Immune checkpoint inhibitor for different age patients with NSCLC in efficacy: a systematic review and Meta-analysis

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Research Article

Keywords: immune checkpoint inhibitor, NSCLC, age, systematic review, Meta-analysis

Posted Date: October 19th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2165411/v1

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Abstract

Objective

This article is a Meta-analysis aiming to systematically evaluate the difference in efficacy of immune checkpoint inhibitor in patients with non-small cell lung cancer (NSCLC) by age.

Methods

We performed a Meta-analysis of published randomized controlled trials concerning for patients with NSCLC by age. We compared overall survival among three groups (age < 65 years, age ≥ 65 years, age ≥ 75 years). Hazard ratios (HRs) and 95% confidence intervals (CIs) were collected and pooled.

Results

A total of 10,291 patients from 17 RCTs were included. In the group under age 65 years, immune checkpoint inhibitor can significantly prolong the overall survival of patients with NSCLC (HR = 0.73, 95% CI: 0.66~0.81, P < 0.00001). Meanwhile, it can extend the overall survival of patients with NSCLC (HR = 0.78, 95% CI:0.71~0.84, P < 0.00001) in the group older than 65 years. However, it has no significant effect on the overall survival of NSCLC patients (HR = 0.88, 95% CI:0.72~1.08, P > 0.05) in the group older than 75 years.

Conclusions

According to the Meta-analysis, immune checkpoint inhibitor can prolong the overall survival of patients with NSCLC between the two groups (age < 65 years and age ≥ 65 years). However, it has no significant effect on the overall survival in the group older than 75 years, which may be related to the poor physique of elderly patients and impacted by other diseases.

Introduction

Non-small cell lung cancer (NSCLC) is the most common malignancy in the world, with the highest morbidity and mortality, which causes that the 5-year survival rate is less than 15% [1–2]. Patients with early lung cancer can be cured by surgical resection, but most patients are clinically advanced as there are no obvious signs and symptoms in the early stage [3]. First-line treatment for patients with non-small cell lung cancer currently relies on dual combination chemotherapy with platinum-based drugs and third-generation agents [4]. However, chemotherapy is prone to complications such as bone marrow suppression and severe gastrointestinal symptoms. In addition, this therapy is not effective [5]. In recent years, the study of tumor immune escape mechanism has revealed that some immune monitoring sites play an important role in tumor formation [6]. Immune checkpoint inhibitors have shown significant efficacy in the treatment of advanced non-small cell lung cancer by blocking tumor immune escape mechanisms and activating endogenous anti-tumor immune responses [7–8]. In non-small cell lung cancer, immunosuppression has demonstrated long-lasting responses and improved survival, which can be regarded as a kind of monotherapy or combination therapy. Age plays a major role in the onset, progression and prognosis of disease [9]. The immune system of older people undergoes a remodeling process during ageing compared to younger people, which reduces the function and anti-tumor capacity of various immune cells, thereby reducing the efficacy of immune checkpoint inhibitors [10–11]. Therefore, a systematic evaluation and Meta-analysis on the therapeutic effects of immune checkpoint inhibitors on non-small cell lung cancer patients with different ages was conducted in this study, with a view to providing a reference for clinical treatment.

1. Materials And Methods

1.1. Inclusion and Exclusion Criteria

1.1.1. Inclusion Criteria: Articles that meet all of the following criteria can be included: Patients with non-small cell lung cancer; Interventions should include different immune checkpoint inhibitors; Overall survival (OS) outcomes for non-small cell lung cancer patients in different age groups should be reported; The trial should be a randomized controlled trials (RCT).

1.1.2. Exclusion Criteria: Using the following exclusion criteria: The study is only an abstract, not the full text; Studies with incomplete reporting of data information, duplication of data or inability to extract.

1.2. Literature Search Strategy

We searched a great number of eligible studies published before 30 May 2022 through several databases using keyword index, such as PubMed, Embase, Cochrane library, web of science, China National Knowledge Infrastructure, China Science and Technology Journal Database, Wanfang Data Knowledge Service Platform and the Chinese Biomedical Literature Database (in Chinese). References included in the study were also searched for additional access to relevant information. The search keywords included: “immune checkpoint inhibitor”, “non-small cell lung cancer”, “NSCLC”, “Randomized controlled trials” and “RCTs”.

1.3. Literature Screening and Data Extraction
The literature was screened, extracted and cross-checked by two independent researchers. If there is a disagreement, it will be resolved through discussion or negotiation with a third party. The literature was screened by first reading the title of the text. Then after excluding obviously irrelevant literature, we further read the abstract and full text to determine which can be included. If required, the authors of these articles were contacted by email or telephone to obtain information that was not published but was important to this study. The information extract includes: Basic information about the included studies, such as title of the study, first author and journal of publication; Baseline characteristics of the study population and interventions; Key elements of the risk of bias assessment; Study-related outcome indicators and outcome measures data.

1.4. Evaluation Of Quality And Bias Risk Assessment
The risk of bias about the included studies was evaluated independently by two investigators and the results were cross-checked. Risk of bias was evaluated using the RCT risk of bias assessment tool, which was recommended by the Cochrane Handbook.

1.5. Statistical Analysis
Statistical analysis was carried out using RevMan5.4.1 software. Overall survival in different age groups was assessed by overall Hazard ratio (HR) and 95% confidence interval (CI). Heterogeneity between studies was assessed by the \( I^2 \) test. When \( I^2 \leq 50\% \), the heterogeneity between studies is considered small and a fixed effects model is used to calculate. When \( I^2 > 50\% \), a large heterogeneity between studies is considered to exist and a random effects model is used to calculate. The test level is bilateral \( \alpha = 0.5 \).

2. Results
2.1. Literature Search and Screening
We searched 729 relevant articles. Specifically, duplicated articles were removed, 218 articles were screened according to titles and abstracts, 201 articles with abnormal data, incomplete information or non-comparative studies that could not be utilized were excluded after full text analysis and detailed assessment, and finally 17 documents were included for systematic evaluation and Meta-analysis. The literature screening process is shown in Fig. 1 (literature search flowchart). There were 5500 patients under 65 years and 4791 patients older than 65 years. Table 1 (Basic characteristics of included studies) summarizes the basic characteristics and key evaluation indicators of the included studies.
### Table 1: Baseline characteristics of the included retrospective studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Experimental group</th>
<th>Control group</th>
<th>Treatment line</th>
<th>Number of patients</th>
<th>Number of patients (≥ 65 years)</th>
<th>Overall survival</th>
<th>Total risk ratio (95%CI)</th>
<th>Risk ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borghaei[12]</td>
<td>2015</td>
<td>Nivolumab 3 mg/kg q2w</td>
<td>Docetaxel 75 mg/m2 q3w</td>
<td>2</td>
<td>582</td>
<td>339</td>
<td>243</td>
<td>0.73 (0.59–0.89)</td>
<td>0.81 (1.04)</td>
</tr>
<tr>
<td>Brahmer[13]</td>
<td>2015</td>
<td>Nivolumab 3mg/kg q2w</td>
<td>Docetaxel 75 mg/m2 q3w</td>
<td>2</td>
<td>272</td>
<td>152</td>
<td>120</td>
<td>0.59 (0.44–0.79)</td>
<td>0.62 (0.89)</td>
</tr>
<tr>
<td>Govindan[14]</td>
<td>2017</td>
<td>Ipilimumab</td>
<td>Placebo + Paclitaxel and Carboplatin</td>
<td>1</td>
<td>749</td>
<td>380</td>
<td>369</td>
<td>0.91 (0.77–1.07)</td>
<td>0.82 (1.04)</td>
</tr>
<tr>
<td>Hellmann[15]</td>
<td>2019</td>
<td>Nivolumab + Ipilimumab</td>
<td>Nivolumab + Chemotherapy or Chemotherapy</td>
<td>1</td>
<td>793</td>
<td>406</td>
<td>387</td>
<td>0.79 (0.65–0.96)</td>
<td>0.70 (0.89)</td>
</tr>
<tr>
<td>Paz-Ares[16]</td>
<td>2018</td>
<td>Pembrolizumab + Chemotherapy</td>
<td>Placebo + Chemotherapy</td>
<td>1</td>
<td>559</td>
<td>254</td>
<td>305</td>
<td>0.64 (0.49–0.85)</td>
<td>0.52 (0.80)</td>
</tr>
<tr>
<td>West[17]</td>
<td>2019</td>
<td>Atezolizumab + Carboplatin + Nab-paclitaxel</td>
<td>Carboplatin + Nab-paclitaxel</td>
<td>1</td>
<td>451</td>
<td>227</td>
<td>224</td>
<td>0.79 (0.64–0.98)</td>
<td>0.79 (1.08)</td>
</tr>
<tr>
<td>Gandhi[18]</td>
<td>2018</td>
<td>Pembrolizumab + Pemetrexed + Platinum-based drug</td>
<td>Placebo + Pemetrexed + Platinum-based drug</td>
<td>1</td>
<td>616</td>
<td>312</td>
<td>304</td>
<td>0.49 (0.38–0.64)</td>
<td>0.43 (0.61)</td>
</tr>
<tr>
<td>Papadimitrakopoulou[19]</td>
<td>2018</td>
<td>Atezolizumab + Carboplatin + Pemetrexed</td>
<td>Carboplatin/Cisplatin + Pemetrexed</td>
<td>1</td>
<td>578</td>
<td>320</td>
<td>258</td>
<td>0.81 (0.64–1.03)</td>
<td>0.89 (1.21)</td>
</tr>
<tr>
<td>Socinski[20]</td>
<td>2018</td>
<td>Atezolizumab + Bevacizumab + Carboplatin + Pemetrexed</td>
<td>Bevacizumab + Carboplatin + Pemetrexed</td>
<td>1</td>
<td>800</td>
<td>441</td>
<td>359</td>
<td>0.78 (0.64–0.96)</td>
<td>0.65 (0.82)</td>
</tr>
<tr>
<td>Carbone[21]</td>
<td>2017</td>
<td>Nivolumab 3 mg/kg q2w</td>
<td>Platinum-based chemotherapy</td>
<td>1</td>
<td>541</td>
<td>281</td>
<td>260</td>
<td>1.08 (0.87–1.34)</td>
<td>1.13 (1.54)</td>
</tr>
<tr>
<td>Antonia[22]</td>
<td>2018</td>
<td>Durvalumab</td>
<td>Placebo</td>
<td>1</td>
<td>713</td>
<td>391</td>
<td>322</td>
<td>0.68 (0.54–0.86)</td>
<td>0.62 (0.86)</td>
</tr>
<tr>
<td>Fehrenbacher[23]</td>
<td>2018</td>
<td>Atezolizumab  1200mg q3w</td>
<td>Docetaxel 75 mg/m2 q3w</td>
<td>2</td>
<td>1225</td>
<td>661</td>
<td>564</td>
<td>0.80 (0.70–0.92)</td>
<td>0.84 (1.01)</td>
</tr>
<tr>
<td>Rittmeyer[24]</td>
<td>2016</td>
<td>Atezolizumab 1200mg q3w</td>
<td>Docetaxel 75 mg/m2 q3w</td>
<td>2</td>
<td>850</td>
<td>453</td>
<td>397</td>
<td>0.73 (0.62–0.87)</td>
<td>0.80 (1.00)</td>
</tr>
<tr>
<td>Herbst[25]</td>
<td>2015</td>
<td>Pembrolizumab</td>
<td>Docetaxel 75 mg/m2 q3w</td>
<td>2</td>
<td>1033</td>
<td>604</td>
<td>429</td>
<td>0.67 (0.56–0.80)</td>
<td>0.63 (0.79)</td>
</tr>
<tr>
<td>Barlesi[26]</td>
<td>2018</td>
<td>Avelumab 10mg/Kg q2w</td>
<td>Docetaxel 75mg/m² q3w</td>
<td>2</td>
<td>529</td>
<td>279</td>
<td>250</td>
<td>0.90 (0.73–1.12)</td>
<td>0.84 (1.13)</td>
</tr>
<tr>
<td>Spigel[27]</td>
<td>2019</td>
<td>Atezolizumab</td>
<td>Platinum-based chemotherapy</td>
<td>1</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Nosaki[28]</td>
<td>2019</td>
<td>Pembrolizumab  10mg/Kg q3w</td>
<td>Platinum-based chemotherapy</td>
<td>1</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

#### 2.2. Quality Evaluation Results

The results of the quality assessment are shown in Fig. 2 (Risk of bias summary). Most studies had a low risk of bias, with random sequence generation reported in 11 trials. These articles except six of the trials provided detailed information on allocation concealment. The information on participant and personnel blinding was clearly reported in eight trials. Detailed information on detection bias and wear bias was provided for all trials. Selective reporting was present in two trials. No other bias was evident in all but four trials.

#### 2.3. Overall Survival

##### 2.3.1. Patients (< 65 years)

Fifteen RCTs reported overall survival in patients under 65 years, with relatively large statistical heterogeneity between studies ($I^2 = 54\%$). Meta-analysis showed that immune checkpoint inhibitors significantly prolonged overall survival in non-small cell lung cancer patients under 65 years (Fig. 3: OS forest plot).
for age < 65 years), with a statistically significant difference (HR = 0.73, 95% CI: 0.66~0.81, P < 0.00001). The funnel plot for age < 65 years is shown in Fig. 4, with no significant publication bias.

2.3.2. Patients (≥ 65 years)

Twelve RCTs reported overall survival at age ≥ 65 years, with little statistical heterogeneity between studies (I^2 = 11%). Meta-analysis showed that immune checkpoint inhibitors prolonged overall survival in elderly patients aged ≥ 65 years (Fig. 5: OS forest plot for age ≥ 65 years), with a statistically significant difference (HR = 0.78, 95% CI:0.71~0.84, P < 0.00001). The funnel plot for age ≥ 65 years is shown in Fig. 6, with no significant publication bias.

2.3.3. Patients (≥ 75 years)

Seven RCTs reported overall survival at age ≥ 75 years, with little statistical heterogeneity between studies (I^2 = 0%). Meta-analysis showed that immune checkpoint inhibitors had no significant effect on overall survival in non-small cell lung cancer patients aged ≥ 75 years (Fig. 7: OS forest plot for age ≥ 75 years) and the difference was not statistically significant (HR = 0.88, 95% CI:0.72~1.08, P > 0.05).

2.4. Publication bias testing and sensitivity analysis

Publication bias was assessed only in the age < 65 years group and in the age ≥ 65 years group. The funnel plot is symmetrical, indicating no significant publication bias. Sensitivity analysis of the results, when each study was ignored, Meta-analysis was conducted by ignoring each study in turn, and no significant changes were found, indicating this study has robust and reliable results.

3. Discussion

Lung cancer is one of the most malignant tumors threatening the health and lives of the population due to its high morbidity and mortality[29]. Among the different pathological types, non-small cell lung cancer accounts for 80% of all lung cancers[30]. In recent years, significant breakthroughs have been made in the study of immune checkpoint inhibitors that block the immune escape mechanism of tumors by blocking the binding of their corresponding ligands[31]. This approach offers new ideas for oncology treatment with better efficacy and safety compared to original Platinum-based drug chemotherapy[32]. Compared to younger people, the immune system's ability to fight tumors in the elderly decreases with age, and the function of various immune cells decreases due to aging of the hematopoietic stem cell compartment, reduced release of tumor antigens, uptake and processing of antigen-presenting cells, altered function of antigen-presenting cells, impairment of T cell activation, and reduced ability of senescent T cells to clear tumor cells[33]. Currently, it is unknown about the efficacy of immune checkpoint inhibitors in patients with non-small cell lung cancer at different ages. Therefore, this study systematically evaluated the effectiveness of immunotherapy in patients with non-small cell lung cancer at different ages.

Activation of the immune checkpoint inhibitor signaling pathway contributes to tumor immune escape and blocking this pathway enhances the endogenous anti-tumor immune effect[34]. Various relevant drugs are now applied to clinical practice. Nivolumab monoclonal antibody is a programmed death receptor 1 (PD-1) blocker[35]. As a new class of anti-tumor drug, it has the ability to treat a wide range of tumors and significantly improve the survival time of tumor patients. Pembrolizumab is a monoclonal antibody that binds to programmed death receptor-1 (PD-1)[36]. Blocks the PD-1 pathway-mediated immunosuppressive response by blocking the interaction between PD-1, PD-L1 and PD-L2. Atezolizumab is an engineered humanized monoclonal antibody[37]. It can inhibit activated T cells by modifying the structural domain of the crystal fragment to eliminate its antibody-dependent cytotoxicity. The results of this paper showed as follows: in the age < 65 years group, immune checkpoint inhibitors significantly prolonged the overall survival of NSCLC patients (HR = 0.73, 95% CI:0.66~0.81, P < 0.00001); in the age ≥ 65 years group, immune checkpoint inhibitors prolonged the overall survival of NSCLC patients (HR = 0.78, 95% CI:0.71~0.84, P < 0.00001); however, in the age ≥ 75 years group, immune checkpoint inhibitors had no significant effect on the overall survival of patients with NSCLC (HR = 0.88, 95% CI:0.72~1.08, P > 0.05). This may be related to the increased proportion of coexisting disease in older patients influenced by several factors such as age and poor health. Coexisting disease can affect the effectiveness of immunotherapy in older lung cancer patients in many ways, and severe co-morbidities can reduce the life expectancy of patients and reduce the potential longevity benefit of immunotherapy.

There are some limitations to this study. Firstly, only 17 articles were included in this study for Meta-analysis, which is a small amount of literature. Secondly, differences in PD-L1 positive thresholds, smoking status and histological type of non-small cell lung cancer may affect the outcome. Thirdly, there was greater heterogeneity in the age < 65 years group, which may affect the credibility of the results. Although there were some limitations to the included studies, this study was reported strictly in accordance with the PRISMA project in order to minimize bias.

4. Conclusions

In summary, PD-1/PD-L1 immune checkpoint inhibitors prolonged the overall survival of NSCLC patients in both the age < 65 years group and the age ≥ 65 years group, but in the age ≥ 75 years group, there was no significant effect on overall survival, which may be related to the poor physical condition of elderly patients and the combined influence of other diseases.

Declarations

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.
Author contributions

Contributions: (I) Conception and design: Qi Zhang, Tian-Tian Zheng; (II) Administrative support: Kun-Peng Qu; (III) Provision of study materials or patients: Jin-Wei Gao Ze-Sheng Wang; (IV) Collection and assembly of data: Yi-bin Guo Sheng-chang Liang; (V) Data analysis and interpretation: Lin Xu, Qi Zhang, Tian-Tian Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Funding

This work was supported by following grants: Natural Science Foundation of Gansu Province of China(145RJZA116); Special Fund for Clinical Research of Wu Jieping Medical Foundation 320.6750.16216 .

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References


Figure 1

Flow diagram of the selection of the included studies
Figure 2
Risk of bias summary

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antonia 2018</td>
<td>-0.478</td>
<td>0.1709</td>
<td>5.6%</td>
<td>0.62 [0.44, 0.87]</td>
</tr>
<tr>
<td>Barlesi 2018</td>
<td>-0.174</td>
<td>0.1491</td>
<td>6.4%</td>
<td>0.84 [0.63, 1.13]</td>
</tr>
<tr>
<td>Borghesi 2015</td>
<td>-0.211</td>
<td>0.1319</td>
<td>7.2%</td>
<td>0.81 [0.63, 1.05]</td>
</tr>
<tr>
<td>Brahmer 2015</td>
<td>-0.478</td>
<td>0.1796</td>
<td>5.2%</td>
<td>0.62 [0.44, 0.88]</td>
</tr>
<tr>
<td>Carbone 2017</td>
<td>0.122</td>
<td>0.1577</td>
<td>6.1%</td>
<td>1.13 [0.83, 1.54]</td>
</tr>
<tr>
<td>Fehrenbacher 2018</td>
<td>-0.174</td>
<td>0.0935</td>
<td>9.2%</td>
<td>0.84 [0.70, 1.01]</td>
</tr>
<tr>
<td>Gandhi 2018</td>
<td>-0.843</td>
<td>0.1727</td>
<td>5.5%</td>
<td>0.43 [0.31, 0.60]</td>
</tr>
<tr>
<td>Govindan 2017</td>
<td>-0.198</td>
<td>0.1239</td>
<td>7.6%</td>
<td>0.82 [0.64, 1.05]</td>
</tr>
<tr>
<td>Hellmann 2019</td>
<td>-0.357</td>
<td>0.1228</td>
<td>7.7%</td>
<td>0.70 [0.55, 0.89]</td>
</tr>
<tr>
<td>Herbst 2015</td>
<td>-0.462</td>
<td>0.1167</td>
<td>8.0%</td>
<td>0.63 [0.50, 0.79]</td>
</tr>
<tr>
<td>Papadimitriakopoulou 2018</td>
<td>-0.117</td>
<td>0.1706</td>
<td>5.6%</td>
<td>0.89 [0.64, 1.24]</td>
</tr>
<tr>
<td>Paz-Ares 2018</td>
<td>-0.654</td>
<td>0.2183</td>
<td>4.1%</td>
<td>0.52 [0.34, 0.80]</td>
</tr>
<tr>
<td>Ritmeyer 2016</td>
<td>-0.223</td>
<td>0.1139</td>
<td>8.1%</td>
<td>0.80 [0.64, 1.00]</td>
</tr>
<tr>
<td>Socinski 2018</td>
<td>-0.431</td>
<td>0.1211</td>
<td>7.7%</td>
<td>0.65 [0.51, 0.82]</td>
</tr>
<tr>
<td>West 2019</td>
<td>-0.236</td>
<td>0.1586</td>
<td>6.0%</td>
<td>0.79 [0.58, 1.08]</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.73 [0.66, 0.81]
Heterogeneity: Tau² = 0.02; Ch² = 30.49, df = 14 (P = 0.007); I² = 54%
Test for overall effect: Z = 5.81 (P < 0.000001)

Figure 3
OS forest plot for age < 65 years
Figure 4
funnel plot for age < 65 years

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antonia 2018</td>
<td>-0.2744</td>
<td>0.1674</td>
<td>6.5%</td>
<td>0.76 [0.65, 1.06]</td>
</tr>
<tr>
<td>Barlesi 2018</td>
<td>-0.0202</td>
<td>0.1621</td>
<td>6.9%</td>
<td>0.98 [0.71, 1.35]</td>
</tr>
<tr>
<td>Carbone 2017</td>
<td>0.0392</td>
<td>0.1543</td>
<td>7.7%</td>
<td>1.04 [0.77, 1.41]</td>
</tr>
<tr>
<td>Fehrenbacher 2018</td>
<td>-0.2877</td>
<td>0.1021</td>
<td>17.9%</td>
<td>0.75 [0.61, 0.92]</td>
</tr>
<tr>
<td>Gandhi 2018</td>
<td>-0.4463</td>
<td>0.2022</td>
<td>4.5%</td>
<td>0.64 [0.43, 0.95]</td>
</tr>
<tr>
<td>Hellmann 2019</td>
<td>-0.0943</td>
<td>0.1222</td>
<td>12.2%</td>
<td>0.91 [0.72, 1.16]</td>
</tr>
<tr>
<td>Herbst 2015</td>
<td>-0.2744</td>
<td>0.1484</td>
<td>8.3%</td>
<td>0.76 [0.57, 1.02]</td>
</tr>
<tr>
<td>Papadimitrakopoulou 2018</td>
<td>-0.3425</td>
<td>0.1793</td>
<td>5.7%</td>
<td>0.71 [0.50, 1.01]</td>
</tr>
<tr>
<td>Paz-Ares 2018</td>
<td>-0.3011</td>
<td>0.1891</td>
<td>5.1%</td>
<td>0.74 [0.51, 1.07]</td>
</tr>
<tr>
<td>Rittmeyer 2016</td>
<td>-0.4155</td>
<td>0.1193</td>
<td>12.8%</td>
<td>0.66 [0.52, 0.83]</td>
</tr>
<tr>
<td>Socinski 2018</td>
<td>-0.5108</td>
<td>0.1919</td>
<td>4.9%</td>
<td>0.60 [0.41, 0.87]</td>
</tr>
<tr>
<td>West 2019</td>
<td>-0.2485</td>
<td>0.1514</td>
<td>8.0%</td>
<td>0.78 [0.58, 1.05]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.0% 0.78 [0.71, 0.84]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 12.38, df = 11 (P = 0.34); I² = 11%
Test for overall effect: Z = 5.94 (P < 0.00001)

Figure 5
OS forest plot for age ≥ 65 years
**Figure 6**

Funnel plot for age ≥ 65 years

![Funnel plot](image)

**Figure 7**

OS forest plot for age ≥ 75 years

![OS forest plot](image)

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- searchstrategy.docx