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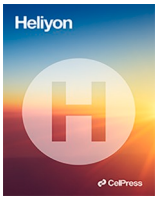

Research article

Efficacy of immunotherapy in *RET* fusion-positive NSCLC: A meta-analysis

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ABSTRACT

Background: The Rearranged during Transfection (*RET*) gene represents a rare driver mutation in non-small cell lung cancer (NSCLC) occurring in only 1 %–2 % of cases, with implications in targeted carcinogenesis. Despite the significant efficacy demonstrated by immunotherapy in advanced NSCLC with wild-type driver genes, its validation in *RET* fusion-positive patients is yet to be established.
Objectives: This meta-analysis aims to systematically evaluate the effectiveness of immunotherapy in patients with *RET* fusion-positive NSCLC.
Data sources: and Methods: PubMed and Web of Science databases were systematically searched for relevant studies. Outcomes including objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were extracted for further analysis.
Results: Ten real-world evidence (RWE) studies involving 7145 patients were enrolled in this meta-analysis. In terms of tumor response, the pooled ORR and DCR were 24.0 % and 61.0 %, respectively. Regarding survival analysis, the pooled median PFS and median OS were 4.17 months [95 % confidence interval (CI): 3.40–5.02) and 17.22 months (95 % CI: 11.58–23.91)], respectively. Subgroup analyses showed that immunotherapies plus chemotherapy were superior to single-immunotherapy in terms of ORR, DCR, and median PFS, which were 43 % (95 % CI: 31%–55 %) vs. 17 % (95 % CI: 11%–25 %), 74 % (95 % CI: 60%–84 %) vs. 45 % (95 % CI: 31%–59 %) and 6.69 months (95 % CI: 4.91–8.93) vs. 2.96 months (95 % CI: 2.25–3.78), respectively.
Conclusions: To date, *RET* fusions appear to be associated with poor response to immunotherapy in NSCLC patients, and immunotherapy combined with chemotherapy seems to offer greater clinical benefits than mono-immunotherapy.

1. Introduction

Rearranged during transfection (*RET*) fusion is a rare oncogenic driver in 1–2% of non-small cell lung cancer (NSCLC) patients [1]. It is closely associated with tumor cell proliferation, invasion, and migration, with the most common subtype being *KIF5B-RET*(53.8 %) and *CCDC6-RET*(17 %) [2,3]. NSCLC patients with *RET* fusion share clinical characteristics with *ALK/ROS1* fusion-positive patients,

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Abbreviations

RET	rearranged during transfection
NSCLC	non-small cell lung cancer
ORR	objective response rate
DCR	disease control rate
PFS	progression-free survival
OS	overall survival
PRISMA	Preferred Reporting Items for Systematic and Meta-Analyses
RWE	real-world evidence
CI	confidence interval
TKIs	tyrosine kinase inhibitors
ICIs	immune checkpoint inhibitors
PD-L1	programmed death ligand-1
PD-1	programmed death-1
ICPi	immune checkpoint inhibitors
ICBs	immune checkpoint blockades
JBI	Joanna Briggs Institute
GLMM	generalized linear mixed model
TMB	tumor mutational burden
MSI	microsatellite instability

including higher incidences in younger, female, and non-smoking populations, and a common adenocarcinoma subtype [4]. Additionally, *RET* fusion-positive NSCLC patients have an elevated risk of brain metastases compared to *RET* fusion-negative patients [5]. The majority of *RET* fusion-positive NSCLC patients are diagnosed at advanced stages, with only 5.4–14 % at early stage (stage I/II) [6–8].

In recent years, significant progress has been made in treating *RET* fusion-positive NSCLC. Selective *RET* tyrosine kinase inhibitors (TKIs) like pralsetinib and selpercatinib have demonstrated remarkable efficacy, with median progression-free survival (PFS) of 13–22 months and objective response rate (ORR) of approximately 59–84 % [9,10]. However, their clinical use is constrained by drug accessibility and eventual resistance. Traditional chemotherapy remains a limited option for *RET* fusion-positive NSCLC patients, yielding a median PFS of 5–9 months and ORR of approximately 50–60 % [6,8,11]. Yet, chemotherapy is often limited by drug resistance or intolerable toxicity effects. Immune checkpoint inhibitors (ICIs), such as anti-programmed death ligand-1 (anti-PD-L1) and anti-programmed death-1 (anti-PD-1) antibodies, have revolutionized cancer treatment, being recommended as first and second-line options for advanced wild-type NSCLC [12]. However, data on the efficacy of immunotherapy in *RET* fusion-positive NSCLC patients are currently lacking. Therefore, we conducted this meta-analysis to systematically evaluate the efficacy of immunotherapy in patients with *RET* fusion-positive NSCLC.

2. Methods

2.1. Search strategy

This meta-analysis adheres to the Preferred Reporting Items for Systematic and Meta-Analyses (PRISMA) guidance. A completed PRISMA checklist is included in Supplementary Material S1 (PRISMA Checklist). We searched databases including PubMed and Web of Science, for relevant studies from their inception until August 2023. Studies were identified using any of the following key words: "*RET* fusion OR *RET*-aberrant OR *RET*-Rearranged OR *RET* rearrangement OR *RET*-translocation OR Rare targetable drivers" AND "immunotherapy OR immune checkpoint blocker OR immune checkpoint inhibitor OR ICI OR ICPi OR ICBs OR pembrolizumab" AND "Non-small Cell Lung Cancer OR Lung Cancer OR NSCLC OR non-small lung cancer" (See Supplementary Material S2). We also checked reference lists of relevant review articles and related studies to prevent omissions. This meta-analysis was restricted to human studies published in English due to accessibility and data availability considerations.

Only real-world evidence (RWE) studies that assessed the efficacy of ICIs in patients with *RET* fusion-positive NSCLC were included. Systematic reviews, meta-analysis, letters, case reports, and non-English publications were excluded. Additionally, RWE studies with unclear data on treatment related effectiveness were also excluded. The studies identified through the search were independently screened by two authors (Zhongsheng Peng and Kaibo Ding) for inclusion. Any disagreements were arbitrated by a third author (Mingying Xie).

2.2. Data extraction

The study protocol was registered on PROSPERO (registration ID: CRD42023479763). The required data from all included studies were independently extracted by two investigators. Subsequently, we conducted a quality assessment of the studies. Extracted

characteristics included the authors' names, publication year, nation, sample size, *RET*-fusion patients receiving ICI treatment, gender, PD-L1 expression, intervention, number of treatment lines, and reported endpoints. Clinical outcome measures comprised ORR, disease control rate (DCR), overall survival (OS) and PFS. We assessed retrospective studies using the Joanna Briggs Institute (JBI) critical appraisal checklist for case series [13].

2.3. Statistical analysis

Meta-analyses were conducted in R 4.1.3(R Programming), using the meta and metafor packages. A generalized linear mixed model (GLMM) was implemented for the meta-analysis of proportions [14]. Heterogeneity among studies was comprehensively evaluated using the I^2(I-squared) statistic, Cochran's Q test, and visual inspection of forest plots. Studies were categorized according to I^2 values: <40 % for low heterogeneity, 40–75 % for moderate, and >75 % for high heterogeneity [15]. Cochran's Q test with a p-value <0.1 indicated significant inter-study variability. A random-effects model was applied for analyses showing substantial heterogeneity ($p < 0.1$, I^2>50 %), ensuring robustness in the face of varying effect sizes. Otherwise, a fixed-effects model was used. Forest plots visually depicted study outcomes and confidence intervals, aiding in the qualitative assessment of heterogeneity and effect size consistency. Possible publication bias was assessed with funnel plots and Egger' s test.

3. Result

3.1. Search results and study characteristics

A total of 2382 references were identified. The reference flow is depicted in Fig. 1. Ten RWE studies including a total of 7145 patients were included [7,16–24]. It is important to note that the two original studies, Bhandari N.R. et al. and Aldea M. et al., each comprised two distinct subgroups of data [16,19]. Following a series of sensitivity analyses, all four groups of data from both studies met the pre-defined inclusion criteria. Consequently, we proceeded to define each of the two groups of data from these two articles, respectively, as the data sets from the original studies by Bhandari N.R. et al. (1), Bhandari N.R. et al. (2), and Aldea M. et al. (1), Aldea M. et al. (2) which were included in the meta-analysis, resulting in a total of 12 data sets from the 10 original studies. All 12 data sets were extracted from the 10 studies, all of which reported median PFS and ORR. Additionally, 7 data sets reported median OS, 8 data sets reported DCR, and only 3 data sets reported associated adverse events. The articles included in the meta-analysis were published

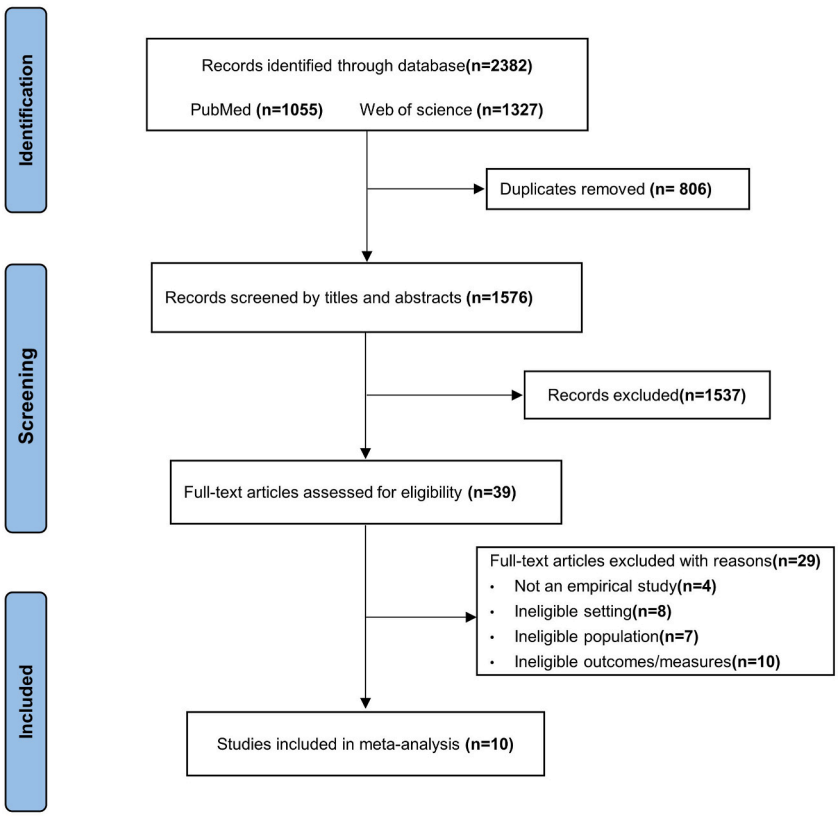

Fig. 1. Flow chart of articles identified, included and excluded.

between 2018 and 2023.These studies included five data sets involving immunotherapies plus chemotherapy [16–19], and seven data sets involving single-immunotherapy [7,16,20–24]. Important details about the included studies are presented in Table 1. The quality assessment details are shown in Table 2. Supplementary material S3 provides the quality assessment criteria for the included studies. Supplementary Table S1 summarizes the ORR, DCR, PFS and OS of the 12 data sets included in the meta-analysis, along with their 95 % CI.

3.2. Efficacy

3.2.1. ORR and DCR

A forest plot displaying all the pooled studies is presented in Fig. 2. The pooled ORR and its corresponding 95 % confidence interval (CI) were calculated. A p-value of 0.05 for the heterogeneity measure suggests the use of a random effects model, indicating an overall estimated ORR of 24 % (95 % CI: 14%–38 %). Furthermore, we divided the ten studies into two treatment regimen subgroups: mono-immunotherapy group and the immunotherapy combination chemotherapy group. We also performed a meta-analysis within each treatment regimen subgroup for exploratory purposes. Less heterogeneity was observed in the subgroup meta-analysis; hence, common-effect models were employed to estimate ORR and DCR. The ORR estimate was higher in patients treated with immunochemotherapy (43 %,95 % CI: 31%–55 %) compared to those receiving immunotherapy alone (17 %,95 % CI: 11%–25 %), as illustrated in Fig. 3A and B. The overall estimate of DCR for all studies was 61 % (95 % CI: 46%–74 %), as shown in Fig. 4. Additionally, the estimated DCR for the immunochemotherapy subgroup was 74 % (95 % CI: 60%–84 %) (see Fig. 5A), while for the mono-immunotherapy subgroup, it was 45 % (95 % CI: 31%–59 %) (shown in Fig. 5B).

3.2.2. PFS and OS

Due to the limited information in the published papers, we only had access to summary level data, such as median PFS and median OS. We used simulation techniques to estimate the median survival time. As demonstrated in previous meta-analysis of ORR and Darwen single-immunotherapy studies and immunochemotherapy studies were separately analyzed, the clinical outcomes showed less

Table 1
Characteristics of the studies included in the meta-analysis.

Authors	Year	Publication of journals	Nation	Sample size(n)	patients of RET+ with ICI(n)	Male (n)	PD-L1 (TPS%: /0/ 1–100)	Intervention	Line	Endpoints
Guisier F. et al.	2020	Journal of Thoracic Oncology	France	107	9	5	1/5/3	Single-immunotherapy	≥second-line	ORR, DCR, PFS and OS
Dudnik E. et al.	2018	Lung Cancer	Israel	82	4	–	–	Single-immunotherapy	≥first-line	ORR, PFS and OS
Offin M. et al.	2019	Journal of Clinical Oncology: Precision Oncology	America	74	16	–	5/7/4	Single-immunotherapy	≥first-line	ORR, PFS and AEs
Lu C. et al.	2020	Journal of Hematology & Oncology	Chian	129	10	–	2/2/6	Single-immunotherapy	≥first-line	ORR, DCR and PFS
Lee J. et al.	2020	Japanese Journal of Clinical Oncology	Korean	59	13	–	–	Single-immunotherapy	≥first-line	ORR, DCR, PFS and OS
Mazieres J. et al.	2019	Annals of Oncology	France	551	16	7	10/2/4	Single-immunotherapy	≥first-line	ORR, DCR, PFS and OS
Hess L.M. et al.	2021	BioMed Central Cancer	America	5807	9	–	–	ICI + chemotherapy	first-line	ORR, DCR, PFS and OS
Bhandari N.R. et al. (1)	2021	Immunotherapy	America	69	17	16	16/7/6	ICI + chemotherapy	first-line	ORR, DCR, PFS and OS
Bhandari N.R. et al. (2)	2021	Immunotherapy	America	49	11			ICI + chemotherapy	first-line	ORR, DCR, PFS and OS
Meng Y. et al.	2022	Frontiers in Oncology	Chian		26	–	13/9/4	ICI + chemotherapy	≥first-line	ORR, DCR and PFS
Aldea M. et al. (1)	2023	Journal of Thoracic Oncology	Europe	218	37	18	3/10/24	ICI + chemotherapy	first-line	ORR, PFS and AEs
Aldea M. et al. (2)	2023	Journal of Thoracic Oncology	Europe		52	35	15/18/ 19	Single-immunotherapy	≤second-line	ORR, PFS and AEs

RET, rearranged during transfection; RET+, RET-fusion positive; ICI, immune checkpoint inhibitor; PD-L1, programmed death ligand-1; TPS, tumor proportion score; -: not report; NR, not reach; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; AEs, adverse events.

Table 2
JBI critical appraisal quality assessment of the studies included in the meta-analysis.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Proportion of Y
Guisier F. et al., 2020	Y	Y	Y	N	Y	Y	Y	Y	N	Y	8/10
Dudnik E. et al., 2018	Y	Y	Y	Y	N	Y	Y	Y	N	Y	8/10
Offin M. et al., 2019	Y	Y	Y	N	Y	Y	Y	Y	N	Y	8/10
Lu C. et al., 2020	N	Y	Y	Y	N	Y	Y	Y	N	N	6/10
Lee J. et al., 2020	N	Y	Y	Y	N	Y	Y	Y	N	N	6/10
Mazieres J. et al., 2019	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	9/10
Hess L.M. et al., 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/10
Bhandari N.R. et al., 2021	Y	N	Y	Y	Y	Y	Y	Y	N	N	7/10
Meng Y. et al., 2022	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	9/10
Aldea M. et al., 2023	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	9/10

Y: Yes; N: No; For a detailed explanation of the quality assessment criteria (Q1-Q10), see Supplementary Material S2.

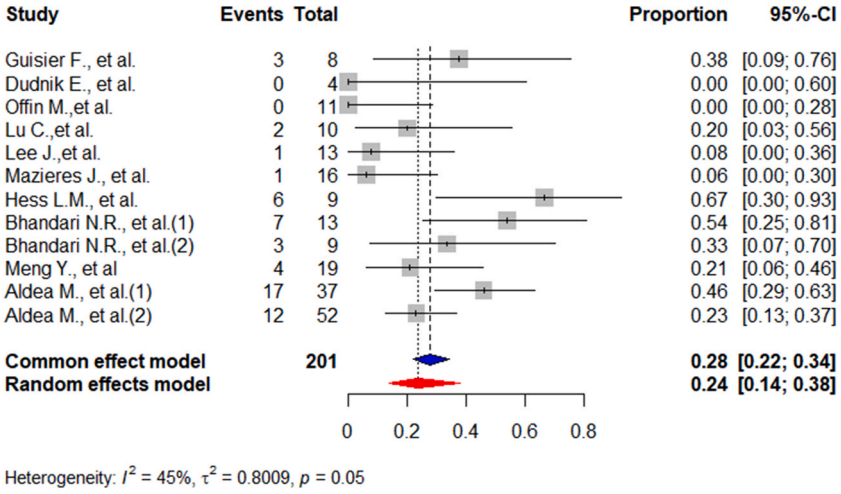

Fig. 2. Forest plot of objective response rate (ORR) for all pooled studies. The Forest plot shows the pooled overall ORR for all studies, with an estimated ORR of 24 % (95 % CI: 14%–38 %, p = 0.05, I^2 = 45 %).

heterogeneity. Based on this assumption, we simulated survival times separately for single-immunotherapy and immunochemotherapy. Taking OS as an example, assuming that the survival time obeys the exponential distribution with expectation λ, each study generates n random numbers obeying the exponential distribution according to their respective mOS for the expectation λ. Combine the results of the five studies to find the combined median, 2.5 % quantile and 97.5 % quantile, with the random seed set to 1234; repeat the above steps for 10,000 times, and obtain 10,000 median, 2.5 % quantile and 97.5 % quantile, respectively, 2.5 % quantile and 97.5 % quantile, respectively. Their mean values were used as the median time to death (mOS) and the lower limit of the 95 % CI and the upper limit of the 95 % CI estimated from the simulation. Based on 10000 simulations, the estimate of median PFS is 2.96 months (95 % CI: 2.25–3.78) for single-immunotherapy and 6.69 months (95 % CI: 4.91–8.93) for immunochemotherapy. Studies with both known PFS and OS were pooled, resulting in a median PFS of 4.17 months (95 % CI: 3.40–5.02) and a median OS of 17.22 months (95 % CI: 11.58–23.91). Table 3 summarizes the original and simulated PFS and OS data for the studies included in the Meta-analysis. One limitation is that the follow-up time was not reported for the majority of the studies. The variability in follow-up time could reduce comparability of the studies and therefore the interpretability of the simulation results.

3.2.3. Publication bias

Publication bias was assessed using funnel plots and Egger's test. The funnel plot for DCR (supplementary Figure S1) did not demonstrate significant asymmetry, and Egger's test found no evidence of publication bias (p = 0.241). Regarding ORR, no publication bias was observed through visual inspection of a funnel plot and an Egger test (p = 0.153) (supplementary Figure S2). Limitations exist due to the limited disclosure of relevant data.

3.2.4. Heterogeneity

The forest plots visually depicted ORR and DCR estimates and intervals, revealing broad data ranges and minimal confidence interval overlaps, suggesting high heterogeneity. Analysis across twelve studies consistently indicated moderate heterogeneity, with an I^2 of 45 %, a Cochran's Q test p-value nearing 0.05, and comparable DCR heterogeneity levels. Regression analyses explored heterogeneity sources, factoring in publication year, immunotherapy line (first/second), and combination therapy use. Findings

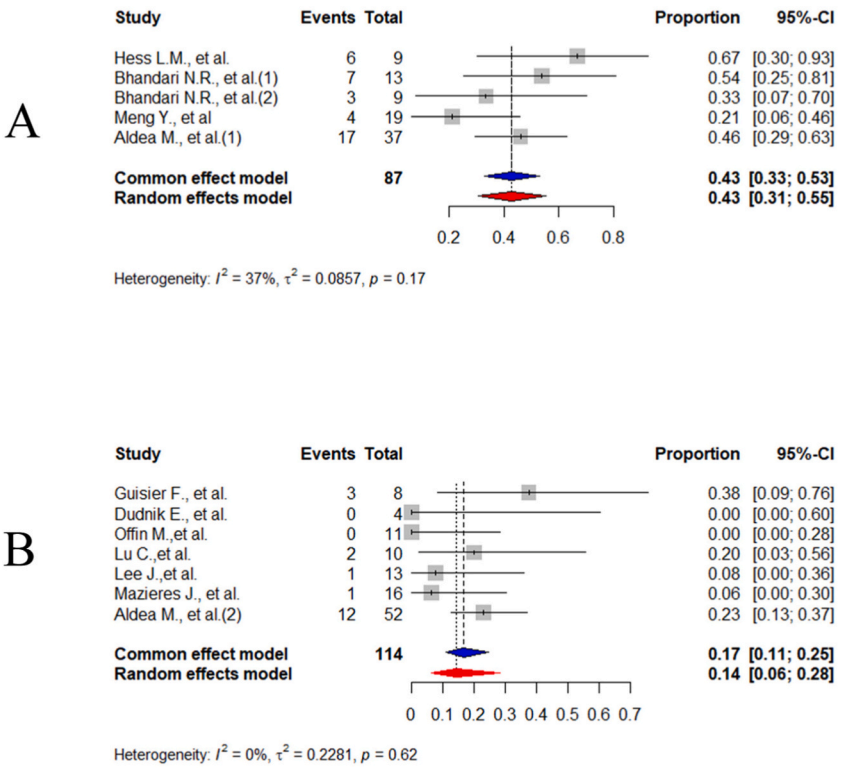

Fig. 3. **A**:Forest plot of objective response rate (ORR) for studies with immunochemotherapy. This forest plot displays the ORR for studies involving immunochemotherapy, with an estimated ORR of 43 % (95 % CI: 31%–55 %, p = 0.17, I^2 = 37 %). **B**: Forest plot of ORR for studies with mono-immunotherapy. This forest plot displays the ORR for studies involving mono-immunotherapy, with an estimated ORR of 17 % (95 % CI: 11%–26 %, p = 0.62, I^2 = 0 %).

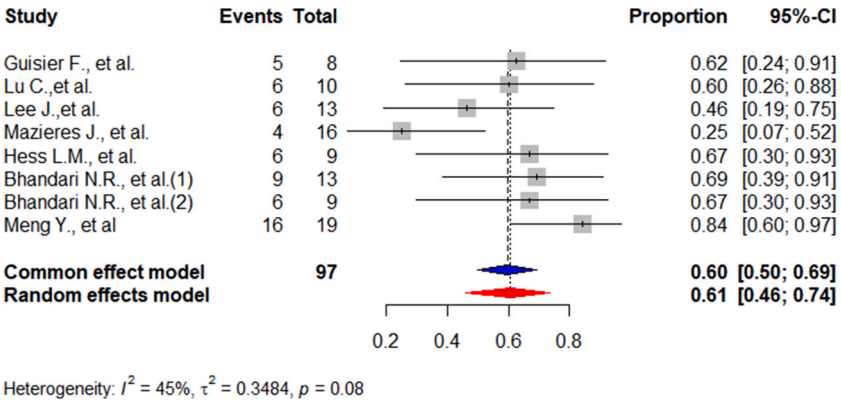

Fig. 4. Forest plot of disease control rate (DCR) for all pooled studies. The forest plot illustrates the overall DCR across all studies, estimating a DCR of 61 % (95 % CI: 46%–74 %, p = 0.08, I^2 = 45 %).

showed significant effects of these factors on ORR heterogeneity (publication year: p = 0.0449; therapy line: p = 0.0019; combination therapy: p = 0.00017). Publication year and combination therapy similarly impacted DCR heterogeneity (p = 0.0006 and p = 0.0039, respectively). Notably, therapy line did not significantly influence DCR heterogeneity (p = 0.3997). The bubble plots can be found in Supplemental Fig. S3.

4. Discussion

Immunotherapy is a highly relevant and critical topic in NSCLC treatment. Its goal is to establish or enhance an effective immune response against tumors, thereby increasing anti-tumor activity [12,25]. Currently, the most widely used predictive biomarkers with

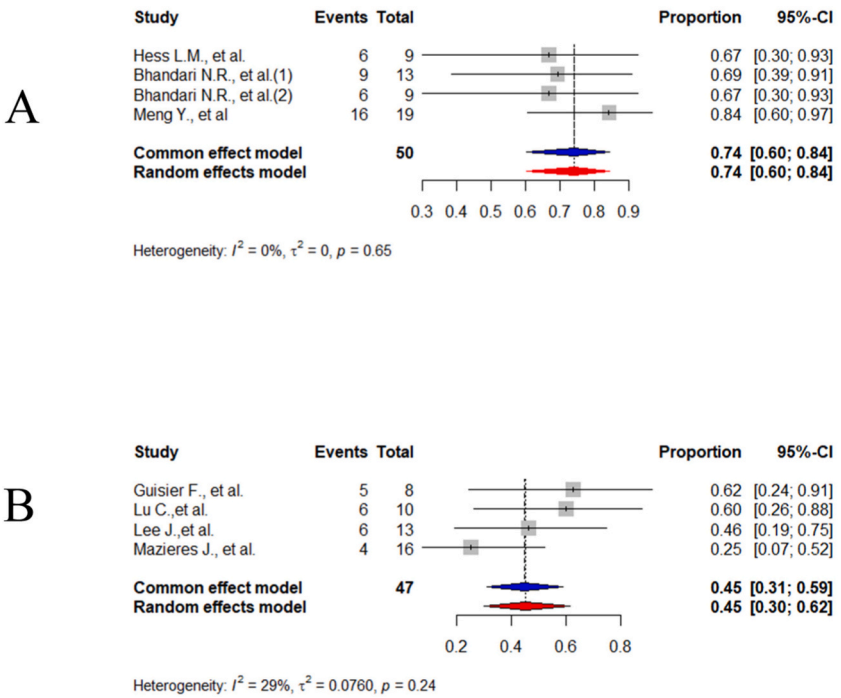

Fig. 5. A: Forest plot of disease control rate (DCR) for studies with immunochemotherapy. This forest plot depicts the DCR for studies with immunochemotherapy, demonstrating a DCR of 74 % (95 % CI: 60%–84 %, p = 0.65, I^2 = 0 %). **B:** Forest plot of DCR for studies with mono-immunotherapy. This forest plot depicts the DCR for mono-immunotherapy studies, with an estimated DCR of 45 % (95 % CI: 31%–59 % p = 0.24, I^2 = 29 %).

ICIs include PD-1/PD-L1, TMB, and microsatellite instability (MSI) [26]. These biomarkers help predict the effectiveness of immunotherapy. Our meta-analysis included 12 data sets from the 10 original studies, comprehensively assessing the effectiveness of ICIs for the treatment of advanced *RET* fusion-positive NSCLC. The pooled analysis demonstrated the efficacy of immunotherapy through a comprehensive evaluation of the data from multiple studies. Despite variations in disease conditions and treatments approaches, the pooled results revealed an ORR of 24.0 %, a DCR of 61.0 %, a median PFS of 4.17 months and a median OS of 17.22 months. Subgroup analyses showed that the combination of immunotherapy and chemotherapy outperformed single-immunotherapy in terms of ORR, DCR, and median PFS, with rates of 43 % (95 % CI: 31%–55 %) vs. 17 % (95 % CI: 11%–25 %), 74 % (95 % CI: 60%–84 %) vs. 45 % (95 % CI: 31%–59 %), and 6.69 months vs. 2.96 months, respectively.

While single-immunotherapy can provide some survival benefit to patients to some extent, its effect does not appear to be significant. In oncogene-driven NSCLC, PD-11/PD-L1 inhibitors tend to have limited efficacy. This limitation arises from the fact that the primary oncogenic drivers are associated with intrinsic resistance to ICIs [25,27]. For instance, *RET* is involved in promoting cancer-related inflammation and suppressing anti-cancer immune responses [28]. Previous studies have shown that *RET* fusion NSCLC usually exhibits low PD-L1 expression and low TMB [29,30]. These factors may explain the poor efficacy of immunotherapy in this population. Several studies have shown that immune-combination chemotherapy demonstrates stronger efficacy compared to immune monotherapy. Moreover, it offers benefits irrespective of the PD-L1 expression level, making it the most common first-line treatment modality for advanced NSCLC today [31–34]. In the subgroup of *RET* fusions, two prospective studies are currently underway. While no data have been published yet from the ongoing LIBRETTO-431 Phase 3 study, which is evaluating the first-line use of immune-combination chemotherapy in *RET* fusion-positive NSCLC, we eagerly anticipate its results [35]. Similarly, the Poseidon trial in China, a prospective study assessing the efficacy of ICIs in *RET*-fusion positive NSCLC, is also currently underway [36]. The forthcoming publication of these findings holds significant promise for advancing our understanding of treatment options in these patients.

Compared to immunotherapy, Chemotherapy is the traditional treatment. A study by Drilon A et al. demonstrated that pemetrexed resulted in a 45 % ORR and a median PFS of 19 months in patients with *RET*-fusion NSCLC, which is comparable to the efficacy seen in ALK/ROS1 fusion cases [37]. Additionally, a Chinese study also indicated that pemetrexed-based chemotherapy outperformed other chemotherapy regimens in this subgroup [11]. In 2018, two RET-TKIs emerged with significant efficacy. In the phase I/II clinical trial of LIBRETTO-001, selpercatinib exhibited an ORR of up to 61 % and a median PFS of 24.9 months in patients with *RET* fusion-positive NSCLC who had received prior platinum-based chemotherapy [9]. Similarly, selpercatinib also demonstrated excellent efficacy in treatment-naive *RET* fusion-positive NSCLC patients. These patients achieved an ORR of 84 % and a median PFS of 22.0 months [9]. Prasertinib achieved similar efficacy in phase I/II of the ARROW study, with an ORR of 78 % and a median PFS of 12.6 months in untreated patients; patients who had previously received platinum therapy also had an ORR of 63 % and a median PFS of 12.6 months

Table 3
The summary of original and simulated PFS and OS data from studies included in Meta-analysis.

Factors	Single-immunotherapy							Immunochemotherapy				
	Guisier F. et al.	Dudnik E. et al.	Offin M. et al.	Lu C. et al.	Lee J. et al.	Mazieres J. et al.	Aldea M. et al. (2)	Hess L. M. et al.	Bhandari N.R. et al. (1)	Bhandari N.R. et al. (2)	Meng Y. et al.	Aldea M. et al. (1)
The Samples(n)	9	4	16	10	13	16	52	9	17	11	26	37
The median PFS in Months (95%CI)	7.6 (2.3-NR)	3.0 (1.9–3.1)	3.4 (2.1–5.6)	2.5 (1.1–5.8)	2.1 (1.6–2.6)	2.1 (1.3–4.7)	9.6 (5.2–13.8)	6.6 (0.4-NR)	4.2 (1.4–8.4)	4.4 (1.5-NR)	6.7 (2.9–10.5)	3.1 (2.4–7.0)
The estimate of median PFS in Months(95%CI)	2.96 (95 % CI: 2.25–3.78)							6.69 (95 % CI: 4.91–8.93)				
The estimated overall median PFS in Months (95%CI)	4.17 (95 % CI: 3.40–5.02)											
The median OS in Months (95%CI)	NR	14.9 (7.2–19.7)	-	-	12.4 (2.9–21.8)	21.3 (3.8–28.0)	-	NR	19.1 (6.9-NR)	16.0 (3.7-NR)	-	-
The estimated overall median OS in Months (95%CI)	17.22 (95 % CI: 11.58–23.91)											

PFS: progression-free survival; OS: overall survival; CI: confidence interval; NR, not reach; -: not reported.
The median PFS/OS in Months(95%CI): Original median PFS and OS data from studies included in the Meta-analysis.
The estimate of median PFS in Months(95%CI): Median PFS and 95 % confidence intervals for studies receiving mono-immunotherapy and immune-combination chemotherapy, respectively, in included meta-analyses derived from simulation methods.
The estimated overall median PFS/OS in Months (95%CI): Median PFS, OS and 95 % confidence intervals for all studies included in the meta-analysis based on simulation methods.

[38]. Notably, they showed superior efficacy compared to previous treatment modalities. These findings highlight the potential of RET-TKIs as a treatment option for patients with *RET* fusion-positive NSCLC. Overall, based solely on efficacy data, both pemetrexed chemotherapy and RET-TKIs were more effective than immunotherapy.

This meta-analysis, marking the initial evaluation of immunotherapy's efficacy in RET-fusion NSCLC, acknowledges several limitations. Firstly, inherent to a single-arm study design, considerable heterogeneity exists amongst the included studies, exacerbated by inadequate baseline data, precluding a thorough exploration of heterogeneity origins, and our analysis was confined to subgroup examinations based on prior treatment regimens. Secondly, the included studies were all non-controlled trials with small sample size, and thus, our assessment focused solely on efficacy without drawing definitive conclusions. Thirdly, the scarcity of detailed raw data posed challenges in assessing the adverse reactions associated with immunotherapy. Moreover, the absence of a control group in this single-arm meta-analysis precluded direct comparisons of immunotherapy's effectiveness against alternative treatments in advanced RET fusion-positive NSCLC scenarios. Further, larger-scale studies are required to ascertain the efficacy of ICIs in patients with RET fusion-positive NSCLC and to address the limitations.

5. Conclusions

In conclusion, our meta-analysis demonstrated that *RET* fusion seems to imply a poorer response to immunotherapy in NSCLC patients and a greater clinical benefit of immunotherapy combined with chemotherapy compared to single immunotherapy. Evidence is provided for its future clinical application. However, due to limited clinical data, future large-scale, multicenter research trials are needed to confirm this conclusion.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Availability of data and materials

The original contributions presented in the study are included in the article/Supplementary Material.

CRediT authorship contribution statement

Zhongsheng Peng: Writing – review & editing, Writing – original draft, Data curation. **Kaibo Ding:** Writing – review & editing, Supervision, Investigation. **Mingying Xie:** Writing – review & editing, Visualization. **Yanjun Xu:** Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34626.

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