REVIEW ARTICLE

Effectiveness of PD1/PD-L1 combined with anti-angiogenic drugs in patients with advanced nonsmall cell lung cancer: A systematic review and meta-analysis

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Background: Protein-1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1) therapy have become an important treatment approach for patients with advanced nonsmall cell lung cancer (NSCLC), but primary or secondary resistance remains a challenge for some patients. PD-1/PD-L1 combined with anti-angiogenic drugs (AAs) in NSCLC patients have potential synergistic effects, and the survival benefit may vary based on a treatment order. To investigate the efficacy of PD-1/PD-L1 combined with AAs as the treatment for patients with advanced NSCLC. **Materials and Methods:** We comprehensively searched EMBASE, PubMed, Web of Science, CNKI, VIP, and Wanfang databases from January 2017 to September 2022. The Cochrane risk bias tool evaluated the quality of included randomized clinical trials. Newcastle-Ottawa-Scale score was used to evaluate the quality of retrospective studies. Publication bias was evaluated by funnel plot, Begg's test, and Egger's test. **Results:** Seventeen articles were finally selected, involving 5182 patients. Meta-analysis results showed that PD1/PD-L1 combined with AAs therapy significantly improved progression-free survival (PFS) (hazard ratio [HR] = 0.61, 95% confidence interval [CI]: 0.50–0.75, $P < 0.00001$), overall survival (OS) (HR = 0.79, 95% CI: 0.71–0.88, $P < 0.00001$), and objective response rate (ORR) (risk ratio = 0.88, 95% CI: 0.81–0.96, $P = 0.004$), with the statistically significant difference. The sensitivity analysis demonstrated the robustness of the PFS, ORR, and OS. **Conclusion:** The combination of PD-1/PD-L1 inhibitors with AAs in treating advanced patients has exhibited notable therapeutic advantages when contrasted with monotherapy. Specifically, the administration of PD-1/PD-L1 inhibitors in conjunction with AAs, or sequential treatment involving PD-1/PD-L1 followed by AAs, has shown enhanced therapeutic efficacy in this patient population.

Key words: Anti-angiogenic drugs, clinical efficacy, meta-analysis, nonsmall cell lung cancer, protein-1/programmed cell death 1 ligand 1 inhibitors

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INTRODUCTION

Lung cancer, a highly vascularized tumor, is one of the most common types of cancer with the highest mortality rate globally and the leading causes of death in cancer patients.[1] It comprises two main subtypes of small cell lung cancer and nonsmall cell lung cancer (NSCLC), with the latter being the most prevalent type of disease, encompassing adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, representing over 85% of all lung cancers.[1,2] Regrettably, the absence of early diagnostic indicators may result in over 70% of patients presenting with locally invasive disease, lymph node involvement, and distant metastases at the time of diagnosis, consequently leading to an unfavorable prognosis and a significantly diminished 5-year survival rate.[3,4]

In recent years, immunotherapy has been emerged as a fundamental treatment for lung cancer in combination

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with other therapeutic measures. Immune checkpoint inhibitors (ICIs), which target the programmed cell death protein-1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1), have revolutionized breakthrough therapy for NSCLC by blocking the PD-1/PD-L1 signaling pathway and reactivating the body's immune cells to attack tumor cells, leading to significant improvements in patient survival. However, the efficacy of PD-1/PD-L1 monotherapy for solid tumors is limited, and some patients may still experience resistance to ICIs.[5,6]

The investigators explored the potential benefits of combining immunotherapy with other drugs. They found that anti-angiogenic drugs (AAs) were promising therapeutic strategy for NSCLC, which can be broadly classified into multitargeted anti-angiogenic tyrosine kinase inhibitors, monoclonal antibodies targeting anti-angiogenic agents, and other multitargeted inhibitors. AAs achieve antitumor effects by blocking the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) signaling pathway, which is involved in the process of tumorigenesis, progression, and metastasis. AAs also regulate the tumor microenvironment, preventing tumor angiogenesis and proliferation.[7-9] Moreover, PD-1/PD-L1-activated immunity is also known to enhance the anti-angiogenesis activity by downregulating VEGF expression and reducing hypoxic conditions. PD-1/PD-L1 combined with AAs have potential synergistic mechanisms.[10-14] However, several studies[15,16] have reported that PD-1/PD-L1 combined with AAs did not provide any additional progression-free survival (PFS) and overall survival (OS) benefits with a high incidence of treatment-related adverse events. In addition, the impact of the treatment order of PD-1/PD-L1 combined with AAs in patients with advanced NSCLC cancer has yet to be definitively elucidated.

In light of this knowledge gap, this article undertakes a meticulous pooled analysis, leveraging existing studies, to systematically evaluate the therapeutic efficacy of the combined approach of PD-1/PD-L1 inhibitors with AAs in patients afflicted with advanced NSCLC. The ultimate aim is to offer a more dependable, evidence-based foundation to inform the clinical utilization of these combined therapeutic modalities.

METHODS

This meta-analysis was performed and written following the PRISMA standard guidelines and checklists. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42022367960).

Sources and search strategy

Relevant literature about the combination of PD-1/PD-L1 with AAs for advanced NSCLC patients was searched through three medical online medical databases (EMBASE, PubMed, and Web of Science) and three Chinese databases (CNKI, VIP, and Wanfang) from January 2017 to September 2022. A search strategy was developed following the PICOS principles, and medical subject terms (MeSH) and free words were used for the search, such as "non-small cell lung cancer," "NSCLC," "immune checkpoint inhibitors," "ICIs," "Nivolumab," "Pembrolizumab," "Atezolizumab," "Atezolizumab" "Durvalumab," "Camrelizumab," "Toripalimab," "Angiogenesis Inhibitors," "Bevacizumab," "Anlotinib," "Levatinib," "Ramucirumab," and "Nintedanib," etc., Meanwhile, randomized clinical trials (RCTs) or retrospective studies related to PD-1/PD-L1 combined with AAs in treating patients with advanced NSCLC were searched manually to minimize bias.

Inclusion and exclusion criteria

- Inclusion criteria: (1) Phase II or phase III RCTs and retrospective cohort studies were searched, investigating PD-1/PD-L1 inhibitors combined with AAs with or without chemotherapy for advanced NSCLC, and were published in Chinese or English. (2) Patients with cytologically confirmed advanced (III or IV or recurrent) NSCLC, aged 18 years or older, regardless of gender, region, or race. (3) Control group: Monotherapy and treatment group: PD-1/PD-L1 combined with AAs. (4) Outcomes: PFS, OS, and objective response rate (ORR). (5) If multiple papers were from the same study and reported the same or overlapping results, the most recently published article was selected
- Exclusion criteria: (1) Animal studies, (2) full text not provided or missing data, (3) review articles, case reports, cross-sectional studies, conference abstracts, or duplicate publications, (4) sample size (n) <30, and (5) Phase I clinical trials.

Data extraction and quality assessment

First, the retrieved literature was imported into Noteexpress software by one researcher (Xueyu Duan), and duplicates were removed using the check weighing function. Next, two researchers (Xueyu Duan and Yanjiao Pu) independently screened titles, abstracts, and full-text articles to identify potentially relevant articles. If disagreements existed, all disagreements were thoroughly discussed and assessed in the full text accordingly, and the data were extracted independently from each eligible study separately, including first author, year of publication, sample size, clinical trial number, age, gender, tumor stage, clinical trial stage, Eastern Cooperative Oncology Group performance status score, interventions, and outcome (PFS, OS, and ORR). Risk of bias was assessed for RCTs using the Cochrane Risk of Bias Assessment Tool: green indicates low risk, yellow indicates unclear risk, and red indicates high risk.[17] Retrospective studies were assessed for quality using Newcastle-Ottawa-Scale (NOS) score, which focused on three aspects of quality: selectivity, comparability,

and outcomes, with a total score of 9, and ≥ 7 was considered a high-quality study.[18]

Statistical analysis

Rev Man 5.3 and Stata17.0 were used for meta-analysis. ORR was analyzed using risk ratio (RR) and 95% confidence interval (CI) for the combined effect size. OS and PFS were evaluated using hazard ratio (HR) and 95% CI as statistical effect size. The difference was considered statistically significant at $P < 0.05$. The Q-test and I^2 test were used to assess heterogeneity. I^2 values were used to assess the magnitude of heterogeneity. When $I^2 \leq 50\%$ and $P \geq 0.1$, the heterogeneity between studies was considered low, and the fixed-effect model (FE model) was used; conversely, the random-effect model (RE model) was used.[19] We performed exploratory analyses of predefined subgroups based on PD-L1 expression, treatment order, and estimated glomerular filtration rate (EGFR) mutation to examine heterogeneity. Funnel plot, Egger's test, and Begg's test were used to analyze publication bias. To determine the robustness of the results (PFS, OS, and ORR), we conducted a sensitivity analysis by the one-by-one elimination method.

RESULTS

Literature search results

A total of 2728 Chinese and English literature records were retrieved, of which 1720 were included after eliminating duplicates. Upon further screening of titles and abstracts according to the inclusion and exclusion criteria, 17 studies were finally included, as depicted in Figure 1.

Basic characteristics of the included studies

The included studies[20-36] in this analysis were conducted between January 2017 and September 2022 [Table 1]. Of the 1720 studies, 17 met the inclusion and exclusion criteria, comprising 5 randomized controlled trials[21,25,34-36] and 12 retrospective cohort studies.[20,22,26-32] A total of 5182 patients were included. Eight studies investigated PD-1 + AA, three examined PD-L1 + AA, and six investigated PD-1/PD-L1 + AA. Of the 17 studies, five investigated the sequence of treatment, of which three were PD-1/PD-L1 followed by AAs,[20,22,30] while two investigated AAs followed by PD-1/PD-L1.[23,26]

Quality assessment

Four studies[21,34-36] reported specific randomization methods, and three studies[21,34,36] described allocation concealment schemes. Only two studies[21,35] had complete outcome data. In addition, two studies[25,35] were unclear whether other sources of bias existed, as shown in Figure 2. All included retrospective studies in the analysis scored either 6 or 7 on the NOS scale [Table 2].

Meta-analysis results

Progression-free survival

Thirteen studies[20-22,24,26-28,30-35] reported HR values of PFS between the PD-1/PD-L1 plus AAs and monotherapy in NSCLC patients. By heterogeneity test, $I^2 = 75\%$, $P < 0.00001$, using the random-effect model (RE model), the results

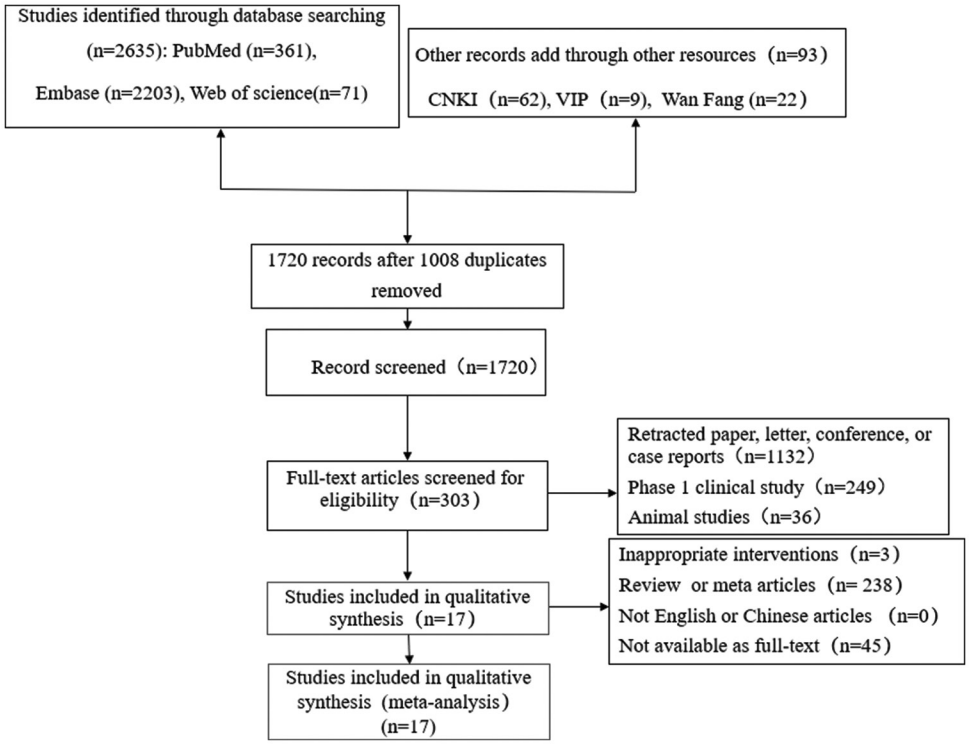

Figure 1: Flow diagram of literature screening

demonstrated a statistically significant prolongation of PFS in the PD-1/PD-L1 plus AAs group compared to the monotherapy group (HR = 0.61, 95% CI: 0.50–0.75, $P < 0.00001$), as shown in Figure 3.

Overall survival

Nine studies[20-22,26-27,30,32,35,36] reported HRs for OS between the PD-1/PD-L1 plus AAs and monotherapy in NSCLC patients. After heterogeneity testing, with $I^2 = 35\%$ and $P = 0.14$, indicating low heterogeneity, the fixed-effect model (FE model) was used for meta-analysis, which demonstrated that PD-1/PD-L1 plus AAs significantly improved OS in NSCLC patients (HR = 0.79, 95% CI: 0.71–0.88, $P < 0.00001$), as illustrated in Figure 4.

Objective response rate

Fifteen studies[20-33,35] reported RR values for ORR in NSCLC patients treated with either PD-1/PD-L1 combination AAs or monotherapy. A meta-analysis was conducted with a heterogeneity test revealing $I^2 = 66\%$ and $P = 0.0002$. The RE model was used; the analysis showed that the combination of PD-1/PD-L1 with AAs group significantly improved ORR in NSCLC patients compared to the monotherapy

Table 1: Basic characteristics of included literature

Author	Design	Sample	Age		Interventions		Outcomes
			Treatment group	Control group	Treatment group	Control group	
Tozuka *et al*., 2020[20]	Retrospective	46	65	59	RAM after NIV/PEM/ATE	RAM after CT	①②③
Sugawara *et al*., 2021[21]	RCT	540	66	66	NIV + BEV	BEV	①②③
Harada *et al*., 2019[22]	Retrospective	39	67	65	RAM after ATE/NIV/PEM	RAM after CT	①②③
Nakahama *et al*., 2017[23]	Retrospective	199	NR	NR	RAM after ATE/NIV/PEM	RAM after CT	③
Shi *et al*., 2022[24]	Retrospective	354	59	59	NIV after ANL	NIV after CT	①③
Lee *et al*., 2022[25]	RCT	66	63	66	TIS/CAM/ATE/DUR/PEM/NIV/SIN + ANL	TIS/CAM/ATE/DUR/PEM/NIV/SIN	③
Tanimura *et al*., 2021[26]	Retrospective	105	69	71	NIV/PEM after AA	NIV/PEM after CT	①②③
Zhang *et al*., 2021[27]	Retrospective	101	60	62	NIV/PEM/CAM/TIS/SIN/ATE + BEV/APA/ARO/SIT	NIV/PEM/CAM/TIS/SIN/ATE	①②③
Zhang *et al*., 2021[28]	Retrospective	99	NR	NR	PEM/SIN/TOR/CAM + ANL	ANL	①③
Wang *et al*., 2021[29]	Retrospective	88	64	65	CAM + ANL	ANL	③
Kato *et al*., 2020[30]	Retrospective	1439	68	69	RAM after NIV/PEM	RAM after CT	①②③
Zhang *et al*., 2021[31]	Retrospective	103	59	62	PEM/TOR + ANL	PEM/TOR	①③
Chen *et al*., 2021[32]	Retrospective	60	59	61	PEM + ANL	PEM	①②③
Xiong *et al*., 2021[33]	Retrospective	54	NR	NR	PEM/NIV/SIN/TOR/ATE + ANL	ANL	①③
Lu *et al*., 2022[34]	RCT	299	59	57	SIN + BEV	SIN	①
Reck *et al*., 2019[35]	RCT	790	63	63	ATE + BEV	BEV	①②③
Socinski *et al*., 2021[36]	RCT	800	63	63	ATE + BEV	BEV	②

①=PFS refers to the duration from the beginning of receiving PD-1/PD-L1 combined with AAs to the first disease progression (including local recurrence, distant metastasis, deterioration of symptoms, death from any cause, or the last followup); ②=OS pertains to the duration from receiving PD-1/PD-L1 combined with AAs to death from any cause or last follow-up; ③=ORR refers to tumors become small after drug treatment, including CR, PR. AAs=Anti-angiogenic drugs; RCT=Randomized clinical trial; NR=Not mentioned; NIV=Nivolumab; PEM=Pembrolizumab; SIN=Sintilizumab; ATE=Atezolizumab; DUR=Durvalumab; TOR=Tremelimumab; CAM=Camrelizumab; TIS=Tirelizumab; BEV=Bevacizumab; RAM=Ramucirumab; ANL=Anlotinib; ARO=Arotinib; APA=Apatinib; SIT=Small molecule inhibitor; CR=Complete response; PR: Partial response; PD-1=Protein-1; PD-L1=Programmed cell death 1 ligand 1; PFS=Progression-free survival; OS=Overall survival; ORR=Objective response rate

Table 2: Results of Newcastle-Ottawa-Scale of the included cohort studies

Author	Selectivity/score	Comparability/score	Outcomes/score	Total/score
Tozuka *et al*., 2020[20]	3	2	1	6
Harada *et al*., 2019[22]	3	2	1	6
Nakahama *et al*., 2017[23]	3	1	2	6
Shi *et al*., 2022[24]	3	2	2	7
Tanimura *et al*., 2021[26]	3	2	2	7
Zhang *et al*., 2021[27]	3	2	1	6
Zhang *et al*., 2021[28]	3	1	2	6
Wang *et al*., 2021[29]	3	1	2	6
Kato *et al*., 2020[30]	3	2	1	6
Zhang *et al*., 2021[31]	3	2	1	6
Xiong *et al*., 2021[33]	3	2	2	7
Chen *et al*., 2021[32]	3	2	2	7

group (RR = 0.88, 95% CI: 0.81–0.96, P = 0.004), as demonstrated in Figure 5.

Subgroup analysis

A subgroup analysis was performed based on PD-L1 expression showed that regardless of the level of PD-L1 expression, the PFS in the PD-1/PD-L1 plus AAs group was higher than the monotherapy group, with a statistically significant difference (HR = 0.61, 95% CI: 0.51–0.73, P < 0.00001) [Figure 6a]. Subgroup analysis for OS based on PD-L1 expression showed that PD-1/PD-L1 plus AAs did not result in a significant OS benefit in PD-L1 ≥50%, PD-L1 1%~49%, and PD-L1 <1% patients (HR = 1.05, 95% CI: 0.52–2.14, P = 0.89) [Figure 6b].

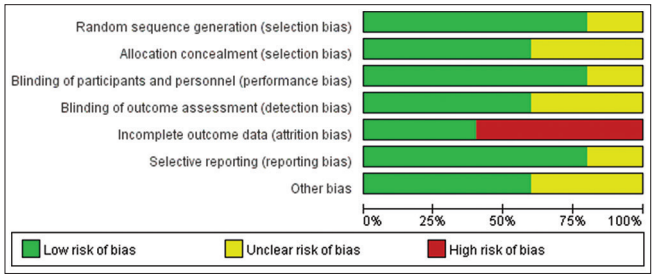

Figure 2: Bias risk assessment of the included randomized clinical trials

A subgroup analysis for PFS was performed based on treatment order and showed that AAs followed by PD-1/PD-L1 did not provide a PFS benefit (HR = 1.83, 95% CI: 1.05–3.19, P = 0.03). On the other hand, PD-1/PD-L1 + AA therapy resulted in a significant PFS benefit (HR = 0.56, 95% CI: 0.46–0.68, P < 0.00001, I^2 = 69%). The therapy of PD-1/PD-L1 followed by AAs also demonstrated an excellent PFS benefit. However, there was no significant difference (HR = 0.57, 95% CI: 0.29–1.15, P = 0.12, I^2 = 72%) [Figure 7a]. Subgroup analysis for OS based on treatment order showed that AAs followed by PD-1/PD-L1 did not result in a significant OS benefit (HR = 1.47, 95% CI: 0.76–2.84, P = 0.25). Conversely, the combination of PD-1/PD-L1 with AAs or PD-1/PD-L1 followed by AAs yielded a favorable OS benefit (HR = 0.79, 95% CI: 0.71–0.89, P < 0.0001, I^2 = 30%) and (HR = 0.58, 95% CI: 0.39–0.86, P = 0.007, I^2 = 0%), as depicted in Figure 7b. Subgroup analysis for ORR based on treatment order showed that the combination of PD-1/PD-L1 with AAs was not statistically different from the monotherapy group (RR = 0.91, 95% CI: 0.80–1.02, P = 0.11, I^2 = 71%). Moreover, in the sequential therapy, the combination of PD-1/PD-L1 with AAs had an improvement in ORR compared to the monotherapy group, with a statistically significant difference (RR = 0.84, 95% CI: 0.72–0.98, P = 0.03, I^2 = 25%), as illustrated in Figure 7c.

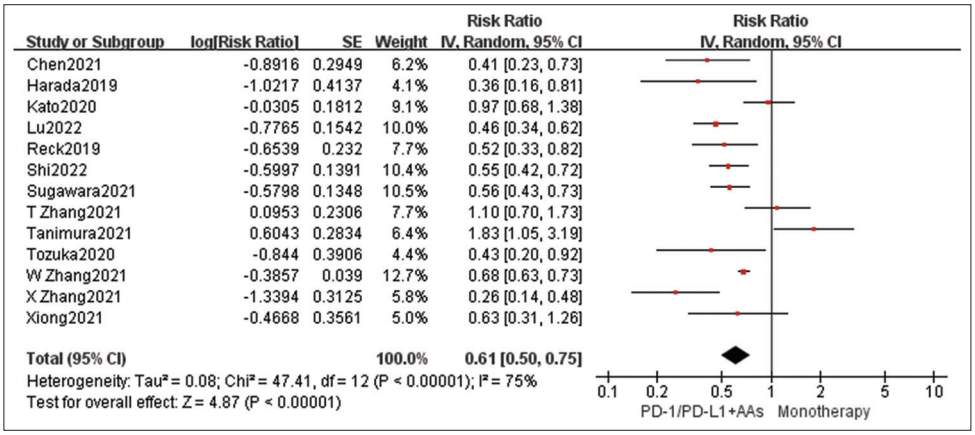

Figure 3: Forest plot of the progression-free survival between protein-1/programmed cell death 1 ligand 1 plus anti-angiogenic drugs therapy group and monotherapy group. SE = Standard error; CI = Confidence interval; PD-1 = Protein-1; PD-L1 = Programmed cell death 1 ligand 1; AAs = Anti-angiogenic drugs

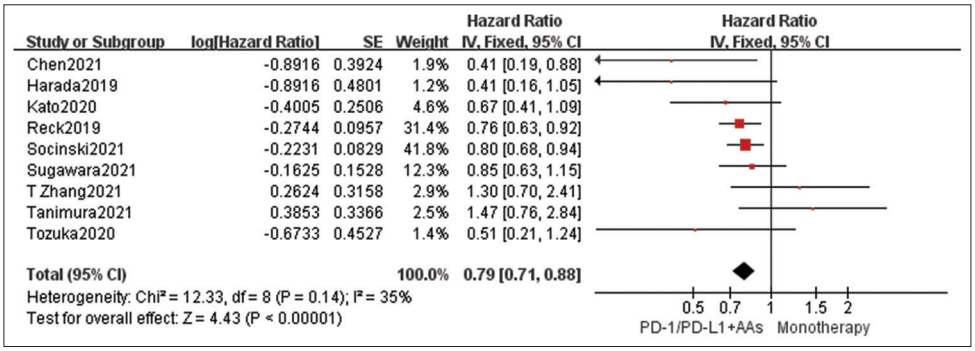

Figure 4: Forest plot of the overall survival between protein-1/programmed cell death 1 ligand 1 plus anti-angiogenic drugs therapy group and monotherapy group. SE = Standard error; CI = Confidence interval; PD-1 = Protein-1; PD-L1 = Programmed cell death 1 ligand 1; AAs = Anti-angiogenic drugs

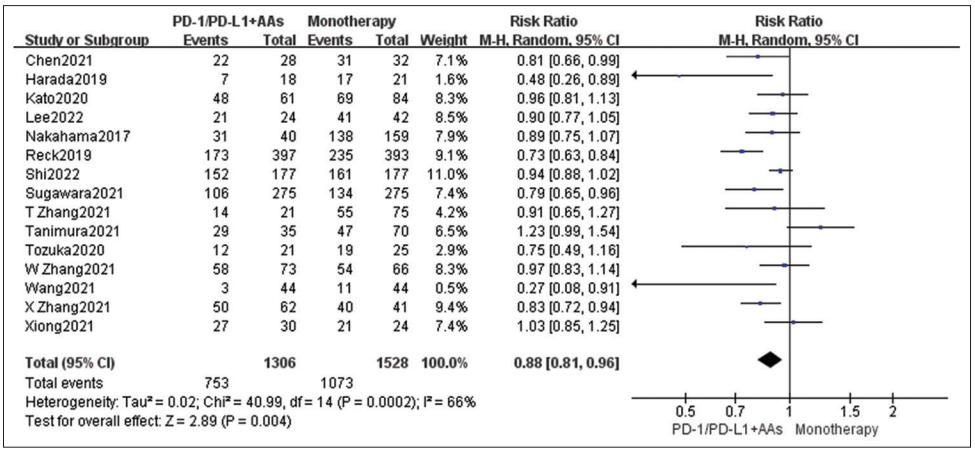

Figure 5: Forest plot of the objective response rate between protein-1/programmed cell death 1 ligand 1 plus anti-angiogenic drugs therapy and monotherapy. CI = Confidence interval; PD-1 = Protein-1; PD-L1 = Programmed cell death 1 ligand 1; AAs = Anti-angiogenic drugs

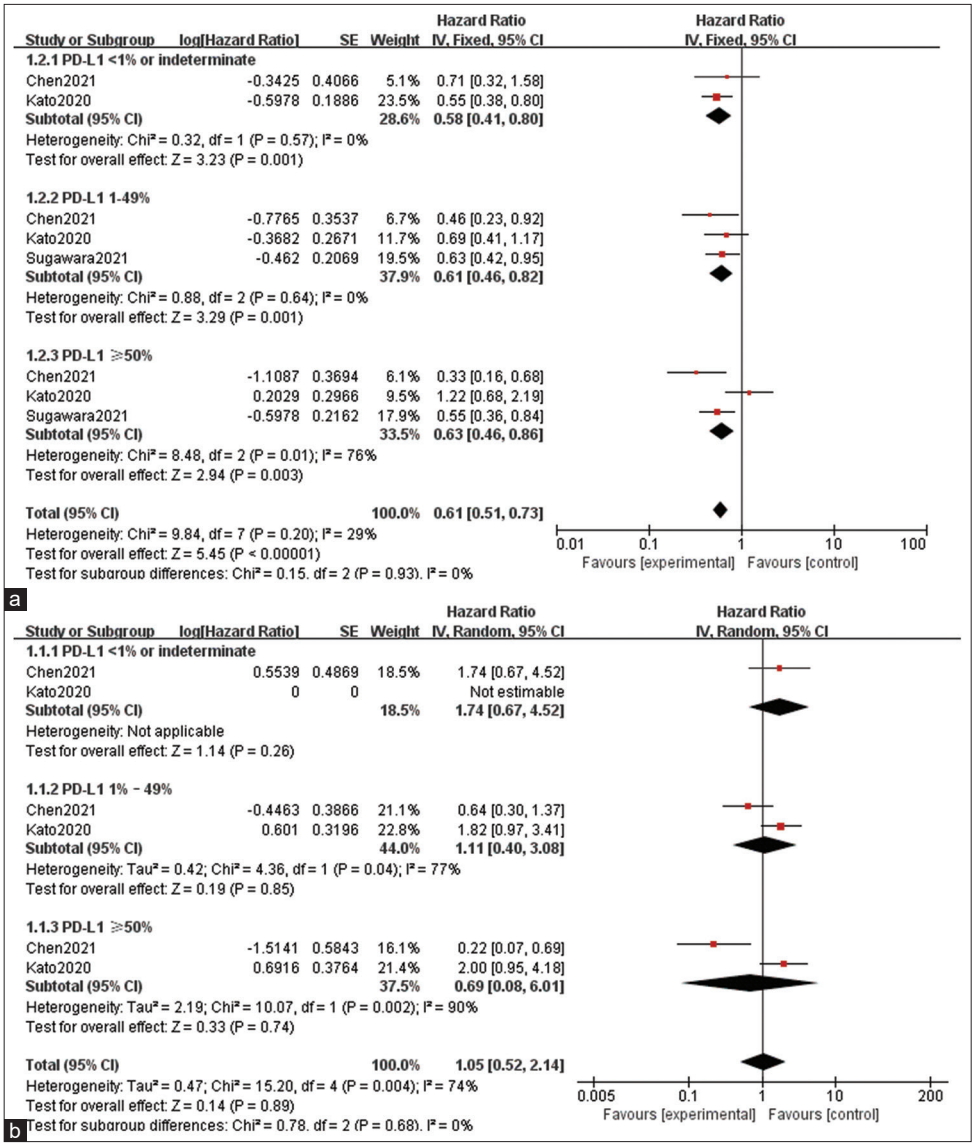

Figure 6: Subgroup analysis based on programmed cell death 1 ligand 1 expression of the progression-free survival (a), overall survival (b). SE = Standard error; CI = Confidence interval; PD-L1 = Programmed cell death 1 ligand 1

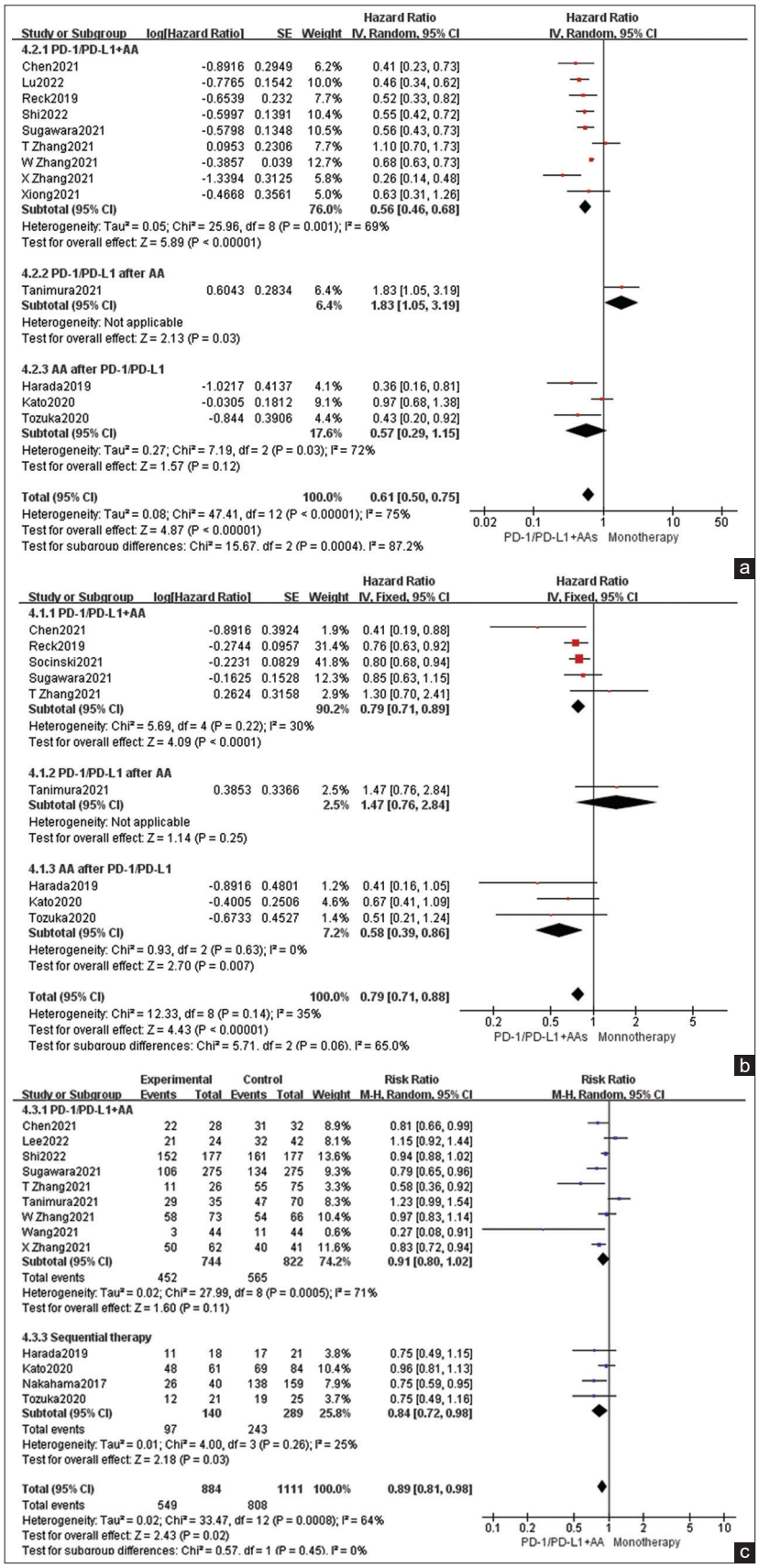

Figure 7: Subgroup analysis based on treatment order of the progression-free survival (a), overall survival (b), objective response rate (c). SE = Standard error; CI = Confidence interval; PD-1 = Protein-1; PD-L1 = Programmed cell death 1 ligand 1; AAs = Anti-angiogenic drugs

A subgroup analysis was performed based on EGFR mutation and showed significantly longer PFS in patients with the mutation [HR = 0.60, 95% CI: 0.39–0.92, P = 0.02, I^2 = 0%; Figure 8a], but not improvement in OS [HR = 0.76, 95% CI: 0.57–1.03, P = 0.07, I^2 = 0%; Figure 8b].

Sensitivity analysis and publication bias

The sensitivity analysis suggested that the results obtained for all indicators (PFS, OS, and ORR) were stable [Supplementary Figures 1-3]. A funnel plot was drawn to assess publication bias in the studies evaluating ORR in patients with advanced NSCLC, as illustrated in Figure 9. For the impact of RR on ORR, no publication bias was detected in Begg's test (P = 0.113) and Egger's test (P = 0.525).

DISCUSSION

In recent years, ICIs, including PD-1/PD-L1, have emerged as a promising approach in cancer therapy. However, there is a limited efficacy of PD-1/PD-L1 monotherapy for cancer patients, which is thought to be closely related to the high antigenicity of the tumor microenvironment due to primary drug resistance.[37] The overexpression of VEGF in tumors leads to abnormal vascular architecture, creating a selective immune cell barrier and deteriorating the hypoxic microenvironment, thus promoting the growth and metastasis of the tumor.[38] In addition, overexpressed vascular growth factor directly activates immunosuppressive cells and promotes tumor angiogenesis, creating a vicious cycle.[39,40] Combining PD-1/PD-L1 with AAs can remodel the tumor microenvironment and normalize blood vessels at tumor sites, leading to synergistic anti-tumor effects. Although several large-scale prospective RCTs have been conducted to evaluate the efficacy and safety of combining immunotherapy, anti-angiogenic therapy, and chemotherapy in treating advanced NSCLC, the results of most trials are still immature and inconclusive.

A total of 12 retrospective studies were included in this study, and five RCTs[21,25,34-36] reported PFS and OS. The meta-analysis results indicated that PD-1/PD-L1 combined with AAs has a better therapeutic effect than monotherapy in patients with advanced NSCLC, which can significantly improve ORR and significantly prolong PFS and OS. However, Lee *et al*.[25] showed that there was no improvement in PFS and ORR, due to the delayed anticancer effect. Similarly, the IMPOWER130 trial[41] showed that there was no significant benefit in terms of PFS or OS in patients with EGFR and ALK alterations, possibly due to a significant improvement in antigen-specific T-cell migration in NSCLC patients with EGFR mutations after AAs therapy. The dose of each drug was not analyzed in this paper. However, related studies have shown[42] based on the complexity of tumor cell signaling pathways, high doses of anti-angiogenic

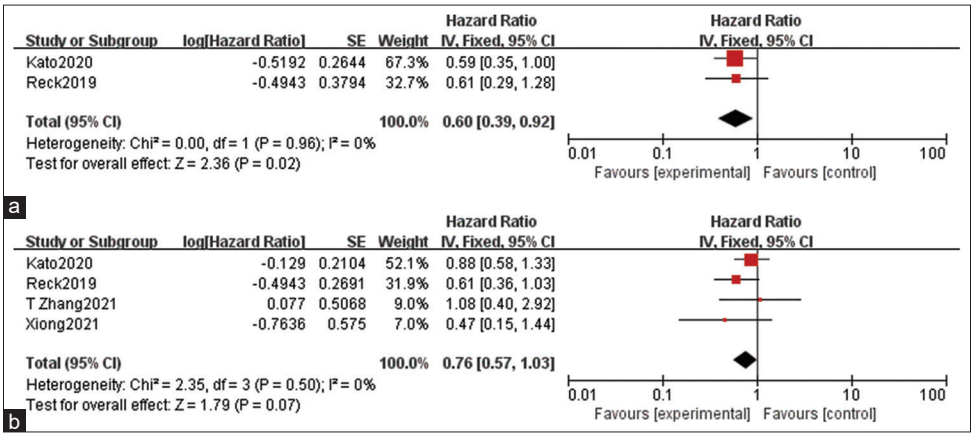

Figure 8: Subgroup analysis based on estimated glomerular filtration rate mutation of the progression-free survival (a) and overall survival (b). SE = Standard error; CI = Confidence interval

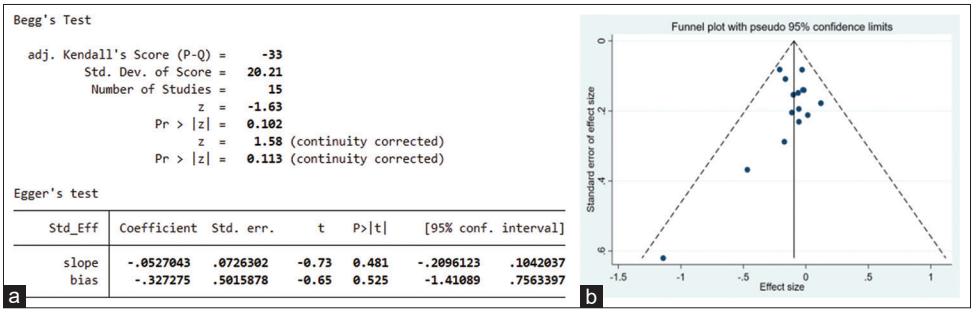

Figure 9: Publication bias plots for the objective response rate using Begg's test and Egger's test (a), and funnel plot (b)

agents may directly disrupt tumor vasculature causing more severe hypoxic and immunosuppressive effects when PD-1/PD-L1 combined with AAs are used in treating patients with advanced NSCLC. Therefore, more optimal doses of each drug need to be explored, and the scientific community working in this area is thus encouraged to evaluate their best dosage efficiency.

Our subgroup analysis based on treatment sequence revealed that AAs followed by PD-1/PD-L1 did not benefit PFS and OS. In contrast, combining PD-1/PD-L1 with AAs or PD-1/PD-L1 followed by AAs showed good PFS and OS benefits. Notably, Yang *et al*.[43] reported that PD-1/PD-L1 affects the efficacy of subsequent chemotherapy. One possibility is that prior PD-1/PD-L1 therapy has produced a beneficial change in the efficacy of cytotoxic chemotherapy in tumors and/or their microenvironment, and another is that treatment with AA overcomes PD-1/PD-L1 resistance mechanisms. Several prospective and retrospective studies[42,44] have demonstrated the efficacy of sequential treatment with AAs immediately after PD-1/PD-L1.

Similarly, the VARGADO trial[45] supported the potential benefits of PD-1/PD-L1 followed by AAs, consistent with our findings. Sensitivity analysis revealed that the results obtained for PFS and OS indicators were stable and reliable. Our meta-analysis involved advanced NSCLC treated with PD-1/PD-L1 + AA with or without chemotherapy. However, we acknowledge that combination therapy with chemotherapy will inevitably increase the toxicity inevitably, whether the use of only AAs drugs in combination with ICI or a "de-chemotherapy" treatment regimen could be an effective strategy for advanced NSCLC in advanced NSCLC, which can become a goal and direction for future exploration. Our study does not confirm whether PD-1/PD-L1 + AAs + chemotherapy is as effective as immunochemotherapy, and the optimal treatment regimen should be further optimized in combination with a comprehensive evaluation of tumor genomics and the tumor microenvironment in further.

However, this study has several limitations, and the results must be interpreted cautiously. First, the majority of the included studies were retrospective studies, with limited RCTs, and confounding factors such as specific diseases or drugs could not be excluded. Selection bias was not completely avoidable, which might have affected the results' reliability to a certain extent. Second, despite searching both Chinese and English databases, all the final included literature was in English, which may have resulted in incomplete data retrieval and language bias, potentially affecting the study results. Third, there were fewer studies on patients receiving AAs followed by PD-1/PD-L1, and some of the studies had a shorter follow-up period, which may have a particular impact on the results, so it is necessary to refer to this article cautiously. Finally, inconsistencies in drug regimens, population characteristics, and doses may have led to biased results.

CONCLUSION

The amalgamation of PD-1/PD-L1 inhibitors with AAs has exhibited notable advantages over monotherapy, with substantial improvements observed in PFS, OS, and ORR among advanced NSCLC patients, especially when PD-1/PD-L1 inhibitors are administered in conjunction with AAs or sequentially with PD-1/PD-L1 followed by AAs. However, it is important to note that no survival advantage was observed with the administration of AAs followed by PD-1/PD-L1. In the context of clinical applications, personalized dosing regimens should be tailored to individual patient characteristics. Future investigations necessitate more profound, rigorous, and high-quality prospective studies to corroborate and consolidate these findings.

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Conflicts of interest

There are no conflicts of interest.

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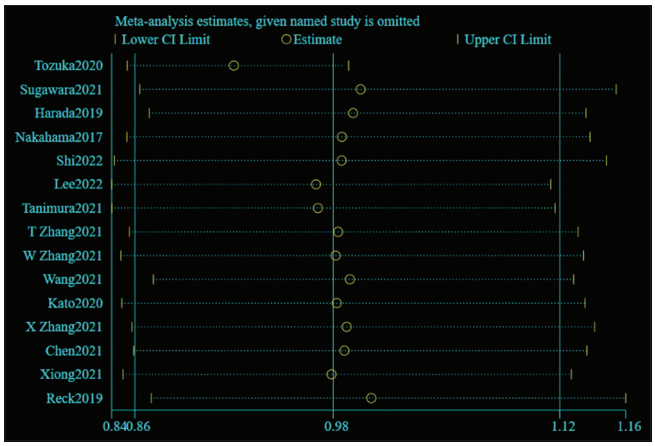
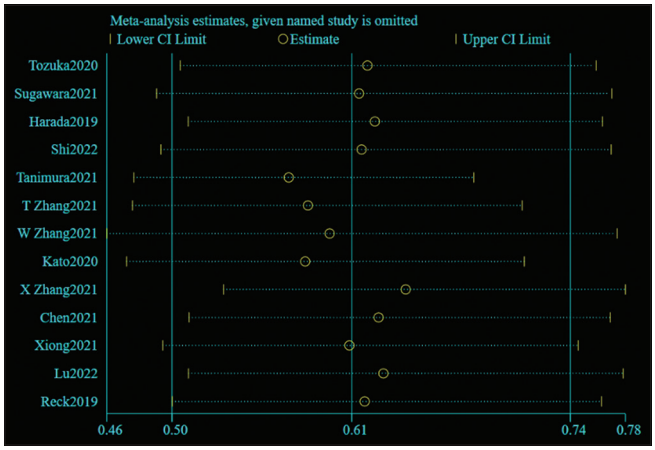
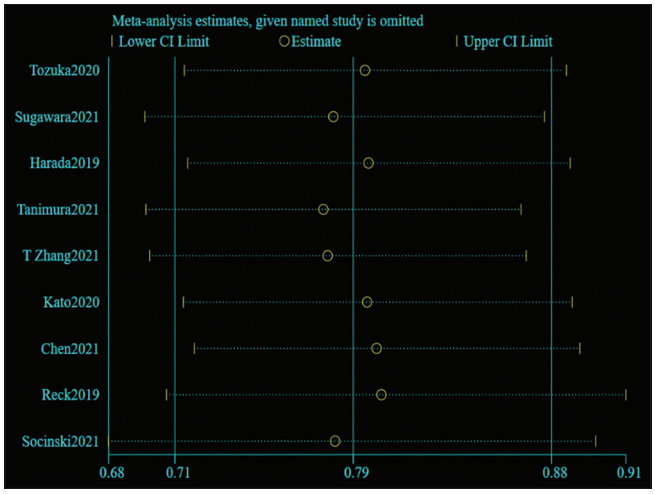


Supplementary Figure 1: Sensitivity analysis of objective response rate. CI = Confidence interval



Supplementary Figure 2: Sensitivity analysis of progression free survival. CI = Confidence interval



Supplementary Figure 3: Sensitivity analysis of overall survival. CI = Confidence Interval