Efficacy and safety of immune checkpoint inhibitors in elderly patients with advanced non-small cell lung cancer: a systematic review and meta-analysis

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Summary

Background Immune checkpoint inhibitors (ICIs) are the preferred treatments for advanced non-small cell lung cancer (NSCLC) without targetable oncogene alterations. However, evidence in the elderly population (aged ≥ 65 years) remains limited.

Methods We searched PubMed, Embase, Cochrane Library, Web of Science, and Scopus databases for eligible publications until September 30, 2024. The primary outcome of interest was overall survival (OS). A random-effects model was used for the statistical analysis.

Findings A total of 35 phase 3 randomized controlled trials (RCTs) involving 9788 patients and 64 real-world studies involving 37,111 patients were included. Results from phase 3 RCTs revealed that ICIs significantly improved OS (hazard ratio [HR] = 0.78, 95% confidence interval [CI]: 0.74–0.82) and progression-free survival (PFS) (HR = 0.67, 95% CI: 0.60–0.75) compared to chemotherapy. The association between ICIs and improved OS was independent of patient characteristics (race and histological type) or treatment-related factors (ICI drug type, treatment mode, and treatment line). However, significantly prolonged OS was not observed in subgroups of aged ≥ 75 years and PD-L1 < 1%. In real-world studies, the pooled median OS of ICIs were 11.8 months (95% CI: 11.2–12.4); Eastern Cooperative Oncology Group (EOCG) score, histological type, PD-L1 status, with immune-related adverse events (irAEs), and treatment mode were predictive for OS; rates of irAEs and discontinuation were numerically higher for combination therapy vs. monotherapy.

Interpretation ICIs are associated with a significant improvement in OS and PFS compared to chemotherapy in elderly patients with advanced NSCLC. Nevertheless, some patient characteristics such as aged ≥ 75 years, ECOG score ≥ 2, and PD-L1 < 1% seem to have a negative impact on the efficacy of ICIs, while these findings require further validation in large RCTs.

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Keywords: Immune checkpoint inhibitors; Overall survival; Non-small cell lung cancer; Elderly; Meta-analysis

Introduction

Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer, and more than 40% of patients with NSCLC are over 70 years old at diagnosis.[1] Currently, immune checkpoint inhibitors (ICIs), such as programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors, are the preferred treatments for advanced NSCLC without targetable oncogene alterations. However, few clinical trials have specifically examined the role of ICIs in elderly patients, mainly because of concerns about their poor health

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Research in context

Evidence before this study

Immune checkpoint inhibitors (ICIs) have become the preferred regimens for advanced non-small cell lung cancer (NSCLC). However, evidence on the elderly population is still limited. We searched PubMed, Embase, Cochrane Library, Web of Science, and Scopus databases for eligible studies until September 30, 2024, mainly using the search terms "checkpoint inhibitor" and "non-small cell lung cancer".

Added value of this study

To our knowledge, this is the most comprehensive meta-analysis focusing on the role of ICIs in elderly patients with advanced NSCLC. Efficacy and safety of ICIs were assessed in phase 3 randomized controlled trials (RCTs) and real-world studies, respectively. Results from phase 3 RCTs revealed that ICIs significantly improved overall survival (OS) compared to chemotherapy, regardless of race, histological type, ICI drug, treatment mode, and treatment line. In real-world studies, EOCG score, histological type, with immune-related adverse events, and treatment mode were predictive for OS; combination therapy was associated with more toxicity compared to monotherapy.

Implications of all the available evidence

ICIs are associated with a significant improvement in OS compared to chemotherapy. Nevertheless, patient characteristics such as aged ≥75 years, ECOG score ≥ 2, and PD-L1 < 1% seem to have a negative impact on the efficacy of ICIs, while the findings require further validation in large RCTs.

status, presence of multiple comorbidities, and age-associated decline in immune system function,[2] which may reduce the efficacy and tolerability of treatments.

Recently, many phase 3 randomized controlled trials (RCTs) examining ICIs vs. chemotherapy (CT) in advanced NSCLC have included a small proportion of elderly patients[3–42] but with inconsistent findings in this population. Results from real-world studies[43–106] are also largely different, with the median overall survival (OS) of ICIs ranging from 2.9 to 42.2 months. Elderly patients comprise a heterogeneous group of patients. Differences in patient physiological conditions (such as baseline comorbidity and performance status) may be associated with the different findings among the studies. For example, several phase 3 RCTs reported an improved OS with ICIs in patients aged 65–74 years but not in those aged ≥ 75 years[3,4,9]; and some real-world studies found a better OS of ICIs in patients with Eastern Cooperative Oncology Group [ECOG] score 0–1 than those with ECOG score ≥ 2.[49,54,55,60,63] In addition, PD-L1 status and treatment mode may also effect the benefits of ICIs. Thus, an individualized assessment of the role of ICIs in elderly patients is essential.

In this systematic review and meta-analysis of elderly patients with advanced NSCLC, we compared the efficacy of ICIs monotherapy or combination therapy with CT alone in phase 3 RCTs, and summarized the survival and safety outcomes of ICIs in real-world studies, aiming to explore the subgroups that could benefit more from ICIs.

Methods

Literature search

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[107] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline.[108] Two authors (JY and SL) independently searched scientific databases including PubMed, Embase, Cochrane Library, Web of Science, and Scopus for potentially eligible publications until September 30, 2024, using the search strategies detailed in Supplementary File Table S1. The reference lists of relevant articles were manually checked for missing studies after an electronic search.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) study design and intervention: RCTs examining ICIs monotherapy or combination therapy vs. CT alone, or real-world studies investigating ICIs with or without control group; (2) study population: elderly patients (aged ≥ 65 years) with advanced NSCLC; (3) outcomes: OS, progression-free survival (PFS), treatment-related adverse events (TRAEs), immune-related adverse events (irAEs), and discontinuation. In cases of overlapping of patient data among studies, the study with the most comprehensive and/or recent data was selected.

Data extraction and quality assessment

Two authors (JY and SL) independently collected the following information from the studies: (1) study characteristics: name or first author of the study, year of publication, design, region, sample size, and follow-up time; (2) patient characteristics, including age, sex, histological type, smoking status, ECOG score, and PD-L1 expression; (3) treatment characteristics: ICI drug, treatment mode, and treatment line; and (4) outcomes: data on OS, PFS, TRAEs, irAEs, and discontinuation. Quality assessment was conducted by using the Cochrane Risk of Bias Tool[109] for RCTs and the Methodological Index for Non-randomized Studies (MINORS)[110] for real-world studies.

Statistics

The primary outcome of interest was OS and the secondary outcomes were PFS, TRAEs, irAEs, and discontinuation. A random-effects meta-analysis was conducted using the Review Manager 5.4 (Cochrane Collaboration, Oxford, UK). For the meta-analysis of a few included studies ($n \leq 5$), we used an alternative methodology of Hartung-Knapp-Sidik-Jonkman (HKSJ) instead of the standard random-effects model.[111] Hazard ratios (HRs) with their 95% confidence intervals (CIs) were used as summary statistics for OS and PFS in phase 3 RCTs. The median OS and OS rates at 12, 24, and 36-months with their 95% confidence intervals (CIs) derived from real-world studies were pooled using the method described by Combescure et al.[112] When the median OS and/or OS rates at 12, 24, and 36-months were not directly reported, they were calculated from the reported Kaplan–Meier curves using the method described by Liu et al.[113] The inverse variance method was used to calculate the pooled risks of TRAEs and irAEs. Heterogeneity was assessed using Q- and I-square (I^2) tests. Univariate and multivariate meta-regression analyses were performed to explore potential sources of heterogeneity. The details of the meta-regression model are summarized on page 7 of the Supplementary File. Subgroup analyses were performed according to age, race, histological type, ICI, treatment mode, treatment line, and PD-L1 expression levels. Publication bias was investigated using Egger's linear regression test[114] and a funnel plot. The stability of the results was assessed using sensitivity analysis.

Role of funding source

This study received no funding.

Results

Study selection and characteristics

The initial literature search yielded 45,138 results. After removing the duplicates, 30,459 publications remained. Of these, 30,301 articles were excluded based on title and abstract reviews. The remaining 158 studies underwent a full-text assessment. Ultimately, 104 studies[3–106] were included in the meta-analysis. A summary of the study selection process and the reasons for exclusion are shown in Fig. 1. Among the 104 included studies, 40 studies[3–42] reporting 35 phase 3 RCTs involving 9788 patients examined ICIs vs. CT, and 64 real-world studies[43–106] involving 37,111 patients examined ICIs with or without a control group.

Of the 35 phase 3 RCTs (40 studies), only two enrolled elderly patients. The remaining trials included patients aged ≥ 18 years, with data for patients aged ≥ 65 years extracted for analysis. Most patients had an ECOG score of 0–1 without epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations. Ten RCTs were conducted in Asian countries, six in non-Asian countries, and 19 in both regions. Sixteen RCTs examined ICIs monotherapy (10 anti-PD-1 and 6 anti-PD-L1), 18 examined combination therapy (11 anti-PD-1+CT, 5 anti-PD-L1+CT, and 2 dual ICIs), and one examined anti-PD-L1 with and without anti-CTLA-4. ICIs were used as first-line (1 L) and second- or later line (≥2 L) settings in 27 and 8 RCTs, respectively. The frequently used CT regimens were cisplatin/carboplatin with pemetrexed (non-squamous NSCLC) or with paclitaxel/nab-paclitaxel (squamous NSCLC) in 1 L setting, and docetaxel in ≥2 L setting. The median sample sizes of the ICIs and CT arms were 139 (interquartile range [IQR]: 84–190) and 118 (IQR: 68–171) patients, respectively. The median duration of follow-up was 16.4 months (IQR, 11.7–28.1 months). The primary outcomes were OS, PFS, and co-primary endpoints of OS and PFS in 17, 10, and eight RCTs, respectively. The characteristics and main outcomes of the phase 3 RCTs are summarized in Table 1.

As for the 64 real-world studies, three studies assessed ICIs vs. CT,[62,80,92] and the remaining 61 studies investigated ICIs alone. Regarding the three studies on ICIs vs. CT, only data from the ICIs group were used for the analysis. Most studies included patients with ECOG scores of 0–1 and ≥2, and without reporting EGFR/ALK status. Twenty-seven studies were conducted in Asian countries, thirty-four in non-Asian countries, and three in the both regions. Forty-two studies assessed ICIs monotherapy (23 of anti-PD-1 and 19 of mixed drugs), eight studies assessed ICIs combination therapy (seven of anti-PD-1+CT and one of dual ICIs + CT), and 14 studies assessed both modes. ICIs were administered in 1 L and ≥2 L settings in 31 and 18 studies, respectively, and both 1 L and ≥2 L ICIs were used in 15 studies. The median sample size was 100 patients (IQR, 47–179 months), with a median follow-up time of 18.2 months (IQR, 11.1–22.0 months). The characteristics of the real-world studies are shown in Table 2, and the main outcomes are summarized in Supplementary File: Table S2.

Outcomes in phase 3 RCTs

OS

Thirty-two studies reported the HRs and their 95% CIs for OS. Compared with CT, ICIs significantly improved OS (HR = 0.78, 95% CI: 0.74–0.82; I^2 = 14%) (Fig. 2). In subgroup analyses (Fig. 3), ICIs was associated with a significantly longer OS in all subgroups, including aged 65–74 years (HR = 0.75, 95% CI: 0.63–0.88; I^2 = 55%), Asian (HR = 0.70, 95% CI: 0.55–0.90; I^2 = 42%), non-Asian (HR = 0.78, 95% CI: 0.64–0.95; I^2 = 50%), squamous cell carcinoma (SCC) (HR = 0.79, 95% CI: 0.65–0.96; I^2 = 41%), non-SCC (HR = 0.78, 95% CI: 0.68–0.89; I^2 = 0%), monotherapy (HR = 0.76, 95% CI: 0.70–0.83; I^2 = 22%), combination therapy (HR = 0.79, 95% CI: 0.73–0.86; I^2 = 1%), anti-PD-1

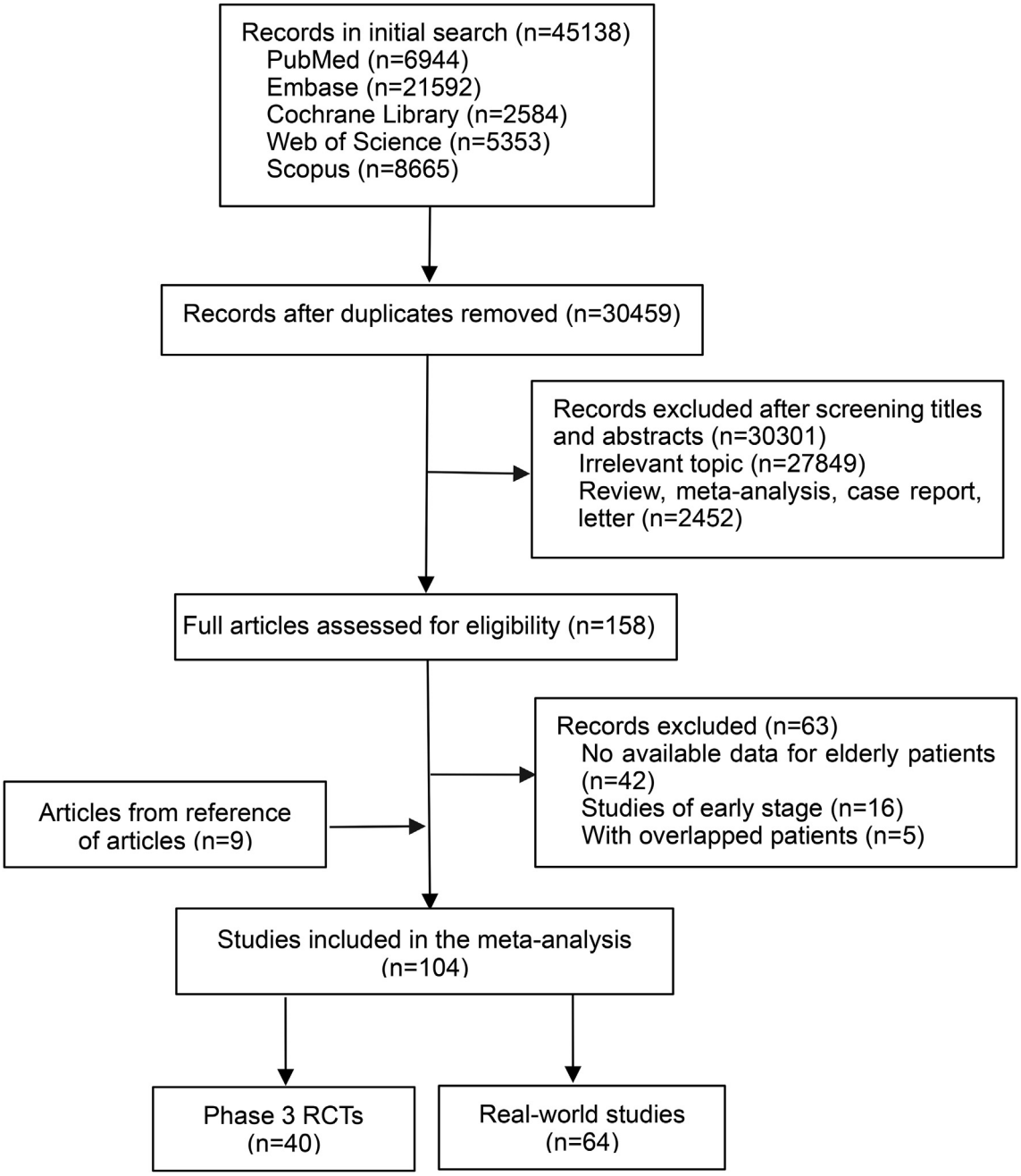

Fig. 1: Literature search and selection. RCTs, randomized controlled trials.

(HR = 0.75, 95% CI: 0.68–0.82; I^2 = 19%), anti-PD-L1 (HR = 0.78, 95% CI: 0.72–0.85; I^2 = 0%), 1 L setting (HR = 0.78, 95% CI: 0.73–0.84; I^2 = 4%), ≥2 L setting (HR = 0.76, 95% CI: 0.67–0.87; I^2 = 37%), PD-L1 ≥ 1% (HR = 0.81, 95% CI: 0.73–0.89; I^2 = 8%), and PD-L1 ≥ 50% (HR = 0.55, 95% CI: 0.45–0.66; I^2 = 0%), except subgroups of aged ≥ 75 years (HR = 0.89, 95% CI: 0.77–1.04; I^2 = 0%) and PD-L1 < 1% (HR = 0.66, 95% CI: 0.05–9.03; I^2 = 43%). Forest plots for the results of the subgroup analyses are presented in Supplementary File: Figs. S1–S7.

We conducted subgroup analyses of patients who received ICIs monotherapy and combination therapy (Supplementary File: Fig. S8). Regarding ICIs monotherapy, except aged ≥ 75 years (HR = 0.90, 95% CI: 0.73–1.11; I^2 = 0%), significantly improved OS was

Trial name/year	Region	Median follow-up time (IQR, m)	Treatment (sample size)	Treatment line	Age (years)	Histological type	PD-L1 level	HR (95% CI) for OS	HR (95% CI) for PFS
CheckMate-017/2015[3]	Muti	11.1[a]	Niv/CT (45/46)	≥2	65–74	SCC	NA	0.56 (0.34–0.91)	0.51 (0.32–0.82)
			Niv/CT (11/18)	≥2	≥75	SCC	NA	1.85 (0.76–4.51)	1.76 (0.77–4.05)
CheckMate-057/2015[4]	Muti	13.2[a]	Niv/CT (200 T)	≥2	65–74	non-SCC	NA	0.63 (0.45–0.89)	0.94 (0.69–1.27)
			Niv/CT (20/23)	≥2	≥75	non-SCC	NA	0.90 (0.43–1.87)	0.97 (0.45–1.95)
CheckMate-026/2017[5]	Muti	13.5	Niv/CT (123/137)	1	≥65	NSCLC	≥1%	1.04 (0.77–1.41)	1.21 (0.91–1.62)
CheckMate-078/2020[6]	Muti	25.9[a]	Niv/CT (87/40)	≥2	≥65	NSCLC	NA	0.53 (0.36–0.79)	0.69 (0.46–1.03)
CheckMate-227 (Part1)/2019[7]	Multi	29.3[a]	Niv + Ipi/CT (157/149)	1	65–74	NSCLC	≥1%	0.91 (0.70–1.19)	NA
			Niv + Ipi/CT (40/41)	1	≥75	NSCLC	≥1%	0.92 (0.57–1.48)	NA
			Niv + Ipi/CT (136)	1	65–74	NSCLC	<1%	0.49 (0.32–0.75)	NA
			Niv + Ipi/CT (32)	1	≥75	NSCLC	<1%	0.75 (0.31–1.82)	NA
CheckMate-227 (part2)/2023[8]	Multi	19.5[a]	Niv + CT/CT (125/149)	1	65–74	NSCLC	NA	0.87 (0.65–1.17)	NA
			Niv + CT/CT (38/33)	1	≥75	NSCLC	NA	0.86 (0.47–1.55)	NA
CheckMate-9LA/2021[9]	Multi	9.7 (6.4–12.8)	Niv + Ipi + CT/CT (148/147)	1	65–74	NSCLC	NA	0.62 (0.46–0.85)	0.75 (0.57–0.98)
			Niv + Ipi + CT/CT (37/33)	1	≥75	NSCLC	NA	1.21 (0.69–2.12)	1.17 (0.68–2.03)
Keynote-010-/2016[10,11]	Muti	42.6	Pem/CT (295/134)	≥2	≥65	NSCLC	≥1%	0.79 (0.63–1.00)	0.93 (0.72–1.19)
Keynote-024/2016[12,13]	Muti	25.2	Pem/CT (164)	1	≥65	NSCLC	≥50%	0.64 (0.42–0.98)	0.45 (0.29–0.70)
Keynote-042/2019[14]	Muti	12.8 (6.0–20.0)	Pem/CT (278/289)	1	≥65	NSCLC	≥1%	0.82 (0.66–1.01)	NA
Keynote-010,-024,-042/2019[15]	Muti	11.7	Pem/CT (149/115)	1, ≥2	≥75	NSCLC	≥1%	0.76 (0.56–1.02)	NA
Keynote-189/2018[16]	Multi	10.5	Pem + CT/CT (213/91)	1	≥65	non-SCC	NA	0.64 (0.43–0.95)	0.75 (0.55–1.02)
Keynote-407/2018[17]	Multi	7.8	Pem + CT/CT (151/154)	1	≥65	SCC	NA	0.74 (0.51–1.07)	0.63 (0.47–0.84)
Keynote-407-China/2021[18]	China	28.1	Pem + CT/CT (51 T)	1	≥65	SCC	NA	0.45 (0.23–0.91)	0.37 (0.20–0.69)
Keynote-189,-407, NCT03950674, NCT03875092/2024[19]	Muti	60.7	Pem + CT/CT (190/217)	1	≥65	NSCLC	<1%	0.80 (0.60–1.07)	0.83 (0.63–1.09)
IMpower-110/2020[20]	Multi	15.7	Ate/CT (33/47)	1	65–74	NSCLC	≥50%	0.63 (0.34–1.19)	NA
			Ate/CT (15/8)	1	≥75	NSCLC	≥50%	0.79 (0.18–3.56)	NA
IMpower-130/2019[21]	Multi	18.5 (15.2–23.6)	Ate + CT/CT (224/114)	1	≥65	non-SCC	NA	0.78 (0.58–1.05)	0.64 (0.50–0.82)
IMpower-131/2020[22]	Multi	26.8	Ate + CT/CT (134/145)	1	65–74	SCC	NA	0.84 (0.63–1.13)	NA
			Ate + CT/CT (39/38)	1	≥75	SCC	NA	0.74 (0.45–1.23)	NA
IMpower-132/2021[23]	Multi	28.4	Ate + CT/CT (139/118)	1	≥65	non-SCC	NA	0.84 (0.63–1.13)	0.55 (0.42–0.73)
IMpower-150/2018[24]	Multi	15.5	Ate + CT/CT (149/132)	1	65–74	non-SCC	NA	NA	0.52 (0.39–0.69)
			Ate + CT/CT (33/39)	1	≥75	non-SCC	NA	NA	0.78 (0.42–1.45)
IMpower-210/2024[25]	China	30.2	Ate/CT (144/144)	2	≥65	NSCLC	NA	1.05 (0.69–1.60)	NA
IPSOS/2023[26]	Multi	41.0 (36.7–47.8)	Ate/CT (80/43)	1	65–69	NSCLC	NA	0.75 (0.49–1.14)	NA
			Ate/CT (125/65)	1	70–79	NSCLC	NA	0.68 (0.49–0.94)	NA
			Ate/CT (97/43)	1	≥80	NSCLC	NA	0.97 (0.66–1.44)	NA
OAK/2017[27]	Muti	21.0	Ate/CT (190/207)	≥2	≥65	NSCLC	NA	0.66 (0.52–0.83)	NA
EMPOWER-Lung 1/2021[28]	Multi	10.8 (7.6–15.8)	Cem/CT (126/133)	1	≥65	NSCLC	≥50%	0.48 (0.30–0.76)	0.60 (0.43–0.84)
EMPOWER-Lung 3/2022[29]	Multi	16.3 (13.9–19.1)	Cem + CT/CT (128/60)	1	≥65	NSCLC	NA	0.88 (0.56–1.37)	0.56 (0.39–0.81)
JAVELIN Lung 200/2018[30]	Multi	18.9 (13.5–23.1)	Ave/CT (130/120)	≥2	≥65	NSCLC	≥1%	0.98 (0.71–1.34)	1.07 (0.76–1.50)
JAVELIN Lung 100/2024[31]	Multi	48.8	Ave/CT (71/98)	1	≥65	NSCLC	≥1%	0.73 (0.51–1.06)	0.57 (0.38–0.86)
MYSTIC/2020[32]	Muti	30.2	Dur/CT (81/81)	1	≥65	NSCLC	≥25%	0.66 (0.45–0.95)	NA
POSEIDON/2023[33]	Multi	34.9	Dur/CT (169/161)	1	≥65	NSCLC	NA	0.81 (0.64–1.03)	NA
			Dur + Tre/CT (147/161)	1	≥65	NSCLC	NA	0.74 (0.58–0.94)	NA
RATIONALE-303/2023[34]	Multi	16.0	Tis/CT (171/90)	≥2	≥65	NSCLC	NA	0.73 (0.55–0.99)	NA
RATIONALE-304/2021[35]	China	9.8	Tis + CT/CT (60/37)	1	≥65	non-SCC	NA	NA	0.73 (0.41–1.30)
RATIONALE-307/2021[36]	China	8.6	Tis + CT-A/CT (39/36)	1	≥65	SCC	NA	NA	0.60 (0.31–1.18)
			Tis + CT-B/CT (52/36)	1	≥65	SCC	NA	NA	0.56 (0.30–1.05)
CameL/2023[37]	China	24.2	Camr + CT/CT (45/53)	1	≥65	non-SCC	NA	0.71 (0.43–1.15)	0.53 (0.32–0.86)
CameL-sq/2022[38]	China	13.5	Cam + CT/CT (84/71)	1	≥65	SCC	NA	0.64 (0.40–1.04)	0.49 (0.33–0.71)
GEMSTONE-302/2022[39]	China	17.8 (15.1–20.9)	Sug + CT/CT (118/68)	1	≥65	NSCLC	NA	NA	0.53 (0.38–0.75)
CHOICE-01/2023[40]	China	16.2	Tor + CT/CT (130/55)	1	≥65	NSCLC	NA	0.89 (0.58–1.40)	0.53 (0.37–0.76)
ASTRUM-004/2024[41]	China	31.0	Ser + CT/CT (154/73)	1	≥65	SCC	NA	NA	0.52 (0.35–0.77)
Study-104/2017[42]	Muti	12.5	Ipi + CT/CT (152/146)	1	65–74	SCC	NA	1.06 (0.81–1.37)	NA
			Ipi + CT/CT (38/33)	1	≥75	SCC	NA	0.85 (0.51–1.43)	NA

RCTs, randomized controlled trials; Niv, nivolumab; Pem, pembrolizumab; Ate, atezolizumab; Cem, cemiplimab; Ave, avelumab; Dur, durvalumab; Tre, tremelimumab; Tis, tislelizumab; Cam, camrelizumab; Sug, sugemalimab; Tor, toripalimab; Ser, serplulimab; Ipi, ipilimumab; CT, chemotherapy; SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; m, month; HR, hazard ratio; CI, confidence interval; NA, not available. [a]The minimum follow-up time.

Table 1: **Characteristics and main outcomes of phase 3 RCTs.**

First author/year	Region	Median follow-up time (IQR,m)	Treatment (sample size)	Treatment line	Age (median) (years)	Male (%)	ECOG 0–1 (%)	Never smoker (%)	Histological type	PD-L1 level
Sabatier/2018[43]	France	8.2	Nivolumab (30)	≥2	≥70 (75)	73	69	NA	NSCLC	NA
Juergens/2018[44]	Canada	NA	Nivolumab (199)	≥2	65–74	NA	NA	NA	NSCLC	NA
			Nivolumab (60)	≥2	≥75	NA	NA	NA	NSCLC	NA
Dudnik/2018[45]	Israel	18.5	Nivolumab (60)	≥2 (94%)	≥75	NA	NA	NA	NSCLC	NA
Grossi/2018[46]	Italy	NA	Nivolumab (175)	≥2	65-74 (70)	82	94	8	SCC	NA
			Nivolumab (70)	≥2	≥75 (77)	87	94	3	SCC	NA
Galli/2019[47]	Italy	NA	ICIs (94)	1, ≥2	70–79	67	84	17	NSCLC	NA
			ICIs (16)	1, ≥2	≥80	88	90	25	NSCLC	NA
Grossi/2019[48]	Italy	8.1	Nivolumab (522)	≥2	≥70 (74)	74	92	20	non-SCC	NA
Muchnik/2019[49]	Canada	NA	ICIs (75)	1, ≥2	≥70 (74)	52	51	NA	non-SCC	NA
Montana/2019[50]	France	NA	Nivolumab (52)	1, ≥2	≥65	NA	NA	NA	NA	NA
Morgan/2019[51]	USA	NA	ICIs ± CT (76)	1, ≥2	70–79	55	56	8	NSCLC	NA
			ICIs ± CT (28)	1, ≥2	≥80	68	58	4	NSCLC	NA
Almazán/2019[52]	Spain	NA	Nivolumab (59)	≥2	≥70	NA	NA	NA	NSCLC	NA
Khozin/2019[53]	USA	NA	ICIs (499)	1, ≥2	65–74	NA	NA	NA	NSCLC	NA
			ICIs (365)	1, ≥2	≥75	NA	NA	NA	NSCLC	NA
Yamaguchi/2020[54]	Japan	11.1	ICIs (131)	≥2	≥75 (77)	75	84	24	NSCLC	NA
Kubo/2020[55]	Japan	18.8	ICIs (95)	1, ≥2	≥75 (79)	81	80	12	NSCLC	NA
Okishio/2020[56]	Japan	NA	Nivolumab (178)	≥2	≥75 (78)	74	80	22	NSCLC	NA
Luciani/2020[57]	Italy	10.3	ICIs (86)	1, ≥2	≥75 (79)	83	80	7	NSCLC	NA
Facchinetti/2020[58]	Italy	18.2	Pembrolizumab (74)	1	≥70	NA	0	NA	NSCLC	≥50%
Ahmed/2020[59]	USA	NA	ICIs (100)	1, ≥2	≥70	NA	29	NA	NSCLC	NA
Adachi/2020[60]	Netherlands	26.6	Nivolumab (296)	1, ≥2	≥65	70	76	20	NSCLC	NA
Elkrief/2020[61]	Multi	19.3	ICIs (124)	≥2 (88%)	≥70	62	84	8	NSCLC	NA
Nakamura/2020[62]	Japan	NA	ICIs (31)/CT (35)	≥2	≥70 (75)	70	68	27	NSCLC	NA
Imai/2020[63]	Japan	10.1	Pembrolizumab (47)	1	≥75 (79)	85	79	9	NSCLC	≥50%
Joris/2020[64]	Belgium	NA	Nivolumab (108)	≥2	≥70 (74)	65	74	9	NSCLC	NA
Smit/2020[65]	Netherlands	NA	ICIs (207)	≥2 (94%)	≥75	NA	NA	NA	NSCLC	NA
Cavaille/2020[66]	France	7.6	Pembrolizumab (18)	1	≥65	NA	NA	NA	NSCLC	≥50%
Nebhan/2021[67]	Multi	NA	ICIs (345)	1, ≥2	≥80 (83)	64	71	NA	NSCLC	NA
Grosjean/2021[68]	Canada	NA	Pembrolizumab (169)	1	≥70	52	74	7	NSCLC	≥50%
Morimoto/2021[69]	Japan	13.9	Pembrolizumab + CT (43)	NA	≥75 (77)	81	93	14	NSCLC	NA
Kehl/2021[70]	USA	18.0	Pembrolizumab (3079)	1	≥65 (74)	49	NA	NA	NSCLC	NA
			Pembrolizumab + CT (1425)	1	≥65 (74)	52	NA	NA	NSCLC	NA
Waterhouse/2021[71]	USA	NA	ICIs (2340) ICIs + CT (2811)	1, ≥2 1, ≥2	≥65 ≥65	NA NA	NA NA	NA NA	NSCLC NSCLC	NA NA
Matsubara/2021[72]	Japan	13.8	ICIs (15)	1, ≥2	≥75	NA	NA	NA	NSCLC	NA
Chikaishi/2021[73]	Japan	13.0	ICIs (10)	1, ≥2	≥80 (85)	70	90	20	non-SCC	NA
Ron/2021[74]	Spain	NA	Nivolumab (38)	≥2	≥70 (75)	95	95	13	NSCLC	NA
Fujimoto/2021[75]	Japan	11.7 (9.8–13.6)	Pembrolizumab + CT (43)	1	≥75	NA	NA	NA	non-SCC	NA
Jiménez Galán/ 2021[76]	Spain	23.0	Pembrolizumab (NA)	1	≥70	NA	NA	NA	NSCLC	≥50%
Dudnik/2021[77]	Israel	22.3 (14.5–28.9)	Pembrolizumab (126)	1	≥65	NA	NA	NA	NSCLC	≥50%
			Pembrolizumab + CT (34)	1	≥65	NA	NA	NA	NSCLC	≥50%
Li/2022[78]	China	9.8	ICIs (68)	≥2	≥65 (72)	63	69	NA	NSCLC	NA
Shiotsu/2022[79]	Japan	9.5	Pembrolizumab (31)	1, ≥2	≥75 (79)	NA	NA	NA	NSCLC	≥1%
Yang/2022[80]	China	NA	Pembrolizumab + CT (43)/ CT (93)	1	≥75 (78)	88	93	NA	NSCLC	NA
Altan/2022[81]	USA	24.7	ICIs (179)	1, ≥2	≥70 (75)	59	80	17	NSCLC	NA
Benguerfi/2022[82]	France	12.6	ICIs (36)	≥2 (92%)	≥80 (82)	72	72	25	NSCLC	NA
Goto/2022[83]	Japan	13.5	Pembrolizumab (138)	1	≥75 (79)	77	57	18	NSCLC	≥50%
Tibaldi/2022[84]	Italy	15.2	Pembrolizumab (NR)	1	≥70	NA	NA	NA	NSCLC	≥50%
Kubo/2023[85]	Japan	NA	ICIs (100)	1, ≥2	≥85 (87)	81	75	6	NSCLC	NA
Burns/2023[86]	Multi	NA	ICIs (3248)	NA	≥80 (84)	51	NA	NA	non-SCC	NA
			ICIs + CT (2393)	NA	≥80 (82)	58	NA	NA	non-SCC	NA

(Table 2 continues on next page)

First author/year	Region	Median follow-up time (IQR,m)	Treatment (sample size)	Treatment line	Age (median) (years)	Male (%)	ECOG 0–1 (%)	Never smoker (%)	Histological type	PD-L1 level
(Continued from previous page)										
Ham/2023[87]	Korea	10.0	ICIs (180)	1, ≥2	≥70 (76; IQR,74–78)	98	96	0	NSCLC	NA
Zhang/2023[88]	China	21.4	ICIs ± CT (43)	1, ≥2	≥65 (70)	86	79	40	NSCLC	NA
Wang/2023[89]	China	9.5 (6.4–12.6)	Camrelizumab ± CT (125)	1, ≥2	≥70	NA	NA	NA	NSCLC	NA
Morinaga/2023[90]	Japan	34.3	ICIs (137)	1, ≥2	≥75 (78)	71	89	26	non-SCC	NA
Blasi/2023[91]	Germany	44.0 (23.0–58.0)	Pembrolizumab (61)	1	≥70 (76)	64	87	15	NSCLC	≥50%
		22.0 (17.0–34.0)	Pembrolizumab + CT (95)	1	≥70 (74)	74	88	12	NSCLC	NA
Mahashabde/2023[92]	USA	NA	ICIs ± CT (178)/CT (1303)	1	≥65 (74)	47	NA	NA	NSCLC	NA
Galán/2023[93]	Spain	NA	Pembrolizumab (38)	1	≥70	NA	NA	NA	NSCLC	≥50%
Takei/2024[94]	Korea	21.9	Pembrolizumab (52)	1	≥70 (76)	82	100	10	NSCLC	≥50%
			ICIs + CT (52)	1	≥70 (73)	74	100	21	NSCLC	≥50%
Zhang/2024[95]	China	NA	ICIs (30)	1	≥75 (80)	80	94	23	NSCLC	NA
			ICIs + CT (20)	1	≥75 (77)	80	95	10	NSCLC	NA
Huang/2024[96]	China	NA	ICIs + CT (40)	1	65–69	85	NA	25	NSCLC	NA
			ICIs + CT (19)	1	70–74	84	NA	26	NSCLC	NA
			ICIs + CT (10)	1	≥75	80	NA	30	NSCLC	≥1%
Cafaro/2024[97]	Italy	19.7	Pembrolizumab + CT (22)	1	≥75	NA	NA	NA	non-SCC	NA
Li/2024[98]	China	NA	ICIs ± CT (58)	1, ≥2	≥70 (76)	81	85	28	NSCLC	NA
Wasamoto/2024[99]	Japan	14.9	Pembrolizumab + CT (30)	1	≥75 (76)	67	93	27	non-SCC	NA
Matsumoto/2024[100]	Japan	18.5 (14.6–22.1)	Nivolumab + Ipilimumab + CT (52)	1	≥65	NA	NA	NA	NSCLC	NA
			Pembrolizumab + CT (103)	1	≥65	NA	NA	NA	NSCLC	NA
Cafaro/2024[101]	Italy	35.1	Pembrolizumab (229)	1	≥75	NA	NA	NA	NSCLC	≥50%
Yagishita/2024[102]	Japan	NA	Pembrolizumab ± CT (99)	1, ≥2	≥75 (78)	71	86	20	NSCLC	NA
Velcheti/2024[103]	USA	60.5	Pembrolizumab (310)	1	≥75	NA	100	NA	NSCLC	≥50%
Ikezawa/2024[104]	Japan	20.2	Pembrolizumab (81)	1	≥75	NA	NA	NA	NSCLC	≥50%
			Pembrolizumab + CT (18)	1	≥75	NA	NA	NA	NSCLC	≥50%
Tsukita/2024[105]	Japan	19.2	ICIs (425)	1	≥75 (78)	NA	NA	NA	NSCLC	NA
			ICIs + CT (354)	1	≥75 (78)	NA	NA	NA	NSCLC	NA
Rousseau/2024[106]	France	25.9	Pembrolizumab (10,935)	1	70–79	NA	NA	NA	NSCLC	NA
			Pembrolizumab (2826)	1	≥80	NA	NA	NA	NSCLC	NA

ICIs, immune checkpoint inhibitors; CT, chemotherapy; NA, not available; NSCLC, Non-small cell lung cancer; SCC, squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group.

Table 2: **Characteristics of real-world studies.**

observed in each subgroup, including aged 65–74 years (HR = 0.61, 95% CI: 0.52–0.72; I^2 = 0%), 1 L setting (HR = 0.78, 95% CI: 0.70–0.86; I^2 = 8%), ≥2 L setting (HR = 0.76, 95% CI: 0.66–0.89; I^2 = 42%), anti-PD-1 (HR = 0.73, 95% CI: 0.63–0.85; I^2 = 48%), anti-PD-L1 (HR = 0.78, 95% CI: 0.70–0.87; I^2 = 0%), PD-L1 expression ≥ 1% (HR = 0.84, 95% CI: 0.75–0.94; I^2 = 0%), or PD-L1 expression ≥ 50% (HR = 0.58, 95% CI: 0.48–0.70; I^2 = 0%). As for combination therapy, significantly better OS was not observed in subgroups of aged 65–74 years (HR = 0.80, 95% CI: 0.62–1.04; I^2 = 62%) and aged ≥ 75 years (HR = 0.88, 95% CI: 0.71–1.08; I^2 = 0%); either ICIs plus CT (HR = 0.78, 95% CI: 0.70–0.87; I^2 = 0%) or dual ICIs (HR = 0.76, 95% CI: 0.66–0.88; I^2 = 45%) were associated with a significantly longer OS.

PFS

Twenty-four studies reported HRs with 95% CIs for PFS. ICIs were associated with a significantly prolonged PFS compared to CT (HR = 0.67, 95% CI: 0.60–0.75; I^2 = 59%) (Supplementary File: Fig. S9). In subgroup analyses, ICIs significantly improved PFS in all subgroups, except subgroups of aged ≥ 75 years, non-Asian, ≥2 L setting, and PD-L1 ≥ 1% (Supplementary File: Fig. S10).

Safety

Only one study (pooled analysis of Keynote-010, -024, and –042 trials)[15] reported data of TRAEs in elderly patients (aged ≥ 75 years). The incidence of all grade and grade ≥ 3 TRAEs in the pembrolizumab arm were 68.5% and 24.2%, respectively, which were numerically low compared to that in CT arm (94.3% and 61.0%), and TRAEs-related discontinuation was 10.7% vs. 15.2%.

Outcomes in real-world studies

Median OS and OS rates at 12-, 24-, and 36-months

The median OS of ICIs extracted from 50 real-world studies with 22,382 patients ranged from 2.9 to 42.2

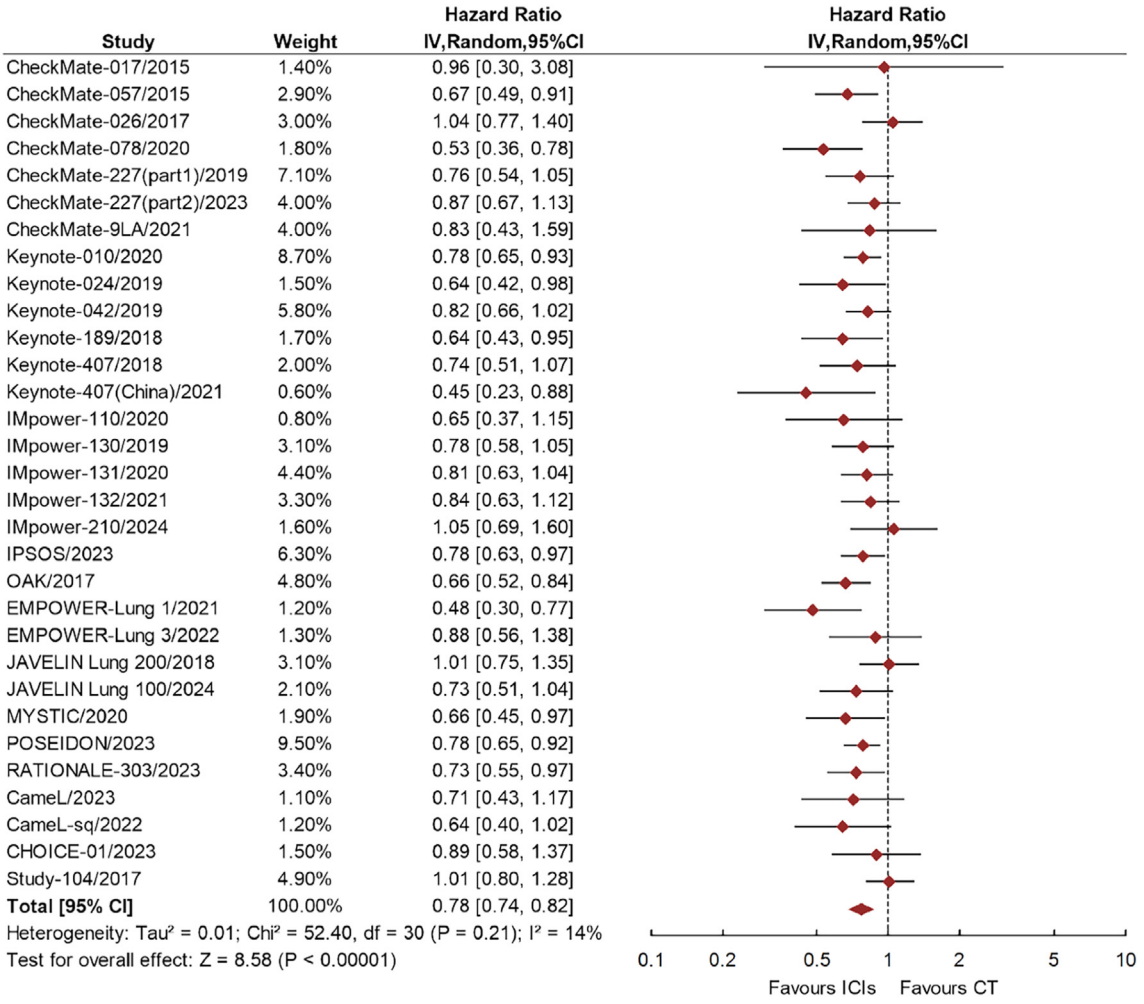

Fig. 2: Forest plot of hazard ratios comparing OS between ICIs and CT in phase 3 RCTs. OS, overall survival; RCTs, randomized controlled trials; ICI, immune checkpoint inhibitor; CI, confidence interval.

months, with a pooled median OS of 11.8 months (95% CI: 11.2–12.4; $I^2 = 91\%$). The pooled OS rates at 12-, 24-, and 36-months were 53% (95% CI: 51%–55%; $I^2 = 90\%$), 35% (95% CI: 33%–37%; $I^2 = 89\%$), and 26% (95% CI: 24%–28%; $I^2 = 88\%$), respectively (Table 3). In subgroup analyses, the pooled median OS and the pooled OS rates at 12-, 24-, and 36-month were numerically high for Asians (15.1 months; 61%, 43%, and 33%) compared to non-Asian (10.9 months; 48%, 31%, and 23%). Similarly, combination therapy (13.6 months; 59%, 41%, and 32%) demonstrated better outcomes than monotherapy (11.0 months; 50%, 33%, and 25%). 1 L (12.8 months; 59%, 41%, and 32%) also outperformed 2 L (10.5 months; 47%, 30%, and 14%) settings. However, outcomes were comparable between patients aged ≥ 70 years (11.9 months; 53%, 35%, and 26%) and ≥75 years (12.2 months; 54%, 37%, and 27%) (Table 3).

Factors associated with OS

Twenty-seven studies investigated factors associated with the OS. ECOG score (0–1 vs. ≥2) (15 studies; HR = 0.42, 95% CI: 0.35–0.49; $I^2 = 0\%$), histological type (non-SCC vs. SCC) (9 studies; HR = 0.68, 95% CI: 0.52–0.90; $I^2 = 65\%$), PD-L1 status (<1% vs. ≥1%) (7 studies; HR = 1.35, 95% CI: 1.10–1.65; $I^2 = 0\%$), irAEs (yes vs. no) (6 studies; HR = 0.59, 95% CI: 0.46–0.76; $I^2 = 0\%$), and treatment mode (monotherapy vs. combination therapy) (6 studies; HR = 1.14, 95% CI: 1.08–1.20; $I^2 = 0\%$) were significantly associated with OS (Fig. 4); while liver metastasis (yes vs. no), brain metastasis (yes vs. no), age (65–74 vs. ≥75 years), gender (males vs. females), smoking status (others/never smokers), and treatment line (1 L vs. ≥2 L) were not significantly associated with OS (Fig. 4).

Considering that many of the HR estimates obtained from real-world studies were unadjusted and subjected

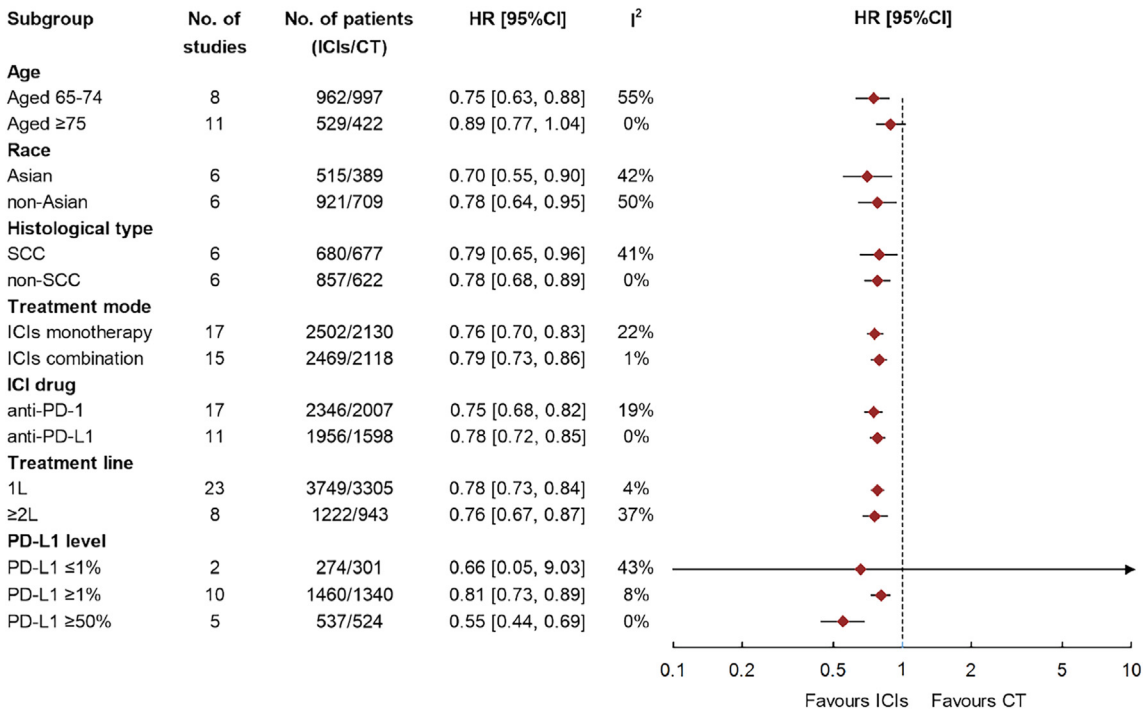

Fig. 3: Subgroup analyses of OS in phase 3 RCTs. OS, overall survival; RCTs, randomized controlled trials; ICI, immune checkpoint inhibitor; CT, chemotherapy; SCC, squamous cell carcinoma; L, line; HR, hazard ratio; CI, confidence interval.

to confounding factors, we further performed subgroup analyses using multivariable-adjusted HRs to measure the effect, while found the similar results (Fig. 4). Nevertheless, the studies reporting adjusted HRs was limited, and the set of adjusted variables varied across the studies. The adjusted variables in each study are summarized in Supplementary File: Table S3. Forest plots for the results shown in Fig. 4 are presented in the Supplementary File as Supplementary Figs. S11–S21.

Safety

Safety outcomes are summarized in Fig. 5. Seven, 19, and 20 studies provided data on TRAEs, irAEs, and drug discontinuation, respectively. The pooled rates of all-grade and grade ≥3 TRAEs were 50.2% (95% CI: 37.1%–63.2%) and 7.7% (95% CI: 4.1%–11.3%), respectively. Patients receiving combination therapy had a higher incidence of all-grade (89.1% vs. 37.7%) and grade ≥3 TRAEs (44.2% vs. 5.7%) than those receiving monotherapy. Nevertheless, the number of studies providing data on TRAEs was small, especially in the combination therapy group (n = 2 for all-grade and n = 1 for grade ≥3). The pooled rates of all-grade and grade ≥3 irAEs were 40.4% (95% CI: 36.3%–44.5%) and 11.3% (95% CI: 8.1%–14.9%), respectively, and were numerically high in combination therapy (45.1% and 19.0%) vs. monotherapy groups (40.1% and 10.1%). For patients aged ≥75 years, the pooled rates of all-grade and grade ≥3 TRAEs and irAEs were 41.6% and 5.5%, and 40.6% and 11.7%, respectively. The pooled discontinuation rate was 18.7% (95% CI: 14.9%–22.4%) overall, 19.6% (95% CI: 14.7%–24.9%) for patients with aged ≥75 years, and 14.5% (95% CI: 11.3%–18.1%) for monotherapy vs. 33.9% (95% CI: 27.0%–41.2%) for combination therapy. The heterogeneity was generally high, with I^2 values ranging from 39% to 98%.

The GRADE assessment in phase 3 RCTs

The results of the GRADE assessment are shown in Supplementary File Table S3. Most evidence for OS had moderate GRADE ratings, except for the subgroups aged 65–74 years and with PD-L1 < 1%, which had low GRADE ratings. The evidence for PFS had moderate GRADE ratings in the Asian, SCC, non-SCC, combination therapy, 1 L setting, and 2 L setting subgroups and had low GRADE ratings in other subgroups.

Meta-regression analysis

Regarding phase 3 RCTs, univariate and multivariable meta-regression analyses showed that sample size, risk bias of study, race, histological type, PD-L1 status, treatment mode, and ICI drug were not significantly associated with the heterogeneity of OS and PFS ($P > 0.05$). In contrast, the treatment line appeared to be a source of heterogeneity of PFS (multivariable, $P = 0.01$) (Supplementary File: Table S5). As for

Group	No. of studies	No. of patients	Median (95% CI)	I^2 (%)
Median OS (months)				
Overall	50	36,134	11.8 (11.2–12.4)	91
Race				
Asian	15	2083	15.1 (13.1–17.4)	76
Non-Asian	33	33,715	10.9 (10.2–11.5)	92
Treatment type				
ICI monotherapy	45	28,611	11.0 (10.3–11.9)	90
ICI combination	10	7370	13.6 (12.1–15.2)	90
Treatment Line				
1 line	18	20,640	12.8 (11.4–14.3)	92
≥2 line	16	2111	10.5 (9.2–12.1)	82
Age				
≥70 years	41	27,279	11.9 (11.2–12.7)	92
≥75 years	22	11,342	12.2 (11.1–13.4)	92
OS rate at 12 months (%)				
Overall	54	36,023	53 (51–55)	90
Race				
Asian	27	2965	61 (57–65)	76
Non-Asian	26	32,713	48 (46–50)	92
Treatment type				
ICI monotherapy	43	27,960	50 (47–52)	90
ICI combination	19	7944	59 (55–63)	89
Treatment Line				
1 line	24	21,082	59 (56–62)	89
≥2 line	15	1961	47 (43–51)	66
Age				
≥70 years	46	27,367	53 (51–55)	87
≥75 years	33	11,846	54 (51–56)	84
OS rate at 24 months (%)				
Overall	42	34,373	35 (33–37)	89
Race				
Asian	21	2424	43 (38–47)	76
Non-Asian	20	31,604	31 (29–33)	92
Treatment type				
ICI monotherapy	34	27,158	33 (31–35)	91
ICI combination	15	7053	41 (37–45)	86
Treatment Line				
1 line	18	20,828	41 (38–44)	88
≥2 line	10	1332	30 (27–33)	18
Age				
≥70 years	34	26,228	35 (33–38)	85
≥75 years	22	11,000	37 (34–40)	85
OS rate at 36 months (%)				
Overall	28	25,423	26 (24–28)	88
Race				
Asian	14	1811	33 (27–39)	86
Non-Asian	13	23,267	23 (21–25)	89
Treatment type				
ICI monotherapy	22	8298	25 (22–27)	90
ICI combination	10	3248	32 (26–39)	86
Treatment Line				
1 line	13	15,824	32 (28–35)	88
≥2 line	3	191	14 (9–19)	86

(Table 3 continues on next page)

real-world studies, univariate meta-regression analysis revealed that race (P = 0.001) and EOCG score (P = 0.02) were significantly associated with the heterogeneity of median OS (Supplementary File: Table S6); multivariable meta-regression analysis was not performed because of too many missing data.

Sensitivity analysis

When one study was omitted at a time, the pooled HRs of OS and PFS in phase 3 RCTs and the pooled median OS in real-world studies did not change markedly, suggesting relatively stable results (Supplementary File: Figs. S22–S24).

Assessment of included studies and publication bias

Among the 35 RCTs, 10[10,16,17,29,30,38–42] were classified as having a low risk of bias, while the remaining 25 RCTs were considered to have a high risk of bias, mainly due to their open-label nature, which resulted in difficulty in the blinding of participants and personnel (Supplementary File: Fig. S25). All real-world studies demonstrated a score of ≥8 (range: 8–12), suggesting moderate quality of them (Supplementary File: Table S7). No publication bias was observed in phase 3 RCTs (P = 0.12; OS: P = 0.10) but was observed in real-world studies (P < 0.001) using Egger's test. Funnel plots are shown in the Supplementary File: Figs. S26–S28.

Discussion

In this study, we investigated the efficacy and safety of ICIs in elderly patients with advanced NSCLC in phase 3 RCTs and real-world studies, respectively. Results from phase 3 RCTs revealed that ICIs significantly improved OS and PFS compared to CT. The association of ICIs with better OS was irrespective of patient characteristics, including race and histological type; or treatment-related factors, including ICIs type, treatment mode, and treatment line. However, in the subgroup analysis according to age, significantly prolonged OS was not observed in patients aged ≥ 75 years. In addition, we did not find an OS benefit with ICIs combination therapy in patients with PD-L1 expression < 1%. Currently, the efficacy of ICIs for PD-L1-negative NSCLC remains controversial because of the different findings in phase 3 trials. For example, the CheckMate-227,[8] CheckMate-9LA,[9] KEYNOTE-189,[16] and Impower-132[23] trials demonstrated a significantly longer OS with ICI plus CT or dual ICIs vs. CT alone in PD-L1-negative patients, whereas the Impower-131,[22] Impower-150,[24] and Empower-Lung 3[29] trials did not find any difference in OS between arms of ICIs plus CT and CT alone in this population. In our meta-analysis, only two studies[7,19] provided OS data for elderly patients with expression < 1%. Limited by the small sample size, our

results require further validation through additional RCTs.

In real-world studies, some findings have been inconsistent with those of phase 3 RCTs. The pooled median OS as well as OS rates at 12-, 24-, and 36-months appeared to be similar between patients aged ≥ 65 years aged ≥ 75 years, and age (65–74/ ≥75 years) was not predictive for OS. In addition, ICIs monotherapy was associated with a worse OS than combination therapy. The unbalanced characteristics of patients between real-world studies and phase 3 RCTs may be related to the different findings. For example, the majority of patients included in phase 3 RCTs had an ECOG score of 0–1, while many patients with ECOG ≥ 2 were included in real-world studies, which might be associated with the worse OS in real-world studies because ECOG ≥ 2 was found to be a negative predictor of OS in our study. In addition, there is the possibility of selection bias in real-world studies. Patients with ECOG ≥ 2 were likely to be treated with ICIs monotherapy, and those with ECOG 0–1 had more chance to receive combination therapy, which might magnify the efficacy of combination therapy.

Moreover, the histological type appears to be associated with OS in real-world studies. Patients with SCC with worse OS in real-world studies are probably due to their heavier history of smoking exposure and more comorbidities such as cardiovascular diseases and chronic obstructive pulmonary diseases,[115,116] which may affect the choice of aggressive treatments and lead to a

Group	No. of studies	No. of patients	Median (95% CI)	I^2 (%)
(Continued from previous page)				
Age				
≥70 years	24	23,788	26 (23–28)	89
≥75 years	15	9123	27 (23–30)	87

OS, overall survival; ICI, immune checkpoint inhibitor; CI, confidence interval.

Table 3: **Median OS and OS rates at 12-, 24-, 36-months in real-world studies.**

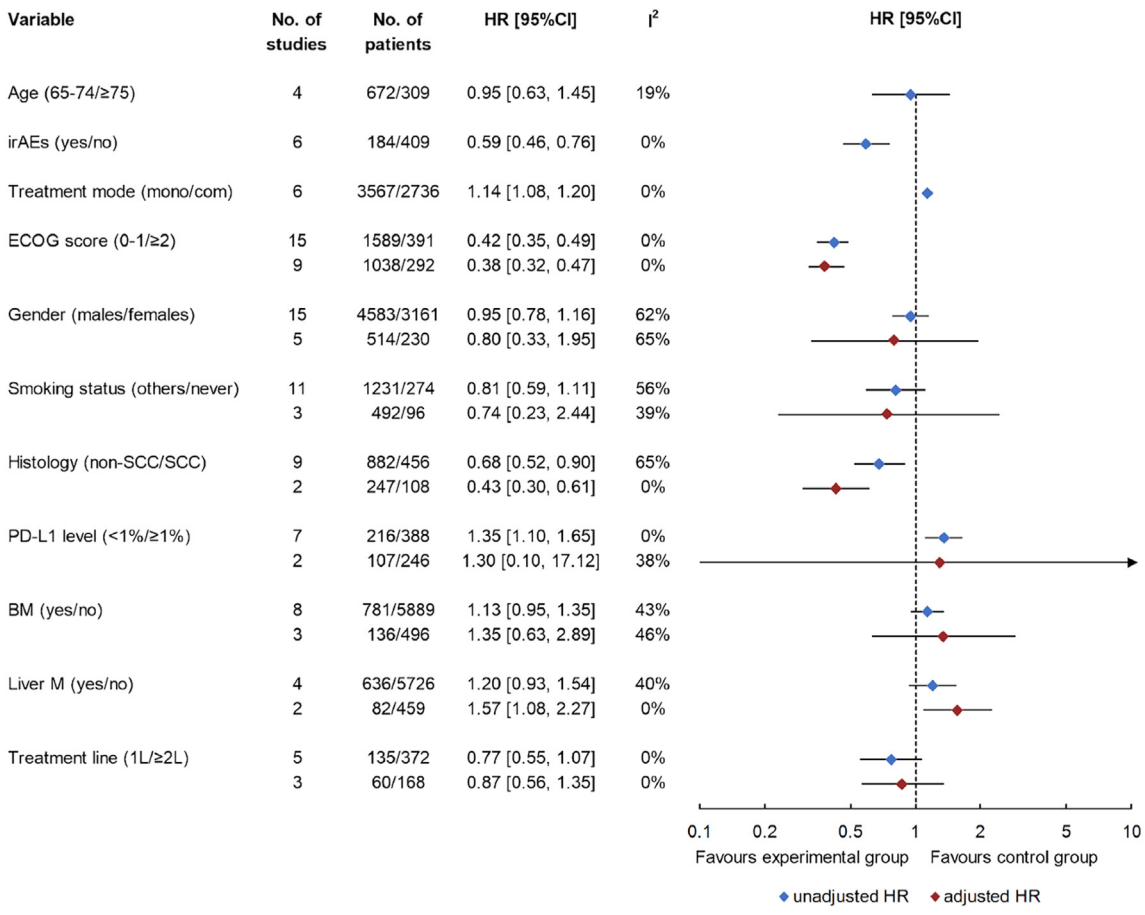

Fig. 4: Analysis of factors associated with OS in real-world studies. OS, overall survival; ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; BM, brain metastasis; irAEs, immune-related adverse events; mono, monotherapy; com, combination therapy; L, line.

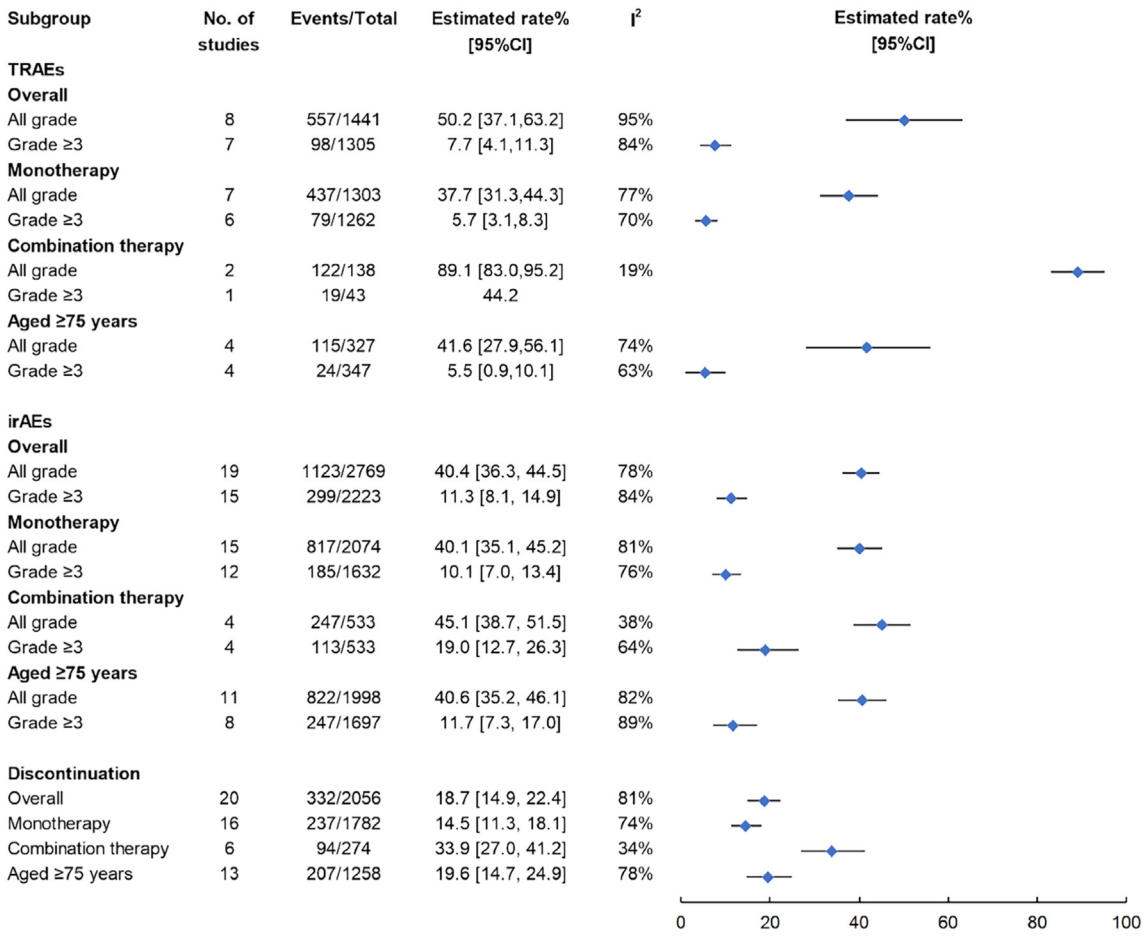

Fig. 5: Safety outcomes in real-world studies. TRAEs, treatment related adverse events; irAEs, immune-related adverse events; CI, confidence interval.

poor prognosis. However, in phase 3 RCTs, patients generally had good physiological conditions and balanced characteristics with non-SCC patients, which might have resulted in a comparable OS benefit with ICIs between the two populations. Additionally, we investigated the effects of liver metastasis, brain metastasis, sex, smoking status, PD-L1 status, and treatment line on ICI efficacy in real-world studies. Except for PD-L1 < 1%, which was likely associated with worse OS, other factors were not found to be significantly predictive of OS. Nevertheless, many of HRs used for the analysis of predictors in real-world studies were unadjusted, which were subject to confounding factors. Although we further performed analyses using multivariable-adjusted HRs to measure the effect and found similar results, the studies reporting the adjusted HRs were limited, and the set of adjusted variables varied over studies. Thus, these findings should be interpreted with caution.

Regarding the safety of ICIs in phase 3 RCTs, only one study (a pooled analysis of four phase 3 trials)[15] provided data on TRAEs in elderly patients (aged ≥ 75 years). The incidence of all grade and grade ≥ 3 TRAEs were 68.5% and 24.2% in the pembrolizumab arm, and 94.3% and 61.0% in the CT arm, respectively; TRAEs related discontinuation was 10.7% vs. 15.2%. In real-world studies, the pooled rates of all grade and grade ≥3 TRAEs and irAEs and discontinuation for ICIs monotherapy were numerically lower compared to that for combination therapy, suggesting more toxicity of combination therapy in elderly patients. However, irAEs were found to be a positive predictor of OS in this study. Similar results were also reported in a more recent meta-analysis of NSCLC.[117] Patients with irAEs after receiving ICIs had prolonged OS compared to those without irAEs; however, those with severe irAEs were associated with a worse OS.[116] Nevertheless, there is still a lack of RCTs designed explicitly for this subject, and the association between the incidence of irAEs and ICIs efficacy in elderly patients requires further investigation.

Several recently published meta-analyses[118–122] also investigated the efficacy of ICIs in elderly patients with NSCLC (Supplementary File Table S4), and with a consistent conclusion that ICIs probably prolonged OS

in patients aged 65–74 years but patients aged ≥ 75 years. However, their findings were insufficient due to the limited number of trials (ranging from 11 to 20) and the lack of subgroup analyses. Our study included more trials (35 phase 3 trials) with more patients than previous meta-analyses. Comprehensive subgroup analyses were performed (according to race, histological type, ICI drug, treatment mode, treatment line, and PD-L1 expression). Moreover, we summarize the survival and safety outcomes of ICIs in real-world studies. Our findings will be helpful for clinicians to develop individualized strategies for the use of ICIs in elderly patients with NSCLC.

However, our study has some limitations. First, the majority of data for elderly patients in phase 3 RCTs were extracted from the subgroup analyses of these trials, which might be due to an imbalance in baseline characteristics between the ICIs and CT arms. Second, significant heterogeneity was observed in the real-world studies. Although the results of the meta-regression analysis suggested that race and treatment line were likely sources of heterogeneity, other characteristics such as EOCG score, PD-L1 status, and treatment mode might also be confounding factors. Third, some data on median OS and OS rates at 12, 24, and 36-months in real-world studies were calculated from the reported Kaplan–Meier curves, which might result in an error compared with the raw data. Fourth, some phase 3 RCTs and real-world studies were excluded because they did not provide data on elderly patients, which might have resulted in a selection bias. Fifth, many of the HR estimates used for the analyses of predictors in real-world studies were unadjusted and subjected to confounding factors. Although subgroup analyses using adjusted HRs were performed, the studies reporting adjusted HRs were limited, and the set of adjusted variables varied across studies. We had considered using external estimates of confounding bias. However, obtaining reliable external estimates for the relevant confounding factors was challenging in our study because of the lack of comprehensive and applicable data sources. Sixth, the number of studies was small in some subgroup analyses, which might result in an inaccurate estimation of the between-study heterogeneity. In addition, unrealistically large HR estimates and/or confidence limits were observed in some studies with small sample sizes, suggesting a potential sparse-data bias in these studies which might have carried over the pooled estimates. Moreover, despite comprehensive subgroup and meta-regression analyses were performed, there might have been a built-in selection bias in the use of HRs, which might have affected the reliability of our results. Finally, Presenting the results with appropriate effects/association measures is crucial for understanding their clinical importance. However, we could not provide HRs estimates with 95% CIs for the outcomes of real-world patients because most real-world studies (61/64) were single-arm studies examining ICIs alone without a CT control group. Nevertheless, we summarized the median OS and OS rates at 12, 24, and 36-months and the toxicity outcomes of ICIs in real-world studies, which would be helpful for clinicians to understand the survival and safety data for the use of ICIs in real-world patients. Larger studies are needed to examine the role of ICIs vs. CT based on the HRs with 95% CIs in real-world patients.

In conclusion, ICIs are associated with a significant improvement in OS and PFS compared to chemotherapy in elderly patients (especially patients aged 65–74 years) with advanced NSCLC. The association of ICIs with better OS was not significantly modified by patient characteristics, including race and histological type; or treatment-related factors, such as the type of ICI drug, treatment mode, and treatment line. Nevertheless, some patient characteristics such as age ≥ 75 years, ECOG score ≥ 2, and PD-L1 < 1% seem to have a negative impact on the efficacy of ICIs, while these findings need further validation in large RCTs. Additionally, ICIs combination therapy is likely to be associated with high toxicity and should be used carefully in elderly patients.

Contributors

The study was designed by JD, JQ. Literature search and data collection were done by JY, SL, LB, JC, JC, and CR. Statistical analyses were done by JY, SL, and TL. JY, SL, and JQ contributed to data analysis and interpretation. TL, JQ, and LB verified the underlying data. All authors had full access to all of the data. The manuscript was drafted by JD, JY, SL, and LB. All authors read and approved the final version of the manuscript. JD had the final responsibility to submit for publication.

Data sharing statement

All data extracted and generated in this study can be shared with others on reasonable request via email to the corresponding author.

Declaration of interests

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103081.

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