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Efficacy of Immune Checkpoint Inhibitors for Lung Cancer According to Patient Age and Eastern Cooperative Oncology Group Performance Status: A Systematic Review and Meta-analysis

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Abstract

Background

For treatment of advanced lung cancer, immune checkpoint inhibitors (ICIs) + chemotherapy or the combination of dual ICIs has become the standard first-line treatment in recent years. Considering the differences among patients' immune systems, the response to ICIs may vary. Therefore, we aimed to evaluate the predictive implications of patient age and Eastern Cooperative Oncology Group (ECOG) performance status (PS) for the efficacy of ICIs for the treatment of lung cancer.

Methods

We searched the PubMed, Cochrane Library, Web of Science, and EMBASE databases for articles published between January 2010 and September 2020 that compared overall (OS) and progression-free survival (PFS) rates between patients with lung carcinoma who were administered ICIs and control treatments.

Results

Twenty-four trials including 15,584 patients were selected. ICIs significantly improved the OS rates in patients aged < 65 (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.65–0.82) and ≥ 65 (0.75 [0.70–0.82]) years, with an age cut-off of 65 years; patients aged < 65 (0.83 [0.72–0.95]) years, when age was classified as < 65, 65–74, and ≥ 75 years; and patients with an ECOG PS score of 0 (0.77 [0.69–0.86]) and 1 (0.78 [0.72–0.85]). However, the differences between the two age groups (p = 0.69), the three age groups (p = 0.43), and the ECOG PS groups (p = 0.82) were not insignificant. Significant advantages of ICIs in terms of PFS rates were found in patients aged < 65 (0.64 [0.52–0.79]) and ≥ 65 (0.73 [0.64–0.84]) years and in those with an ECOG PS score of 0 (0.63 [0.49–0.82]) and 1 (0.66 [0.59–0.75]). No significant difference was observed between the age (p = 0.35) and ECOG PS groups (p = 0.89).

Conclusions

Younger patients benefited more from ICI administration; however, lung cancer treatment cannot be decided based on age. Patients with different ECOG PS could benefit from ICIs, but data on patients with an ECOG PS score of ≥ 2 are lacking. In future studies, more patients with poor ECOG PS scores should be included.

1 Introduction

Lung carcinoma is the main cause of cancer mortality worldwide [1]. It is estimated that approximately 1,796,144 people died because of lung cancer, accounting for 18.0% of all cancer deaths [1]. The advent

of immune checkpoint inhibitors (ICIs), such as durvalumab, atezolizumab, and ipilimumab, resulted in a breakthrough in the treatment of hematological and solid tumors, including lung carcinoma. For patients diagnosed with advanced lung cancer, ICIs + chemotherapy or the combination of dual ICIs has become the standard first-line treatment in recent years [2].

Age is a well-known factor that could affect the immune response. Age-related immune dysfunction has been shown to alter the efficacy of ICIs in a preclinical study [3]. Several retrospective studies have reported better outcomes in older patients who were treated with ICIs [4, 5]. Available data from several meta-analyses were inconsistent concerning the effects of age on ICI efficacy. Wu and colleagues reported that older patients (≥ 65 years) benefited more from ICIs than younger patients (< 65 years) [6]. However, another meta-analysis reported that ICIs improved the overall survival (OS) in both younger and older patients, but the difference was not significant [7]. Similarly, Fang Yang et al. [8] reported that there was no correlation between the different age groups and survival benefit of cancer immunotherapy. Numerous studies have reported inconsistent conclusions; hence, it is worth exploring whether age is an important factor in clinical decision-making in this setting.

Apart from age, the Eastern Cooperative Oncology Group (ECOG) performance status (PS) is also a factor that could affect ICIs' efficacy, as confirmed in a clinical study [9]. The ECOG scale is widely used in clinical settings. Patients need to be evaluated using the ECOG scale before receiving anti-cancer drugs, and the scale has become the most commonly used parameter for evaluating a patient's ability for daily living [10]. In addition, ECOG PS is an important independent prognostic factor for different types of cancers, including advanced lung cancer [11]. Studies have showed that a worse ECOG PS was related to a lower efficiency of ICIs [12, 13]. However, the OS rate was not significantly different between the different ECOG PS groups among patients treated with ICIs, as revealed by a meta-analysis [14].

Considering the differences among patients' immune systems, it is reasonable to assume that the response to ICIs may vary depending on age and the ECOG PS. Considering the contradictory results of the relationship between age and benefits from ICIs and the lack of research on the correlation between ECOG PS and ICI treatment efficacy, we conducted this study to clarify the survival benefits in relation to age and the ECOG PS and their potential association with the treatment of patients with advanced lung cancer using ICIs. We only included randomized controlled studies and pooled the hazard ratios (HRs) of OS or progression-free survival (PFS) rate to assess the efficacy of ICIs in published studies.

2 Methods

2.1 Literature Search

The PRISMA guidelines were used to guide the progress of this meta-analysis [15]. We reviewed the results of all randomized controlled trials comparing the OS and PFS rates with ICIs and control treatments in patients with lung cancer. Two investigators independently performed the computerized literature search using the PubMed, the Cochrane Library, Web of Science, and EMBASE databases

(January 2010–September 2020). The search words were “lung neoplasm,” “non-small cell lung cancer,” “small cell lung cancer,” “cytotoxic T-lymphocyte-associated protein 4 (CTLA-4),” “cytotoxic T-lymphocyte-associated protein 4,” “programmed death receptor 1 (PD-1),” “programmed death receptor 1,” “programmed cell death ligand 1 (PD-L1),” “programmed cell death ligand 1,” “immune checkpoint inhibitor,” “durvalumab,” “atezolizumab,” “ipilimumab,” “tremelimumab,” “nivolumab,” “avelumab,” and “pembrolizumab.” We used MeSH terms and free test words for the literature search to ensure a more comprehensive search. We also searched for abstracts from conference proceedings in the field of cancer and immunotherapy from 2010 to 2020, and the references of the included articles, to identify other potential publications.

2.2 Inclusion and exclusion criteria

The inclusion criteria for studies were as follows: (i) all cases were pathologically identified as lung cancer; (ii) phase 2 or 3 randomized trials; (iii) the intervention-group treatment included inhibitors of CTLA-4, PD-1, PD-L1, or their combinations; (iv) available information on OS or PFS rates for calculating the HR of death considering the patients’ age or ECOG PS; (v) most recent and complete report of controlled trials with full text available; and (vi) articles reported in English.

The exclusion criteria were as follows: (i) full text not available; (ii) non-randomized trials; and (iii) duplicated text.

2.3 Outcomes

The primary outcome was the difference in the efficacy of ICIs with respect to the patients’ age and ECOG PS.

2.4 Data extraction

Articles initially included in the study were independently reviewed by two researchers. Then, two other researchers independently extracted all data from these studies. All researchers discussed and resolved the differences together. Details regarding the selection process are presented in Fig. 1.

2.5 Data analysis

The main results were based on the OS and PFS benefits of ICI treatment. We derived the HRs for death in the intervention and control groups. Patients in the treatment group received at least one kind of ICI, and those in the control group received different types of anti-cancer drugs (such as chemotherapy, targeted therapies, ICIs, or placebo). We also derived the 95% confidence intervals (CIs) from each study, separately, for two age groups (< 65 vs. ≥65 years), three age groups (< 65 vs. 65–74 vs. ≥75 years), and two ECOG PS groups (0 vs. 1). Using randomized models, we calculated the pooled HR for the OS and PFS rates between the different age or ECOG PS groups. Heterogeneity was evaluated using the Q-test and I^2 statistics. Heterogeneity existed when the I^2 value was > 50% [16]. The subgroup analysis involved the lung cancer type, clinical phase, intervention (single ICI or combination), and line of therapy. Meta-

regression analyses were performed to compare the summary estimates of the different subgroups and to assess the potential sources of heterogeneity.

Publication bias was assessed using Begg's and Egger's tests [17], and all reported p-values were two-sided. The level of significance was set at $p < 0.05$. Analyses were performed using Stata16.0 software (Stata Corporation, College Station, TX, USA).

3 Results

3.1 Liteature Search

The study selection flowchart is presented in Fig. 1. Initially, we identified 985 articles that met the inclusion criteria after excluding 214 studies owing to duplication. Subsequently, 633 studies met the exclusion criteria after browsing the titles and abstracts. After re-examining the full text of 138 potentially qualified papers, 114 articles were excluded because 10, 20, and 84 papers were retrospective studies, were not from the field of interest, and had no data available, respectively. Finally, the data reported from 24 randomized controlled trials, which were published from January 2010 to September 2020, were analyzed [18–41].

3.2 Study characteristics

We found 10 randomized controlled trials using anti-PD-1 (two using nivolumab and eight using pembrolizumab), eight trials using PD-L1 inhibitors (one, three, and four using avelumab, durvalumab, and atezolizumab, respectively), two trials using ipilimumab, one trial using pembrolizumab plus natural killer cells in combination, and three trials using ipilimumab plus nivolumab in combination (Additional File 1).

The studies included a total of 15,584 patients, with the number of patients in each trial ranging from 92 to 1,274. There were one, 20, one, and one phase 2, phase 3, phase 1/2, and phase 2/3 trials, respectively, while one article did not indicate the phase (Additional File 1). Eighteen trials were performed for patients with non-small cell lung cancer (NSCLC), five for patients with small cell lung cancer (SCLC), and one included both patients with NSCLC and SCLC. ICIs were used as the first-line treatment or as the second or further line of treatment in 15 and nine studies, respectively. Nineteen trials used 65 years as the cut-off value to divide patients into two subgroups, and the remaining five trials divided patients into three groups for analysis: <65, 65–74, and ≥ 75 years. All patients included in the studies were diagnosed with advanced lung cancer.

We conducted quality evaluations on the 24 included studies (Fig. 2). The random allocation method was used in all trials, specific allocation methods were applied in 12 studies [19, 21, 25, 28, 29, 31, 32, 34, 37, 38, 40, 41], and the remaining studies did not provide sufficient information. Most studies did not mention allocation concealment. Eleven studies [18, 20–22, 26, 32–34, 37] used the open-label method, four studies [24, 29, 31, 38] used the double-blind method, and the other studies did not mention the relevant

information. Most studies were sponsored by pharmaceutical companies; hence, other biases in these studies were assessed as high risk. Most included studies had a low risk of reporting and attrition biases.

3.3 Meta-analysis results on overall survival

In total, 15 trials involving 8,826 patients reported data on the HR of OS based on two age groups (< 65 and ≥ 65 years). Compared to the corresponding control therapy, ICIs showed a significant OS benefit in younger (< 65 years: HR, 0.73; 95% CI, 0.65–0.82) and older (≥ 65 years: HR, 0.75; 95% CI, 0.70–0.82) patients (Fig. 3). However, no significant difference was found between the two groups (p = 0.69). There was significant heterogeneity in younger (< 65 years: Q = 31.08; p = 0.005; I2 = 55%) patients, whereas no heterogeneity was found for older (≥ 65 years: Q = 15.69; p = 0.33; I2 = 10.8%) patients. There was no significant difference between the subgroups (Table 1). Five trials reported separate survival data for three age groups (< 65, 65–74, and ≥ 75 years). Compared to the corresponding control therapy, ICIs showed a significant OS benefit in patients aged < 65 years (HR, 0.83; 95% CI, 0.72–0.95). However, no improvement in OS was observed in patients aged 65–74 (HR, 0.90; 95% CI, 0.75–1.07) and ≥ 75 years (HR, 0.85; 95% CI, 0.67–1.07) (Fig. 4). Moreover, significant heterogeneity was found among patients aged < 65 years (Q = 10.12; p = 0.07; I2 = 50.6%) and those aged 65–74 years (Q = 11.22; p = 0.05; I2 = 55.4%), whereas no heterogeneity was found in patients aged ≥ 75 years (Q = 0.71; p = 0.98; I2 = 0.0%). The difference among the three age groups was not significant (p = 0.43). Moreover, subgroup analysis was not performed for these three age groups because few included studies involved these age divisions.

Table 1
Differences in the overall survival rate between younger and older patients

Subgroups	Number of trials	Pooled HR (95% CI)		Test for difference	
		< 65 years	≥ 65 years	I^2 (%)	p value
Overall	15	0.73 (0.65–0.82)	0.75 (0.70–0.82)	40.14	0.69
Cancer type					
NSCLC	11	0.70 (0.60–0.81)	0.75 (0.69–0.82)	45.28	0.42
SCLC	4	0.83 (0.70–0.97)	0.76 (0.59–0.99)	25.29	0.56
Phase					
3	11	0.74 (0.64–0.86)	0.75 (0.68–0.82)	46.15	0.97
Other	4	0.67 (0.58–0.78)	0.80 (0.64–1.0)	10.68	0.22
Lines of therapy					
1	9	0.74 (0.62–0.88)	0.74 (0.66–0.84)	53.77	0.99
≥2	6	0.71 (0.62–0.82)	0.77 (0.68–0.88)	12.04	0.43
Intervention therapy					
ICI monotherapy	7	0.78 (0.67–0.91)	0.82 (0.73–0.92)	40.89	0.66
Combination therapy	8	0.68 (0.57–0.81)	0.69 (0.62–0.77)	26.32	0.87

CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

A total of 18 trials that recruited 12,898 patients reported data on the HR for OS based on the patients' ECOG PS. A significant OS advantage in using ICIs over control therapy was found for those with an ECOG PS score of 0 (HR, 0.77; 95% CI, 0.69–0.86) and 1 (HR, 0.78; 95% CI, 0.72–0.85) (Fig. 5). The difference between the two groups was not significant (p = 0.82). No heterogeneity was observed between patients with an ECOG PS score of 0 (Q = 26.56; p = 0.09; I2 = 32.2%) and 1 (Q = 35.57; p < 0.05; I2 = 49.4%). There was no significant difference between the subgroups (Table 2).

Table 2
Differences in the overall survival rate between patients with ECOG PS scores of 0 and 1

Subgroups	Number of trials	Pooled HR (95% CI)		Test for difference	
		ECOG PS 0	ECOG PS 1	I^2 (%)	p value
Overall	18	0.77 (0.69–0.86)	0.78 (0.72–0.85)	42.05	0.82
Cancer type					
NSCLC	13	0.75 (0.68–0.82)	0.76 (0.69–0.83)	29.7	0.74
SCLC	5	0.85 (0.64–1.14)	0.87 (0.75–1.0)	51.89	0.96
Phase					
3	15	0.77 (0.69–0.87)	0.79 (0.73–0.85)	44.08	0.91
Other	3	0.72 (0.55–0.95)	0.81 (0.54–1.22)	44.91	0.67
Lines of therapy					
1	11	0.77 (0.66–0.91)	0.79 (0.72–0.86)	51.22	0.97
≥2	7	0.75 (0.65–0.86)	0.78 (0.67–0.91)	23.79	0.67
Intervention therapy					
ICI monotherapy	8	0.76 (0.67–0.86)	0.77 (0.67–0.87)	25.31	0.87
Combination therapy	10	0.68 (0.63–0.91)	0.80 (0.72–0.88)	52.24	0.82

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PS, performance status; SCLC, small cell lung cancer

3.4 Meta-analysis results on progression-free survival

In total, 11 trials that enrolled 5,543 patients reported data on PFS based on patient age. A significant advantage in terms of PFS when using immunotherapy over control therapy was found in patients aged < 65 (HR, 0.64; 95% CI, 0.52–0.79) and ≥ 65 years (HR, 0.73; 95% CI, 0.64–0.84) (Fig. 6). No significant difference was observed between the two groups (p = 0.35). However, significant heterogeneity was found in patients aged < 65 (Q = 53.44; p < 0.05; I2 = 81.3%) and ≥ 65 years (Q = 79.82; p < 0.05; I2 = 73.7%). There was no significant difference between the subgroups (Table 3).

Table 3. Differences in the progression-free survival rate between younger and older patients					
Subgroups	Number of trials	Pooled HR (95% CI)		Test for difference	
		< 65 years	≥ 65 years	I^2 (%)	p value
Overall	11	0.64 (0.52–0.79)	0.73 (0.64–0.84)	73.56	0.35
Cancer type					
NSCLC	9	0.62 (0.48–0.80)	0.73 (0.61–0.87)	78.03	0.34
SCLC	2	0.76 (0.62–0.93)	0.73 (0.59–0.89)	0	0.79
Phase					
3	8	0.74 (0.64–0.86)	0.75 (0.68–0.82)	46.15	0.97
Other	3	0.67 (0.58–0.78)	0.80 (0.64–1.0)	10.68	0.22
Lines of therapy					
1	4	0.67 (0.52–0.86)	0.72 (0.59–0.87)	75.16	0.71
≥2	7	0.60 (0.39–0.92)	0.78 (0.64–0.95)	76.9	0.37
Intervention therapy					
ICI monotherapy	7	0.72 (0.47–1.11)	0.80 (0.57–1.12)	85.37	0.77
Combination therapy	4	0.59 (0.48–0.73)	0.69 (0.61–0.77)	42.29	0.99

CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

A total of eight trials that enrolled 3,760 patients reported data on PFS according to patients' ECOG PS. A significant advantage in terms of PFS in using immunotherapy over control therapy was found for patients with an ECOG PS score of 0 (HR, 0.63; 95% CI, 0.49–0.82) and 1 (HR, 0.66; 95% CI, 0.59–0.75) (Fig. 7). No significant difference was observed between the two groups (p = 0.89). However, significant heterogeneity was observed for patients with an ECOG PS score of 0 (Q = 22.11; p < 0.05; I2 = 68.3%), whereas no heterogeneity was found in those with an ECOG PS score of 1 (Q = 10.10; p = 0.18; I2 = 30.7%). There was no significant difference between the subgroups (Table 4).

Table 4
Differences in the progression-free survival rate associated between patients with ECOG PS scores of 0 and 1

Subgroups	Number of trials	Pooled HR (95% CI)		Test for difference	
		ECOG PS 0	ECOG PS 1	I^2 (%)	p value
Overall	8	0.63 (0.49–0.82)	0.66 (0.59–0.75)	56.54	0.89
Cancer type					
NSCLC	5	0.59 (0.39–0.90)	0.63 (0.54–0.70)	69.97	0.85
SCLC	2	0.72 (0.52–1.0)	0.76 (0.64–0.9)	0	0.81
LC	1	0.62 (0.38–1.02)	0.55 (0.38–0.8)	/	/
Phase					
3	6	0.57 (0.46–0.70)	0.63 (0.55–0.73)	32.51	0.44
Other	2	0.91 (0.55–1.5)	0.76 (0.64–0.91)	1.76	0.28
Lines of therapy					
1	6	0.57 (0.46–0.70)	0.63 (0.55–0.73)	32.51	0.44
≥ 2	2	0.91 (0.55–1.5)	0.76 (0.64–0.91)	1.76	0.28
Intervention therapy					
ICI monotherapy	2	0.72 (0.31–1.69)	0.64 (0.44–0.95)	82.66	0.77
Combination therapy	6	0.59 (0.48–0.72)	0.66 (0.58–0.75)	21.58	0.42

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PS, performance status; SCLC, small cell lung cancer

3.5 Publication bias

Publication bias was found with respect to the OS rates among the ECOG groups (Begg's test: p = 0.03; Egger's test: p = 0.03). No publication bias was found with respect to the OS rates among the two (Begg's test: p = 0.31; Egger's test, p = 0.54) and three age groups (Begg's test: p = 0.94; Egger's test: p = 0.42). Similarly, no publication bias was observed concerning the PFS rates among the age (Begg's test: p = 0.37; Egger's test: p = 0.30) and ECOG PS groups (Begg's test: p = 0.56; Egger's test: p = 0.17).

4 Discussion

In this study, we explored whether patient age and their ECOG PS had a potentially positive effect on the efficacy of ICIs. To clarify the predictive value of age and ECOG PS in lung carcinoma when using ICIs, we performed this meta-analysis and pooled the HRs for the OS and PFS rates. Our results showed that ICIs

increased the OS and PFS rates in both age groups when the cut-off value was set at 65 years and in the ECOG PS 0 and 1 groups among patients diagnosed with advanced lung cancer. The remaining results demonstrated that when patients were divided into three groups (< 65, 65–74, and ≥ 75 years), no benefit was noted for those aged 65–74 and ≥ 75 years.

These results showed that younger and older patients could benefit from ICIs with respect to OS and PFS rates when the cut-off of 65 years is used. There was a trend toward better long-term survival outcomes in younger patients, although the difference between the two groups was not significant. Similarly, one study found an OS benefit in patients treated with immunotherapy in different age groups [8]. A study reported that the OS and PFS rates were better in younger and older patients when using ICIs than in controls, but older patients could gain more benefits from ICIs than younger patients [6]. When the patients were divided into three groups by age, our results showed that only those aged < 65 years could benefit from ICIs, and those aged 65–74 and ≥ 75 years were unlikely to benefit in terms of OS. Likewise, another meta-analysis showed that no OS benefit was observed in patients aged ≥ 65 years treated with PD-1 inhibitors [42]. However, Corbaux et al. [43] reported that patients treated with single-agent ICIs for various cancer types had greater OS and PFS rates, especially when they were older than 70 years. There may be several reasons for these inconsistent results. The first reason is immunosenescence, which is the phenomenon of decreasing immune function with increasing age [44]. Second, the different grouping standards for age can partly explain some of the contradictory results. Third, the ICI types, whether they were used in combination or individually, differed between the treatment and control groups. Moreover, several recently published large trials [39–41] on lung cancer were included in our study, making our conclusions more reliable.

Furthermore, we analyzed the relationship between the efficacy of ICIs and the patients' ECOG PS. Patients with different ECOG PS scores could benefit from ICIs in different situations. For example, one study showed that patients with an ECOG PS score of 0 benefited more from ICIs than those with an ECOG PS score of 1 [45], but another study reached the opposite conclusion [46]. Therefore, it remains controversial whether differences in ECOG PS scores could affect the anti-tumor efficacy of ICIs in patients with lung cancer. The results of a previous study showed that the OS benefit was not significantly different between patients with a PS score of 0 and those with a PS score of 1–2 treated with ICIs [14]. Likewise, the results of another study showed that no significant difference was noted in patients with different ECOG PS scores (0–1) [8]. However, a meta-analysis of retrospective and prospective studies suggested that caution should be exercised when deciding on administering ICIs to patients with poor PS (score > 2) [47]. Few patients with an ECOG PS score of 2 who received ICIs were included in the examined randomized controlled clinical trials in this meta-analysis. Thus, we analyzed whether patients in the ECOG PS 0 or 1 group could benefit from ICI treatments; interestingly, no difference between these groups was observed. Therefore, ECOG PS should not be the basis for selecting patients for ICI treatment.

Heterogeneity was also observed between studies. The following aspects may be the source of the heterogeneity. Clinical heterogeneity mainly comes from patients in the control group who received

different types of anti-cancer drugs (such as chemotherapy, targeted therapies, or ICIs); hence, it may be difficult to distinguish the prognostic effects in the intervention versus the control group in some trials. There have been some studies that used the open-label method, others that used the double-blind method, and others that did not mention the relevant information, which may be sources of methodological heterogeneity. Additionally, the following measures have been applied to address the heterogeneity: (i) The included data were checked again to ensure that all data were correct; (ii) the random-effect model was used to perform calculations with the data; (iii) subgroup and meta-regression analyses were performed to compare summary estimates at the different subgroups and to assess the potential sources of heterogeneity.

Our meta-analysis had several strengths. First, we considered all recently available evidence and included 24 randomized controlled studies focused on the treatment of lung cancer with ICIs published until September 2020. Second, a total of 15,321 patients with OS and PFS data were included in our meta-analysis, and inclusion of such a large number of patients increased the reliability of our results. Third, we strictly grouped patients according to the original age grouping in the literature and did not merge the data of patients with inconsistent ages, thus, obtaining more credible results. Finally, a detailed assessment of the credibility of the evidence was performed to critically appraise the results.

Nevertheless, there were three studies in our analysis that may have caused a bias in the results. One of the studies was a phase 1/2 study update, whereas one did not mention staging; nevertheless, both studies had qualified data and thus, were included in the analysis. Another study reported the HRs of OS and PFS rates for the control versus experimental arms. Then, we recalculated the HR of the experimental arm versus that of the control, as described by Tierney et al. [48]. Besides, publication bias was found with respect to the OS rates among the ECOG groups. The possible reason was that our study included only published works written in English. Furthermore, our analysis had several other limitations. Especially, our report excluded individual patient data and only included published results. Furthermore, there are always missing values in published articles. In addition, some confounding factors, such as the expression of PD-L1, were not included in the analysis because of the presence of inconsistent cut-off values.

5 Conclusion

Younger patients could benefit more from ICIs, but age cannot be used as a reference for making treatment decisions for patients with lung cancer. Those with different ECOG PS scores could benefit from ICIs, but data on patients with an ECOG PS score of ≥ 2 are lacking. In future studies, more patients with poorer ECOG PS scores should be included to assess whether more patients with lung cancer could benefit from ICIs.

Abbreviations

CTLA-4

cytotoxic T-lymphocyte-associated protein 4
CI
confidence interval
ECOG
Eastern Cooperative Oncology Group
HR
hazard ratio
ICIs
immune checkpoint inhibitors
NSCLC
non-small cell lung cancer
PS
performance status
PD-1
programmed death receptor 1
OS
overall survival
SCLC
small cell lung cancer

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: XBL and WYC conceptualized the study. XLZ curated the data and wrote the original draft. GYZ, HK, JY, and QT performed the statistical analysis. QC, SZ, LZL, QY, JL, CJZ, and QHY reviewed and edited the manuscript. All authors read and approved the final manuscript.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021.
2. Ettinger DS, Wood DE, Aggarwal C, Aisner DL, Akerley W, Bauman JR, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020. Journal of the National Comprehensive Cancer Network: JNCCN. 2019;17(12):1464–72. https://doi.org/10.6004/jnccn.2019.0059.
3. Hurez V, Padrón ÁS, Svatek RS, Curiel TJ. Considerations for successful cancer immunotherapy in aged hosts. Clin Exp Immunol. 2017;187(1):53–63. https://doi.org/10.1111/cei.12875.
4. Perier-Muzet M, Gatt E, Péron J, Falandry C, Amini-Adlé M, Thomas L, et al. Association of Immunotherapy With Overall Survival in Elderly Patients With Melanoma. JAMA dermatology. 2018;154(1):82–7. https://doi.org/10.1001/jamadermatol.2017.4584.
5. Kugel CH 3rd, Douglass SM, Webster MR, Kaur A, Liu Q, Yin X, et al. Age Correlates with Response to Anti-PD1, Reflecting Age-Related Differences in Intratumoral Effector and Regulatory T-Cell Populations. Clinical cancer research: an official journal of the American Association for Cancer Research. 2018;24(21):5347–56. https://doi.org/10.1158/1078-0432.Ccr-18-1116.
6. Wu Q, Wang Q, Tang X, Xu R, Zhang L, Chen X, et al. Correlation between patients' age and cancer immunotherapy efficacy. Oncoimmunology. 2019;8(4):e1568810. https://doi.org/10.1080/2162402x.2019.1568810.
7. Kasherman L, Siu DHW, Lee KWC, Lord S, Marschner I, Lewis CR, et al. Efficacy of immune checkpoint inhibitors in older adults with advanced stage cancers: A meta-analysis. Journal of geriatric oncology. 2020;11(3):508–14. https://doi.org/10.1016/j.jgo.2019.05.013.
8. Yang F, Markovic SN, Molina JR, Halfdanarson TR, Pagliaro LC, Chintakuntlawar AV, et al. Association of Sex, Age, and Eastern Cooperative Oncology Group Performance Status With Survival Benefit of Cancer Immunotherapy in Randomized Clinical Trials: A Systematic Review and Meta-analysis. JAMA network open. 2020;3(8):e2012534. https://doi.org/10.1001/jamanetworkopen.2020.12534.
9. Felip E, Ardizzoni A, Ciuleanu T, Cobo M, Laktionov K, Szilasi M, et al. CheckMate 171: A phase 2 trial of nivolumab in patients with previously treated advanced squamous non -small cell lung cancer, including ECOG PS 2 and elderly populations. Eur J Cancer. 2020;127:160–72.
10. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–55.
11. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group exp erience. J Clin Oncol. 1991;9(9):1618–26.
12. Gridelli C, Ardizzoni A, Le Chevalier T, Manegold C, Perrone F, Thatcher N, et al. Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel. Ann Oncol. 2004;15(3):419–26.
13. Gebbia V, Galetta D, De Marinis F. Non small cell lung cancer patients with ECOG PS2: unsolved questions and lessons from clinical trials. Ann Oncol. 2005;16(Suppl 4):iv123–31.

14. Bersanelli M, Brighenti M, Buti S, Barni S, Petrelli F. Patient performance status and cancer immunotherapy efficacy: a meta-analysis. Med Oncol (Northwood Lond Engl). 2018;35(10):132. https://doi.org/10.1007/s12032-018-1194-4.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. International journal of surgery (London England). 2009;62(10):1006–12. https://doi.org/10.1016/j.ijsu.2021.105906.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical researched.). 2003;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557.
17. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–101.
18. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. New England journal of medicine. 2015;373(17):1627–39. https://doi.org/10.1056/NEJMoa1507643.
19. Reck M, Luft A, Szczesna A, Havel L, Kim S-W, Akerley W, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol. 2016;34(31):3740–48. https://doi.org/10.1200/jco.2016.67.6601.
20. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New England journal of medicine. 2016;375(19):1823–33. https://doi.org/10.1056/NEJMoa1606774.
21. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–50. https://doi.org/10.1016/S0140-6736(15)01281-7.
22. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017;376(25):2415–26. https://doi.org/10.1056/NEJMoa1613493.
23. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. New England journal of medicine. 2017;377(20):1919–29. https://doi.org/10.1056/NEJMoa1709937.
24. Govindan R, Szczesna A, Ahn MJ, Schneider CP, Gonzalez Mella PF, Barlesi F, et al. Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2017;35(30):3449–57. https://doi.org/10.1200/jco.2016.71.7629.
25. Barlesi F, Vansteenkiste J, Spigel D, Ishii H, Garassino M, de Marinis F, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncol. 2018;19(11):1468–79. https://doi.org/10.1016/s1470-2045(18)30673-9.

26. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med. 2018;378(22):2093–104. https://doi.org/10.1056/NEJMoa1801946.
27. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. New England journal of medicine. 2018;379(24):2342–50. https://doi.org/10.1056/NEJMoa1809697.
28. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. New England journal of medicine. 2018;379(23):2220–29. https://doi.org/10.1056/NEJMoa1809064.
29. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. New England journal of medicine. 2018;379(21):2040–51. https://doi.org/10.1056/NEJMoa1810865.
30. Fehrenbacher L, von Pawel J, Park K, Rittmeyer A, Gandara DR, Ponce Aix S, et al. Updated Efficacy Analysis Including Secondary Population Results for OAK: a Randomized Phase III Study of Atezolizumab versus Docetaxel in Patients with Previously Treated Advanced Non-Small Cell Lung Cancer. Journal of thoracic oncology. 2018;13(8):1156–70. https://doi.org/10.1016/j.jtho.2018.04.039.
31. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. New England journal of medicine. 2018;378(22):2078–92. https://doi.org/10.1056/NEJMoa1801005.
32. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819–30. https://doi.org/10.1016/S0140-6736(18)32409-7.
33. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Updated Analysis of KEYNOTE-024: pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. Journal of clinical oncology. 2019;37(7):537–46. https://doi.org/10.1200/JCO.18.00149.
34. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. The lancet. Oncology. 2019;20(7):924–37. https://doi.org/10.1016/S1470-2045(19)30167-6.
35. Theelen W, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts J, et al. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. JAMA oncology. 2019;5(9):1276–82. https://doi.org/10.1001/jamaoncol.2019.1478.

36. Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2020;15(3):426–35. https://doi.org/10.1016/j.jtho.2019.10.004.
37. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394(10212):1929–39. https://doi.org/10.1016/S0140-6736(19)32222-6.
38. Reck M, Mok TSK, Nishio M, Jotte RM, Cappuzzo F, Orlandi F, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. The Lancet Respiratory medicine. 2019;7(5):387–401. https://doi.org/10.1016/s2213-2600(19)30084-0.
39. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. New England journal of medicine. 2019;381(21):2020–31. https://doi.org/10.1056/NEJMoa1910231.
40. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csőszi T, et al. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2020;38(21):2369–79. https://doi.org/10.1200/jco.20.00793.
41. Lin M, Luo H, Liang S, Chen J, Liu A, Niu L, et al. Pembrolizumab plus allogeneic NK cells in advanced non-small cell lung cancer patients. J Clin Investig. 2020;130(5):2560–69. https://doi.org/10.1172/jci132712.
42. Nishijima TF, Muss HB, Shachar SS, Moschos SJ. Comparison of efficacy of immune checkpoint inhibitors (ICIs) between younger and older patients: A systematic review and meta-analysis. Cancer treatment reviews. 2016;45(30 – 7. https://doi.org/10.1016/j.ctrv.2016.02.006.
43. Corbaux P, Maillet D, Boespflug A, Locatelli-Sanchez M, Perier-Muzet M, Duruisseaux M, et al. Older and younger patients treated with immune checkpoint inhibitors have similar outcomes in real-life setting. European journal of cancer (Oxford England: 1990). 2019;121:192–201. https://doi.org/10.1016/j.ejca.2019.08.027.
44. Pawelec G, Derhovanessian E, Larbi A. Immunosenescence and cancer. Critical reviews in oncology/hematology. 2010;75(2):165 – 72. https://doi.org/10.1016/j.critrevonc.2010.06.012.
45. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019;381(21):2020–31.
46. Herbst RS, Baas P, Kim DW, Felip E, P¨¦rez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung c ancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–50.

47. Dall'Olio FG, Maggio I, Massucci M, Mollica V, Fragomeno B, Ardizzoni A. ECOG performance status ¡Ý2 as a prognostic factor in patients with advanced non small cell lung cance r treated with immune checkpoint inhibitors-A systematic review and meta-analysis of real world data. Lung Cancer. 2020;145:95–104.
48. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;816. https://doi.org/10.1186/1745-6215-8-16.

Figures

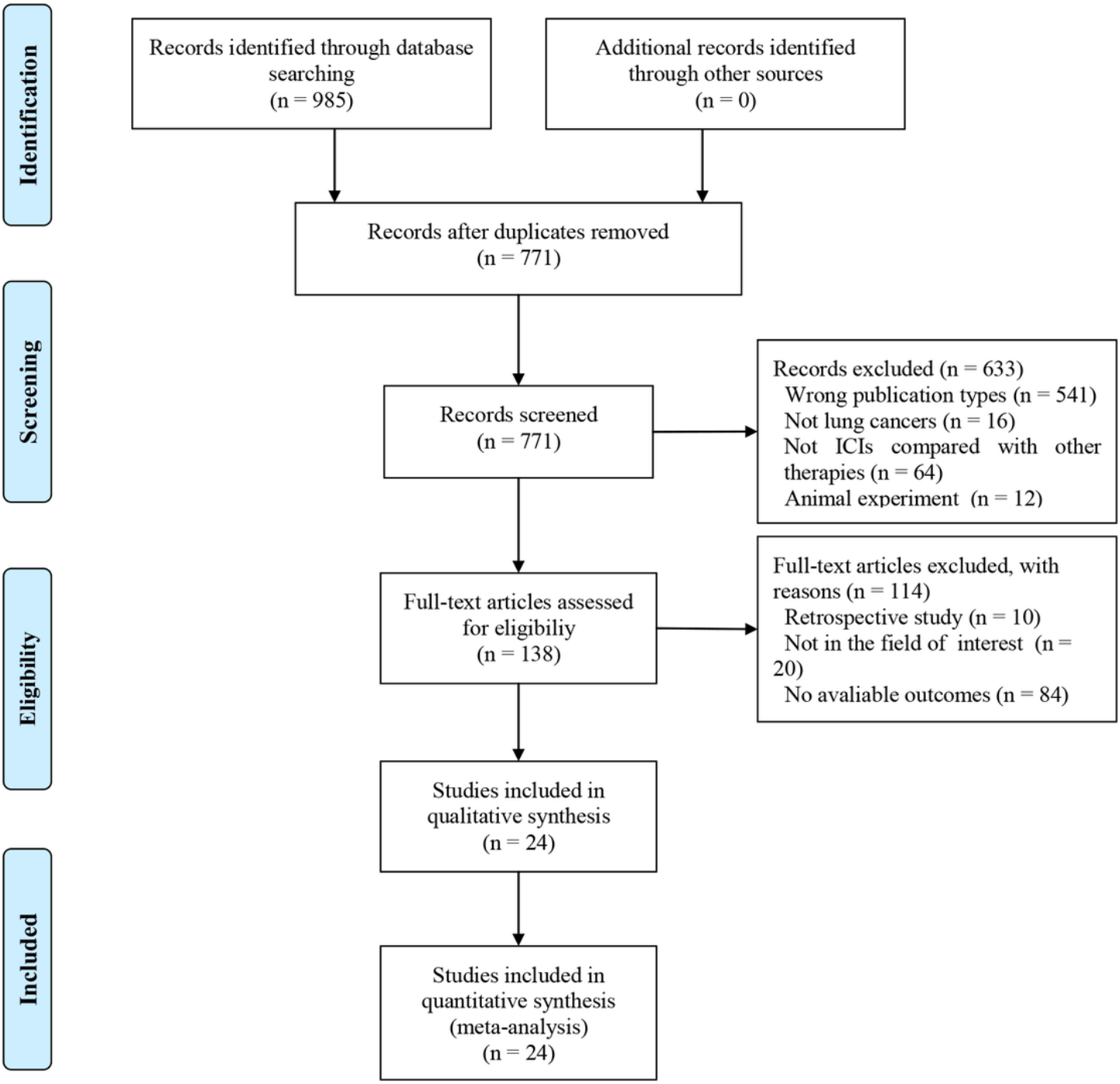


Figure 1

Overview of the search for selection of trials

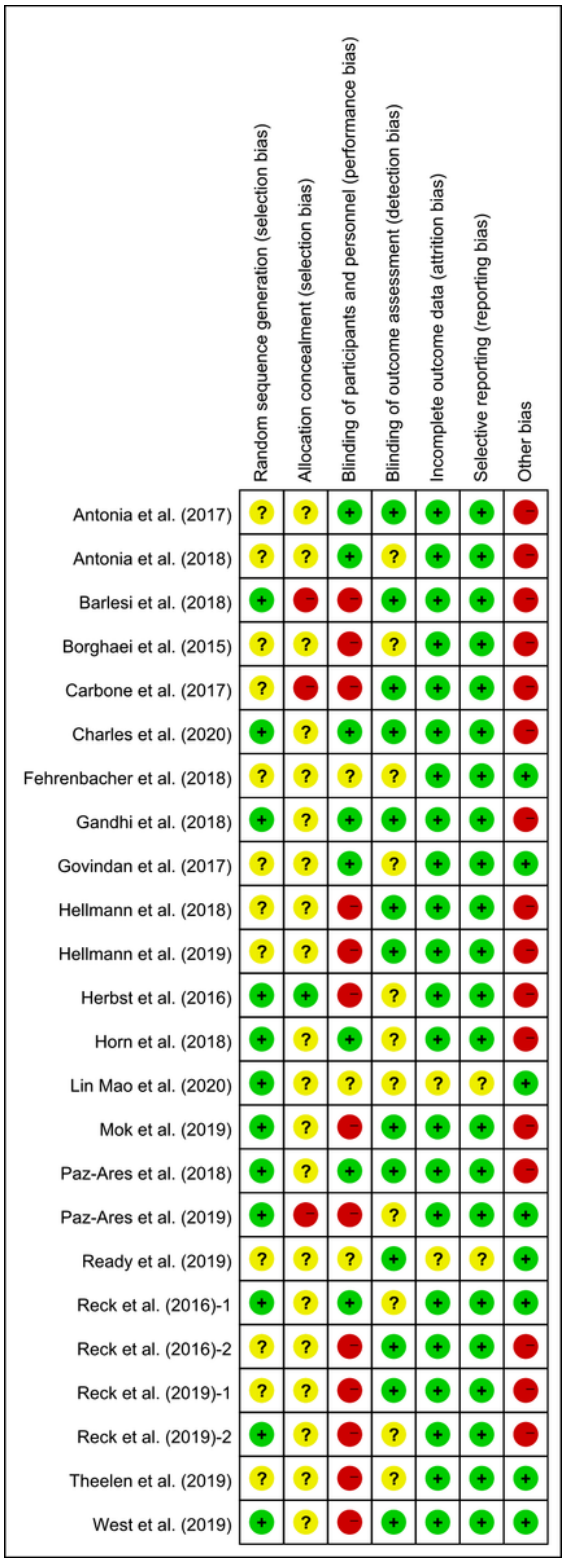


Figure 2

Methodological quality of the studies included in the meta-analysis

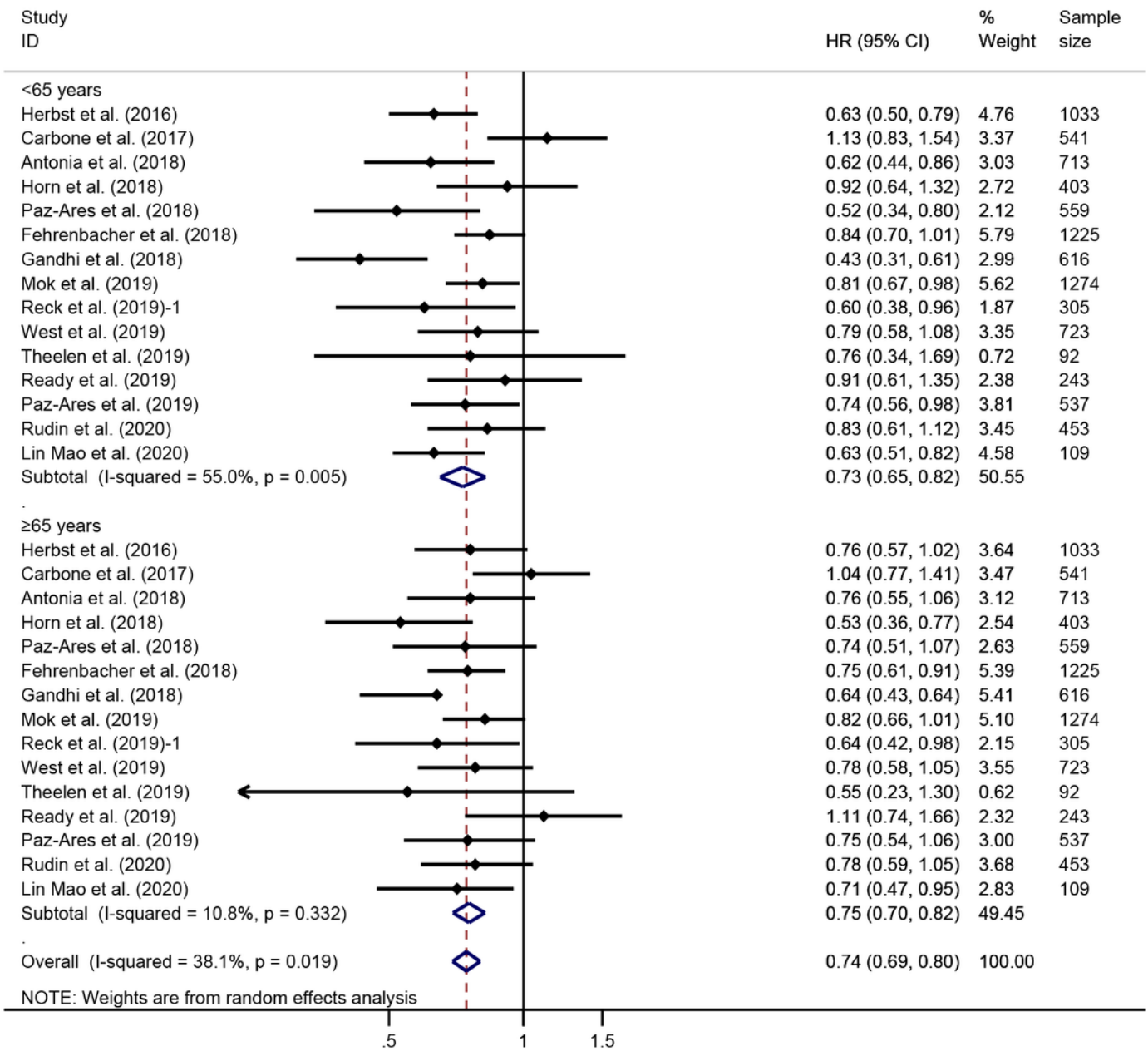


Figure 3

Evaluation of efficacy of ICIs by OS rate in patients classified into two age groups Forest plot of the efficacy of ICIs with respect to the OS rate among patients with lung cancer classified into two age groups were made. CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival

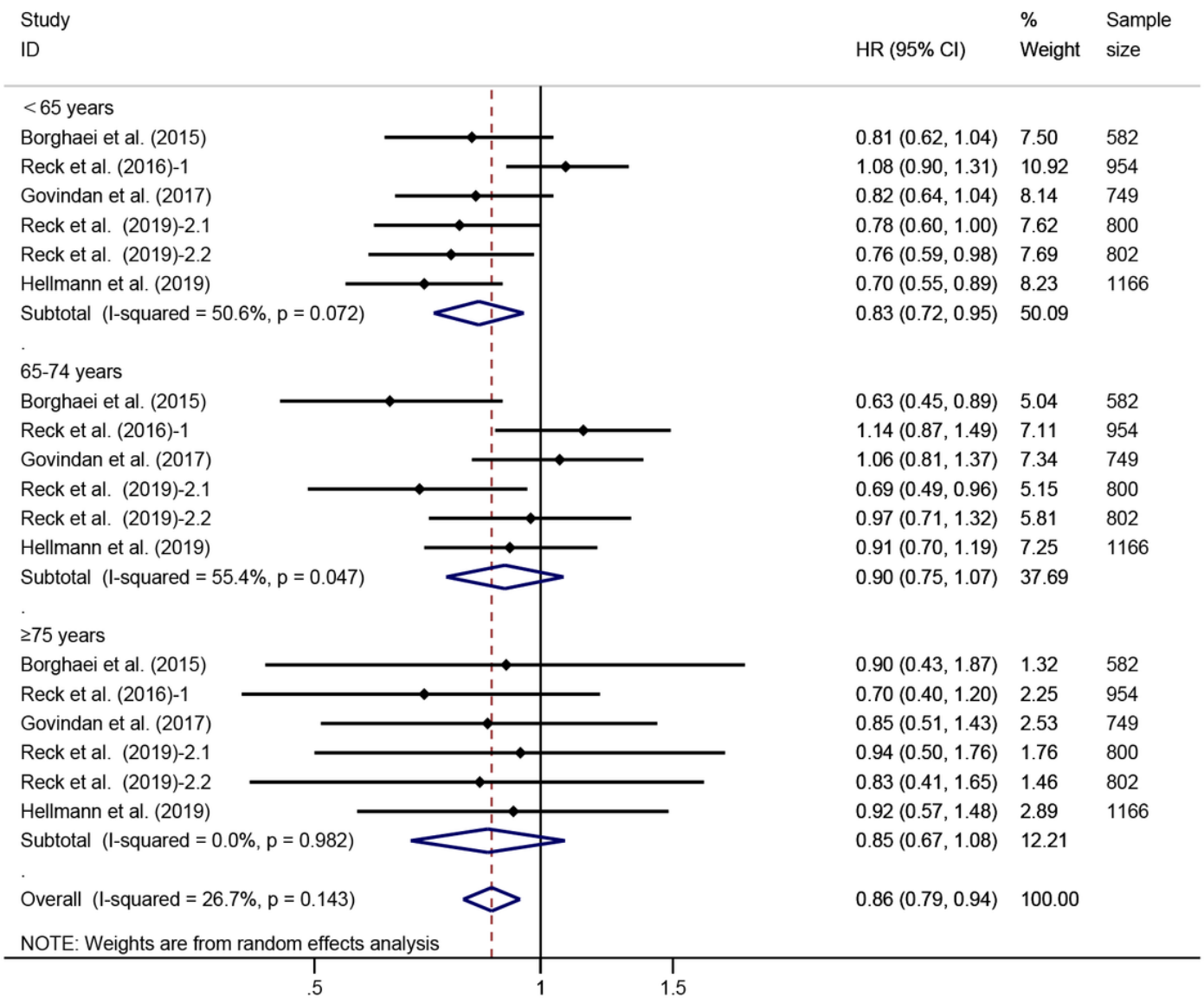


Figure 4

Evaluation of efficacy of ICI by OS rate in patients classified into three age groups Forest plot of the efficacy of ICI with respect to the OS rate among patients with lung cancer classified into three age groups were made. CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival 2.1: comparison of atezolizumab + bevacizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel 2.2: comparison of atezolizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel

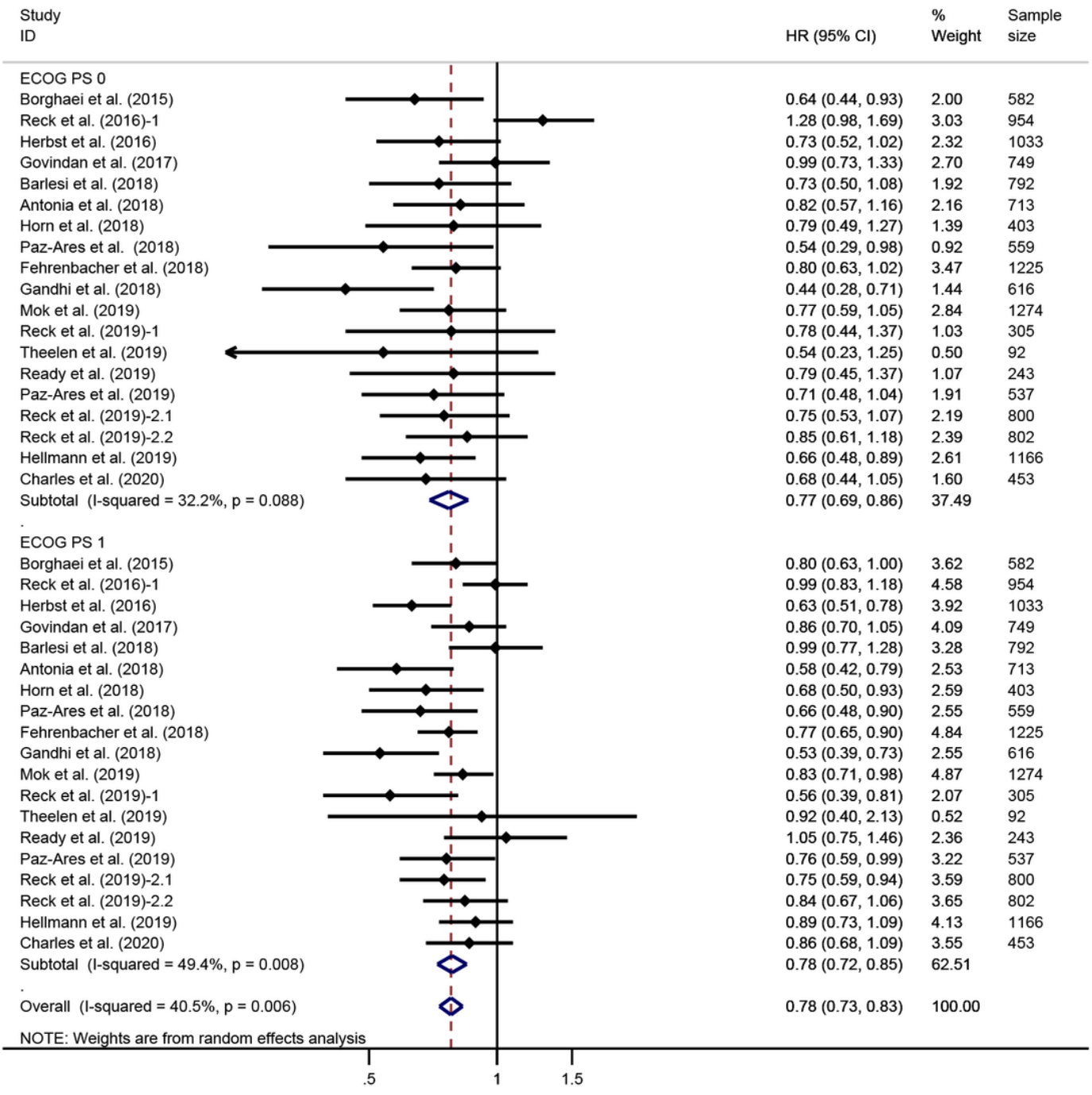


Figure 5

Evaluation of efficacy of ICIs by OS rate based on ECOG PS scores Forest plot of the efficacy of ICIs with respect to the OS rate in patients with lung cancer classified according to ECOG PS scores were made. CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; PS, performance status 2.1: comparison of atezolizumab + bevacizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel 2.2: comparison of atezolizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel

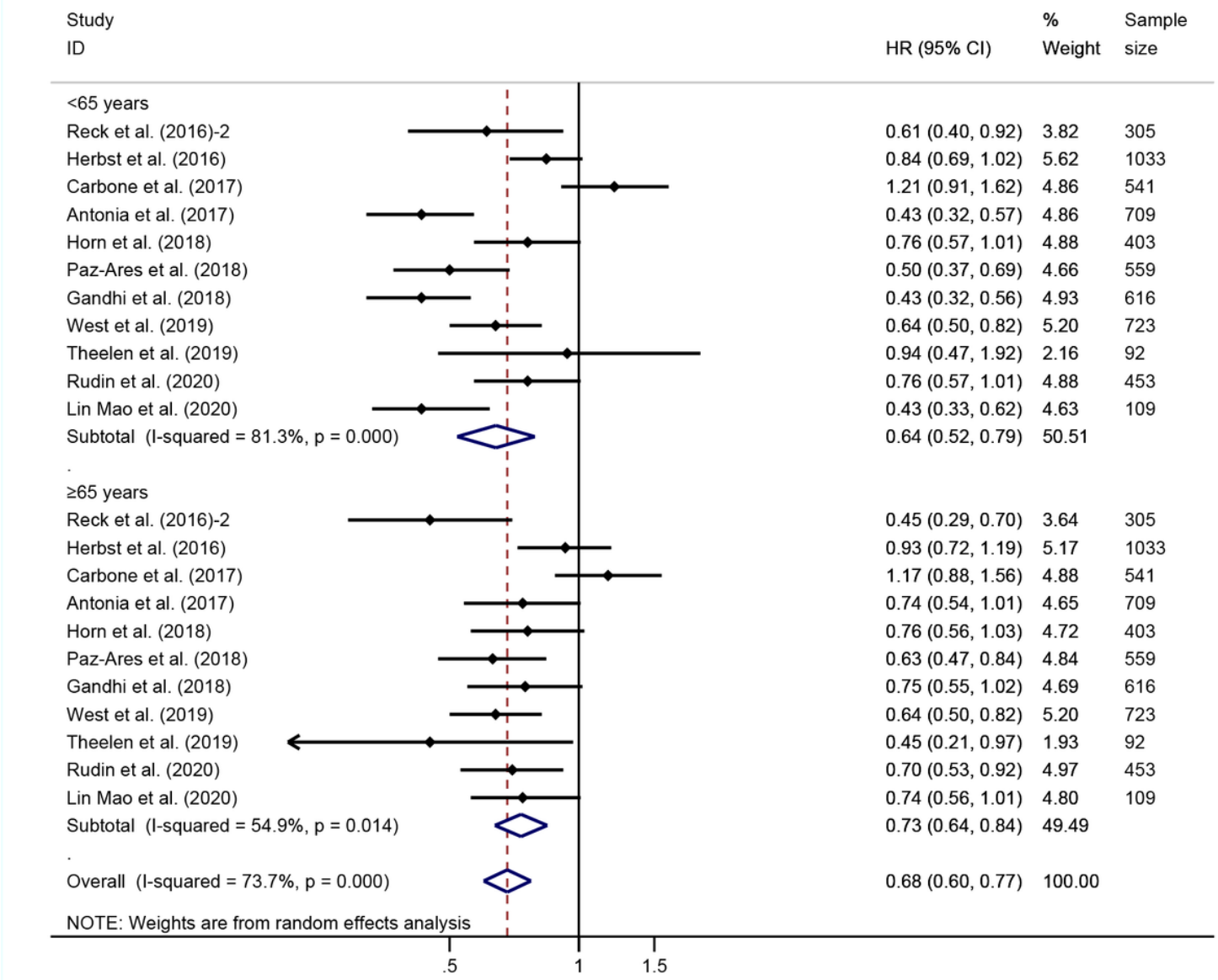


Figure 6

Evaluation of efficacy of ICIs by PFS rate in patients classified into two age groups Forest plot of the efficacy of ICIs with respect to the PFS rate in patients with lung cancer classified into two age groups were made. CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; PFS, progression-free survival

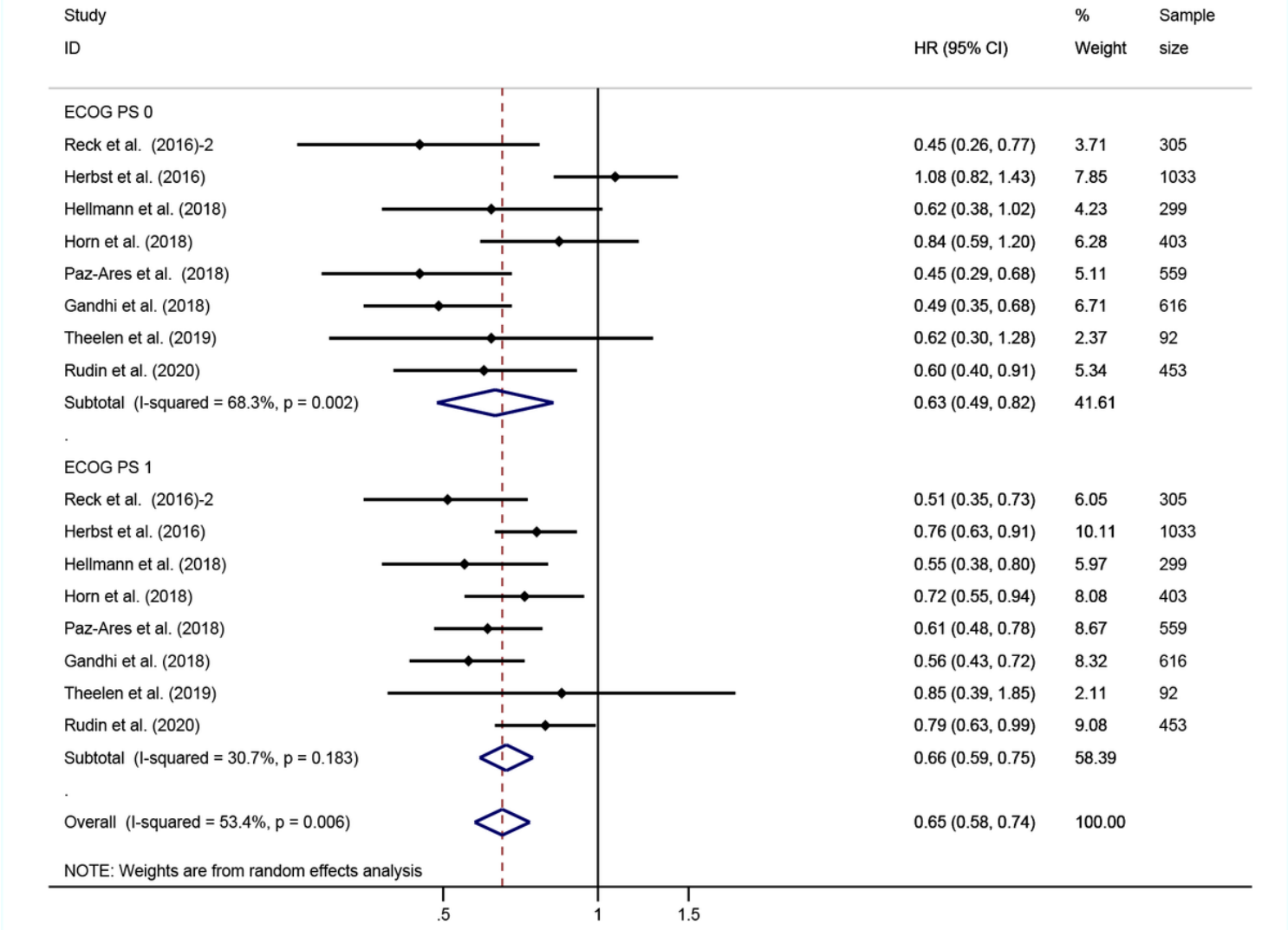


Figure 7

Evaluation of efficacy of ICIs by PFS rate based on ECOG PS scores Forest plot of the efficacy of ICIs with respect to the PFS rate in patients with lung cancer classified according to ECOG PS scores were made. CI, confidence interval; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ICI, immune checkpoint inhibitor; PFS, progression-free survival

Supplementary Files

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