Meta-analysis of the clinical efficacy of anti-PD-1/L1 + paclitaxel/albumin-paclitaxel + platinum vs. paclitaxel/albumin-paclitaxel + platinum in the treatment of patients with advanced non-small cell lung cancer

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Received July 23, 2025; Accepted October 14, 2025

DOI: 10.3892/ol.2026.15454

Abstract. Platinum-based dual-drug chemotherapy is the standard first-line treatment for non-small cell lung cancer. It inhibits tumor proliferation through cytotoxic effects. However, in clinical practice, 30-40% of patients will experience disease progression due to primary or secondary drug resistance. The present study aimed to analyze the clinical efficacy and adverse reactions of anti-PD-1/L1 + paclitaxel/albumin-paclitaxel + platinum and paclitaxel/albumin-paclitaxel + platinum in the treatment of advanced non-small cell lung cancer. Computer searches were conducted in PubMed, The Cochrane Library, EMbase, China National Knowledge Infrastructure, Wanfang Data, VIPernet and China Biology Medicine databases. Randomized controlled trials on the clinical efficacy of taxel/albumin-paclitaxel + platinum and the combination of taxel/albumin-paclitaxel + platinum immunotherapy drugs in patients with non-small cell lung cancer were collected from the establishment of the database to May 2025. Meta-analysis was conducted using RevMan 5.4 software. A total of five randomized controlled trials were included, involving a total of 3,683 patients. The meta-analysis showed that the median survival rate and the incidence of asymptomatic recurrence in the experimental group (anti-PD-1/L1 + paclitaxel/albumin-paclitaxel + platinum combined immunotherapy drugs) for the treatment of non-small cell lung cancer were higher than those in the control group (paclitaxel/albumin-paclitaxel + platinum). The median progression-free and overall survival time in the experimental group were longer than those in the control group, and the incidence of side effects was higher than that in the control group. The experimental group had advantages in treating non-small cell lung cancer during the asymptomatic remission period and prolonging survival time, but the incidence of adverse reactions decreased.

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Key words: paclitaxel/albumin-paclitaxel, platinum, anti-PD-1/L1, non-small cell lung cancer, meta-analysis

Introduction

Lung cancer is the most common malignant tumor worldwide (1). In 2022, there were 2.48 million new cases of lung cancer worldwide (accounting for 12.4% of all new cancer cases) and 1.81 million deaths (accounting for 18.7% of all cancer deaths in 2022), both ranking first among all malignant tumors (2). Lung cancer is classified into small cell and non-small cell lung cancer (NSCLC) on the basis of pathology, and NSCLC accounts for 80-85% of all lung cancer cases (3). The primary histological subtypes of NSCLC include adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma and not otherwise specified NSCLC (4). Patients with early-stage lung cancer usually have no symptoms. Most confirmed cases cannot be resected or have metastasized and the 5-year survival period of these patients is short (5).

Platinum-based drug therapy is currently the main treatment option for the first-line treatment of NSCLC. Treatment with monotherapy drugs may lead to drug resistance (6). At present, the first-line treatment for NSCLC is immunotherapy combined with chemotherapy for tumors with PD-L1 expression <50%. For tumors with PD-L1 ≥50%, immunotherapy is administered. Studies (7-9) have shown that after first-line immunotherapy, patients with advanced NSCLC and high PD-L1 expression (PD-L1 ≥50%) treated with platinum-based drugs as second-line therapy experience improved overall survival (OS), progression-free survival (PFS) and objective response Rate (ORR). To the best of our knowledge, however, the effect of chemotherapy and immunotherapy in these patients has not been analyzed. Therefore, the present study aimed to analyze the use of chemotherapy combined with immunotherapy in patients with advanced NSCLC harboring tumors with high, medium and low PD-L1 expression (10).

A number of clinical studies have confirmed that third-generation chemotherapy drugs paclitaxel, pemetrexed, gemcitabine and vincristine combined with platinum are effective treatment regimens for NSCLC (11,12). The paclitaxel + carboplatin regimen is one of the most widely used regimens in clinical practice (13).

The immune system is the primary defense mechanism in humans against pathogens and abnormal cells, and T cells serve a key role in immune surveillance and attacking tumor cells (14). However, tumor cells often evade the surveillance of the immune system through various mechanisms (such as defects in antigen presentation function.), and thus proliferate. Immune checkpoints are key regulatory factors for maintaining immune tolerance and regulating immune responses. Tumor cells use these checkpoints to inhibit the activity of T cells, thereby evading immune attack. Immune checkpoint inhibitors (ICIs) restore the immune surveillance function and enhance recognition and attack of tumor cells, thereby improving the prognosis of patients (15). ICIs relieve the immunosuppression of T cells and restore their anti-tumor ability by blocking these inhibitory signals. The programmed death receptor 1 (PD-1)/PD-L1 pathway is an important mechanism for tumor cells to escape immunity (16). PD-1 is one of the key targets of ICIs (17).

To explore whether the addition of immunosuppressants in platinum-based regimens has a more obvious effect compared with immunosuppressants alone, the present study aimed to analyze studies that examined paclitaxel + platinum-based treatment regimens with and without immunosuppressants for patients with NSCLC in terms of patient survival, asymptomatic survival and adverse reactions.

Materials and methods

Literature retrieval. Randomized controlled trials (RCTs) on the clinical efficacy of paclitaxel + carboplatin with and without immunosuppressants in patients with NSCLC were searched in PubMed (pubmed.ncbi.nlm.nih.gov/), The Cochrane Library (cochranelibrary.com/), Embase (embase.com), China National Knowledge Infrastructure (cnki.net/), Wanfang Data (wanfangdata.com.cn/), VIP (cqvip.com/) and China Biology Medicine (sinomed.ac.cn) from the establishment of the databases to May 2025. The search method used subject words + free words, including Chinese key words 'immunosuppressant, paclitaxel, carboplatin, non-small cell lung cancer, lung' and the English search keywords 'paclitaxel, carboplatin, non-small cell lung cancer, atezolizumab, pembrolizumab'. Literature retrieval was conducted independently by two people.

A total of two researchers screened the selected literature by reading the full text and then cross-checked the results. Inclusion criteria were as follows: i) Published RCTs; ii) patients with NSCLC confirmed by pathology or cytology; iii) pathological stage III to V; and iv) treatment measure for the experimental group was paclitaxel + platinum + anti-PD-1/L1 and the treatment for the control group was paclitaxel + platinum. For publications containing overlapping data, the most comprehensive report was included. Exclusion criteria were as follows: i) County-level research centers; ii) animal experiments; iii) studies with missing or incomplete data; and iv) ongoing clinical trials. Outcome indicators included OS and PFS. The safety indicator was the incidence of side effects. PFS is defined as from the start of treatment to the onset of disease progression or death), and OS was defined as the time from the initiation of chemotherapy to the patient death. Certain studies contained three groups as follows: PD-1/PD-L1 + NAB-paclitaxel (Group ICICa) and carboplatin (Group ICICb); Or paclitaxel plus carboplatin (Group Che).We conducted a secondary group comparison of the research, namely:PD-1/L1 combined with paclitaxel and carboplatin (Group ICICa) vs. paclitaxel and carboplatin (Group Che).PD-1/L1 combined with NAB-paclitaxel and carboplatin (Group ICICb) VS paclitaxel and carboplatin (group Che).

A total of two researchers independently screened the literature and extracted the data, including: i) First author and country; ii) patient and tumor characteristics, including age, pathological classification, tumor stage and treatment methods; iii) outcome/safety indicators; and iv) evaluation indicators of risk of bias.

Risk of bias assessment. RevMan 5.4 (Revman International Inc.) was used for risk of bias assessment. The assessment included the following: i) Random allocation method; ii) allocation sequence concealment; iii) blinding method; iv) integrity of outcome data; v) selective outcome reporting; and vi) other sources of bias.

Statistical analysis. Data were analyzed using RevMan5.4 software. Heterogeneity was evaluated by the Q test, with $P<0.1$ or $I^2 \geq 50\%$ indicating heterogeneity, and the random-effects model was used; when heterogeneity was absent, the fixed-effect model was used (18-20). OS, PFS and adverse reactions were expressed using hazard ratio (HR) or the relative odds ratio (OR). HR and OR >1 indicated that the effect size of the experimental group was larger than that of the control group. $P \leq 0.05$ was considered to indicate a statistically significant difference.

Results

Literature screening. A total of 1,378 studies were obtained by searching the databases (Fig. 1). Duplicate studies were removed and irrelevant literature was screened and removed after reading the titles and abstracts. After reading the full text, five clinical studies were included, all of which were RCTs (21-25). Of 3,683 included patients, there were 2,069 patients in the test (T) group and 1,614 patients in the control (C) group (Table I). There were 1,447 (69.93%) male patients in the T group and 1,141 (70.69%) in the C group. The mean age range of patients in the T group was 60.0-69.5 years and that in the C group was 62-69 years. A total of 1,593 patients (76.99%) in the T group and 1,302 (81.78%) in the C group had a smoking history. There were 718 patients with an ECOG score of 0 in the T group (34%).

Basic characteristics of the patients. Tumor tissue in the T group showed high-medium PD-L1 expression in 464 cases (22.43%), low PD-L1 expression in 685 cases (33.11%), and negative or unknown PD-L1 expression in 920 cases (44.47%;

Table I. Randomized control trials included in meta-analysis.

First author/s, year	Country	Number of cases		Median age, years (range)		Male/female (%)		ECOG		History of smoking (%)		(Refs.)
		T	C	T	C	T	C	T (%)	C (%)	T	C	
Wang *et al*, 2024	China (ICICa-Che-C Group)	120.0	121.0	60.0 (41.0-74.0)	62.0 (34.0-74.0)	107.0 (89.2)	111.0 (91.7)	31.0 (25.8)	32.0 (26.4)	96.0 (80.0)	98.0 (81.0)	(21)
	China (ICICb-Che Group)	119.0	121.0	63.0 (38.0-74.0)	62.0 (34.0-74.0)	112.0 (94.1)	111.0 (91.7)	22.0 (18.5)	32.0 (26.4)	107.0 (89.9)	98 (81.0)	
Jotte *et al*, 2020	USA (ICICa-Che Group)	338.0	340.0	66.0 (43.0-85.0)	65.0 (38.0-86.0)	278.0 (82.2)	277.0 (81.5)	109.0 (32.2)	110.0 (32.4)	308.0 (91.1)	316.0 (92.9)	(22)
	USA (ICICb-Che Group)	343.0	340.0	65.0 (23.0-83.0)	65.0 (38.0-86.0)	280.0 (81.6)	277.0 (81.5)	115.0 (33.5)	110.0 (32.4)	311.0 (90.7)	316.0 (92.9)	
Sugawara *et al*, 2023	Japan	22.0	28.0	69.5 (45.0-87.0)	69.0 (43.0-82.0)	19.0 (86)	24.0 (86)	10.0 (45)	13.0 (46.0)	21.0 (95.0)	26.0 (93.0)	(23)
Ren *et al*, 2022	China	193.0	196.0	64.0 (34.0-74.0)	62.0 (34.0-74.0)	179.0 (93.0)	180.0 (92.0)	38.0 (20.0)	43.0 (22.0)	171.0 (89.0)	173.0 (88.0)	(24)
West *et al*, 2019	USA (ICICa-Che Group)	483.0	240.0	64.0 (18.0-86.0)	65.0 (38.0-85.0)	206.0 (43.0)	138.0 (58.0)	204.0 (42.0)	93.0 (39.0)	160.0 (33.0)	73.0 (30.0)	(25)
	USA (ICICb-Che Group)	451.0	228.0	64.0 (18.0-86.0)	65.0 (38.0-85.0)	266.0 (59.0)	134.0 (59.0)	189.0 (42.0)	91.0 (40.0)	419.0 (87.0)	220.0 (92.0)	

T, Experimental; C, Control group; ECOG, Eastern Cooperative Oncology Group.

Table II. Expression of PD1/L1 and tumor staging.

First author/s, year	Country	T PD-1/L1 expression (%)			C PD-1/L1 expression (%)			Stage IIIb (%)		Stage IV (%)		(Refs.)
		High-medium	Low	Negative/unknown	High-medium	Low	Negative/unknown	T	C	T	C	
Wang *et al*, 2024	China (ICICa-Che Group)	42.0 (35.0)	42.0 (35.0)	47.0 (39.2)	41.0 (33.9)	31.0 (25.6)	49.0 (37.2)	3.08.0 (31.7)	44.0 (36.4)	82.0 (68.3)	77.0 (63.6)	(21)
	China (ICICa-Che Group)	42.0 (35.3)	30.0 (25.2)	46.0 (38.7)	41.0 (33.9)	31.0 (25.6)	49.0 (37.2)	40.0 (33.6)	44.0 (36.4)	79.0 (66.4)	77.0 (63.6)	
Jotte *et al*, 2020	USA (ICICa-Che Group)	48.0 (14.2)	110.0 (35.5)	170.0 (50.3)	44.0 (12.9)	125.0 (36.8)	171.0 (50.3)	NA	NA	338.0 (100)	340.0 (100)	(22)
	USA (ICICb-Che Group)	47.0 (13.7)	136.0 (39.7)	160.0 (46.6)	44.0 (12.9)	125.0 (36.8)	171.0 (50.3)	NA	NA	343.0 (100)	340.0 (100)	
Sugawara *et al*, 2023	Japan	13.0 (59.0)	9.0 (41.0)	2.0 (9.0)	22 (78.6)	6.0 (21.0)	0.00	NA	NA	22.0 (100.0)	28.0 (100.0)	(23)
Ren *et al*, 2022	China	95 (68.3)	91.0 (47.0)	7 (4)	93 (66.0)	97.0 (49.0)	6.0 (3.0)	54.0 (28.0)	55.0 (28.0)	139.0 (72.0)	141.0 (72.0)	(24)
West *et al*, 2019	USA (ICICa-Che Group)	91.0 (19.0)	139.0 (29.0)	253.0 (52.0)	43.0 (18.0)	68.0 (28.0)	129.0 (54.0)	NA	NA	483.0 (100.0)	240.0 (100.0)	(25)
	USA (ICICb-Che Group)	88.0 (20.0)	128.0 (28.0)	235.0 (52.0)	42.0 (18.0)	65.0 (29.0)	121.0 (53.0)	NA	NA	451.0 (100.0)	228.0 (100.0)	

NA, not available; T, test; C, control; PD-1/L1, programmed death 1/programmed cell death-ligand1.ICIC, immune checkpoint inhibitor + chemotherapy; ICICa: anti-PD-1/L1 + paclitaxel + platinum; ICICb: anti-PD-1/L1 + albumin-paclitaxel + platinum; Che: paclitaxel/albumin-paclitaxel + platinum.

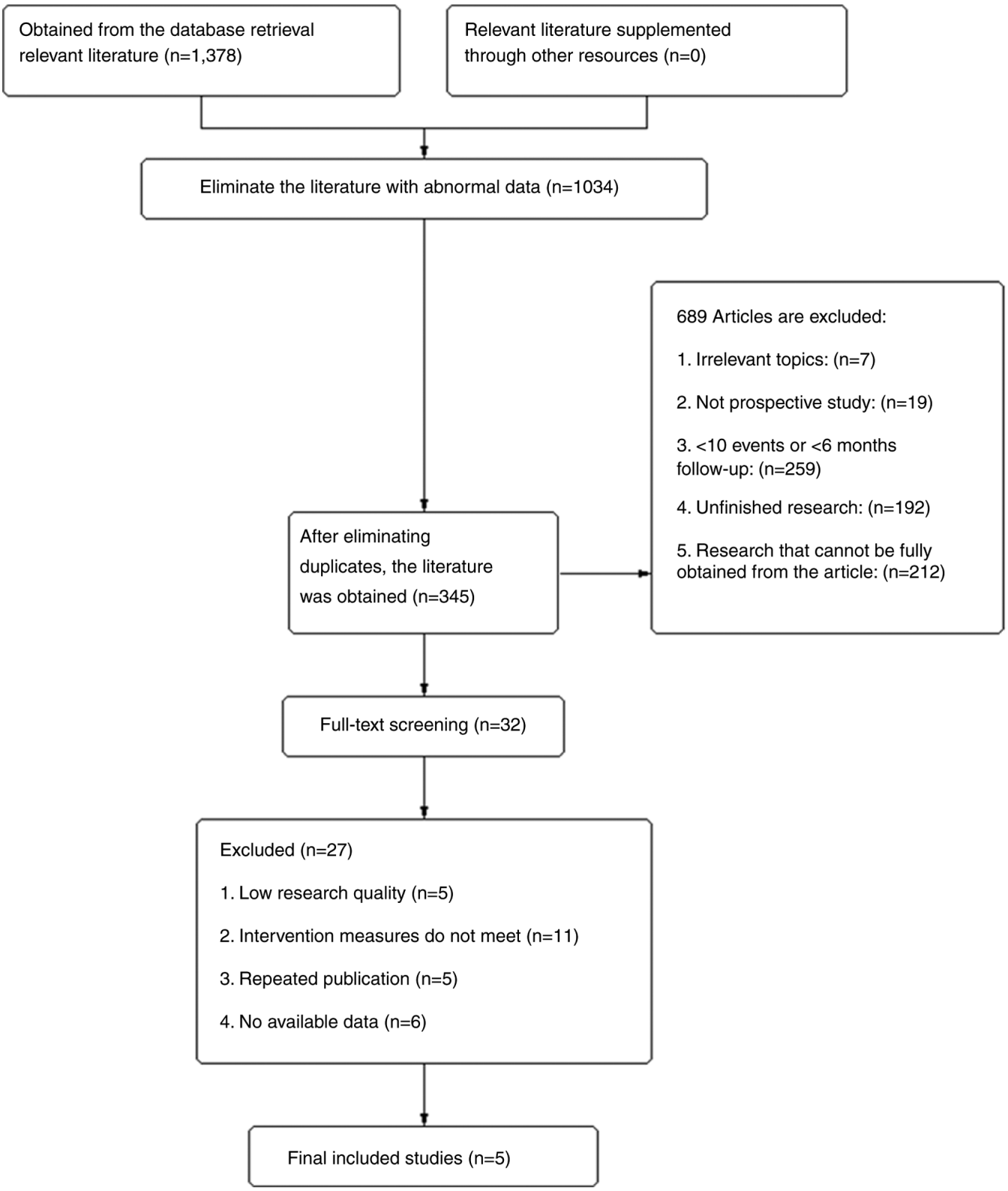

Figure 1. Literature screening process.

Table II). In the C group, there were 370 cases (22.992%) with high-medium PD-L1 expression, 556 (34.45%) with low PD-L1 expression and 688 cases (42.63%) with negative or unknown PD-L1 expression. In the T group, there were 132 cases (6.38%) of stage IIIb (According to the INM classification method for malignant tumors) (26) and 1,937 cases (93.62%) of stage IV cancer, while in the C group, there were 143 cases (8.86%) of stage IIIb and 1,471 cases (91.14%) of stage IV cancer.

Bias risk assessment. Publication bias assessment was not performed as <10 studies were included (27). As all the studies used centralized randomization allocation schemes for RCTs

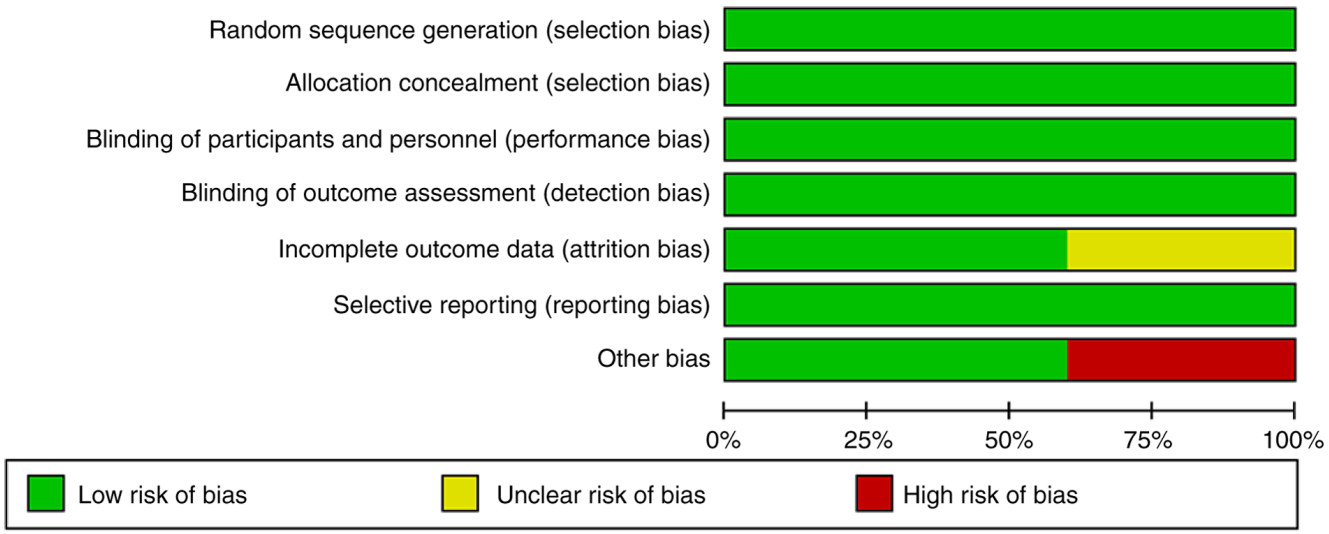

Figure 2. Risk of bias map. RCT, randomized control trial.

and blinding of both researchers and participants, selection bias and implementation bias were judged as low-risk (Fig. 2). All studies reported the methods of randomization. The outcome data studies were complete, and it was not clear whether there were other sources of bias. One cohort study (24) did not report the number of occurrences of specific side effects in the follow-up population, indicating a certain degree of bias. One study (23) had a small number of participants, poor representativeness and selection bias.

Meta-analysis results

Median OS and PFS. There was statistical heterogeneity between these studies. (P=0.07, I^2=49; Fig. 3). A random-effects model was used for meta-analysis; OS of the T group was significantly higher than that of the C group [OR=20.43, 95% confidence interval (CI) (18.81, 22.19), P<0.001]. There was no statistical heterogeneity among studies on PFS.(P=0.14, I^2=38; Fig. 4). A random-effects model was used for meta-analysis; PFS of the T group was significantly higher than that of the C group [HR=7.24, 95% CI (6.93, 7.78), P<0.001].

Safety indicators. The safety assessment of patient medication mainly included the evaluation of the incidence of adverse events. There was no statistical heterogeneity among the studies (P<0.00001, I^2=84; Fig. 5). A random-effects model was used for meta-analysis; incidence of adverse events in the T group was significantly lower than that in the C group [OR=2.47, 95% CI (1.16, 5.25), P=0.02].

Discussion

The meta-analysis showed that in terms of controlling the progression of NSCLC, the anti-PD-1/L1 + paclitaxel/albumin-paclitaxel + carboplatin treatment regimen was significantly superior to the paclitaxel/albumin-paclitaxel + carboplatin treatment regimen. Several reasons may explain the improved efficacy of anti-PD-1/L1 + paclitaxel/albumin-paclitaxel + carboplatin treatment. The regime enhances the anti-tumor immune response: Chemotherapy induces immunogenic cell death, releasing tumor antigens, while immunotherapy eliminates the inhibition of T cells, enabling the immune system to recognize and attack tumor cells, forming a cycle of antigen release-immune activation (28). The regime overcomes chemotherapy resistance: Certain tumor cells may develop resistance through mutations or other mechanisms during chemotherapy. However, immunotherapy does not rely on chemotherapy drugs that directly kill tumor cells, but activates immune pathways, such as T cells, to attack drug-resistant cells and overcome chemotherapy resistance (29). The regime reduces the risk of recurrence and metastasis: Chemotherapy combined with immunotherapy not only enhances the efficacy of the initial treatment but also decreases the risk of tumor recurrence and metastasis by establishing a lasting immune memory. Especially in cases where minimal residual lesions are difficult to eliminate through chemotherapy, immunotherapy provides long-term protection (30).

The present study analyzed OS, PFS and the incidence of adverse events, and verified the hypothesis that the combination of chemotherapy and immunotherapy alters the antigen release-immune activation cycle. Chemotherapy creates the prerequisite conditions for immunotherapy to take effect, and immunotherapy converts the short-term killing effect of chemotherapy into long-term, and potentially curative immune memory. Chemoimmunotherapy improved the initial treatment effect and decreased the risk of tumor recurrence and metastasis (22). Since both the OS and PFS data are medians with significant differences, and there are certain errors in the meta-analysis of survival data using the original data rows obtained from the literature, a random mode was adopted for comparative analysis. The median PFS in terms of Teff high was 6.9 months in the T group and 5.6 months in the C group [HR 0.61, 95% CI (0.46-0.81)]. The median PFS in Teff low was 6.0 months in the T and 5.7 months in the C group [HR 0.84, 95% CI (0.67-1.05)]. The median OS in Teff high was 17 months in the T group and 15.9 months in the C group [HR 0.88, 95% CI (0.66-0.9)]. The median PFS in terms of Teff low was 13.2 months in the T group and 12.6 months in the C group [HR 0.86, 95% CI (0.69-1.13)].

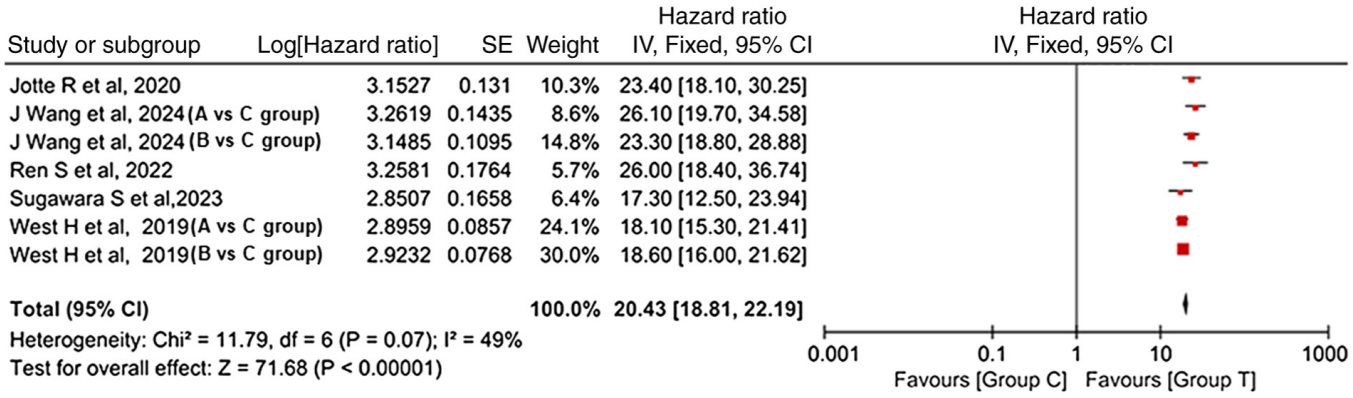

Figure 3. Forest plot of the median overall survival rate of patients with non-small cell lung cancer. There was no statistical heterogeneity among the studies (P=0.07, I^2=49). A random-effects model was used for meta-analysis; overall survival of the T group was significantly higher than that of the C group [OR=20.43, 95%CI (18.81, 22.19), P<0.001]. C, control; T, test;-HR, Hazard Ratio; df, degrees of freedom; IV, Information Value; CI, confidence interval.

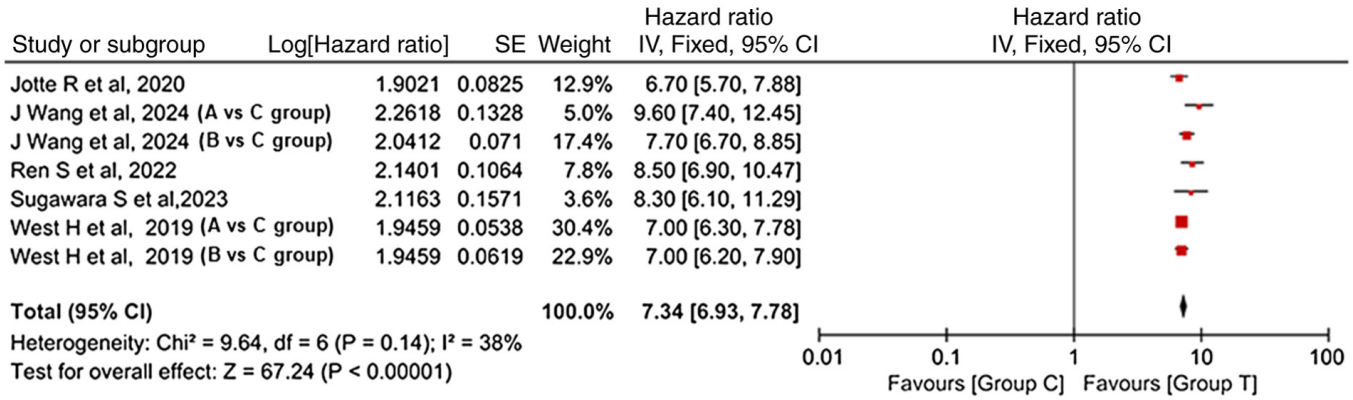

Figure 4. Forest plots of the median asymptomatic survival of patients with non-small cell lung cancer. There was no statistical heterogeneity among the studies (P=0.14, I^2=38). A random-effects model was used for meta-analysis; asymptomatic survival of the T group was significantly higher than that of the C group [OR=7.24, 95%CI (6.93, 7.78), P<0.001]. C, control group; T, the test group; HR, Hazard Ratio; df, degrees of freedom; IV, Information Value; CI, confidence interval.

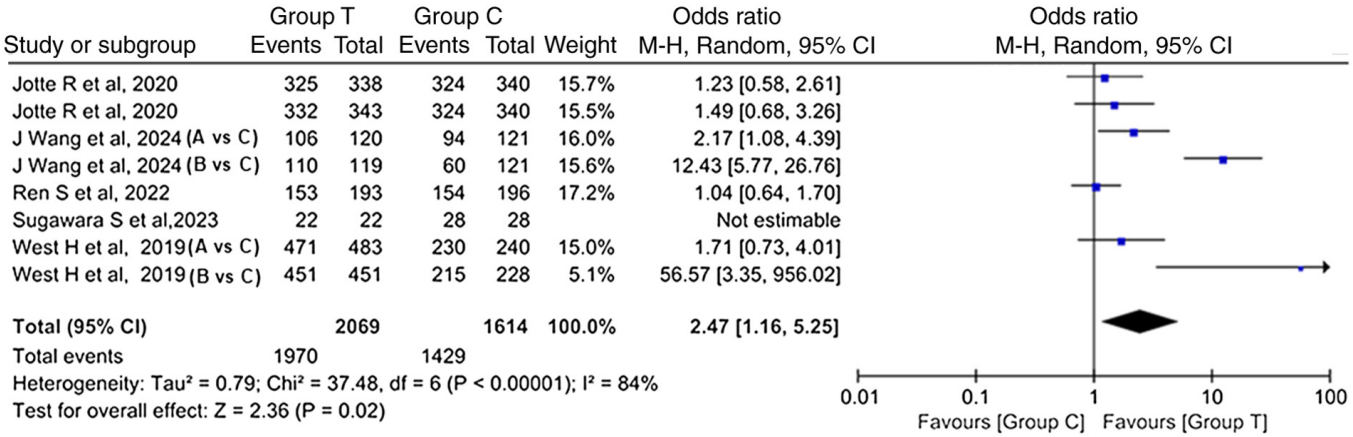

Figure 5. Forest plots of the occurrence of adverse reactions in patients with non-small cell lung cancer. There was no statistical heterogeneity among the studies (P<0.00001, I^2=84). A random-effects model was used for meta-analysis; incidence of adverse events in the T group was significantly lower than that in the C group [OR=2.47, 95%CI (1.16, 5.25), P=0.02]. C, control; T, test; OR, odds ratio; df, degrees of freedom; IV, Information Value; CI, confidence interval.

The meta-analysis showed that patients in the T group had a longer survival time than those in the C group, reflected in the median OS and PFS. Although anti-PD-1/L1 combined with paclitaxel/albumin and platinum-based drugs better controls the condition and prolongs the survival time of patients, it is essential to recheck indicators such as blood cells, coagulation function, electrolytes, liver and kidney function and blood pressure during medication. For patients with severe adverse reactions, daily

monitoring is suitable. Patients experiencing particularly severe adverse reactions need to decrease the dosage, stop the medication or switch regimens to avoid worsening condition and death. For those with serious related diseases before chemotherapy, medication should be used with caution or avoided altogether.

The majority of patients with NSCLC are elderly, and their physical functions, organ condition and psychological states are different from those of younger patients. They have a poorer tolerance to toxic drugs (31) and a lower acceptance of large fluctuations in condition, making them more likely to be negative or resistant to medication. Therefore, clinicians need to be cautious when administering drugs to this patient population.

The present study has several limitations. Only five articles were included, resulting in a small overall sample size that lacked representativeness. As the included studies had already excluded patients with contraindications during the trial design stage, such as those with a bleeding tendency, the results cannot be applied to all patients with NSCLC. The overall disease control and survival rates of patients with NSCLC in the clinic are lower than the research data (32,33). For patients with a tendency to bleed, the use of immunosuppressants should be applied with caution and a switch to other targeted drugs should be considered. Differences in date, region and ethnicity between the included studies introduce bias.

Compared with the paclitaxel/albumin-paclitaxel + carboplatin regimen, the anti-PD-1/L1 + paclitaxel/albumin-paclitaxel + platinum regimen prolonged the survival time of patients with NSCLC. Although patients treated with anti-PD-1/L1 + paclitaxel/albumin-paclitaxel + platinum were more prone to drug toxicity and side effects such as leukopenia, bleeding, proteinuria, and hypertension, in patients with no serious toxic side effects, anti-PD-1/L1+ paclitaxel/albumin-paclitaxel + platinum is a more effective choice. The cost of immunosuppressants remains high, and a large number of patients do not adhere to regular and adequate use. The identification of alternative drugs or strategies using combinations of immune drugs to decrease the dose of a single immune drug may improve the treatment efficacy, shortening the treatment cycle and lowering the cost. This treatment plan can be promoted and used in patients with advanced NSCLC. PFS may also be improved and the side effects of this treatment plan may be decreased. More research into the side effects and methods to alleviate the toxic and side effects of this treatment plan is required. Overall, the present study provides support for the use of chemoimmunotherapy in patients with advanced NSCLC and low expression of PD-L1.

Acknowledgements

The authors would like to thank Mrs Gabrielle White Wolf for editing the manuscript.

Funding

No funding was received.

Availability of data and materials

The data generated in this study may be requested from the corresponding author.

Authors' contributions

FL wrote and revised the manuscript, performed the literature review and constructed figures. LL and FL performed the literature review, designed the study and revised the manuscript. SY and LL analyzed data. All authors have read and approved the final manuscript. FL, LL and SY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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