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Comparison of survival outcomes between clinical trial participants and non-participants of patients with advanced non-small cell lung cancer: A retrospective cohort study

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ABSTRACT

Background: Clinical trials for advanced non-small cell lung cancer (NSCLC) have been conducted extensively. However, the effect of participation in clinical trials on survival outcomes remains unclear. This study aimed to assess whether participation in clinical trials was an independent prognostic factor for survival in patients with advanced NSCLC.

Methods: We analyzed the medical records of patients aged ≥18 years who were newly diagnosed with stage IIIB or IV NSCLC and received chemotherapy or immunotherapy from September 2016 to June 2020 in this retrospective cohort study. To reduce the impact of confounding factors, propensity score matching (PSM) was performed. The Kaplan-Meier method and log-rank test were used to calculate and compare the overall survival (OS) and progression-free survival (PFS) of the patients. Finally, Cox proportional hazards regression was employed to examine the correlation between clinical trial participation and survival outcomes.

Results: The study enrolled 155 patients in total, of which 62 (40.0 %) patients participated in NSCLC clinical trials. PSM identified 50 pairs of patients in total. The median PFS and OS of clinical trial participants and non-participants were 17.2 vs. 13.9 months ($p = 0.554$) and 32.4 vs. 36.5 months ($p = 0.968$), respectively. According to the results of multivariate Cox proportional hazards regression analysis, clinical trial participation was not an independent prognostic factor for advanced NSCLC patients (*HR*: 0.89, 95 % *CI*: 0.50–1.61; $p = 0.701$).

Conclusions: The clinical trial participants with advanced NSCLC displayed similar survival outcomes compared with the non-participating patients in this cohort.

1. Introduction

Lung cancer is the leading cause among all cancer-related deaths globally [1]. For example, the World Health Organization reported over 820,000 new cases of lung cancer and over 710,000 related death cases in China in 2020, accounting for 17.9 % of the total newly diagnosed cancer cases and 23.8 % of all cancer-related deaths, ranking the first among all cancers [2]. Statistically, 80%–85 % of lung cancers are non-small cell lung cancer (NSCLC), and about 75 % of NSCLC patients are in the advanced stages at their first diagnosis, making the medical treatment of NSCLC in high demand [3–5].

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In recent years, rapid development has been seen in the research and treatment of NSCLC, including the applications of immunotherapy and targeted therapy [6]. However, advanced NSCLC still has a poor prognosis, with a 5%–26 % 5-year survival rate [7–9]. Hence, the need for ongoing research and the evaluation of novel therapies to lessen the disease burden remains urgent. In 2020, 722 anti-cancer drug trials were registered in China, and 108 (15.0 %) were anti-lung cancer drugs, ranking the second among those on solid tumors [10]. Meanwhile, among the 1595 registered clinical trials of anti-lung cancer drugs from 2005 to 2020 in mainland China, 1254 (78.6 %) were on NSCLC [11].

Whether participation in a clinical trial benefits survival outcomes is important information for both physicians and patients when making decisions on the enrollment. It is generally believed that participation in clinical trials may benefit the patients in a variety of ways, such as early access to novel therapies or medications, improved observations, or adjustments in the behaviors of patients or investigators as a consequence of being observed [12]. Several studies have shown that participation in clinical trials prolonged survival time in various advanced cancers such as glioblastoma, melanoma, and gastric carcinoma [13–15]. However, it remained controversial that how clinical trial participation affects the survival outcomes of patients with advanced NSCLC. Some evidence indicated that participating in such clinical trials showed improved prognosis [16], while other studies failed to observe better outcomes compared to those outside the trials [17,18]. It has been noticed that most of these studies did not take sources of bias sufficiently into account by applying appropriate statistical methods, or were based on data obtained before 2010.

Therefore, we aimed to compare the survival outcomes between clinical trial participants and non-participants in patients with advanced NSCLC. Cohort data from recent years was used to represent current clinical trials, and the statistical method of propensity score matching (PSM) was performed to eliminate the impacts of potential confounding factors.

2. Methods

2.1. Study population

In this retrospective cohort study, we analyzed the medical records of patients who were newly diagnosed with advanced NSCLC and received chemotherapy or immunotherapy from September 2016 to June 2020 at Chongqing University Cancer Hospital. The sample size was the total number of patients during this period. The following were the inclusion criteria: (1) NSCLC was confirmed histologically or cytologically; (2) the patients were initially diagnosed as stage IIIB or IV NSCLC according to the staging system of the American Joint Committee on Cancer (AJCC); (3) the patients were not younger than 18 years; (4) medical records and follow-up data were complete; (5) the patients had received no fewer than one cycle of chemotherapy or immunotherapy. The exclusion criteria were: (1) the patients had received radiation therapy or targeted therapy; (2) the Eastern Cooperative Oncology Group (ECOG) performance status (PS) was higher than 1 or Karnofsky performance status (KPS) was lower than 70. A total of 155 patients were included in the

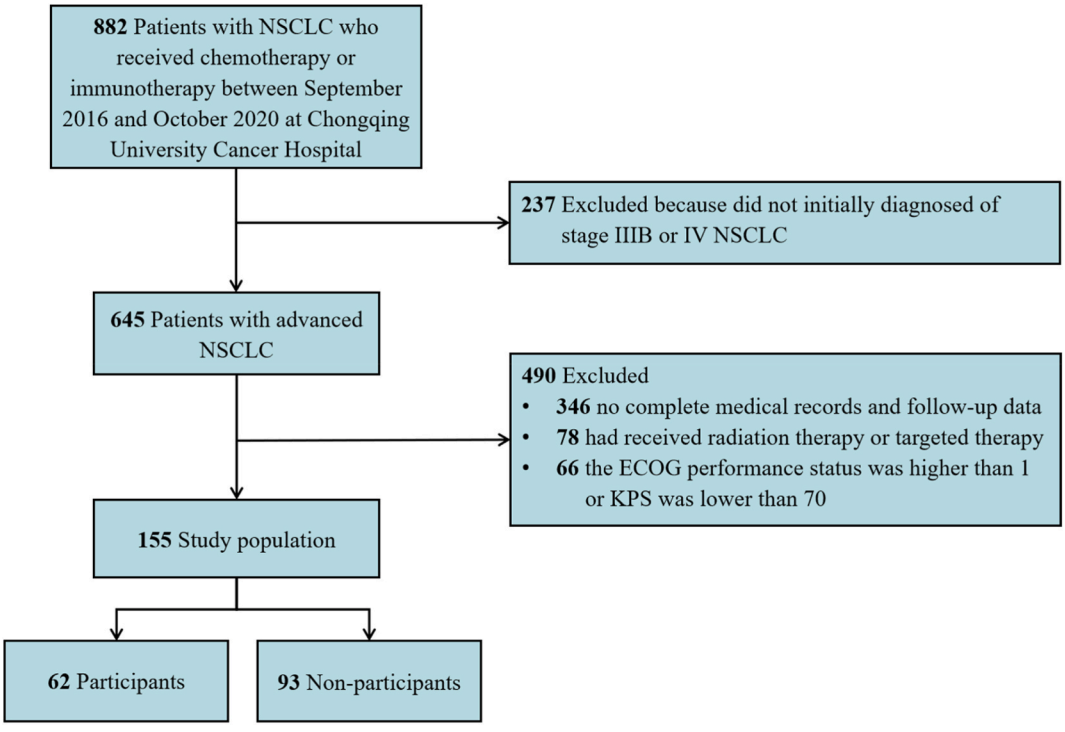

Fig. 1. The flow diagram of the study population included in the analysis.
Abbreviations: NSCLC, non-small cell lung cancer; ECOG, the Eastern Cooperative Oncology Group; KPS, Karnofsky performance status.

study (Fig. 1).

The Ethics Committee of Chongqing University Cancer Hospital had approved this study (protocol number: CZLS2016023-A). All patients provided written informed consent for the analysis and anonymous publication of clinical data.

2.2. Data collection and variable definitions

The baseline data of patients, including age, gender, smoking history, tumor stage, histology type, imaging examination, tumor metastasis, comorbidities, and therapy status, were collected. We also measured the baseline sum of longest diameters (BSLD) using computed tomography (CT) or magnetic resonance imaging (MRI) in accordance with RECIST version 1.1 [19,20]. Tumor size was defined as the maximum diameter measured with the chest CT [21].

Overall survival (OS) was measured from the beginning of anti-tumor therapy to death or the final follow-up visit. The time between the start of anti-tumor therapy and disease progression, the final follow-up visit, or death was defined as progression-free survival (PFS). Every three months after completing the therapy, we conducted telephone interviews and follow-up visits with patients to assess disease progression or survival status. Patients with missing follow-up data or without disease progression until the end of the study were regarded as having censored values. The follow-up period ceased on October 27, 2022.

2.3. Statistical analysis

For descriptive analysis, the median, 95 % confidence interval (CI), and interquartile range (IQR) for continuous variables (skewed distribution) and numbers (ratios) for categorical variables were calculated. To compare the baseline characteristics between participants and non-participants, the Chi-square test, Fisher's exact test, or Kruskal-Wallis test were conducted. To minimize the impact of confounding factors related to clinical trial participation and survival outcomes, PSM was performed to adjust the baseline characteristics of patients. Logistic regression analysis was employed to obtain the propensity scores. Then, we used the nearest available neighbor algorithm with a 1:1 matching ratio to perform PSM. To counteract potential selective bias, the caliper was set at 0.15. The OS

Table 1
Differences in baseline characteristics between clinical trial participants and non-participants.

Characteristics	Total population [*n* (%)]				Propensity-matched population [*n* (%)]			
	Total (*n* = 155)	Participants (*n* = 62)	Non-participants (*n* = 93)	*p*	Total (*n* = 100)	Participants (*n* = 50)	Non-participants (*n* = 50)	*p*
Age (years) [Median (IQR)]	59.0 (52.0–66.0)	60.5 (52.8–67.0)	59.0 (50.0–66.0)	0.219	61.0 (52.0–66.0)	61.0 (52.0–67.0)	60.5 (52.0–66.0)	0.707
Gender				0.945				1.000
Male	103 (66.4)	41 (66.1)	62 (66.7)		70 (70.0)	35 (70.0)	35 (70.0)	
Female	52 (33.6)	21 (33.9)	31 (33.3)		30 (30.0)	15 (30.0)	15 (30.0)	
Smoking history				0.689				0.534
Yes	92 (59.4)	38 (61.3)	54 (58.1)		63 (63.0)	33 (66.0)	30 (60.0)	
No	63 (40.7)	24 (38.7)	39 (41.9)		37 (37.0)	17 (34.0)	20 (10.0)	
Stage				0.103				0.249
IIIB	21 (13.6)	5 (8.1)	16 (17.2)		14 (14.0)	5 (10.0)	9 (18.0)	
IV	134 (86.4)	57 (91.9)	77 (82.8)		86 (86.0)	45 (90.0)	41 (82.0)	
Histology type				**0.002**				0.064
AC	113 (72.9)	42 (67.7)	71 (76.3)		74 (74.0)	33 (66.0)	41 (82.0)	
SCC	37 (23.9)	20 (32.3)	17 (18.3)		25 (25.0)	17 (34.0)	8 (16.0)	
Other	5 (3.2)	0	5 (5.4)		1 (1.0)	0	1 (2.0)	
BSLD (mm) [Median (IQR)]	55.0 (34.0–76.0)	68.5 (50.8–92.5)	41.0 (31.0–66.5)	<**0.001**	59.5 (40.0–80.8)	61.5 (44.0–85.0)	53.0 (37.0–73.3)	0.057
Tumor size (cm) [Median (IQR)]	4.0 (2.8–5.3)	4.5 (3.0–5.9)	3.6 (2.7–5.1)	**0.027**	4.1 (2.8–5.4)	4.3 (2.8–5.8)	3.4 (2.8–5.3)	0.464
Metastasis				0.074				0.161
Yes	133 (85.8)	5 (8.1)	17 (18.3)		85 (85.0)	45 (90.0)	40 (80.0)	
No	22 (14.2)	57 (91.9)	76 (81.7)		15 (15.0)	5 (10.0)	10 (20.0)	
Comorbidity				1.000				0.817
Yes	120 (77.4)	48 (77.4)	72 (77.4)		75 (75.0)	38 (76.0)	37 (74.0)	
No	35 (22.6)	14 (22.6)	21 (22.6)		25 (25.0)	12 (24.0)	13 (26.0)	
Surgical treatment				0.424				0.485
Yes	19 (12.3)	6 (9.7)	13 (14.0)		9 (9.0)	6 (12.0)	3 (6.0)	
No	136 (87.7)	56 (90.3)	80 (86.0)		91 (91.0)	44 (88.0)	47 (94.0)	
First-line cycles				<**0.001**				0.372
1–2	55 (35.5)	11 (17.7)	44 (47.3)		28 (28.0)	11 (14.0)	17 (34.0)	
3–4	71 (45.8)	33 (53.2)	38 (40.9)		52 (52.0)	29 (58.0)	23 (46.0)	
≥5	29 (18.7)	18 (29.0)	11 (11.8)		20 (20.0)	10 (20.0)	10 (20.0)	
Second-line therapy				**0.007**				0.407
Yes	102 (65.8)	33 (53.2)	69 (74.2)		66 (66.0)	26 (52.0)	40 (80.0)	
No	53 (34.2)	29 (46.8)	24 (25.8)		34 (34.0)	24 (48.0)	10 (20.0)	

Abbreviations: IQR, interquartile range; AC, adenocarcinoma; SCC, squamous cell carcinoma; BSLD, baseline sum of longest diameters.

and PFS between the two groups were calculated and compared using the Kaplan-Meier method and log-rank test. Variables significantly associated with OS or PFS in the univariate Cox proportional hazards analysis at the level of p-value <0.05 were included in the multivariate Cox regression model, controlling for other confounding factors. P-values <0.05 were regarded as having statistical significance in this study. R software version 4.2.1 (https://www.r-project.org/) was used for statistical calculation and analysis.

3. Results

3.1. Sample characteristics

Among the 155 eligible patients, the median age was 59.0 (IQR, 52.0–66.0) years, 103 (66.4 %) were males, and 62 (40.0 %) had participated in NSCLC clinical trials. Most patients (92, 59.4 %) had smoking histories. The majority of them were initially diagnosed with stage IV NSCLC (134, 86.4 %), had adenocarcinoma histology (113, 72.9 %), metastases (133, 85.8 %) or comorbidities (120, 77.4 %), and were not treated with surgery (136, 87.7 %). Of the 155 patients, 55 (35.5 %) received 1–2 cycles of first-line therapy, and 71 (45.8 %) received 3–4 cycles of first-line therapy. The median BSLD and tumor size were 55.0 mm and 4.0 cm, respectively. About two-thirds of patients (102, 65.8 %) received second-line therapy (Table 1).

A total of 10 clinical trials were included in this study, all of which were multi-center, randomized, phase III NSCLC clinical trials. Most of the studies were double blind (7, 70.0 %) and enrolled ≥5 patients (6, 60.0 %) (Table 2).

The results showed disparities in certain characteristics between the two groups, including the histology type ($p = 0.002$), BSLD ($p < 0.001$), tumor size ($p = 0.027$), cycles of first-line therapy ($p < 0.001$), and second-line therapy status ($p = 0.007$). PSM identified 50 pairs of patients in total, and all baseline characteristics were well balanced.

3.2. Kaplan-Meier survival analysis

There was no significant difference in median PFS or OS between participants and non-participants (median PFS: 17.2 vs. 13.9 months, $p = 0.554$; median OS: 32.4 vs. 36.5 months, $p = 0.968$), as indicated in Table 3 and Fig. 2 (a & b). The 1-year, 3-year, and 5-year survival rates were 76.0 %, 24.0 %, and 24.0 %, respectively, for the participant group and 90.0 %, 38.0 %, and 24.0 %, respectively, for the non-participant group (Table 3).

3.3. Cox proportional hazards regression analysis

Table 4 summarizes the findings of the univariate and multivariate Cox proportional hazards regression models among the propensity-matched population. In the multivariate analyses, patients diagnosed with adenocarcinoma were associated with a better prognosis (*HR*: 0.11, 95 % *CI*: 0.01–0.95; $p = 0.044$), and those who did not have surgical treatments (*HR*: 4.98, 95 % *CI*: 1.06–23.41; p

Table 2
Summary of NSCLC clinical trials that were included in this study ($n = 10$).

Characteristics	*n* (%)
Year of start-up	
2017	3 (30.0)
2018	4 (40.0)
2019	1 (50.0)
2020	2 (20.0)
Phase	
Phase III	10 (100)
Others	0 (0)
Allocation	
Randomized	10 (100)
Non-randomized	0 (0)
Masking	
Open label	3 (30.0)
Single blind	0 (0)
Double blind	7 (70.0)
Study site	
Single center	0 (0)
Multi-center	10 (100)
Histology type	
Squamous	3 (30.0)
Non-squamous	3 (30.0)
All	4 (40.0)
Number of patients enrolled	
<5	4 (40.0)
≥5	6 (60.0)

Abbreviations: NSCLC, non-small cell lung cancer.

Table 3
Survival outcomes of clinical trial participants and non-participants were compared.

Survival outcomes	Participants ($n = 50$)	Non-participants ($n = 50$)	p
Median PFS (months)	17.2	13.9	0.554
Median OS (months)	32.4	36.5	0.968
1-year survival (%)	76.0	90.0	0.062
3-year survival (%)	24.0	38.0	0.130
5-year survival (%)	24.0	24.0	1.000

Abbreviations: PFS, progression-free survival; OS, overall survival.

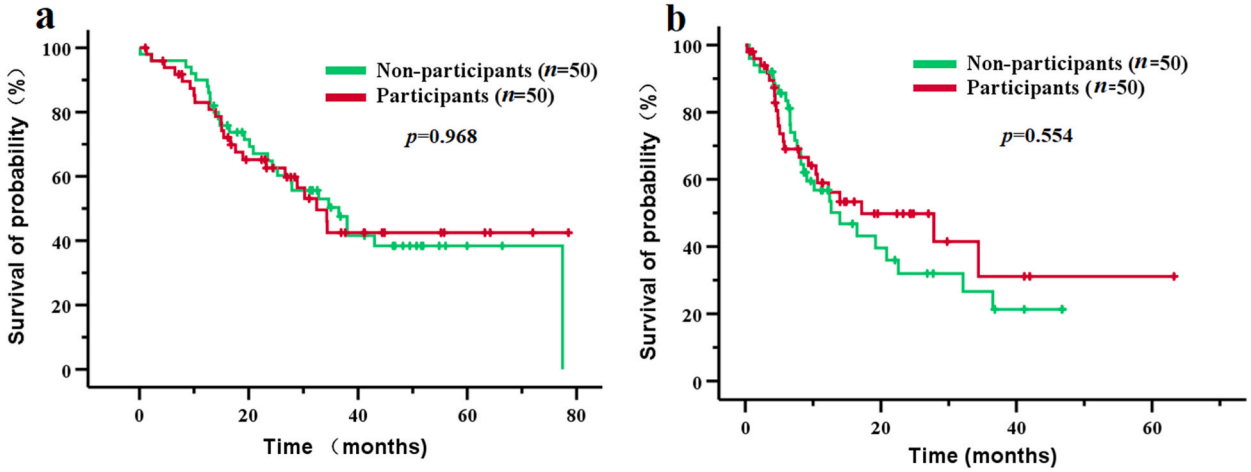

Fig. 2. Comparison of **(a)** overall survival (OS) and **(b)** progression-free survival (PFS) for those who participated and did not participate in trials ($n = 100$).

$= 0.042$) or received 1–2 (*HR*: 3.91, 95 % *CI*: 1.38–11.12; $p = 0.011$) or 3–4 (*HR*: 3.35, 95 % *CI*: 1.22–9.24; $p = 0.019$) cycles of first-line therapy were related to lower odds of survival in patients with advanced NSCLC. No surgical treatment was also found to be a risk factor for disease progression (*HR*: 5.29, 95 % *CI*: 1.25–22.36; $p = 0.024$). Participation in clinical trials was not a predictor of PFS (*HR*: 0.92, 95 % *CI*: 0.51–1.63; $p = 0.767$) or OS (*HR*: 0.89, 95 % *CI*: 0.50–1.61; $p = 0.701$) in the multivariate analysis.

Table 4
Factors related to overall survival and progression-free survival among advanced NSCLC patients were examined in univariate and multivariate analyses ($n = 100$).

Variables	Overall survival				Progression-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95 % *CI*)	p	*HR* (95 % *CI*)	p	*HR* (95 % *CI*)	p	*HR* (95 % *CI*)	p
Did not participate in trials	1.01 (0.58–1.76)	0.968	0.89 (0.50–1.61)	0.701	1.18 (0.68–2.06)	0.555	0.92 (0.51–1.63)	0.767
Age	1.01 (0.98–1.04)	0.630			1.00 (0.97–1.03)	0.818		
Male	1.83 (0.96–3.50)	0.068			2.09 (1.09–4.01)	0.026	1.97 (0.97–3.98)	0.060
Have smoking history	1.37 (0.76–2.47)	0.291			1.75 (0.97–3.16)	0.063		
IV stage	0.99 (0.45–2.21)	0.983			1.12 (0.50–2.50)	0.778		
AC	0.09 (0.01–0.70)	0.022	0.11 (0.01–0.95)	**0.044**	0.29 (0.04–2.15)	0.224		
SCC	0.13 (0.02–1.04)	0.055	0.12 (0.01–1.01)	0.051	0.43 (0.06–3.28)	0.425		
BSLD	1.01 (1.01–1.02)	0.017	1.01 (0.99–1.02)	0.090	1.01 (1.01–1.02)	0.028	1.01 (0.99–1.02)	0.207
Tumor size	1.01 (1.00–1.03)	0.058			1.01 (0.99–1.02)	0.193		
Metastasis	1.03 (0.46–2.28)	0.951			1.17 (0.53–2.61)	0.699		
Have any comorbidities	1.50 (0.75–3.00)	0.252			1.38 (0.71–2.70)	0.341		
Did not have surgical treatment	5.22 (1.08–25.09)	0.039	4.98 (1.06–23.41)	**0.042**	5.39 (1.29–22.59)	0.021	5.29 (1.25–22.36)	**0.024**
1-2 cycles of first-line therapy	3.68 (1.35–10.08)	0.011	3.91 (1.38–11.12)	**0.011**	3.24 (1.19–8.86)	0.022	2.75 (0.98–7.72)	0.055
3-4 cycles of first-line therapy	3.42 (1.32–8.86)	0.011	3.35 (1.22–9.24)	**0.019**	2.77 (1.07–7.17)	0.036	1.92 (0.70–5.23)	0.205
Did not have second-line therapy	1.57 (0.88–2.81)	0.124			1.19 (0.67–2.12)	0.554		

Abbreviations: NSCLC, non-small cell lung cancer; HR, hazards ratio; AC, adenocarcinoma; SCC, squamous cell carcinoma; BSLD, baseline sum of longest diameters.

4. Discussion

The number of treatment options for advanced NSCLC is rapidly increasing with the emergence of immunotherapy and targeted therapy. There are thousands of registered clinical trials for lung cancer each year, but only 5 % of new drugs have successfully gone through the process from early-stage studies to clinical practice [6]. Therefore, exploring and identifying the prognostic effect of clinical trial participation is important for clinical decision-making.

In this retrospective cohort study, after balancing the baseline characteristics, we demonstrated that participating or not participating in clinical trials appeared to result in similar survival outcomes in advanced NSCLC patients. This finding was consistent with two recent studies among patients with advanced NSCLC [12,18]. In a multi-center retrospective study conducted in China, after adjusting the baseline characteristics, there was no statistically significant difference in the PFS and OS of patients with advanced NSCLC who were treated with PD-1/PD-L1 inhibitors, either in the real world or in clinical studies [18]. Nevertheless, in a cohort study that enrolled 1042 advanced NSCLC patients, Arrieta et al. [16] found a positive correlation between clinical trial enrollment and OS. The disparities in these studies may be caused by variances in the study design, measurements, ethnicity, treatment regimens, clinicopathological characteristics, *etc*. Importantly, the imbalanced baseline characteristics of the two groups being compared may also influence the results. Patients who were selected for clinical trials tend to be younger, have better health status, and have received normative treatments. Therefore, we conducted the PSM method to eliminate the effects of potential confounding factors in order to improve the reliability of the results.

We also observed that patients who were diagnosed with adenocarcinoma were associated with better prognosis, and those who did not have surgical treatments or received fewer cycles of first-line therapy were related to lower odds of survival in patients with advanced NSCLC. These findings were similar to those in previous studies [22–25].

The reasons for patients with advanced cancers to participate in clinical trials are complex and multi-factorial, such as subject to new treatments, hopes of personal therapeutic benefit, financial provisions, meticulous follow-up, extra medical attention, altruism in contributing to medical progress, *etc* [26,27]. Some cancer patients even have unrealistic hopes for possible gain and high expectations concerning clinical trial benefits [28]. Studies have shown that approximately 50%–70 % of NSCLC patients were willing to participate in trials. But only about 2%–8% of patients were enrolled in clinical trials [29,30]. On the one hand, clinical trials were conducted only in qualified institutions. Thus, trials may not be available in a real-world setting for patients who are willing to participate. In addition, patients were often excluded because of the strict inclusion criteria.

Our study provided clinical insights for those who need to evaluate the trade-offs of advanced NSCLC clinical trial enrollment. The findings of this study could be helpful for the clinical decision-making of patients. In addition, it is important to highlight that although we did not find the direct positive effect of survival in the clinical trial participants, patients still received various collateral benefits brought by participation, such as meticulous care, financial subsidies, *etc*. In a trial recruitment context, it is essential that clinicians better inform patients about the benefits and drawbacks of clinical trial participation.

Nonetheless, the following limitations remained in this study: Firstly, it was a retrospective study with a small sample size that was conducted at one institution. We used PSM to minimize potential selection bias, but it also reduced the sample size at the same time. Secondly, this study focused on advanced NSCLC patients who received chemotherapy or immunotherapy, and thus the generalizability of our findings was limited.

To our knowledge, this is the first study in China which employed the PSM methodology to examine the association between clinical trial participation and survival outcomes in advanced NSCLC patients. In conclusion, participation in clinical trials was not an independent factor in patients prognosis. Comprehensive analyses in large-scale multi-center prospective cohort studies will be required to validate our findings in the future.

Ethics statement

This study was reviewed and approved by the Ethics Committee of Chongqing University Cancer Hospital, with the approval number: CZLS2016023-A. All participants provided informed consent to participate in the study.

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Data availability statement

The data associated with the study has not been deposited into a publicly available repository. Data will be made available on request.

CRediT authorship contribution statement

Qingqing Jiang: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xiaolin Yue:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Haike Lei:** Writing – review & editing, Methodology, Investigation, Data

curation. **Weiran Mao:** Writing – review & editing, Methodology, Investigation, Data curation. **Yongsheng Li:** Writing – review & editing, Formal analysis. **Xia Chen:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Reports a relationship with that includes:. Has patent pending to. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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