had a statistically significant benefit on the patients' OS benefit was the presence of serious adverse events (AEs) during treatment. 83.83% and 24.55% of patients experienced any grade AEs and grade 3–5 AEs, respectively. *Conclusions*. In our research, therapy lines and history of smoking had influence on the efficacy of immunotherapy, while serious AEs during treatment were prognostic factors that affected the OS benefit of immunotherapy. Patients we studied did not die from treatment-related causes, and PD-1 inhibitors did not cause additional toxicity in elderly patients. However, further investigations and multicenter studies are needed.

1. Introduction

New data show that lung cancer is a major cause of mortality with almost 2.1 million new cases and 1.8 million deaths in 2020 worldwide [1]. Approximately 85% of lung cancer cases result from non-small-cell lung cancer (NSCLC). The disease was locally advanced or advanced in more than 60% of Chinese patients with NSCLC [2]. At the same time, for patients with stage IIIB/IV NSCLC, the survival rate after 5 years ranged from 13% to 36% and from 0% to 10%, respectively [3]. Fortunately, most patients with locally advanced or advanced NSCLC can benefit from immune checkpoint inhibitors' (ICI) treatments.

Current pivotal studies (Camel, Camel-sq, ORIENT-11, ORIENT-12, and CHOICE-01) have shown that combination chemotherapy with camrelizumab, sintilimab, or

toripalimab significantly improves progression-free survival (PFS) and overall survival (OS) in patients with advanced NSCLC compared to chemotherapy alone [4–8]. The combination treatment programme of camrelizumab, sintilimab, or toripalimab with standard chemotherapy, as the first-line therapy for patients with advanced NSCLC without epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) mutation, was approved by the National Medical Products Administration in China. These treatment regimens had also been included in the Guidelines of Chinese Society of Clinical Oncology (CSCO) [9].

However, randomized controlled trials (RCTs) are known to have strict inclusion criteria to ensure internal stability, which will result in the loss of external scalability. Patients with poor prognosis, such as older patients, or patients with an Eastern Cooperative Oncology Group score ≥2 were rarely included in RCTs [10]. These patients who failed to be included in RCTs tended to have less clinical benefit and were more likely to have a toxic response, so the results of RCTs did not fully reflect real clinical situations. In light of this, the current real-world study was conducted to evaluate the efficacy and safety of the PD-1 inhibitors (camrelizumab, sintilimab, and toripalimab) among Chinese patients with advanced NSCLC and explore the factors which impact the efficacy of PD-1 inhibitors.

2. Methods

2.1. Patients. We retrospectively recorded consecutive locally advanced and advanced NSCLC patients receiving PD-1 inhibitors (camrelizumab, sintilimab, and toripalimab) therapy between April 2019 and March 2023 at a large Class A tertiary Hospital. The inclusion criteria included (1) clinical diagnosis was NSCLC; (2) age ≥18 years; (3) received at least 2 cycles of immunotherapy; (4) at least 1 measurable lung lesion; (5) routine baseline tests must be completed before treatment. Patients were excluded if they were receiving other therapeutic programme of immunotherapy or had other primary tumors. Patients with incomplete medical records would also be excluded.

2.2. Data Collection. The study data were extracted from the Hospital His system, including sex, age, TNM stage, smoking history, pathological type, PD-L1 expression level, driver gene variants, medication regimen of antibiotic during immunotherapy, baseline of immunotherapy, medication regimen of immunotherapy, and adverse events.

2.3. Assessments. Tumor response was assessed according to the iRECIST version 1.1 [11], including progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). The objective response rate (ORR) and the disease control rate (DCR) were the proportion of patients with CR or PR and CR, PR, or SD as the best response, respectively. PFS was calculated from the start of treatment until the date of PD or death from any cause or last follow-up (March 1, 2023). OS was estimated from the start date until death from any cause or last follow-up. Adverse events (AEs) were judged according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [12]. Immune-related adverse events (irAEs) were defined according to the Guidelines of CSCO Management of Toxicity Related to Immune Checkpoint Inhibitor [13].

2.4. Statistical Analyses. The statistical analysis and graphs were generated and plotted using SPSS software (version 26.0) and GraphPad Prism (version 9.0), respectively. Descriptive statistics were used to describe the clinical characteristics of patients. The chi-square test and Fisher's exact probability method (Monte Carlo, MC) were used for counting data. PFS and OS were assessed by the Kaplan–Meier method, with the log-rank test for comparison. Covariates ($P < 0.1$ in univariate analyses) were included in the multivariate analysis, and differences were considered statistically significant at $P < 0.05$.

3. Results

3.1. Baseline Characteristics. A total of 167 patients with NSCLC were included in our research. Demographic characteristics and baseline of the 167 patients are displayed in Table 1. 48 (28.74%), 72 (43.11%), and 29 (17.37%) patients received therapy with camrelizumab, sintilimab, and toripalimab, respectively. Due to the costs and AEs of ICIs, 18 (10.78%) patients changed the types of PD-1 inhibitors.

3.2. Efficacy. All the 167 patients were available for the efficacy assessment. Only one patient in our study presented with CR. Of the 167 patients, there were 67 cases of PR and 87 of SD, for an ORR of 40.72% (68/167) and DCR of 92.81% (155/167). The median PFS (mPFS) and median OS (mOS) for all patients were 13.90 months (95% confidence interval [CI], 10.66–17.14 months) and 30.10 months (95% confidence interval [CI], 22.14-38.06 months), respectively.

All of the factors we evaluated (Table 2) had no significant effect on the clinical benefit of immunotherapy on ORR.

Furthermore, we analyzed the correlation between PFS (Figure 1), OS (Figure 2) and subgroups of baseline characteristics, and the results presented by mPFS and mOS are illustrated in Tables 3 and 4, respectively. In univariate analysis, the factors with the P value less than 0.1 included the presence or absence of serious AEs during immunotherapy, therapy lines, and smoking history. Multivariate analysis identified therapy lines and smoking history as predictors of PFS, while serious AEs were predictors of OS.

We also compared the PFS of 22 patients with EGFR mutation in second or more line therapy and 52 patients without genetic mutations, and there was no difference in PFS (mPFS: 9.9 vs. 14.8 months, $P = 0.870$) or OS (mOS: not reached vs. 28.6 months, $P = 0.631$). In our research, most of the factors serious such as AEs, therapy lines, and smoking history did not significantly influence the PFS or OS of immunotherapy.

Table 1: Baseline characteristics of 167 patients.

Variables	*n* (%)
Ages (years)	
Median age	61.5 (35–83)
≥65	66 (39.52)
Sex	
Male	129 (77.25)
Female	38 (22.75)
Smoking history	
Never-smoker	98 (58.68)
Current or ex-smoker	69 (41.32)
Histology	
Nonsquamous	111 (66.47)
Squamous	56 (33.53)
Genetic mutation	
EGFR	22 (13.17)
ALK	3 (1.80)
KARS	11 (6.59)
Other	16 (9.58)
None	54 (32.34)
Unknown	61 (36.53)
Pathological staging	
III	38 (20.75)
IV	129 (77.25)
Therapy lines	
First-line	107 (64.07)
Posterior-line	60 (35.93)
Presence of treating with antibiotic during immunotherapy	
Yes	54 (32.34)
No	113 (67.66)
Types of PD-1 inhibitors used	
Camrelizumab	48 (28.74)
Sintilimab	72 (43.11)
Toripalimab	29 (17.37)
Camrelizumab, sintilimab	5 (2.99)
Camrelizumab, toripalimab	8 (4.79)
Sintilimab, toripalimab	4 (2.40)
Camrelizumab, sintilimab, and toripalimab	1 (0.60)

3.3. Safety. The occurrence of AEs and irAEs in the patients during immunotherapy is described in Table 5. 140 patients (83.83%) experienced any grade of adverse reactions in total, and 41 patients (24.55%) were observed to have grade 3/4 AEs. No patient had died as a result of treatment in our study. The three most common AEs were anemia (73.05%), white blood cell count decreased (25.15%), and alanine aminotransferase increased (22.16%). Anemia (11.98%) and white blood cell count decreased (5.99%), and neutrophil count also decreased (5.99%); these were discovered to be the three most grade 3/4 of AEs. IrAEs was observed in 19 patients (11.38%), and the most common irAEs were reactive cutaneous capillary endothelial proliferation (RCCEP) which was an adverse reaction unique to camrelizumab.

4. Discussion

We refined the efficacy of camrelizumab, sintilimab, and toripalimab in a real-world clinical setting. The ORR and DCR in this research were 40.72% (68/167) and 92.81% (155/167), respectively. Our results found that the patients with NSCLC receiving ICIs had 13.9 months of mPFS and 30.1 months of mOS. At the same time, the results suggested that smoking history and therapy lines were independent factors for PFS of immunotherapy, and serious AEs were OS-related factors.

According to epidemiological data, smoking was one of the greatest risks by far for developing lung cancer [14]. It is estimated that 75.04% of male lung cancer patients and 18.35% of female lung cancer patients died as a result of smoking [15]. Our results found that the patients without smoking history had a better benefit on PFS rather than those with smoking history. However, majority of studies identified smoking history as positive predictors associated with immunotherapy [16]. The retrospective studies had reported significantly longer PFS and OS in NSCLC smokers receiving ICIs compared to patients with no smoking history [17–20]. Furthermore, compared with heavy smokers, mPFS was numerically shorter in never and light smokers (mPFS 3.0 vs 4.0 vs 5.4 months) [17]. The underlying mechanism which increased efficacy of smokers in immunotherapy was that smoking regulated the immune microenvironment and immunogenicity, inducing high tumor mutational burden (TMB) and positive PD-L1 expression [21, 22]. Both positive PD-L1 expression and TMB had reported to influence on the efficacy of immunotherapy [23]. Interestingly, in previous studies of patients with NSCLC receiving immunotherapy, a trend of better efficacy for chemotherapy in nonsmokers compared to single-agent ICIs' treatment was shown [24, 25]. But when the treatment regimen was changed from ICIs monotherapy to ICIs in combination with chemotherapy, compared with chemotherapy, nonsmokers receiving ICIs in combination with chemotherapy had better efficacy [26, 27]. The reason for this might be that cytotoxic chemotherapy regulated the immune microenvironment resulting in increased efficacy of immunotherapy. Referenced to the Guidelines of CSCO, platinum and paclitaxel analogues are the most commonly used chemotherapy agents. It was showed that platinum-based chemotherapy could increase PD-L1 expression and TMB in tumor cells of NSCLC patients [28]. Furthermore, tumor cells could also be induced by paclitaxel to overexpress PD-L1 via κ pathway [29]. Thus, PD-1 inhibitors might achieve significant therapeutic effects in this situation. Our study also validated this possibility. The majority of patients in our research received combination treatment, and the mPFS had a 5-month extension in patients who had nonsmoking history than those in the smoker group. Overall, PD-1 inhibitors in combination with chemotherapy may be a therapeutic option for nonsmoker with NSCLC in the real world.

It had been reported that the gut microbiome governs the efficacy of immunotherapy [30]. Furthermore, gut microbiome diversity was found to be correlated with the responses to immunotherapy in Chinese patients with NSCLC [31]. The use of antibiotics was considered to be a negative prognostic factor due to the disturbance of the gut microbiome. But this view is still controversial [32–36]. The majority of treatment options were found in the studies in which the use of antibiotics was found to be a prognostic factor for immunotherapy monotherapy [35, 36]. As with research of combination therapy as a treatment option [37],

Table 2: Relationship between patient clinical characteristics and treatment responses.

Variables	OR (95% CI)	P value
Ages (<65 years vs. ≥65 years)	1.259 (0.632, 2.505)	0.513
Smoking history (current or ex-smoker vs. never-smoker)	0.492 (0.235, 1.027)	0.059
Sex (male vs. female)	1.815 (0.746, 4.420)	0.189
Histology (nonsquamous vs. squamous)	1.315 (0.653, 2.645)	0.443
Presence of treating with antibiotic during immunotherapy (yes vs. no)	1.526 (0.617, 2.567)	0.526
Pathological staging (III vs. IV)	0.755 (0.345, 1.653)	0.482
Therapy lines (first-line vs. posterior-line)	0.610 (0.306, 1.216)	0.160
Presence of irAEs (yes vs. no)	0.947 (0.337, 2.658)	0.917
Presence of serious AEs (yes vs. no)	0.872 (0.403, 1.888)	0.728

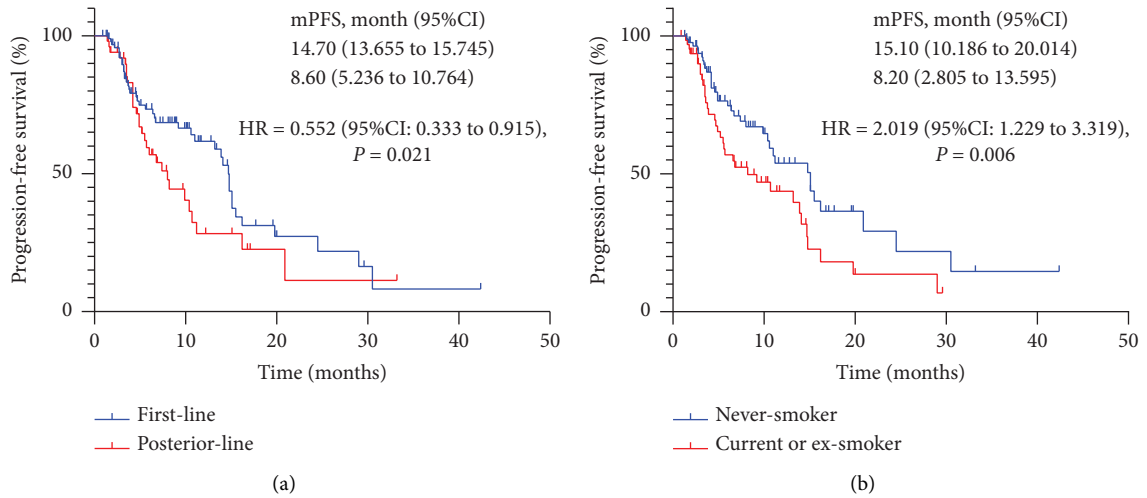

Figure 1: Kaplan–Meier survival curves of PFS by therapy lines (a) and smoking status (b).

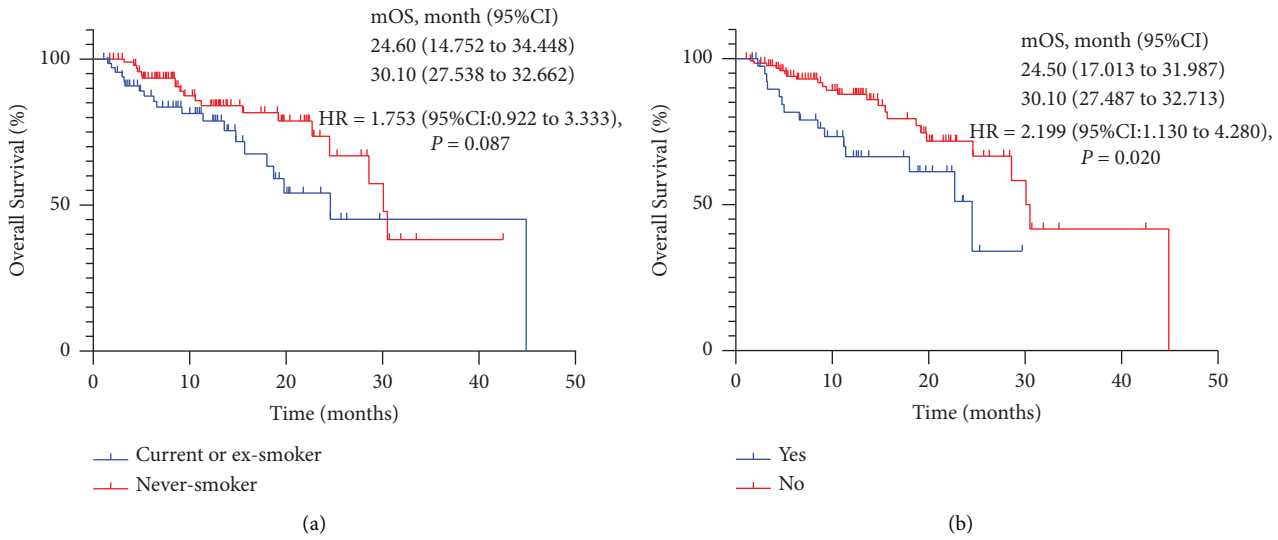

Figure 2: Kaplan–Meier survival curves of OS by smoking status (a) and presence of serious AEs (b).

our study did not demonstrate the differences in the efficacy of ICIs' treatment between patients receiving antibiotic during immunotherapy and those who did not. This might be due to the fact that combination therapy was less dependent on gastrointestinal flora compared with immunotherapy alone, or the negative influence of antibiotics might be compensated by the interaction between cytotoxic chemotherapy and ICIs.

Table 3: Univariate and multivariate analysis of PFS in patients treated with immune checkpoint inhibitors.

Baseline characteristics	Median PFS (95% CI)	*P* value (univariate analysis)	HR (95% CI)	*P* value (multivariate analysis)
Ages (years)		0.250		
<65	13.20 (9.173–17.227)			
≥65	14.80 (10.526–19.074)			
Sex		0.224		
Male	12.10 (7.401–16.799)			
Female	16.20 (13.223–19.177)			
Therapy lines		0.096		
First-line	15.10 (14.567–15.633)		0.604 (0.383–0.955)	0.031
Second or more-line	8.60 (5.248–11.952)			
Smoking history		0.010		
Never-smoker	15.40 (14.114–16.686)		1.976 (1.247–3.133)	0.004
Current or ex-smoker	8.60 (4.161–13.039)			
Histology		0.688		
Nonsquamous	13.20 (9.001–17.399)			
Squamous	14.10 (11.276–16.924)			
Pathological staging		0.323		
III	6.60 (0.000–13.417)			
IV	14.10 (11.589–16.611)			
Presence of treating with antibiotic during immunotherapy		0.754		
Yes	11.20 (6.271–16.129)			
No	14.70 (10.299–19.101)			
Presence of serious AEs		0.749		
Yes	11.20 (2.929–19.471)			
No	14.10 (10.882–17.318)			
Presence of irAEs		0.504		
Yes	15.40 (10.657–17.143)			
No	13.20 (10.191–16.209)			

Table 4: Univariate and multivariate analysis of OS in patients treated with immune checkpoint inhibitors.

Baseline characteristics	Median OS (95% CI)	*P* value (univariate analysis)	HR (95% CI)	*P* value (multivariate analysis)
Ages (years)		0.944		
<65	30.10 (17.525–42.675)			
≥65	28.60 (20.881–36.319)			
Sex		0.454		
Male	30.50 (21.816–39.184)			
Female	28.60 (17.757–39.443)			
Therapy lines		0.643		
First-line	30.10 (22.787–37.413)			
Second or more-line	No reached			
Smoking history		0.067		
Current or ex-smoker	24.60 (14.752–34.448)		1.753 (0.922–3.333)	0.087
Never-smoker	30.10 (27.538–32.662)			
Histology		0.166		
Nonsquamous	28.60 (22.304–34.896)			
Squamous	30.10 (20.205–39.995)			
Pathological staging		0.323		
III	30.10 (18.009–42.191)			
IV	28.60 (22.700–34.500)			
Presence of treating with antibiotic during immunotherapy		0.622		
Yes	28.60 (22.352–34.848)			
No	30.10 (18.092–42.108)			
Presence of serious AEs		0.014		
Yes	24.50 (17.013–31.987)		2.199 (1.130–4.280)	0.020
No	30.10 (27.487–32.713)			
Presence of irAEs		0.839		
Yes	24.60 (19.453–29.747)			
No	30.10 (27.698–32.502)			

Table 5: Treatment-related adverse events.

Adverse reactions	Total (*N*, %)	Grade 1-2 (*N*, %)	Grade ≥3 (*N*, %)
Any AEs	140 (83.83)	99 (59.28)	41 (24.55)
Anemia	122 (73.05)	102 (61.08)	20 (11.98)
White blood cell count decreased	42 (25.15)	32 (19.16)	10 (5.99)
Neutrophil count decreased	32 (19.16)	22 (13.17)	10 (5.99)
Platelet count decreased	19 (11.38)	13 (7.78)	6 (3.59)
Creatinine elevation	33 (19.76)	33 (19.76)	0 (0.00)
Alanine aminotransferase increased	37 (22.16)	34 (20.36)	3 (1.80)
Aspartate aminotransferase increased	14 (8.38)	13 (7.78)	1 (0.60)
Rash	6 (3.59)	6 (3.59)	0 (0.00)
Pruritus	7 (4.19)	7 (4.19)	0 (0.00)
Pyrexia	11 (6.59)	11 (6.59)	0 (0.00)
Hypothyroidism	3 (1.80)	3 (1.80)	0 (0.00)
Hyperthyroidism	5 (2.99)	5 (2.99)	0 (0.00)
Any irAEs	19 (11.38)	11 (6.59)	8 (4.79)
RCCEP	10 (5.99)	5 (2.99)	5 (2.99)
ICI-induced pneumonitis	6 (3.59)	4 (2.40)	2 (1.20)
ICI-induced immune mediated hepatitis	1 (0.60)	1 (0.60)	0 (0.00)
ICI-associated cardiotoxicity	2 (1.20)	2 (1.20)	0 (0.00)
ICI-induced gastrointestinal toxicity	1 (0.60)	0 (0.00)	1 (0.60)
ICI-induced endocrinopathy	1 (0.60)	1 (0.60)	0 (0.00)
ICI-induced myositis	1 (0.60)	1 (0.60)	0 (0.00)

Unlike other studies [38–41], we did not find that EGFR mutation was a prognostic factor affecting the efficacy of immunotherapy. This might be caused by two reasons. Firstly, the PD-L1 expression of patients was not detected, while high expression of PD-L1 was found to be associated with increased efficacy in patients with EGFR mutations in second-line treatment [38]. Secondly, the mutated patients in our study all received ICIs in combination with chemotherapy with or without antiangiogenic agents, both of which were of greater benefit to patients with EGFR mutations compared with immunotherapy monotherapy [42, 43].

As with other studies [44–47], we did not observe the differences in PFS and OS between patients with nonsquamous and squamous. Pathological staging was not a prognostic factor affecting the efficacy of immunotherapy. We examined that there were no differences in PFS and OS between young patients and old patients (mPFS: 13.20 vs. 14.80 months, $P = 0.250$; mOS: 30.10 vs. 28.60 months, $P = 0.944$). In a retrospective study that included 11,157 individuals with cancer, those elder patients had better benefit [48]. However, based on alternative real-world data, the mPFS (4.8 vs. 3.3 months, $P = 0.159$) and mOS (12.3 vs. 13.0 months, $P = 0.559$) was similar between the younger and elderly groups [49]. Overall, all the above studies indicated that advanced age was not a risk factor for the efficacy of immunotherapy. PD-1 inhibitors might be an acceptable treatment option for elderly patients with NSCLC. Furthermore, the differences in safety between the 66 elder patients and 101 younger patients in our study were also presented in this study (Table 6). We found that there were no differences in the incidence of any AEs and irAEs between the elder and younger patients, which had also been reported in other real-world studies [50–52], implying that there was no additional toxicity in elderly patients receiving PD-1 inhibitors. However, the prognosis of older patients with irAEs was poorer. These patients required systemic steroids for a longer period of time in the events of irAEs, as well as ICIs were discontinued due to irAEs higher among older patients compared with younger patients [53, 54].

Neither univariate nor multivariate analyses found differences in the efficacy of immunotherapy between patients with or without irAEs in our study. Unlike our findings, other research studies had shown that the presence of irAEs correlated with ICI efficacy, and patients with irAEs had a greater benefit from ICI treatment than those who did not appear irAEs [55–57]. For the patients with cancer, the presence of irAEs was associated with the better efficacy of ICIs; however, gastrointestinal, pulmonary, and hepatobiliary irAEs were not significantly associated with a favorable PFS [58, 59]. In our study, eight of the 19 patients with irAEs experienced such irAEs which were not associated with the favorable PFS and seven patients discontinued PD-1 inhibitors because of irAEs. These two reasons might have led to a lack of difference in PFS and OS benefit between patients with or without irAEs in our study. It was worth noting that the duration of treatment with ICIs was a risk factor for the occurrence of multisystem irAEs, with the greater the number of times the patients received ICIs, the greater the risk of irAEs [56]. Therefore, for the patients who had received irAEs, it is necessary to closely monitor the reoccurrence of irAEs if they choose to continue treatment with PD-1 inhibitors. Furthermore, we found that PD-1 inhibitors applied in first-line treatment had a better benefit on PFS than in posterior-line treatment. This was in line with the findings of the two prospective studies KEYNOTE-189 and KEYNOTE-407 [60, 61], where the immunotherapy group showed a greater benefit on PFS2 than the chemotherapy group. PFS decreased with the increasing number of previous therapy lines [56]. Thus, we recommend PD-1 inhibitors that should be used first-line for the patients with advanced NSCLC.

Table 6: Differences in the incidence of AEs between the elder and younger patients.

Type of AEs	Age <65 years $N = 101$ (%)	Age ≥65 years $N = 66$ (%)	P
Total AEs	86 (85.15)	54 (81.82)	0.568
Serious AEs	26 (25.74)	15 (22.73)	0.658
irAEs	10 (9.90)	9 (13.64)	0.457

Among the many factors, we identified the occurrence of serious AEs during treatment as a prognostic factor affecting the OS benefit of NSCLC patients. Patients who experienced serious AEs during treatment had a shorter benefit in OS than those who did not experience serious AEs during treatment. This might be caused by the type of serious AEs that occurred in the patients. Anemia was the most common serious AEs in our study, with 48.78% of patients experiencing severe anemia. In contrast, the occurrence of tumor-associated anemia was found to be an influential factor in the OS of cancer patients, with patients without anemia having longer OS compared to those presenting anemia. The effect increases with anemia grade, with shorter OS in grades 3 and 4 anemia compared to grades 1 and 2 anemia [62, 63].

This study has some limitations. The major limitations of this retrospective research included the small sample size; only 167 patients were included for analysis. In addition, more than half of the patients did not receive genetic testing and PD-L1 testing due to the cost of tests. Lastly, the follow-up period was not long enough to obtain data on OS in all subgroups. Therefore, follow-up studies could further expand the sample size and supplement the efficacy evaluation as well as the safety evaluation of these three domestic PD-1 inhibitors.

5. Conclusion

According to our study, patients without history of smoking or using PD-1 as the first-line therapeutic agent had better efficacy benefit in PFS, while patients who did not receive serious AEs had better efficacy benefit in OS. Therefore, our study may provide a reference for clinical use.

Data Availability

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

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Wan Ning, Chen Yongbang, and Lu Liqing contributed equally to this work.

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