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REVIEW

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The efficacy of immunotherapy in non-small cell lung cancer with KRAS mutation: a systematic review and meta-analysis

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Abstract

Purpose The KRAS mutation is highly prevalent in NSCLC and is associated with poor efficacy of immunotherapy. Nevertheless, the impact of KRAS mutation, mutation subtypes, and co-mutations on the effectiveness of immunotherapy remains uncertain. This study aimed to assess the influence of the KRAS mutation on the effectiveness of immunotherapy in NSCLC, specifically examining different subtypes of KRAS mutations and co-mutations.

Methods We performed an extensive search of multiple databases, covering the period from January 1, 2000, to December 5, 2023. A total of 24 articles met our inclusion criteria and were included in this study. A comparative analysis assessed the influence of different subgroups, including KRAS mutation, KRAS wild-type, KRAS G12C mutation, KRAS G12D mutation, and KRAS with co-mutations in NSCLC with immunotherapy. The study outcomes include HR, with corresponding 95% CI and P-values for OS and PFS using Review Manager 5.4 software for the meta-analysis.

Result The KRAS mutation appears to have a more beneficial impact on OS (HR 0.54 [95% CI: 0.41–0.71]; $P < 0.00001$) and PFS (HR 0.63 [95% CI: 0.53–0.76]; $P < 0.00001$) in NSCLC patients receiving immunotherapy compared to those without immunotherapy. The presence of KRASG12C mutation has been found to have a positive impact on PFS (HR 0.39 [95% CI: 0.25–0.62]; $P < 0.0001$) in NSCLC patients who undergo immunotherapy, compared to those who did not receive immunotherapy. KRAS non-G12D mutation is considerably associated with longer OS (HR 1.52 [95% CI: 1.10–2.10]; $P = 0.01$). The clinical benefit in OS between patients without STK11 co-mutation and those who have KRAS mutation with STK11 is significant (HR 1.46 [95% CI: 1.10–1.93]; $P = 0.008$). Comparing the impact of OS patients without KEAP1/NFE2L2 mutation to those with KRAS and KEAP1/NFE2L2 co-mutations showed a significant impact (HR 1.89 [95% CI: 1.33–2.68]; $P = 0.0004$).

Conclusion The KRAS mutation and KRAS G12C mutation confer benefits that impact OS and PFS in NSCLC patients treated with immunotherapy. However, the KRAS G12D mutation negatively impacts OS compared to the KRAS non-

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G12D mutation. Furthermore, KRAS co-mutations involving STK11 and KEAP1/NFE2L2 are associated with a negative impact on the efficacy of immunotherapy in NSCLC patients.

Keywords KRAS mutation, KRAS mutation subtype, KRAS co-mutation, Immunotherapy, NSCLC, Meta-analysis, Systematic review

Introduction

The Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) mutation is a prevalent form of mutation in non-small cell lung cancer (NSCLC), representing about 28% of cases. The primary mutation site is codon 12 [1]. Despite discovering KRAS mutation in NSCLC over four decades ago, there is no effective treatment strategy for KRAS mutant NSCLC. The current international guidelines suggest using platinum-based chemotherapy as the initial therapy for most NSCLC cases, including those with KRAS mutations [2]. Nevertheless, individuals with a KRAS mutation typically experience unfavorable results, considerably affecting their overall survival time [3, 4].

KRAS mutations seem to influence prognosis, a finding that is supported by many studies. In a previous study observed that patients with KRAS mutations experienced shorter OS compared to those with KRAS wildtype (HR: 1.22; 95% CI: 1.05–1.43; $P=0.011$) [5]. And then, other related studies similarly observed that patients with KRAS codon 13 mutant tumors had a shorter OS compared to those with codon 12 mutant tumors [6, 7]. In the KRYSTAL-1 study, the research found that NSCLC patients with KRAS G12C mutations derive benefit from adagrasib (objective response rate (ORR)=42.9%; median duration of response (DOR)=8.5 months (95% CI: 6.2–13.8); median progression-free survival (mPFS)=6.5 months (95% CI: 4.7–8.4); median overall survival (mOS)=12.6 months (95% CI: 9.2-NE)) [8]. Thus, KRAS codon 13 mutations appear to be a prognostic factor of adversity for NSCLC patients. However, in the newly developed KRAS G12C inhibitors, it seems that patients with KRAS G12C mutations may benefit from them.

Research has indicated that KRAS is not the sole mutation present in NSCLC. The most common mutation types among KRAS mutations in NSCLC are Tumor Suppressor P53 (TP53) (42%), Serine Threonine Kinase 11 (STK11) (29%), and Kelch-like ECH-associated protein 1/Nuclear factor, erythroid 2 like 2 (KEAP1/NFE2L2) (27%) [9]. Notably, the influence of gene mutation, particularly KRAS and STK11, on NSCLC immunotherapy is significant. A KRAS mutation is a critical component for inflammatory tumor microenvironment and increased tumor immunogenicity, impacting the effectiveness of immunotherapy [3, 4]. Patients with KRAS mutation experience a higher remission rate and 6-month progression-free survival (PFS) rate when undergoing immunotherapy treatment [10]. Studies have indicated a positive association between KRAS and TP53 co-mutation and the efficacy of NSCLC immunotherapy [11]. Conversely, the co-mutation of STK11 and KEAP1 combined with KRAS appears to be a negative influencing factor for immunotherapy [12]. By identifying specific molecular characteristics, clinicians can better predict recurrence risks and tailor more personalized and effective adjuvant therapy for patients with KRAS co-mutations, potentially improving overall outcomes and survival rates.

Immunotherapy has become a central focus in lung cancer research, showing significant improvement in overall survival (OS) compared to traditional chemotherapy [13]. For example, the CheckMate-057 trial revealed that the KRAS mutant subgroup experienced the most significant overall survival (OS) benefit with Natalizumab monoclonal antibody treatment [14]. Immunotherapy has become a prevalent treatment modality for advanced lung cancer, particularly in NSCLC. In the United States, the Food and Drug Administration (FAD) has approved immunotherapy alone or in combination with other immunotherapy and chemotherapy to treat advanced lung cancer. The National Comprehensive Cancer Network (NCCN) considers pembrolizumab plus platinum-based chemotherapy (pembrolizumab-combination) as the standard-of-care first-line treatment for patients with metastatic NSCLC, irrespective of tumor programmed death-ligand 1 (PD-L1) expression [15]. Currently, most NSCLC patients with KRAS mutations choose platinum-based chemotherapy combination with immunotherapy, irrespective of co-mutations within the specific subtypes of KRAS mutations [14].

In 2021, the FDA approved the first KRAS G12C inhibitor, Sotorasib (AMG-510), for treating NSCLC patients with KRAS G12C mutations who have undergone at least one systemic treatment [16]. Subsequently, in 2022, the FDA approved Krazati (adagrasib), a KRAS G12C inhibitor, to be used in the treatment of patients with locally advanced or metastatic NSCLC who have KRAS G12C mutations and have already undergone at least one systemic therapy. This represents the second targeted medication approved by the FDA that specifically inhibits the activity of KRAS mutations. The mPFS of Sotorasib was considerably higher than that of docetaxel (mPFS 5.6 months [95% CI 4.3–7.8] vs. 4.5 months [3.0–5.7]; risk ratio (RR) 0.66 [0.51–0.86]; $P=0.0017$). Sotorasib significantly improved PFS in advanced NSCLC patients with KRAS mutations [17]However, many questions remain unanswered: Should KRAS inhibitors be used

as monotherapy or in combination therapy to improve prognosis? Do different KRAS mutation subtypes and KRAS co-mutation have similar efficacy and prognosis [18]?

The expression of PD-L1 may be a potential biomarker for predicting the efficacy of immunotherapy. There are changes in the expression of PD-L1 in KRAS co-mutations. For example, tumors with the co-mutation of KRAS and STK11 frequently have reduced levels of PD-L1, while tumors with co-mutations, including both KRAS and TP53, show an increase in PD-L1 expression [19, 20].

Currently, NSCLC is the most common form of lung cancer, representing approximately 85% of all lung cancer cases. The KRAS mutation is one of the most prevalent mutations found in NSCLC. Platinum-based chemotherapy and immune checkpoint inhibitors (ICIs) therapy are the standard first-line treatments for NSCLC patients with KRAS mutations [21]. Nevertheless, the effectiveness of immunotherapy for KRAS mutations, particularly the different KRAS mutant subtypes and KRAS co-mutations, remains uncertain. This study primarily focuses on exploring and analyzing the perspectives of KRAS mutation subtypes and KRAS co-mutations, suggesting that the efficacy of immunotherapy may be influenced by different KRAS mutation subtypes, particularly the KRAS G12D mutation. Furthermore, KRAS co-mutations such as TP53, STK11, and KEAP1/NFE2L2 are also influencing factors. The results of this meta-analysis provide clinical evidence to explore cancer immune biomarkers in future clinical research, to enhance clinical treatment guidance.

Materials and methods

This meta-analysis investigated the impact of the KRAS mutation, mutation subtypes and co-mutation in NSCLC treated with immunotherapy conducted by the PRISMA checklist [22].

Data sources and strategy

A systematic search was performed on databases including PubMed, Embase, Cochrane Library, Web of Sciences (WOS), China National Knowledge Infrastructure (CNKI) databases and China Biology Medicine (CBM) and other databases, covering the period from January 1, 2000, to December 5, 2023. The following keywords were used to search: (Carcinoma, Non Small Cell Lung) OR (Carcinomas, Non-Small-Cell Lung)) OR (Lung Carcinoma, Non-Small-Cell)) OR (Lung Carcinomas, Non-Small-Cell)) OR (Non-Small-Cell Lung Carcinomas)) OR (Non-Small-Cell Lung Carcinoma)) OR (Non Small Cell Lung Carcinoma)) OR (Carcinoma, Non-Small Cell Lung)) OR (Non-Small Cell Lung Carcinoma)) OR (Non-Small Cell Lung Cancer)) OR (Nonsmall Cell Lung Cancer)) OR ("Carcinoma, Non-Small-Cell Lung"[Mesh])) AND (("Immune Checkpoint Inhibitors") OR (Checkpoint Inhibitors, Immune) OR (Immune Checkpoint Inhibitor)) OR (Checkpoint Inhibitor, Immune)) OR (Immune Checkpoint Blockers)) OR (Checkpoint Blockers, Immune)) OR (Immune Checkpoint Blockade)) OR (Checkpoint Blockade, Immune)) OR (Immune Checkpoint Inhibition)) OR (Checkpoint Inhibition, Immune)) OR (PD-L1 Inhibitors)) OR (PD L1 Inhibitors)) OR (PD-L1 Inhibitor)) OR (PD L1 Inhibitor)) OR (Programmed Death-Ligand 1 Inhibitors)) OR (Programmed Death-Ligand 1 Inhibitors)) OR (PD-1-PD-L1 Blockade)) OR (Blockade, PD-1-PD-L1)) OR (PD 1 PD L1 Blockade)) OR (CTLA-4 Inhibitors)) OR (CTLA 4 Inhibitors)) OR (CTLA-4 Inhibitor)) OR (CTLA 4 Inhibitor)) OR (Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitors)) OR (Cytotoxic T Lymphocyte Associated Protein 4 Inhibitors)) OR (Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitor)) OR (Cytotoxic T Lymphocyte Associated Protein 4 Inhibitor)) OR (PD-1 Inhibitors)) OR (PD 1 Inhibitors)) OR (PD-1 Inhibitor)) OR (Inhibitor, PD-1)) OR (PD 1 Inhibitor)) OR (Programmed Cell Death Protein 1 Inhibitor)) OR (Programmed Cell Death Protein 1 Inhibitors)) OR (pembrolizumab)) OR (atezolizumab)) OR (nivolumab)) OR (ipilimumab)) OR (durvalumab)) OR (tremelimumab)) OR (camrelizumab)) OR (tislelizumab)) OR (sintilimab)))) AND (((KRAS mutation) OR (KRAS) OR (KRAS wild-type).

Inclusion and exclusion criteria

Inclusion criteria

1. Patients diagnosed with advanced NSCLC based on histology or cytology were included.
2. The studies were focused on patients who received immune checkpoint inhibitor therapy (IO therapy) or combination therapy, such as immune checkpoint inhibitors.
3. The study aimed to compare the treatment outcomes among different subtypes of KRAS mutation or co-mutation with KRAS.
4. OS was defined as the time from randomization to the death of the patient from any cause.
5. PFS was defined as the time from randomization to disease progression or death from any cause.
6. The results were reported with hazard ratios (HR), 95% confidence intervals (95% CI) and P value.

Exclusion criteria

1. Trials involving patient-targeted treatments, such as surgery, radiotherapy, anti-angiogenesis, immune

cells cancer vaccines, or drugs that are not currently available.
2. Studies that reported maintenance treatment outcomes or had unclear clinical outcomes were excluded.

Data extraction

Two researchers (Zhao and Shu) conducted the data extraction process independently, adhering to the predefined inclusion and exclusion criteria. For a particular article, if there are any disputes, they will be independently reviewed and screened again by a third researcher (Xu). The three researchers will then resolve their differences through discussion. The following information was extracted for each study: the trial name, first author, source, study period, publication region, study design, number of patients, patient age and sex distribution, KRAS status, co-mutation status, and treatment. The primary outcomes included HR, 95% CI, and P-values for OS and PFS.

Evaluation of quality

The risk of bias was assessed using the methodological index for non-randomized studies (MINORS) quality assessment. We considered the following criteria for the evaluation of quality: a clearly stated aim, prospective collection of data, endpoint appropriate to the aim of the study, unbiased assessment of the study endpoint, follow-up period appropriate to the aim of the study, loss of follow-up less than 5%, and prospective calculation of the study size. This quality assessment has additional criteria for comparative studies, which are as follows: an adequate control group, a contemporary group, a baseline equivalent of the group, and adequate statistical analysis. Every study had a score to show the quality.

The risk of bias was evaluated through the MINORS quality assessment, and each study was assigned a score ranging from 9 to 12 for high-quality research, 6–9 for medium-quality research, and less than 5 for low-quality research.

Statistical analysis

Review Manager (RevMan) 5.4 software was used for the meta-analysis. The primary outcomes of OS and PFS were assessed through the HR, 95% CI and P value. Treatment, KRAS subgroup mutation, KRAS with co-mutation and PD-L1 expression in NSCLC were evaluated separately. Statistical heterogeneity was determined through χ^2 tests and I^2 statistics, with $P<0.10$ or $I^2>0$ indicating heterogeneity. The $I^2 \leq 20\%$ denoted low heterogeneity, 25% was the medium heterogeneity threshold, and 75% was the high heterogeneity threshold. The $I^2<50\%$ was considered acceptable in the heterogeneity. Random effect models were applied for $I^2>50\%$, whereas fixed effects models for $I^2 \leq 50\%$. The significance level was set at $P<0.05$. To find potential sources of heterogeneity, subgroup analysis was focused on KRAS subgroup mutation and treatment effects.

Results

Process of inclusion and characteristics of the included study

Initially, the screening of the database yielded 446 relevant references. After excluding 9 duplicate references through screening the title and abstract, an additional 268 references were excluded because they were irrelevant to the study. Following this screening, a total of 169 studies were subjected to full-text review. Finally, based on the predefined eligibility criteria, 24 studies were appropriate to be included in our meta-analysis (Fig. 1).

The 24 articles were included in the study until December 5, 2023. These articles focused on patients with NSCLC harboring KRAS mutations, either having received immunotherapy or not.

The basic characteristics of studies

A total of 24 articles were included in this meta-analysis, comprising two randomized controlled trials that investigated the relationship between KRAS mutation status and the efficacy of immunotherapy. According to the MINORS quality assessment, all articles included in the analysis were deemed high quality. The primary focus of the meta-analysis was on KRAS mutations and their association with the efficacy of immunotherapy. Specifically, ten articles addressed the efficacy of immunotherapy, seven focused on KRAS mutation, five examined KRAS G12C mutation, and two delved into KRAS G12D co-mutation. Additionally, five articles explored KRAS co-mutation (Fig. 2).

Most of the patients included in these studies were more than 60 years old, and adenocarcinoma was the predominant pathological type. All included articles were assessed as high-quality based on the MINORS quality assessment (Table 1).

Assessment of the studies

The 24 articles included in this study were analyzed through the MINORS quality assessment, and the results are shown in the table (Table 2). Only one study had an unclear stated aim. All the articles matched the following criteria: "Inclusion of consecutive patients," "Prospective collection of data," and "Endpoint appropriate to the aim of the study." Almost all studies exhibit a biased assessment regarding the study endpoint. Half of the studies had appropriate follow-up times. All studies had less than a 5% loss of follow-up, but the study size was not estimated.

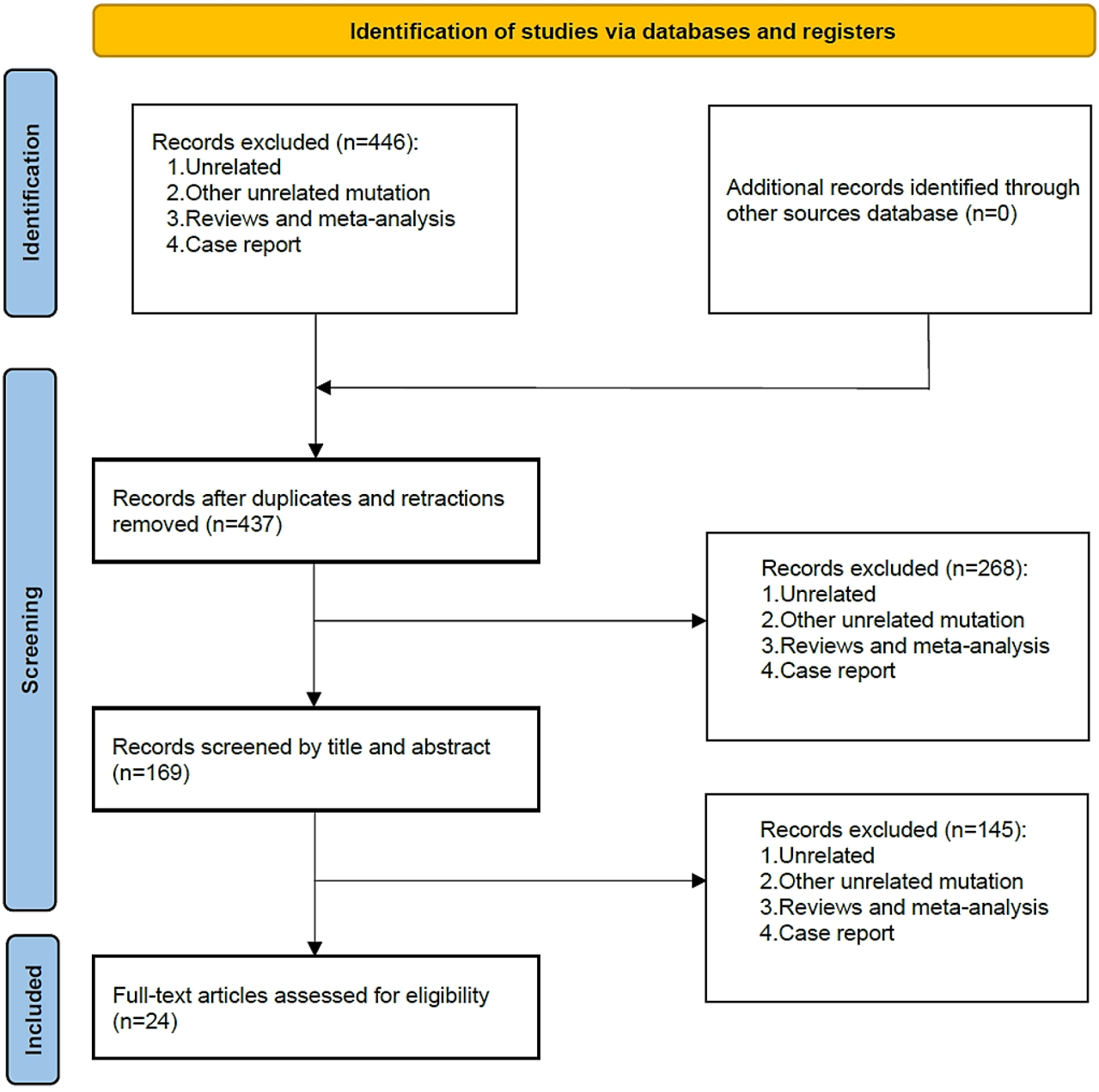


Fig. 1 Flowchart of the literature screening process.

Main results: the efficacy of the immunotherapy

OS

The impact of the KRAS mutation on OS in patients with NSCLC who received immunotherapy was significantly longer compared to those without immunotherapy (HR 0.54 [95% CI: 0.41–0.71]; $P<0.00001$). However, no statistically significant was observed in the KRAS wild-type subgroup in this meta-analysis (HR 0.74 [95% CI: 0.49–1.11]; $P=0.15$). Similarly, the KRAS G12C and co-mutation groups were not found to be statistically significant (HR 0.68 [95% CI: 0.35–1.30]; $P=0.24$) (HR 0.14 [95% CI: 0.01–3.47]; $P=0.23$) (Fig. 3A).

PFS

PFS was significantly improved for patients with KRAS mutation in NSCLC patients who underwent immunotherapy compared to those who did not receive immunotherapy (HR 0.63 [95% CI: 0.53–0.76]; $P<0.00001$) (Fig. 3B). Similarly, the KRAS G12C mutation group exhibited a considerable impact on PFS (HR 0.39 [95% CI: 0.25–0.62]; $P<0.0001$) (Fig. 3C).

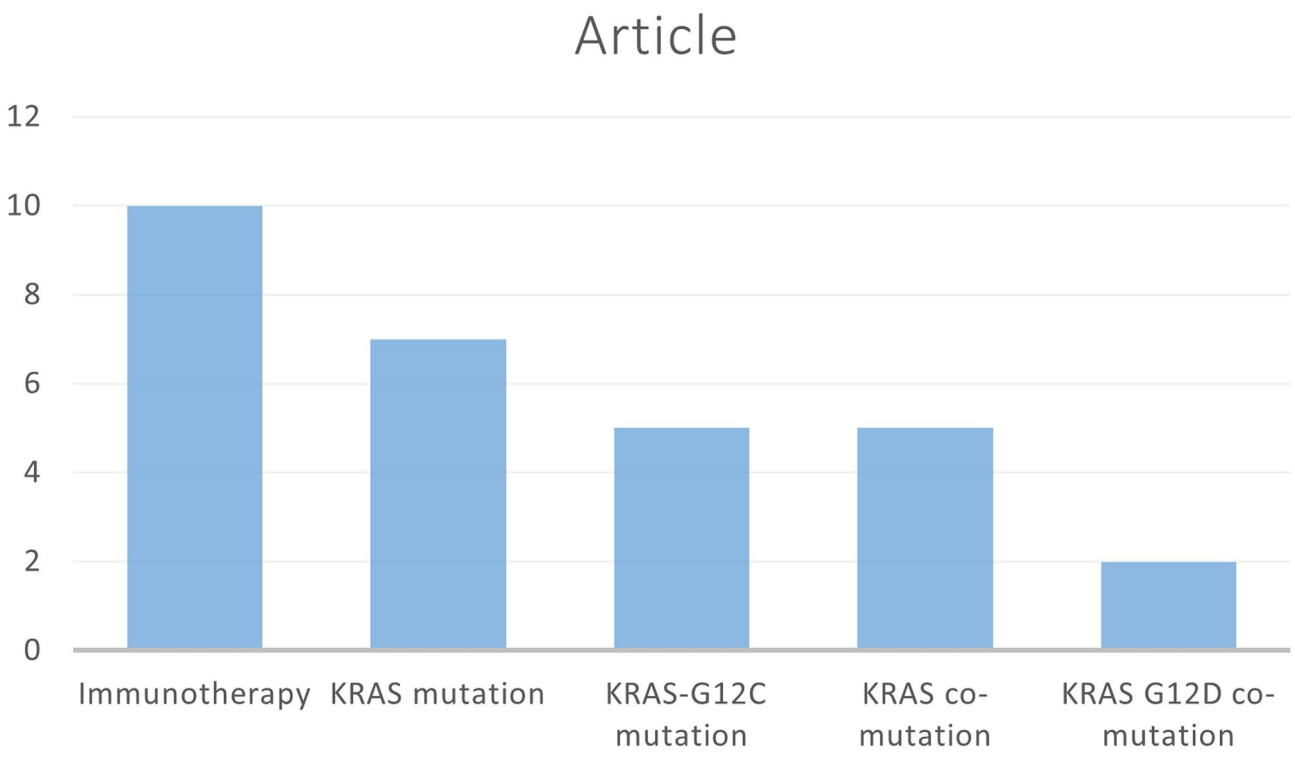


Fig. 2 The types of 24 articles included in the meta-analysis.

Main results: the impact of mutation

KRAS mutation

The meta-analysis included seven studies that compared patients with KRAS mutations to those with KRAS wild-type, and revealed no significant OS benefit (HR 1.01 [95% CI: 0.92–1.11]; P=0.81) (Fig. 4A). Furthermore, the PFS comparing KRAS mutation with KRAS wild-type showed no statistical heterogeneity among five studies (HR 1.02 [95% CI: 0.91–1.15]; P=0.72) (Fig. 4B).

KRAS G12C mutation and KRAS G12D mutation

The KRAS non-G12D mutation appears to significantly benefit OS among patients with NSCLC, whether treated by immunotherapy or not, compared with patients of KRAS G12D mutations (HR 1.52 [95% CI: 1.10–2.10]; P=0.01). However, this effect is not observed in those with KRAS G12C mutations (HR 1.05 [95% CI: 0.91–1.22]; P=0.50) (Fig. 5).

KRAS co-mutation

The three studies exhibited a clinical advantage in OS for patients harboring KRAS mutations without accompanying STK11 co-mutations, when contrasted with those patients presenting both KRAS mutations and STK11 co-mutations (HR 1.46 [95% CI: 1.10–1.93]; P=0.008) (Fig. 6B). Similarly, KRAS mutation without KEAP1/NFE2L2 mutation positively impacted OS in two studies (HR 1.89 [95% CI: 1.33–2.68]; P=0.0004) (Fig. 6C). Conversely, five studies did not demonstrate a significant improvement in OS when comparing the KRAS mutation with TP53 co-mutation to KRAS mutation alone. (HR 0.82 [95% CI: 0.60–1.13]; P=0.23) (Fig. 6A).

The impact of PD-L1

In patients with KRAS mutation, based on three studies, there was no evidence of a difference in PFS when comparing PD-L1 positive and negative groups (HR 0.74 [95% CI: 0.52–1.07]; P=0.11) (Fig. 7A). Similarly, based on two studies, PD-L1 positive did not show a significant benefit of OS compared to PD-L1 negative (HR 0.79 [95% CI: 0.54–1.16]; P=0.24) (Fig. 7B).

Subgroup analysis

About the KRAS mutation subgroup, the subgroup analysis results show that there is no statistically significant subgroup effect (P=0.48) (Fig. 3A), indicating that KRAS mutation subtypes and co-mutations do not affect OS in patients receiving immunotherapy. Furthermore, the distribution of covariates is uneven, with different numbers of studies included between subgroups (KRAS mutation: 8 studies, KRAS wildtype: 4 studies, KRAS G12C: 4 studies and KRAS co-mutation: 2 studies), which suggests that the analysis may not be able to detect subgroup differences. Interestingly, the combined effect of the four subgroups indicates that immunotherapy is beneficial for both KRAS mutated and co-mutated populations.

Table 1 Basic information about selected references.

Study	Study period	Region	Sample number	Median age,	Gender	Histological types[a]	Stage	Quality[b]	Reference
Arbour 2018	2014.1-2016.10	US	330	> 60	Male (41%) Female (59%)	ADC (89%) SCC (3%) Other (8%)	stage IV or recurrent cancer	H	[9]
Gianoncelli 2020	2016–2018	Italy	160	> 60	Male (59%) Female (39%)	NA	stage IV	H	[23]
Uehara 2022	2019.5-2021.7	Japan	78	> 60	Male (69%) Female (31%)	ADC (83%) SCC (10%) Other (7%)	NA	H	[24]
Jeanson 2019	2013,4-2017.6	France	282	< 60	Male (59.5%) Female (40.5%)	ADC (93.9%) SCC (2.1%) Other (4%)	NA	H	[25]
Aredo 2019	2015.1-2017.12	US	186	> 60	Male (43%) Female (57%)	ADC (94.6%) SCC (2.2%) Other (3.2%)	NA	H	[26]
Veccia 2023	2017.3-2021.8	Italy	119	> 60	Male (65.6%) Female (34.4%)	ADC (89.9%) Other (10.1%)	stage IV	H	[27]
Sebastian 2021	2017.3-2021.8	Germany	1039	> 60	Male (61.7%) Female (38.3%)	Non-SCC (89.5%) SCC (10.5%)	stage IV or stage IIIB	H	[28]
Tamiya 2023	2017.3-2021.8	Japan	1258	> 60	Male (66%) Female (34%)	ADC (84%) SCC (4%) Pleom (2%) LCC (1%) Other (9%)	II (4%) III (15%) IV (68%) Recurrence (13%)	H	[29]
Chen 2022	2009.1-2020.10	China	487	< 60 (41.4) > 60 (58.6)	Male (72.8%) Female (27.2%)	ADC (82.9%) SCC (9.1%) Other (8.1%)	I (6.6%) II (3%) III (17.5%) IV (72.9%)	H	[30]
Kartolo 2021	2012–2019	Canada	78	> 60	Male (47%) Female (53%)	Non-SCC (76%) SCC (24%)	III (13%) IV (87%)	H	[31]
Wu 2022	2011.4–2020,3	China	93	> 60	Male (76.3%) Female (23.7%)	ADC (94.6%) SCC (2.2%) Other (3.2%)	IIIB–IIIC (7.6%) IVA–IVB (92.4%)	H	[32]
Ricciuti 2022	2016.10-2021.9	US	2327	> 60	Male (35.5%) Female (64.5%)	Non-SCC (98.5%) SCC (1.5%)	I (21.6%) II (8.2%) III (14.0%) IV (56.2%)	H	[33]
Liu 2023	2019.1-2020.9	China	143	> 60	Male (60%) Female (40%)	ADC (85%) Non-ADC (15%)	IIIB (15%) IV (85%)	H	[34]
Guo 2023	2018.1-2021.9	China	410	> 60	Male (76.9%) Female (23.1%)	ADC (82.3%) SCC (4.2%) Other (13.5%)	I (41.8%) II (8.8%) III (15.8%) IV (30.4%) Unclear (3.2%)	H	[35]
Noordhof 2021	2017.1-2018-12	Netherlands	595	> 60	Male (49.7%) Female (50.3%)	NA	stage IV	H	[36]
Sun 2021	2016.1-2020.5	UA	1127	NA	Male (41.3%) Female (58.7%)	NA	NA	H	[37]
Cortiula 2023	2016–2022	Italy	271	> 60	Male (58%) Female (42%)	NA	IIIA (42%) IIIB (50%) IIIC (8%)	H	[38]
Mok 2023	-2018.9	China	1274	> 60	Male (70.8%) Female (29.2%)	Non-SCC (41.5%) SCC (58.5%)	NA	H	[39]
Garassino 2023	-2019.5	Germany	1174	> 60	Male (81.4%) Female (18.6%)	Non-SCC (47.6%) SCC (52.4%)	NA	H	[40]

Table 1 (continued)

Study	Study period	Region	Sample number	Median age,	Gender	Histological types[a]	Stage	Quality[b]	Reference
Wu 2022	2011.4-2020.3	China	93	> 60	Male (76.3%) Female (23.7%)	ADC (93.5%) SCC (3.3%) Other (3.2%)	IIIB–IIIC (7.6%) IVA–IVB (92.4%)	H	[32]
Attili 2022	2016–2021	Italy	105	> 60	Male (60%) Female (40%)	Non-SCC (100%)	NA	H	[41]
Fancelli 2022	2015-1-2021.12	Italy	219	> 60	Male (61.2%) Female (38.3%)	NA	NA	H	[42]
Zhang 2022	NA	China	748	> 60	Male (61.2%) Female (38.8%)	Non-SCC (71.9%) SCC (28.1%)	NA	H	[20]
Benjamin 2022	2018.1-2019-12	UA	246	> 60	Male (45.5%) Female (54.5%)	ADC (92.3%) SCC (1.6%) Other (6.1%)	NA	H	[43]

[a]ADC adenocarcinoma; SCC squamous carcinoma; Non-SCC non- squamous carcinoma; [b]L low quality; M median quality; H high quality; "NA" no answer

About KRAS G12C and KRAS G12D subgroup, the subgroup analysis results indicate a significant statistical subgroup effect ($P=0.04$) (Fig. 5). Therefore, it is suggested that KRAS mutation subtypes may influence the OS outcomes of patients. However, due to the uneven distribution of covariates, the KRAS G12C subgroup included 7 studies, while the KRAS G12D subgroup included only 2 studies, which suggests that this analysis is less likely to produce useful results.

Sensitivity analysis

The analysis of the effect of immunotherapy in the KRAS wild-type and co-mutation groups for both OS and PFS revealed high heterogeneity. Subgroup analysis of KRAS mutations across nine studies was conducted. Heterogeneity in subgroups of KRAS mutations: KRAS mutation: $I^2=40\%$, KRAS wildtype: $I^2=60\%$; KRAS G12C: $I^2=30\%$; KRAS co-mutation: $I^2=65\%$. Following subgroup analysis for KRAS mutations, the combined heterogeneity is 45% ($I^2=45\%$) (Fig. 3A), which falls within the moderate range and is generally considered acceptable. The observed heterogeneity in subgroup analysis can be attributed to the diverse origins of the nine included studies, which spanned multiple countries including China, the United States, Germany, and Italy. Such geographical spread could account for racial differences, which may contribute to the heterogeneity. Furthermore, in the study conducted by Zhang 2022 [20], it was not established that KRAS mutations alter the OS in patients undergoing immunotherapy. This discrepancy may also contribute to the heterogeneity observed between subgroups.

In the seven included studies, a subgroup analysis was performed based on the KRAS mutation subtypes. The heterogeneity of the meta-analysis for KRAS mutation subtypes was found to be: KRAS G12C: $I^2=44\%$; KRAS G12D: $I^2=47\%$ (Fig. 5). After subgroup analysis of the KRAS mutation subtypes, the combined heterogeneity was 52%, indicating moderate heterogeneity and falling within the acceptable range. In this subgroup, the confidence intervals of the studies overlapped to a lesser extent, and there was a significant difference in the number of studies included between each subgroup. Additionally, the studies included were conducted in different countries, which could contribute to the heterogeneity observed between the studies.

KRAS mutation with TP53 co-mutation exhibits high heterogeneity. Upon excluding the study by Liu 2023 [34], we observed homogeneity ($I^2=0\%$). Consequently, we infer that the heterogeneity may be attributed to disparities among the included studies.

Discussion

This meta-analysis is based on the KRAS mutation to analyze the impact of immunotherapy on NSCLC. The patients with immunotherapy have longer OS and PFS in the KRAS mutation subgroup than those without immunotherapy. The KRAS G12D mutation seems to be a negative factor in patients with immunotherapy. Among the KRAS mutation subtypes, the KRAS non-G12D mutation appears to have a beneficial impact compared to the KRAS G12D mutation. Besides, the clinical benefits in OS between patients with KRAS mutations alone and those with KRAS mutations accompanied by STK11 co-mutation are notable. The comparison of OS between patients with KRAS mutations alone and those with KRAS mutations with KEAP1/NFE2L2 co-mutations demonstrates a significant impact on patient outcomes. Thus, our study found that the KRAS mutation seems to be a significant impact factor of immunotherapy in the NSCLC, especially the KRAS G12C mutation. Notably, the KRAS with co-mutation will also impact the effect of the immunotherapy. And the KRAS G12D mutation appears to be a negative factor in patients receiving immunotherapy.

Table 2 The MINORS quality assessment of the included studies in this meta-analysis. "NA": no answer.

Study	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss of follow-up less than 5%	Prospective calculation of the study size	Additional criteria for comparative studies				Total
									An adequate control group	Contemporary group	Baseline equivalent of groups	Adequate statistical analysis	
Arbour 2018	2	2	1	2	1	2	2	0	NA	NA	NA	NA	12
Gianoncelli 2020	2	2	2	2	1	2	2	0	NA	NA	NA	NA	13
Uehara 2022	1	2	1	2	1	1	2	0	NA	NA	NA	NA	10
Jeanson 2019	2	2	1	2	1	1	2	0	NA	NA	NA	NA	11
Aredo 2019	1	2	2	2	1	2	2	0	NA	NA	NA	NA	12
Veccia 2023	2	2	2	2	1	2	2	0	NA	NA	NA	NA	13
Sebastian 2021	2	2	2	2	1	1	2	0	NA	NA	NA	NA	12
Tamiya 2023	2	2	2	2	1	1	2	0	NA	NA	NA	NA	12
Chen 2022	2	2	2	2	1	1	2	0	NA	NA	NA	NA	12
Kartolo 2021	2	2	2	2	1	1	2	0	NA	NA	NA	NA	12
Wu 2022	2	2	1	2	1	1	2	0	NA	NA		NA	11
Ricciuti 2022	2	2	2	2	1	2	2	0	NA	NA	NA	NA	13
Liu 2023	2	2	1	2	1	2	2	0	NA	NA	NA	NA	12
Guo 2023	1	2	1	2	1	2	2	0	NA	NA	NA	NA	11
Noordhof 2021	1	2	1	1	1	2	2	0	NA	NA	NA	NA	10
Sun 2021	1	2	1	2	1	1	2	0	NA	NA	NA	NA	10
Cortiula 2023	2	2	2	1	1	2	2	0	NA	NA	NA	NA	12
Mok 2023	2	2	2	2	1	2	2	0	2	2	1	2	20
Garassino 2023	2	2	2	2	1	2	2	0	2	2	1	2	20
Wu 2022	2	2	2	2	1	2	2	0	NA	NA	NA	NA	13
Attili 2022	1	2	1	2	1	2	2	0	NA	NA	NA	NA	11
Fancelli 2022	1	2	1	1	1	2	2	0	NA	NA	NA	NA	10
Zhang 2022	2	2	2	2	1	1	2	0	NA	NA	NA	NA	12

Table 2 (continued)

Study	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss of follow-up less than 5%	Prospective calculation of the study size	Additional criteria for comparative studies				Total
									An adequate control group	Contemporary group	Baseline equivalent of groups	Adequate statistical analysis	
Benjamin 2022	1	2	2	2	1	1	2	0	NA	NA	NA	NA	11

Regarding KRAS wild-type, some studies have indicated no significant differences between KRAS mutation and KRAS wild-type in NSCLC regarding mPFS and OS [23, 28]. A recent retrospective study assessed the clinical genomic features of patients with KRAS G12C mutation in NSCLC [29]. In patients with the KRAS mutation who were treated with the ICIs, the mPFS of patients with KRAS G12C mutation (3.4 months) was comparable to that of patients with KRAS G12V mutation (4.2 months, $P=0.90$), but significantly longer than that of patients with KRAS G12D mutation (2.0 months, $P=0.02$) and other KRAS mutation patients (2.5 months, $P=0.02$). This is consistent with our research results. A recent retrospective study of the KRAS G12D mutation subtype produced similar results [33]. KRAS G12D mutation had a poor ORR compared with KRAS non-G12D mutation (15.8% vs. 28.4%, $P<0.03$), correlated with poor PFS (HR 1.51 [95% CI 1.45–2.00]; $P=0.003$), and OS (HR 1.45 [95% CI 1.05–1.99]; $P=0.02$), in which all of were statistically significant.

In some previous studies, PD-L1 expression was higher (≥50%), the efficacy of ICIs tended to be even greater [25, 44]. So, PD-L1 may serve as a potential biomarker for predicting the efficacy of immunotherapy. In our study, we aimed to investigate the potential relationship between PD-L1 expression and KRAS mutation in patients with immunotherapy. However, due to the availability of limited data, we could not identify a correlation between PD-L1 expression and KRAS mutation.

Furthermore, a study investigating KRAS mutation and common co-mutation assessed the efficacy of platinum-based pemetrexed chemotherapy and ICIs. This study revealed that the survival time of patients with a KEAP1/NFE2L2 co-mutation was significantly reduced (HR 1.96 [95% CI: 1.33–2.92]; $P\leq0.001$) [9]. We also observed that KRAS and KEAP1/NFE2L2 co-mutation negatively impact immunotherapy patients.

The previous studies have primarily analyzed patients with NSCLS who received or did not receive immunotherapy based on KRAS mutants and KRAS wild-type. None of these studies compared the KRAS mutant and the KRAS wild-type in all patients with NSCLC who underwent immunotherapy. Furthermore, no previous research focused on the classification of the KRAS subtype. Thus, there is no clear evidence to show whether different KRAS subtypes influence the efficacy of immunotherapy in patients with NSCLC.

Immunotherapy represents a significant advancement in the treatment of NSCLC. However, achieving accurate therapy remains an urgent challenge. To address this issue, our research aimed to investigate the correlation between KRAS mutation, KRAS co-mutation, and immunotherapy and identify potential tumor immune markers. Using this approach, we hope to enhance patient survival rates and prognoses, thus providing better guidance in clinical treatment.

This study has certain limitations. The study divided the treatment based on whether patients had received immunotherapy. However, due to the availability of limited data, further analysis of patients receiving different immunotherapies in the present study was not possible. Therefore, the final results can only indicate whether immunotherapy benefits patients with KRAS mutation, without suggesting which type of immunotherapy may be more beneficial for patients. Simultaneously, due to the lack of more clinical research data, the heterogeneity of some groups is high. However, statistically significant results were still obtained, and after excluding some of the research data, the results remained statistically significant. And the heterogeneity is within an acceptable range ($I^2<50\%$). However, it remains unclear where the source of this high heterogeneity comes from.

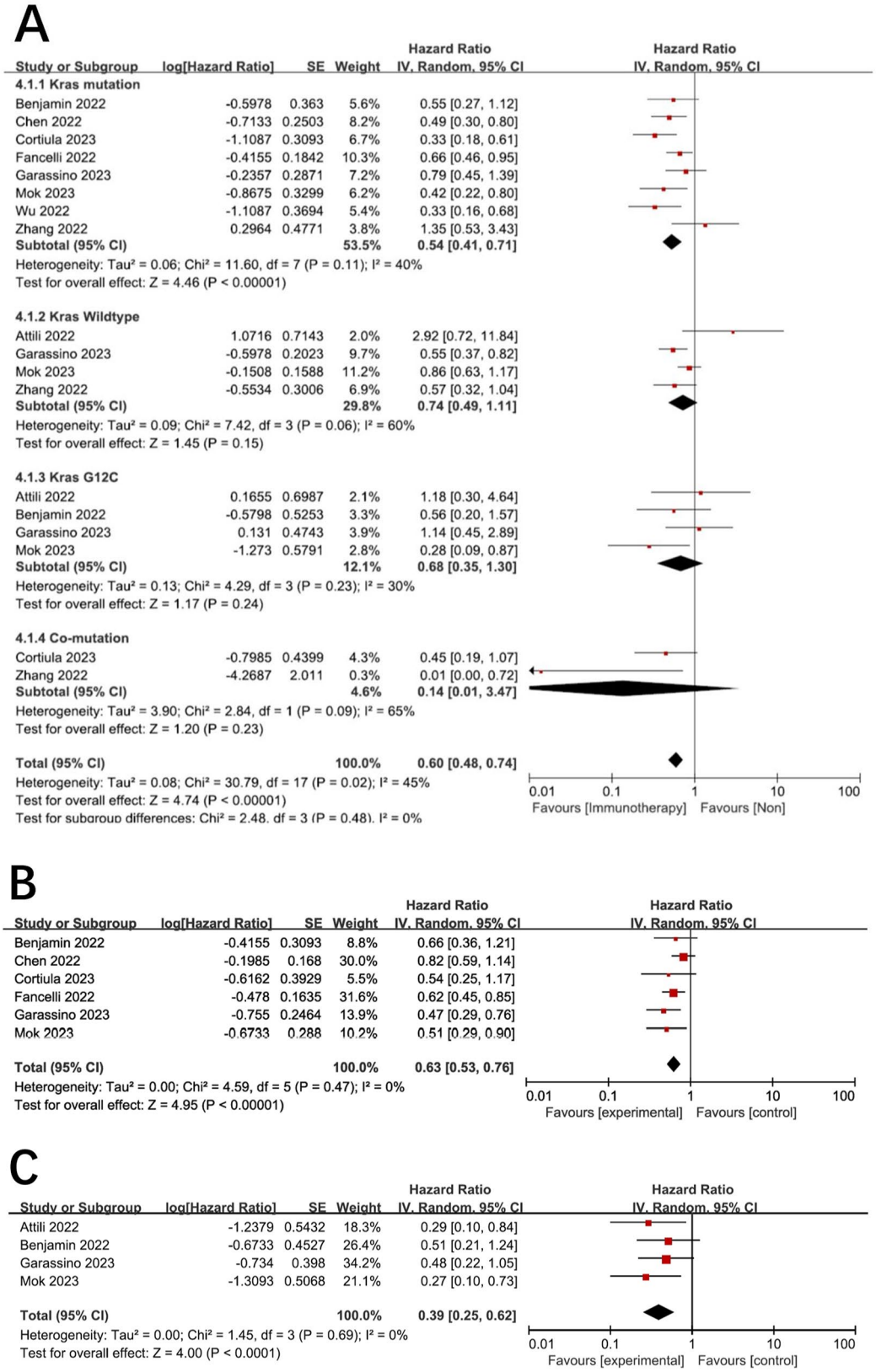
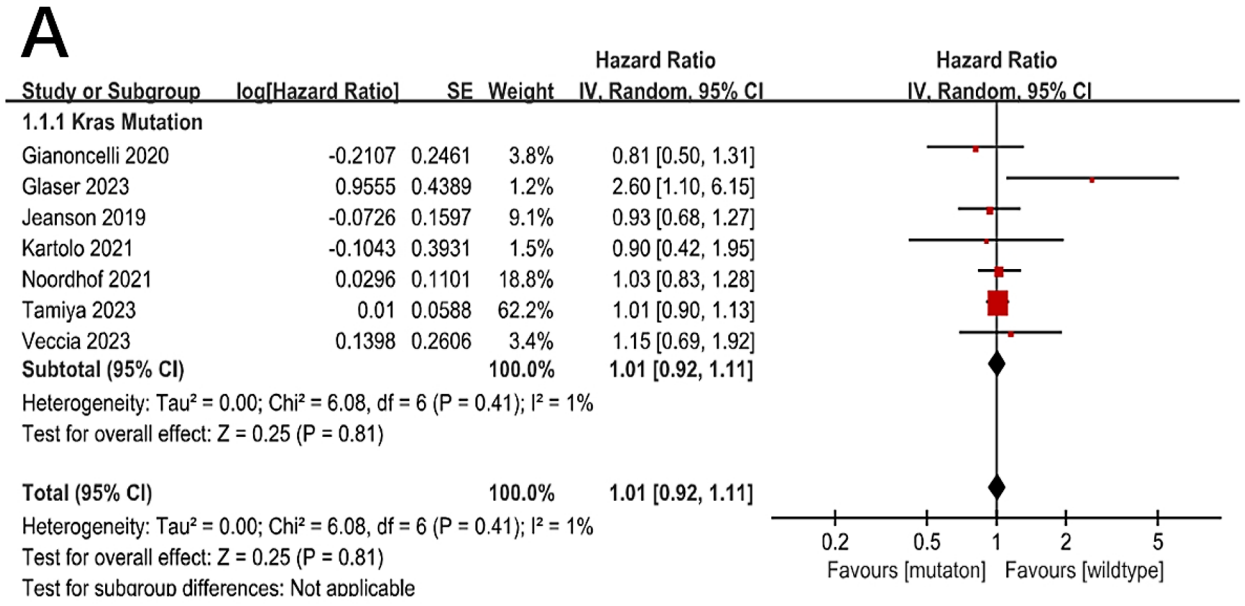


Fig. 3 The forest plots about OS and PFS in NSCLC with KRAS mutation, KRAS wild-type, KRAS G12C mutation, and KRAS co-mutation. (**A**)The forest plots about OS in NSCLC with KRAS mutation, KRAS wild-type, KRAS G12C mutation, and KRAS co-mutation, comparing patients who received immunotherapy therapy (Immunotherapy) to those who did not receive immunotherapy (Non). (**B** and **C**) The PFS in NSCLC with KRAS mutation and KRAS G12C mutation, comparing patients who received immunotherapy therapy (experimental) and those who did not receive immunotherapy (control).



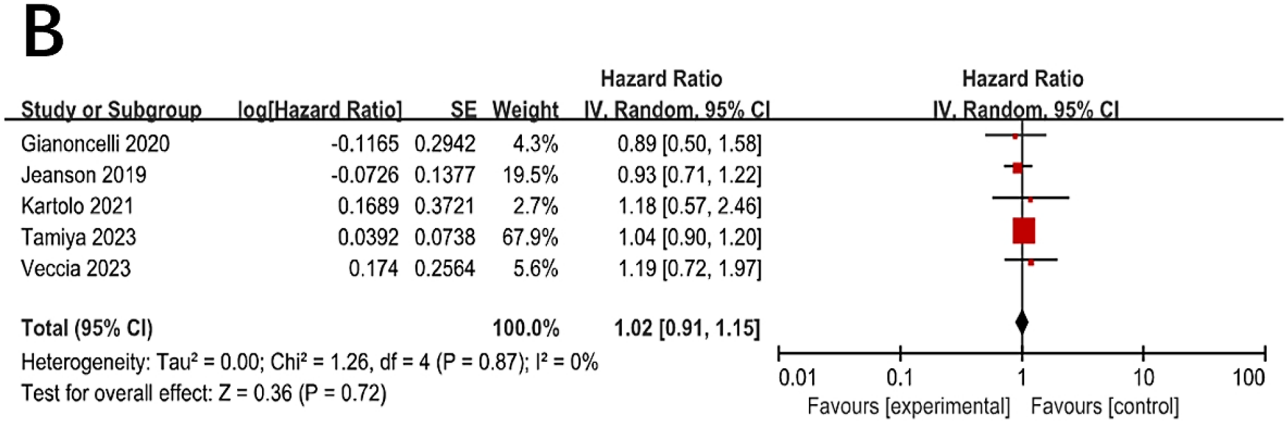


Fig. 4 The forest plots illustrate the comparison of OS and PFS in NSCLC with KRAS mutation. (**A**) The comparison of OS in NSCLC with KRAS mutation (mutation) versus KRAS wild-type (non). (**B**) The comparison of PFS in NSCLC with KRAS mutation (experimental) versus KRAS wild-type (control).

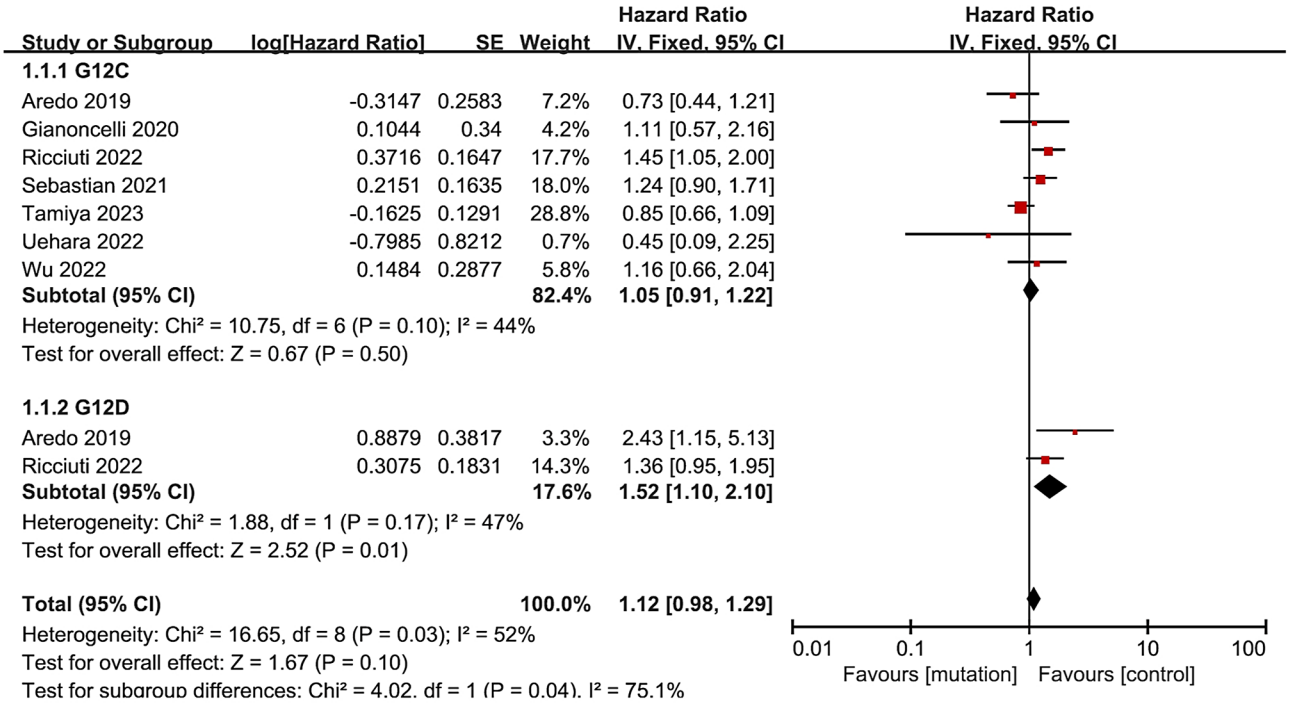


Fig. 5 The forest plots show the OS in NSCLC with the subtype KRAS G12C/KRAS G12D mutation (mutation) compared to KRAS non-G12C/KRAS non-G12D mutation (control).

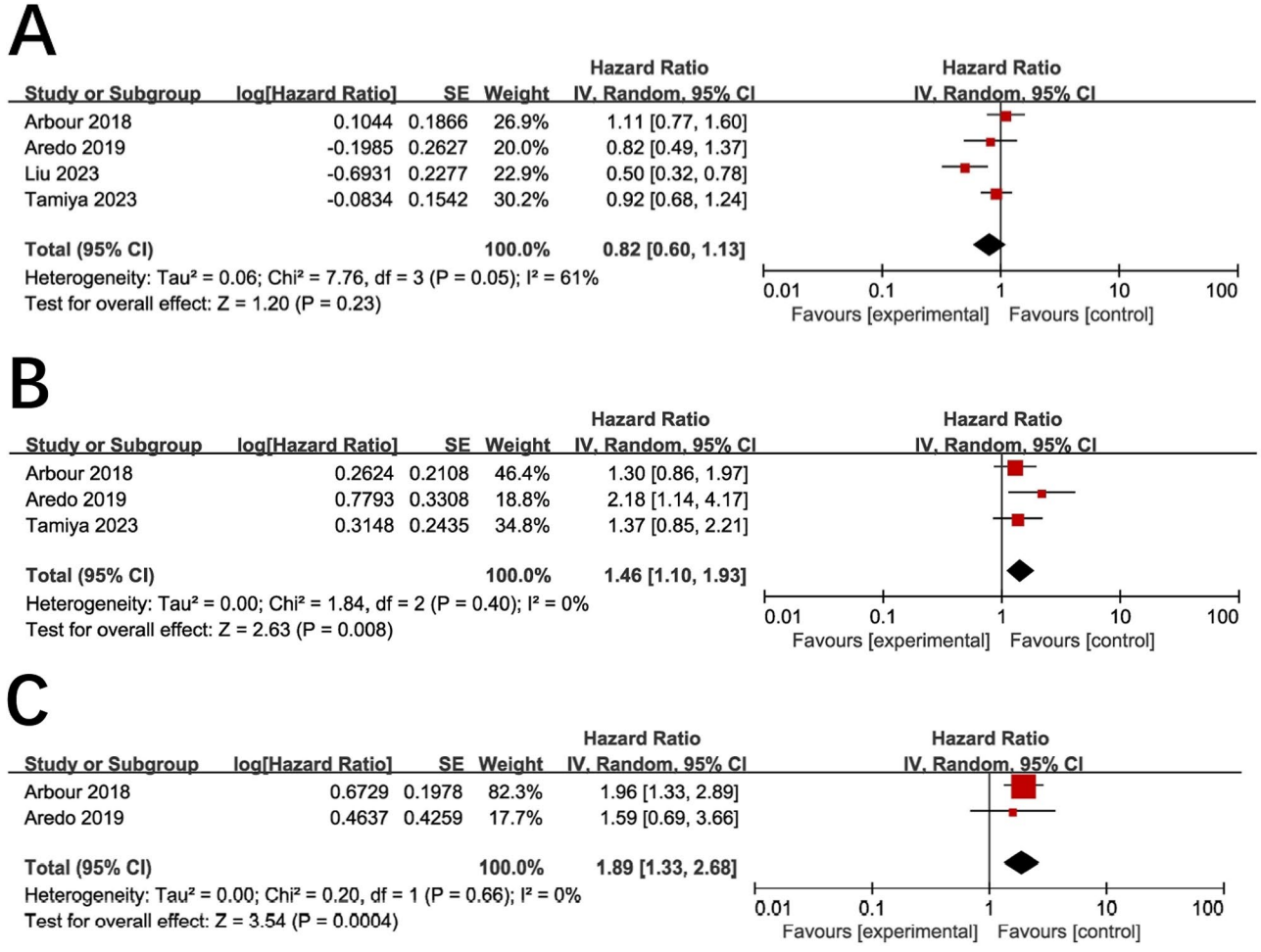


Fig. 6 The forest plots illustrate the comparison of OS between KRAS co-mutation with TP53 (**A**), KRAS co-mutation with STK11 (**B**), and KRAS co-mutation with KEAP1/NFE2L2 (**C**) (experimental) versus KRAS mutation alone (control).

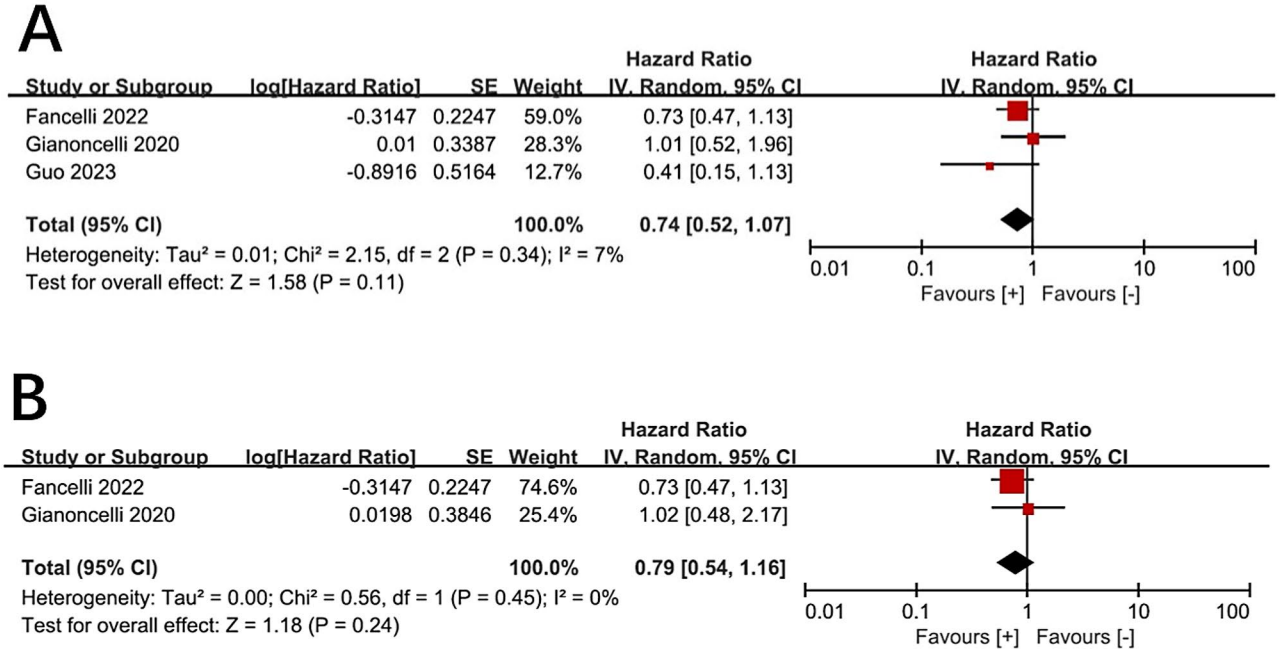


Fig. 7 The forest plots illustrate the comparison of PFS (**A**) and OS (**B**) in PD-L1 positive (+) vs. PD-L1 negative (-).

Conclusion

To summarize, this meta-analysis emphasizes the positive impact of immunotherapy in patients with KRAS mutations in NSCLC compared to those with KRAS wild-type. Notably, individuals harboring KRAS G12C mutation experience significant benefits from immunotherapy. Conversely, the KRAS G12D mutation appears to be a negative factor in patients receiving immunotherapy. Patients with KRAS co-mutations involving STK11 and KEAP1/NFE2L2 may encounter adverse impacts when undergoing immunotherapy. This nuanced understanding of the interplay between KRAS mutations and immunotherapy outcomes provides a valuable foundation for personalized treatment strategies to optimize benefits for patients with specific KRAS mutation profiles.

Abbreviations

CI	Confidence intervals
DOR	Duration of response
HR	Hazard ratios
IO	Immune oncology
ICIs	Immune checkpoint inhibitors
KRAS	Kirsten rat sarcoma viral oncogene homolog
KEAP1	Kelch-like ECH-associated protein 1
STK11	Serine threonine kinase 11
ORR	Objective response rate
OS	Overall survival
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
NSCLC	Non-small cell lung cancer
NFE2L2	Nuclear factor, erythroid 2 like 2
RR	Risk ratio

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Author contributions

Rui Zhao: Conceptualization, Methodology, Visualization, Writing-Original Draft. Yang Shu: Formal analysis, Investigation, Writing-review & editing. Wei Xu: Investigation, Validation. Fengxian Jiang: Software, Data Curation. Pancen Ran: Investigation, Writing-review & editing. Liying Pan: Software, Data Curation. Jingliang Wang: Investigation, Validation. Weihao Wang: Term, Validation, Writing-review & editing. Jing Zhao: Conceptualization, Validation, Writing-review & editing. Yahui Wan: Writing-review & editing.Guobin Fu: Supervision, Project administration, Funding acquisition, Writing-review & editing.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All of the current study data were searched systematically and were used by reference citation, and all of the authors consent to publication.

Competing interests

The authors declare no competing interests.

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