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ORIGINAL ARTICLE

Immunotherapy for resectable NSCLC: neoadjuvant/perioperative followed by surgery over surgery followed by adjuvant. Systematic review and meta-analysis with subgroup analyses

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Background: Immunotherapy has rapidly changed the treatment of early-stage non-small-cell lung cancer (NSCLC) in recent years. We aimed to summarize available evidence on the use of immunotherapy in neoadjuvant/perioperative and adjuvant settings for resectable NSCLC and explore some controversial subgroups.

Materials and methods: Systematic literature research was carried out for randomized controlled trials of neoadjuvant/perioperative chemo-immunotherapy or adjuvant immunotherapy for resectable NSCLC. Separate meta-analyses for neoadjuvant/perioperative or adjuvant immunotherapy were carried out. Subgroup analyses were also carried out to estimate the effect of immunotherapy according to tumor histology, stage, programmed death-ligand 1 (PD-L1), age, sex and smoking status.

Results: Out of 6005 records screened, a total of 11 trials met the inclusion criteria. This pooled analysis showed that patients receiving neoadjuvant or perioperative chemo-immunotherapy had significantly better event-free survival (EFS) compared with those treated with neoadjuvant chemotherapy alone [hazard ratio (HR) 0.58, 95% confidence interval (CI) 0.51-0.66]. Similarly, adjuvant immunotherapy also led to improved outcomes (HR 0.85, 95% CI 0.77-0.94). However, among patients with stage II NSCLC, neoadjuvant/perioperative chemo-immunotherapy demonstrated EFS benefit (HR 0.69, 95% CI 0.54-0.88), while no significant EFS benefit was observed with adjuvant immunotherapy (HR 0.81, 95% CI 0.63-1.05). Similarly, there was an improvement in EFS for patients with squamous-cell carcinoma who received neoadjuvant/perioperative chemo-immunotherapy versus neoadjuvant chemotherapy (HR 0.56, 95% CI 0.45-0.68) and for PD-L1 $<$ 1% (HR 0.77, 95% CI 0.65-0.93), whereas such improvement was not evident with adjuvant immunotherapy (HR 0.93, 95% CI 0.76-1.13 and HR 0.85, 95% CI 0.71-1.01, respectively). Overall survival analysis demonstrated a significant benefit from neoadjuvant/perioperative immunotherapy (HR 0.65, 95% CI 0.53-0.81), but not with adjuvant immunotherapy (HR 0.91, 95% CI 0.76-1.10).

Conclusions: Our results indicate that neoadjuvant/perioperative immunotherapy should be considered the standard. This should be preferred over upfront surgery, also in stage II, PD-L1-negative and squamous histology.

Key words: NSCLC, neoadjuvant, immunotherapy, adjuvant, perioperative, meta-analysis

INTRODUCTION

Lung cancer is still the leading cause of cancer-related deaths worldwide.[1] Non-small-cell lung cancer (NSCLC) accounts for 80%-85% of lung cancer cases, and only 25% of patients have resectable disease at diagnosis.[2] In these settings, surgery remains the main treatment option; however, the probability of recurrence after radical surgery ranges from 30% to over 60%, depending on the pathological stage.[3] Established data have supported chemotherapy as adjuvant or neoadjuvant treatment, with the biological rationale of acting against micrometastatic disease and reducing the risk of recurrence.[4,5] Potential disadvantages of neoadjuvant approach include disease progression or toxicity during treatment, precluding surgery.

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On the other hand, the adjuvant strategy cannot always be carried out due to inadequate post-surgery recovery, thus requiring a careful patient selection based on clinical and biological factors [e.g. programmed death-ligand 1 (PD-L1) expression].[6] In the last few years, several trials assessed the addition of immunotherapy to chemotherapy in both the neoadjuvant and adjuvant settings. To date, the Food and Drug Administration (FDA) approved neoadjuvant nivolumab with platinum doublet chemotherapy for patients with resectable NSCLC based on the results of the phase III CheckMate 816 study.[7] Subsequently, neoadjuvant pembrolizumab in combination with platinum doublet was approved for resectable NSCLC followed by pembrolizumab monotherapy in the adjuvant setting (perioperative approach) after overall survival (OS) results of KEYNOTE-671[8] were presented. The perioperative schemes of the Aegean and CheckMate 77T trials, combining durvalumab or nivolumab, were approved, although their survival is still pending. The year before, atezolizumab as a single agent for 12 months after adjuvant chemotherapy was approved as adjuvant strategy, based on the results of the IMpower010 trial,[9-11] with approval from the European Medicines Agency (EMA) that restricted its use for tumors with PD-L1 tumor proportion score (TPS) $>$50% following a *post hoc* analysis. However, in the adjuvant setting, two other immunotherapy trials reached controversial results: in the phase III KEYNOTE-091 trial, pembrolizumab achieved only one of the two primary endpoints, showing a disease-free survival (DFS) benefit in the overall population, with non-significant DFS advantage in patients with high PD-L1 TPS, leading to FDA and EMA approval irrespective of PD-L1 expression.[12] Lastly, the BR.31 trial compared durvalumab versus placebo after adjuvant chemotherapy; in this case, the study was formally negative since durvalumab did not improve either DFS or OS over placebo.[13] These conflicting data increase the complexity of the decision-making process of a multidisciplinary lung cancer management team, that must define the best therapeutic strategy for patients with resectable NSCLC, minimizing the probability of recurrence. Considering these data, the aim of this meta-analysis is to define the best treatment strategies in some categories, where the hazard ratio (HR) for neoadjuvant, adjuvant and perioperative strategy is controversial for data immaturity or lack of activity. These subgroups specifically are stage II NSCLC, with negative PD-L1 expression, and nonsmokers.

MATERIALS AND METHODS

Study protocol

This is a systematic review and meta-analysis of studies evaluating the addition of immunotherapy to standard chemotherapy as neoadjuvant or adjuvant treatment of resectable NSCLC. The reporting guidelines Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) were used.[14] The protocol of this study was registered with PROSPERO (CRD42024607246).

Search strategy and selection criteria

Eligible studies were identified by systematic literature search of PubMed, Medline and Embase and the most recent presentations to International Congresses from inception to 4 November 2024 without language restrictions. The search strategy was repeated before the final analysis on 15 December 2024 to confirm the retrieval of all possible studies. After this search, one record that was firstly included in the form of abstract[15] was subsequently published; therefore, data from this full manuscript were included.[16] The full search strategy can be found in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105759. Only published articles reporting trial-level data on neoadjuvant/perioperative chemo-immunotherapy or adjuvant immunotherapy were included. Eligible studies had to satisfy the following criteria: (i) phase II or phase III randomized controlled trial (RCT); (ii) neoadjuvant/perioperative chemo-immunotherapy compared with chemotherapy alone or adjuvant immunotherapy compared with placebo/best supportive care (following adjuvant chemotherapy or not); (iii) trials that evaluated only anti-PD-(L)1. Exclusion criteria were as follows: (i) case reports and case series; (ii) observational studies; (iii) clinical trials evaluating the use of radiotherapy or systemic treatments other than chemotherapy; (iv) non-RCT; (v) studies that included only patients with NSCLC with *EGFR* mutations and *ALK* rearrangements; (vi) studies that did not use TNM (tumor—node—metastasis) staging; (vii) ongoing studies with the results not presented or published at the time of the literature search; (viii) trials that evaluated immune checkpoint inhibitors other than anti-PD-(L)1, or vaccines.

All articles were screened for relevance based on title and abstract by two independent reviewers (GR, LB). In case of disagreement, a third reviewer (MT) was involved. Additionally, abstracts from the 2024 American Society of Clinical Oncology Annual Meeting, the 2024 European Society for Medical Oncology Congress, the 2024 European Lung Cancer Congress, the 2024 World Conference on Lung Cancer, and the 2024 American Association for Cancer Research Annual Meeting were reviewed for updates of previously presented RCTs and for results from new RCTs. The most up-to-date results were included for each trial, and online material from conference websites was also used. Cross-referencing from relevant studies was carried out to confirm retrieval of all possible studies. Risk of bias was assessed using the Cochrane risk of bias tool for RCT.

Data extraction

The following variables were extracted independently by two authors (GR and LB) from all included trials, where available and using a predefined form: trial name; first author; year of publication; study design; absolute and relative efficacy outcomes [adjusted HRs for event-free survival (EFS), DFS] with corresponding 95% confidence intervals (CIs), surgery and pathology data and adverse events. Discrepancies were discussed with a third reviewer

(MT) and resolved by consensus. When available, HRs for survival endpoints by subgroup according to sex, age, histology, PD-L1 level, stage, ethnicity and smoking status were also extracted.

Study objectives

The main objective of this analysis was to evaluate EFS and OS in patients receiving chemo-immunotherapy compared with patients treated with chemotherapy alone as neoadjuvant/perioperative treatment, and immunotherapy compared with placebo/best supportive care alone as adjuvant treatment (following adjuvant chemotherapy or not). Subgroup analyses were carried out to evaluate the impact of the addition of immunotherapy in patients with resectable NSCLC according to stage (stage II and III), sex (male, female), smoking habits [current, former smoker irrespective of type of tobacco (including cigarettes, cigar and other), never smoker (less than 100 cigarettes in the whole life)], PD-L1 expression (negative <1%, high expression ≥50%, low expression 1%-49%), tumor histology (squamous and non-squamous) and ethnicity (Asian, Caucasian). Secondary objective was to evaluate the risk of developing high-grade [grade (G) 3-4] toxicity in patients receiving immunotherapy in neoadjuvant/perioperative or adjuvant setting, respectively, as compared with patients not receiving it.

Statistical analysis

A random-effects model was used to calculate pooled HR with 95% CIs.[17] The pooled HR was considered statistically significant if the 95% CI did not include 1.0, with a *P* value <0.05 (two-sided). The Higgins I^2 index was computed to evaluate the heterogeneity between studies, with ≥50% considered as significant heterogeneity.[18] Funnel plot and Egger's test were used to address the potential occurrence of publication bias.[19] To assess whether the pooled HR estimates were stable or dependent on one trial, sensitivity analyses were conducted by interactively recalculating the pooled HR estimates after exclusion of each single trial.

Separate meta-analyses for adjuvant or neoadjuvant/perioperative immunotherapy were carried out, to evaluate the possible differences in effect between therapy settings. Moreover, subgroups analyses were carried out to estimate the effect of addition of immunotherapy according to tumor histology, stage, PD-L1 level, age, sex, ethnicity and smoking status.

Statistical analyses were conducted by VD using package meta, R version 4.3.1 (The R Foundation for statistical computing, Vienna, Austria).

RESULTS

Characteristics of the RCTs included

A total of 6005 records were retrieved (Figure 1). Among the 39 records assessed for eligibility, 15 abstracts were excluded because they were followed (and hence replaced) by full paper publication, while 13 were excluded because they were followed by more updated abstracts and papers. Finally, 11 records were included in the present meta-analysis: 10 full publications[7-9,12,16,20-24] and 1 congress abstract[13] from which we extracted 11 study groups (Figure 1). For seven studies, a follow-up study was found, and the updated data were used in place of the original data.

Details of the 11 trials included are reported in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105759. Briefly, eight trials[7,8,15,20-24] were in the neoadjuvant/perioperative setting and three were in the adjuvant setting,[9,12,13] with a total of 6788 patients included. With respect to histology, 1528 (22.5%) patients had squamous-cell carcinoma. Two adjuvant studies allowed omission of adjuvant chemotherapy before randomization. Among the 3401 patients included in the three RCTs in the adjuvant setting, 3042 (89.4%) patients received chemotherapy before randomization, and 1136 (33.4%) patients had squamous histology; with regard to disease stage, 398 patients (11.7%) had stage Ib disease, 1788 patients (52.6%) had stage II disease, and 1213 (35.7%) patients had stage III disease.

Overall, there was a low risk of bias among the RCTs (Supplementary Table S21, available at https://doi.org/10.1016/j.esmoop.2025.105759).

HR for EFS and OS with neoadjuvant/perioperative and adjuvant immunotherapy

Eleven trials[7-9,13,16,20-22,24-26] were included in this analysis, of which two trials[9,13] included also patients with stage Ib NSCLC, while one[12] included patients with NSCLC from stage II to IIIa (American Joint Committee on Cancer Staging Manual seventh edition). Furthermore, two trials[9,25] included patients with EGFR and ALK alterations, while the BR.31 trial presented data without this subgroup. Pooled EFS favored neoadjuvant/perioperative chemo-immunotherapy (HR 0.58, 95% CI 0.51-0.66, $I^2 = 2\%$, $P = 0.41$) compared with neoadjuvant chemotherapy alone. A smaller effect was observed for immunotherapy in the adjuvant setting compared with chemotherapy alone (HR 0.85, 95% CI 0.77-0.94, $I^2 = 0\%$, $P = 0.76$). Pooled HR for all trials included was 0.66 (95% CI 0.57-0.77, $I^2 = 68\%$, $P < 0.01$) (Figure 2A). Egger's test, carried out separately for the adjuvant and neoadjuvant trials, did not indicate significant evidence of publication bias and sensitivity analysis demonstrated similar results (Supplementary Figure S1 and Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105759).

Seven trials[7,8,16,22,25-27] were included in the OS analysis. Data included only stage II-IIIb patients. Overall, pooled OS favored neoadjuvant/perioperative chemo-immunotherapy compared with neoadjuvant chemotherapy (HR 0.65, 95% CI 0.53-0.81, $I^2 = 0\%$, $P = 0.84$). A smaller and not significant effect was observed for immunotherapy compared with chemotherapy alone in the adjuvant setting (HR 0.91, 95% CI 0.76-1.10, $I^2 = 0\%$, $P = 0.64$). Pooled HR for all trials included was 0.77 (95% CI 0.66-0.91, $I^2 = 15\%$, $P = 0.32$)

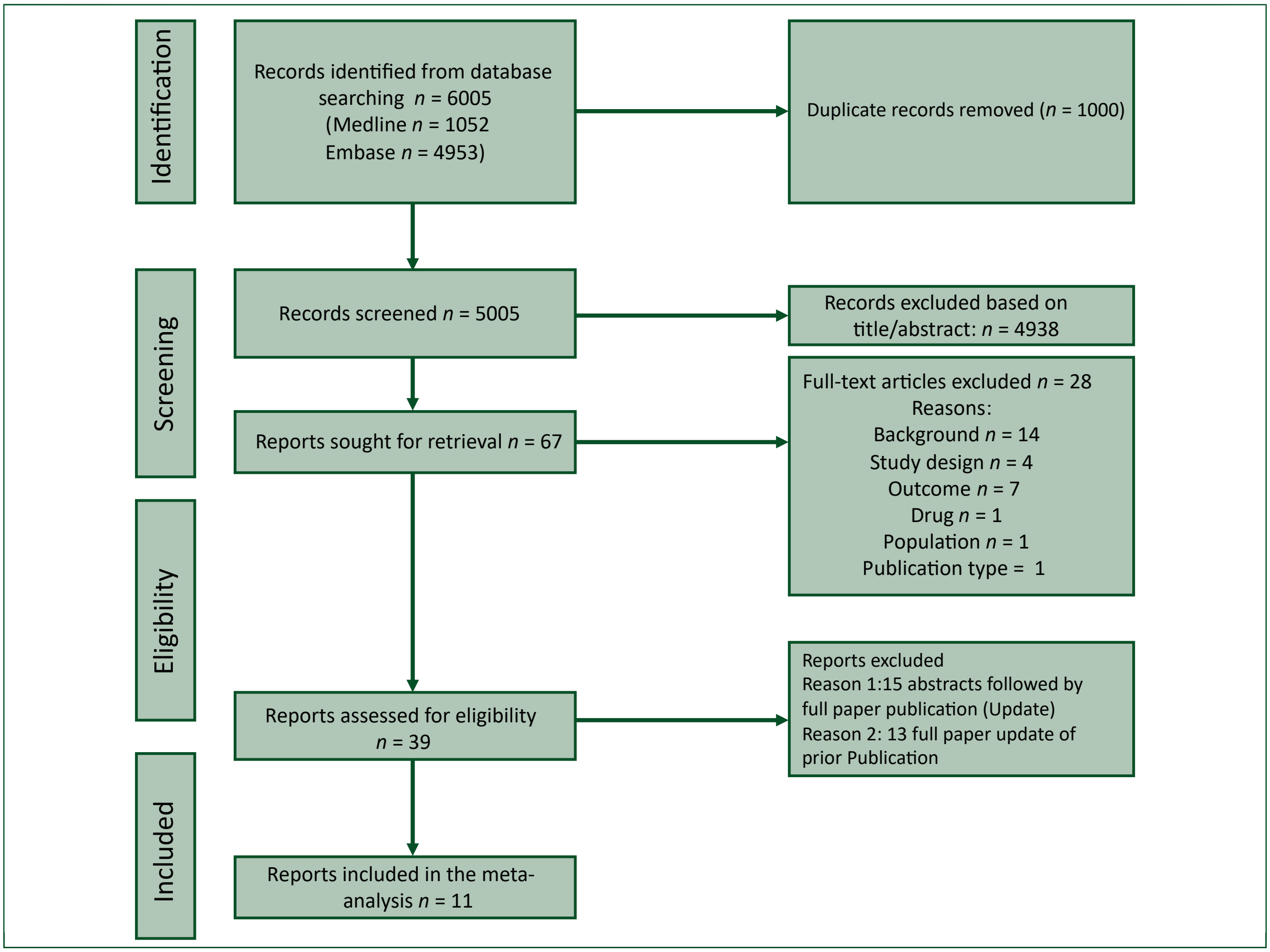

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram.

(Figure 2B). Egger's test, carried out separately for the adjuvant and neoadjuvant trials, did not indicate significant evidence of publication bias in adjuvant trial analysis, while it demonstrated a significant publication bias in neoadjuvant analysis ($P = 0.02$), and sensitivity analysis demonstrated similar results (Supplementary Figure S2 and Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105759).

Sub-analysis by histological type and stage

Figure 2: Forest plot for pooled HR of EFS (A) and OS (B) in the overall population of included trials, and separately in the adjuvant and neoadjuvant/perioperative setting. Random effect model is reported at the bottom of the figure

Nine trials presented data according to disease stage[7-9,13,16,20-22,25] and 10 according to histological subtype.[7-9,13,16,20-22,25,26] In patients with stage II NSCLC, neoadjuvant/perioperative chemo-immunotherapy showed a survival advantage (HR 0.69, 95% CI 0.54-0.88, $I^2 = 0\%$, $P = 0.62$), while no significant advantage was observed with adjuvant immunotherapy (HR 0.81, 95% CI 0.63-1.05, $I^2 = 31\%$, $P = 0.230$) (Figure 3A). In patients with stage III NSCLC, neoadjuvant/perioperative chemo-immunotherapy showed a survival advantage (HR 0.54, 95% CI 0.46-0.62, $I^2 = 0\%$, $P = 0.90$) as did adjuvant immunotherapy (HR 0.81, 95% CI 0.67-0.98, $I^2 = 25\%$, $P = 0.26$) (Figure 3B). There was an improvement in EFS for patients with squamous-cell carcinoma who received neoadjuvant/perioperative chemo-immunotherapy versus neoadjuvant chemotherapy (HR 0.56, 95% CI 0.45-0.68, $I^2 = 36\%$, $P = 0.15$), whereas there was no benefit in patients treated with adjuvant immunotherapy versus chemotherapy alone (HR 0.93, 95% CI 0.76-1.13, $I^2 = 0\%$, $P = 0.60$) (Figure 4A).

For patients with adenocarcinoma histology, neoadjuvant/perioperative chemo-immunotherapy showed a significant benefit over chemotherapy (HR 0.60, 95% CI 0.51-0.71, $I^2 = 0\%$, $P = 0.710$) as well as adjuvant immunotherapy over chemotherapy alone (HR 0.75, 95% CI 0.66-0.85, $I^2 = 0\%$, $P = 0.470$) (Figure 4B).

For all these sub-analyses, Egger's test, carried out separately for the adjuvant and neoadjuvant trials, did not indicate significant evidence of publication bias, and sensitivity analysis demonstrated similar results (Supplementary Figures S3-S6 and Tables S5-S8, available at https://doi.org/10.1016/j.esmoop.2025.105759).

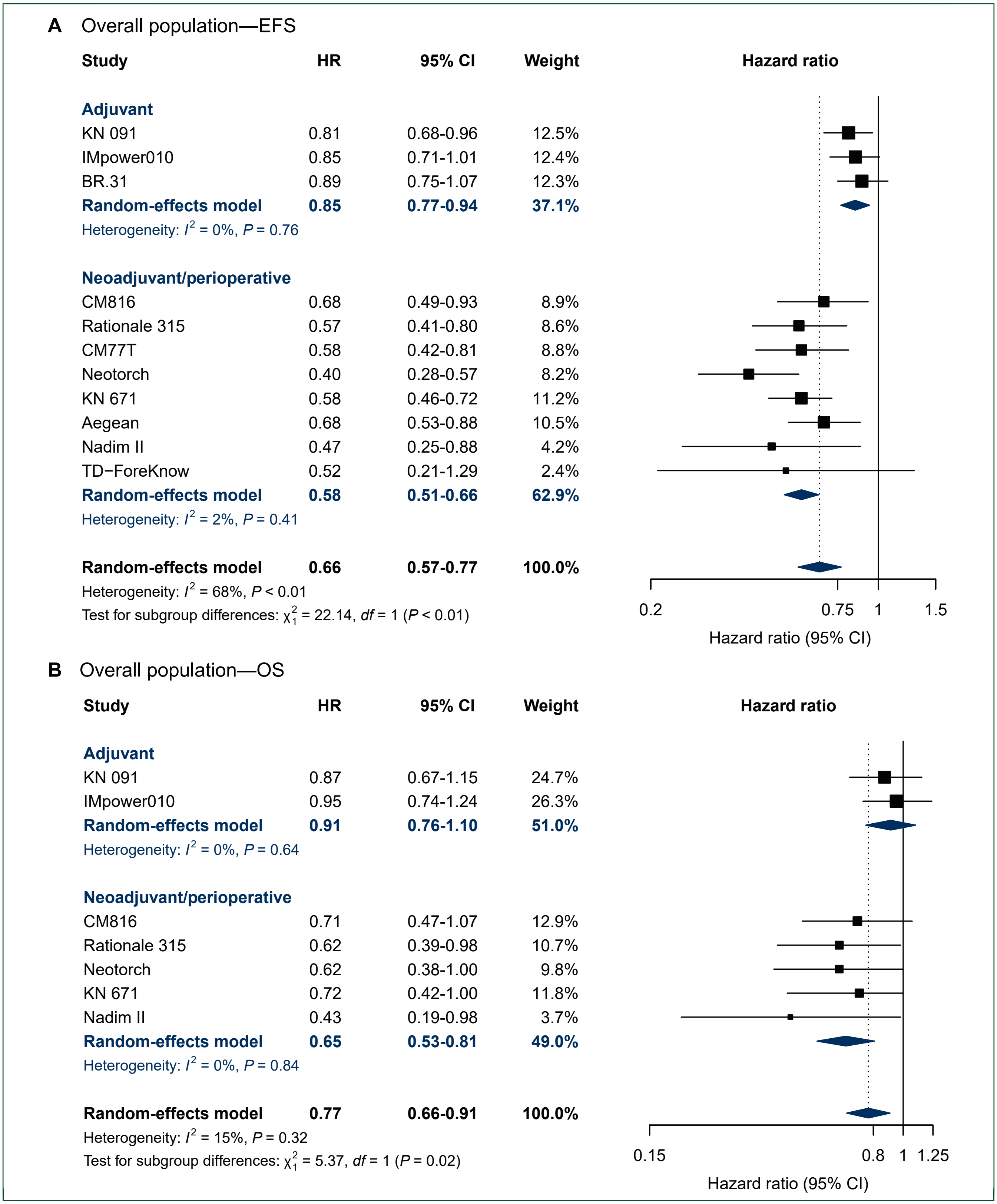

Figure 2. Survival analysis of the whole population in terms of EFS and OS. Forest plot for pooled HR of EFS (A) and OS (B) in the overall population of included trials, and separately in the adjuvant and neoadjuvant/perioperative settings. Random-effects model is reported at the bottom of the figure.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival.

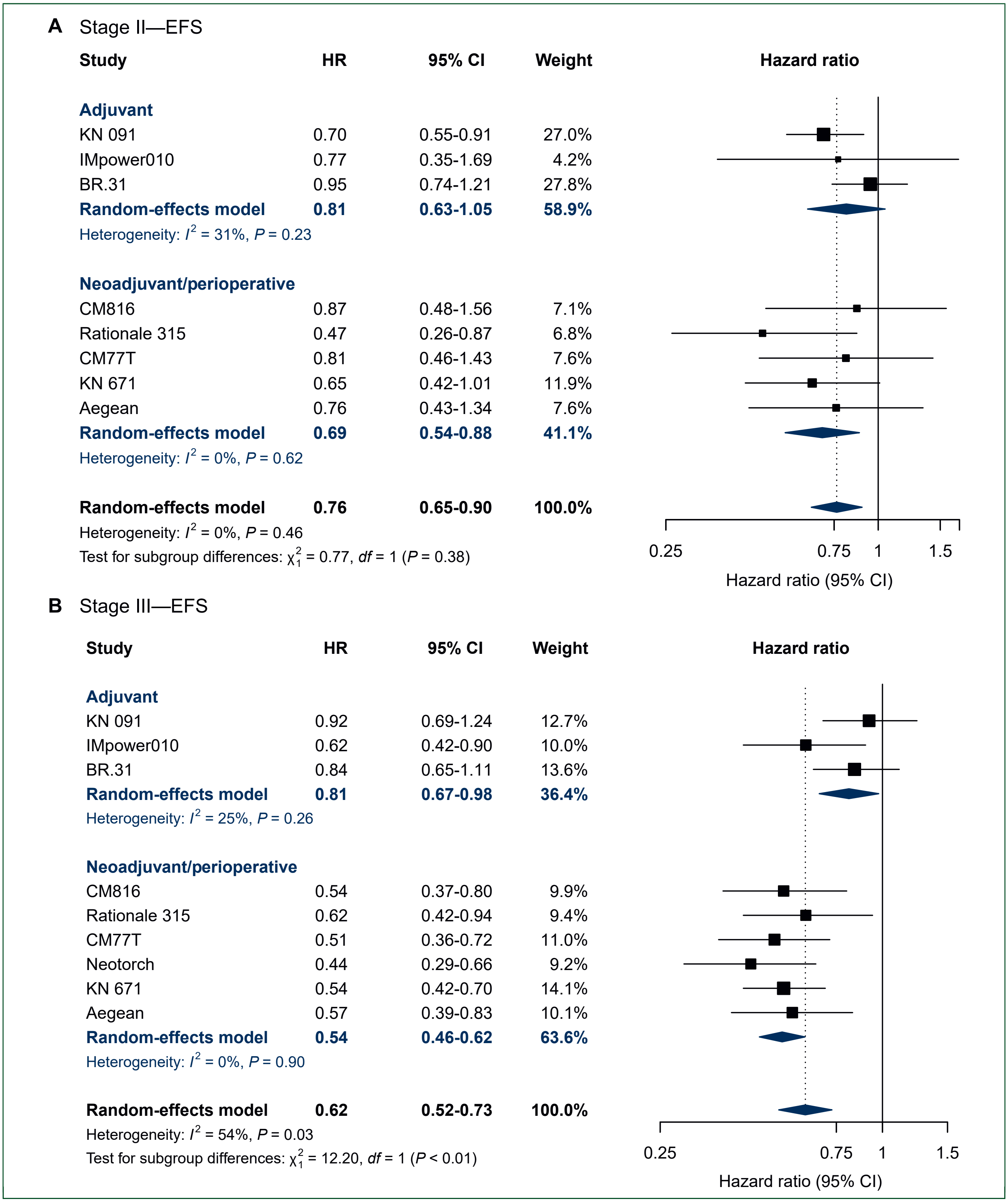

Figure 3. EFS according to TNM stage. Forest plot for pooled HR of EFS in stage II (A) and stage III (B) in the overall population of included trials, and separately in the adjuvant and neoadjuvant/perioperative settings. Random-effects model is reported at the bottom of the figure.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio.

Sub-analysis by PD-L1 expression

Figure 3: Forest plot for pooled HR of EFS in stage II (A) and stage III (B) in the overall population of included trials, and separately in the adjuvant and neoadjuvant/perioperative setting. Random effect model is reported at the bottom of the figure.

Ten trials presented data according to PD-L1 expression.[7-9,13,16,20-22,25,26] There was an improvement in EFS for

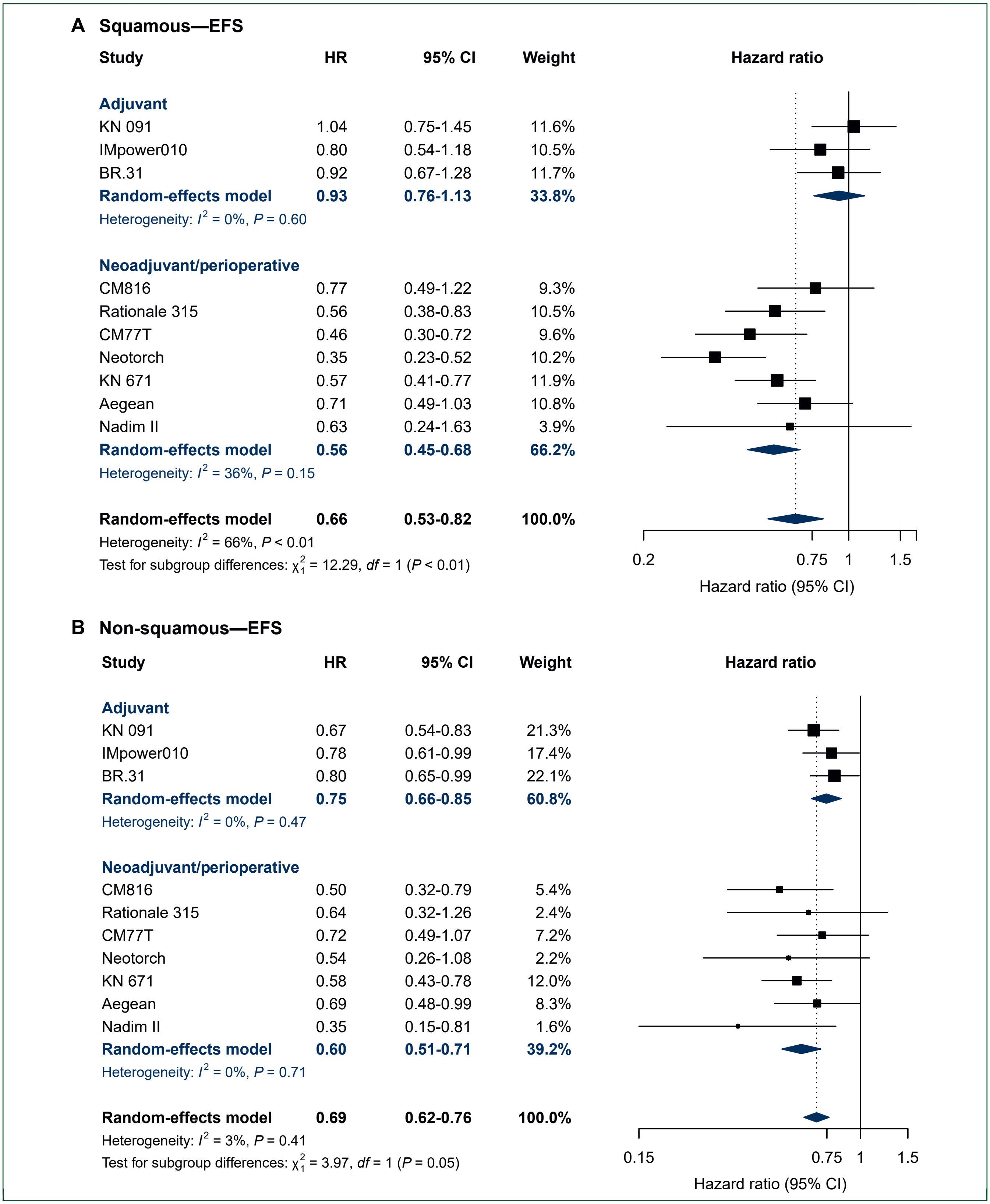

Figure 4. EFS according to histological subtype. Forest plot for pooled HR of EFS for squamous-cell carcinoma (A) and non-squamous-cell carcinoma (B) in the overall population of included trials, and separately in the adjuvant and neoadjuvant/perioperative settings. Random-effects model is reported at the bottom of the figure. CI, confidence interval; EFS, event-free survival; HR, hazard ratio.

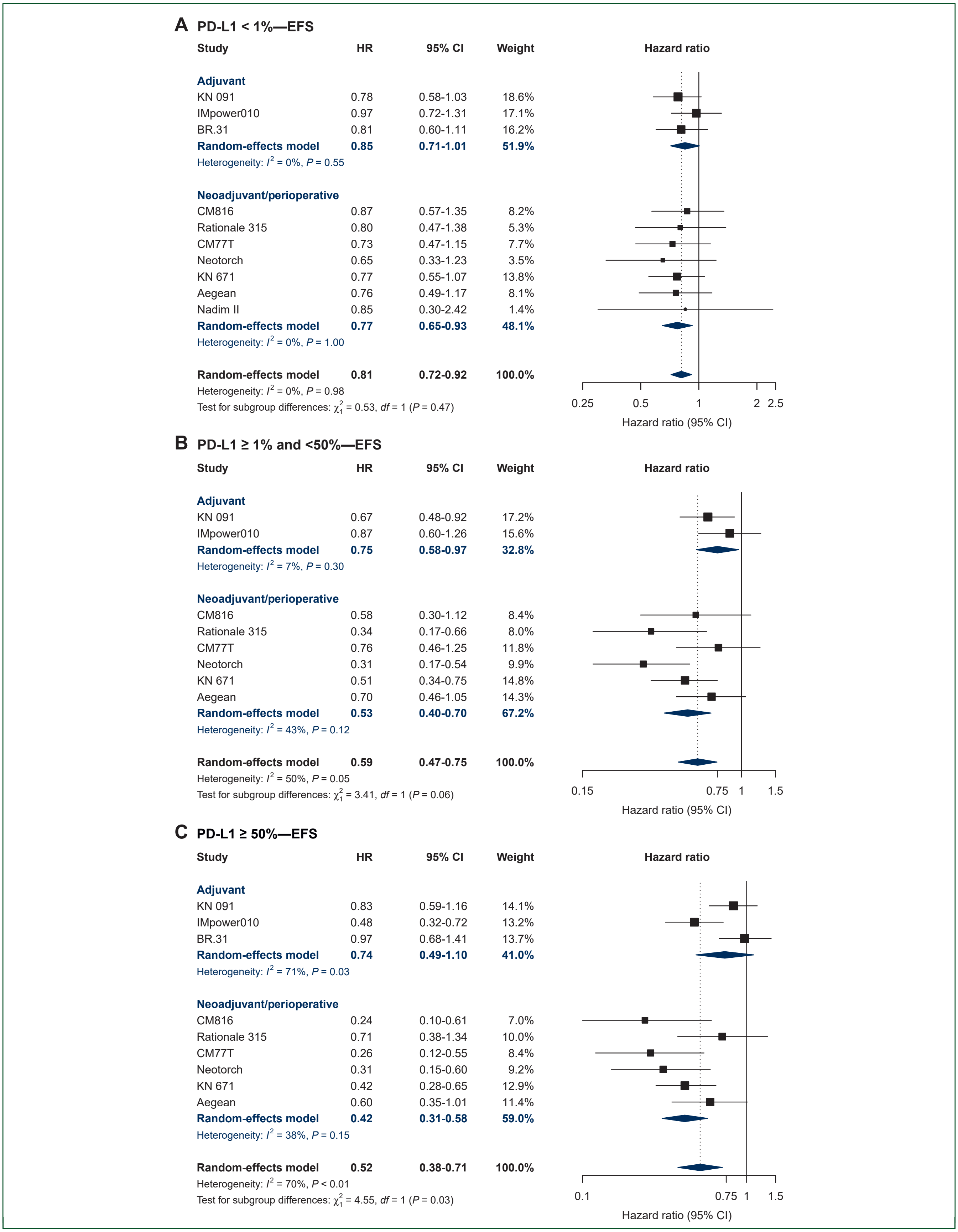

Figure 5. EFS according to PD-L1 expression levels. Forest plot for pooled HR of EFS in PD-L1-negative patients (A), PD-L1 1%-49% patients (B) and PD-L1 ≥ 50% patients (C) in the overall population of included trials, and separately in the adjuvant and neoadjuvant/perioperative settings. Random-effects model is reported at the bottom of the figure.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; PD-L1, programmed death-ligand 1.

patients treated with neoadjuvant/perioperative chemo-immunotherapy compared with neoadjuvant chemotherapy among patients with tumor PD-L1 TPS < 1% (HR 0.77, 95% CI 0.65-0.93, $I^2 = 0\%$, $P = 1.00$), while the benefit was not significant for adjuvant immunotherapy (HR 0.85, 95% CI 0.71-1.01, $I^2 = 0\%$, $P = 0.55$) (Figure 5A). Improved EFS was observed for patients treated with neoadjuvant/perioperative chemo-immunotherapy compared with neoadjuvant chemotherapy among patients with PD-L1 TPS > 50% (HR 0.42, 95% CI 0.31-0.58, $I^2 = 38\%$, $P = 0.15$), but was not significant for those who received adjuvant immunotherapy (HR 0.74, 95% CI 0.49-1.10, $I^2 = 71\%$, $P = 0.03$) (Figure 5C). Finally, improved EFS was observed among patients with PD-L1 expression between 1% and 49% both with neoadjuvant/perioperative treatments (HR 0.53, 95% CI 0.40-0.70, $I^2 = 43\%$, $P = 0.12$) and adjuvant approach (HR 0.75, 95% CI 0.58-0.97, $I^2 = 7\%$, $P = 0.30$) (Figure 5B).

For all these sub-analyses, Egger's test, carried out separately for the adjuvant and neoadjuvant trials, did not indicate significant evidence of publication bias, and sensitivity analysis demonstrated similar results (Supplementary Figures S7-S9 and Tables S9-S11, available at https://doi.org/10.1016/j.esmoop.2025.105759).

Sub-analysis by patients' characteristics

Nine trials presented data according to sex,[7-9,13,16,20-22,25] 10 trials presented data according to age[7-9,13,16,20-22,25,26] and 9 according to smoking status,[8,9,13,16,21,22,25] of which 2 presented aggregated data for current and former smokers.[7,20] Finally, 10 studies reported outcomes stratified by Asian and Caucasian ethnicities.[7-9,13,16,20-22,25,26] Across trials, there is a clinical benefit with the addition of immunotherapy for male patients in adjuvant setting (HR 0.84, 95% CI 0.73-0.95, $I^2 = 0\%$, $P = 0.500$) and in neoadjuvant/perioperative setting (HR 0.57, 95% CI 0.49-0.66, $I^2 = 24\%$, $P = 0.250$) (Supplementary Figure S10, available at https://doi.org/10.1016/j.esmoop.2025.105759), as well as among female patients both in adjuvant (HR 0.79, 95% CI 0.65-0.94, $I^2 = 0\%$, $P = 0.84$) and neoadjuvant/perioperative settings (HR 0.62, 95% CI 0.44-0.86, $I^2 = 18\%$, $P = 0.30$) (Supplementary Figure S12, available at https://doi.org/10.1016/j.esmoop.2025.105759). In younger patients (<65 years), there was a meaningful improvement in EFS with neoadjuvant/perioperative chemo-immunotherapy compared with neoadjuvant chemotherapy (HR 0.55, 95% CI 0.47-0.65, $I^2 = 0\%$, $P = 0.70$) and with immunotherapy adjuvant approach (HR 0.81, 95% CI 0.70-0.94, $I^2 = 0\%$, $P = 0.49$) (Supplementary Figure S14, available at https://doi.org/10.1016/j.esmoop.2025.105759). In patients older than 65 years, EFS with neoadjuvant/perioperative chemo-immunotherapy was better compared with neoadjuvant chemotherapy (HR 0.60, 95% CI 0.51-0.71, $I^2 = 0\%$, $P = 0.50$), as well as with the use of adjuvant immunotherapy over chemotherapy alone (HR 0.83, 95% CI 0.71-0.97, $I^2 = 0\%$, $P = 0.83$) (Supplementary Figure S16, available at https://doi.org/10.1016/j.esmoop.2025.105759). In Asian patients, there was a meaningful improvement in EFS with neoadjuvant/perioperative chemo-immunotherapy compared with neoadjuvant chemotherapy (HR 0.52, 95% CI 0.44-0.61, $I^2 = 0\%$, $P = 0.59$) and with immunotherapy adjuvant approach (HR 0.82, 95% CI 0.62-1.08, $I^2 = 24\%$, $P = 0.27$) (Supplementary Figure S24, available at https://doi.org/10.1016/j.esmoop.2025.105759). In Caucasian patients, there was a significant improvement in EFS with neoadjuvant/perioperative chemo-immunotherapy compared with neoadjuvant chemotherapy (HR 0.64, 95% CI 0.52-0.79, $I^2 = 11\%$, $P = 0.34$) and with immunotherapy adjuvant approach (HR 0.78, 95% CI 0.64-0.95, $I^2 = 35\%$, $P = 0.21$) (Supplementary Figure S26, available at https://doi.org/10.1016/j.esmoop.2025.105759). There was also an EFS improvement with neoadjuvant/perioperative chemo-immunotherapy compared with neoadjuvant chemotherapy for current smokers (HR 0.46, 95% CI 0.37-0.58, $I^2 = 0\%$, $P = 0.67$), whereas this was not evident in patients who received adjuvant immunotherapy compared with chemotherapy alone (HR 0.76, 95% CI 0.43-1.33, $I^2 = 64\%$, $P = 0.06$) (Supplementary Figure S18, available at https://doi.org/10.1016/j.esmoop.2025.105759). There was an improvement in EFS for patients treated with neoadjuvant/perioperative chemo-immunotherapy compared with neoadjuvant chemotherapy among never smokers (HR 0.67, 95% CI 0.47-0.93, $I^2 = 0\%$, $P = 0.44$), but not significant for patients who received adjuvant immunotherapy compared with chemotherapy alone (HR 0.96, 95% CI 0.72-1.26, $I^2 = 19\%$, $P = 0.29$) (Supplementary Figures S20 and S22, available at https://doi.org/10.1016/j.esmoop.2025.105759).

Egger's test, carried out separately for the adjuvant and neoadjuvant trials, demonstrated a significant publication bias only for a subgroup of younger patients (<65 years) in adjuvant trials ($P = 0.02$) and for a subgroup of patients older than 65 years in neoadjuvant/perioperative trials ($P = 0.04$) (Supplementary Figures S11, S13, S15, S17, S19, S23, S25 and S27, available at https://doi.org/10.1016/j.esmoop.2025.105759). Sensitivity analysis demonstrated similar results for all these sub-analyses (Supplementary Tables S12-S20, available at https://doi.org/10.1016/j.esmoop.2025.105759).

High-grade (G3-4) toxicity

All trials presented data about G3-4 toxicities.[7-9,13,16,20-22,24-26] Both neoadjuvant/perioperative chemo-immunotherapy over chemotherapy [odds ratio (OR) 1.27, 95% CI 1.04-1.68] and adjuvant immunotherapy over chemotherapy alone (OR 1.56, 95% CI 1.17-2.08) presented a higher risk to undergo G3-4 toxicities (Supplementary Figure S28, available at https://doi.org/10.1016/j.esmoop.2025.105759).

DISCUSSION

This systematic review and meta-analysis focused on patients with resectable NSCLC,[28] with the aim of summarizing the available evidence on the use of immunotherapy in the neoadjuvant/perioperative and adjuvant setting in resectable NSCLC.[7-9,13,16,20-22,24-26] The aim of this study was to carry out an indirect comparison of different therapeutic strategies based on the timing of surgery, as this is a decision that must be made prospectively by a multidisciplinary team. This objective, along with the inclusion of updated data and newly available trials, represents the main distinction from previous meta-analyses evaluating neoadjuvant or perioperative approaches.[29] Recently, two meta-analyses demonstrated that the efficacy of perioperative treatment does not appear to be superior to neoadjuvant treatment, so we decided to consider trials in the perioperative and neoadjuvant setting together.[30,31] Although the overall data suggested a clinical benefit from adjuvant immunotherapy after chemotherapy, we have highlighted that this advantage is clinically and statistically not significant in several subgroups. Despite some differences, patients enrolled across trials were similar regarding stage, histology and biological characteristics due to inclusion criteria. Previous evidence showed adjuvant therapy to be superior in terms of OS compared with the neoadjuvant approach, although these data were obtained from retrospective studies; notably, clinical practice has seen a clear preference for upfront surgery especially in stage II, relegating neoadjuvant treatment to patients with borderline resectability.[32] In our meta-analysis, neoadjuvant/perioperative chemo-immunotherapy trials have shown a clear benefit in all subgroups, including stage II. In this subgroup, adjuvant immunotherapy did not demonstrate a clinically or statistically significant advantage over chemotherapy alone. This finding persists despite the underrepresentation of this subgroup in one of the three trials, which likely reduced the statistical power of the pooled analysis. Regarding subgroup analysis by PD-L1 expression, for PD-L1 TPS $<$ 1%, the neoadjuvant/perioperative approach showed more promising results than adjuvant immunotherapy as compared with immunotherapy-free regimens. In this population, also taking into account FDA and EMA approvals, the patient should be preferably candidate to a neoadjuvant/perioperative approach.[33] It is interesting to note that adjuvant trials showed inconsistent results in PD-L1 $\geq$ 50% subgroup; indeed, only the IMpower010[9] trial reported a significant survival benefit with immunotherapy in this subgroup, while the pooled EFS of RCTs in this setting is not statistically significant (HR 0.74, 95% CI 0.49-1.10). One possible explanation is biological: patients with high PD-L1 expression may respond more effectively when immunotherapy is administered in the presence of the tumor, due to the presence of tumor antigens and a more immunologically active tumor microenvironment. Consequentially, the neoadjuvant administration of immune checkpoint inhibitors can induce broader and more robust systemic immune responses compared with adjuvant administration.[34] In addition, the lack of a significant PFS benefit in patients with PD-L1 expression $\geq$50% may be related to immature data. The inconsistency of the data in this setting may also be partly attributed to the ability of platinum-based chemotherapy to up-regulate PD-L1 expression—an effect that cannot be assessed in patients with completely resected disease, as no residual tumor tissue is available for evaluation.[35,36]

Contrarily, neoadjuvant/perioperative treatment consistently showed improved outcomes in this patient population. Squamous histology represents another subgroup worth of notice, where data are clear in preferring neoadjuvant chemo-immunotherapy, while they are not clinically and statistically significant in the adjuvant setting. Notably, the difference in this subgroup appears even more evident than in the other ones and cannot be underestimated in the decisions made by a multidisciplinary team. Finally, if quite disappointing results of immunotherapy in never-smoker patients are not surprising, we should certainly be aware of the significant difference we have found in current-smoker patients, where the neoadjuvant/perioperative appears consistent in providing a reproducible benefit across studies, which is not observed in the adjuvant approach. Indeed, it is known that patients who have undergone surgery for NSCLC, especially smokers, face a complex physical and functional recovery phase, frequently leading to exclusion from adjuvant treatment. This aspect is also demonstrated by the proportion of patients in perioperative trials who were not able to start any post-surgery treatment, which ranged between 30% and 40%.[37,38] These data should not be underestimated, since the major difference between neoadjuvant/perioperative and adjuvant immunotherapy trials relies on patient selection. Although they had similar disease staging, biological and histological characteristics, patients who received adjuvant immunotherapy had been able to undergo a previous adjuvant chemotherapy within 8-12 weeks after surgery. This selection bias means patients enrolled in adjuvant trials had better functional recovery and fitness. These data were already known from historical studies, which showed that 42% of patients were unable to face the adjuvant phase after surgery.[39] Moreover, data relating to perioperative trials showed an attrition rate from surgery to adjuvant treatment ranging between 11.5% and 20%-38%.[26] Based on these data, it is evident that if adjuvant trials had enrolled patients at the time of surgery rather than post-operatively, the demonstrated benefit would likely have been even lower, as a significant proportion of patients would have been unable to initiate treatment. This, combined with real-world evidence showing substantial overlap with clinical trial outcomes, even among more vulnerable patient populations,[40-42] further reinforces the rationale for recommending neoadjuvant chemo-immunotherapy in patients with locally advanced disease. Finally, the most recent update on OS that we have analyzed demonstrated a significant impact only for neoadjuvant/perioperative treatment and not for adjuvant immunotherapy, supporting our conclusion in unselected population.

In addition to efficacy data, our analysis aimed to evaluate the toxicity of the different approaches compared with the control arm. Although the comparator is very different between the neoadjuvant/perioperative trials and the pure adjuvant trials (chemotherapy versus placebo/best supportive care, respectively), the immunotherapy arm presented an overall higher risk of severe adverse events. This increase was more evident in the post-surgical therapy trials where the toxicity of adjuvant chemotherapy preceding anti-PD-(L)1 therapy was difficult to assess. However, the markedly different timing of treatments and the sequencing of surgery relative to systemic therapy make it difficult to compare the associated toxicities, due to differences in systemic therapy exposure and the selection of patients undergoing surgery and enrolled in adjuvant therapy trials.

Our analysis has several limitations. Firstly, it compares two different treatment strategies (preoperative versus post-operative), introducing an inherent bias that cannot be fully addressed outside of cross-trial comparisons or dedicated randomized studies. Such trials, as conducted in melanoma (e.g. NADINA and SWOG S1801), directly compared the two approaches and, in both cases, demonstrated a clear advantage of neoadjuvant therapy. Furthermore, it is important to acknowledge that we excluded studies evaluating treatments with anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) agents. This choice inevitably limits the applicability of our conclusions, which cannot be generalized to all forms of immunotherapy. A key limitation is the potential for patient selection bias. Post-operative trials appear more selective by enrolling patients characterized by better performance status and post-surgical recovery; this bias may have affected the results due to a more fit control group, eventually corroborating our conclusions. Secondly, only trial-level data were available, and this could have reduced the accuracy of our results. Finally, another limitation of the analysis is the heterogeneity across trials due to differences in treatment schedule, drug exposure and patient selection. To address this, we carried out a leave-one-out sensitivity analysis within each subgroup, which confirmed the consistency of the results across the different studies.

Conclusions

In conclusion, our findings suggest a greater benefit in the relative reduction of recurrences for patients treated with chemo-immunotherapy in the neoadjuvant setting compared with those who received immunotherapy after surgery. Of note, also in debatable subgroups such as PD-L1 negative, stage II and squamous histology, neoadjuvant/perioperative should be considered the standard approach. Multidisciplinary discussion will be the key to implement this approach.

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DATA SHARING

The query string for the PubMed search adapted for the Embase dataset search used for the systematic review is available in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105759.

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