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The role of PD-L1 in patients with non-small cell lung cancer receiving neoadjuvant immune checkpoint inhibitor plus chemotherapy: a meta-analysis

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Background: The use of immune checkpoint inhibitors (ICIs) as neoadjuvant therapy is a promising novel approach in resectable non-small-cell lung cancer (NSCLC). This study aimed to investigate the prognostic value of PD-L1 in patients with NSCLC receiving neoadjuvant immune checkpoint inhibitor plus chemotherapy (CT). Materials and methods: Several databases (PubMed, Embase, and cochrane central register of controlled trials [CENTRAL]) were systematically searched. Randomized controlled trials (RCTs) investigating pathological and survival outcomes with neoadjuvant ICI + CT versus CT alone in NSCLC were analyzed. Results: Overall, eight RCTs ($n = 3,404$) were included. The analyses showed neoadjuvant ICI + CT significantly improved complete pathological response (pCR) and event-free survival (EFS) in either tumor PD-L1 < 1%, ≥ 1%, 1-49%, or ≥ 50% population (both $p < 0.0001$) compared with neoadjuvant CT alone. The overall survival (OS) data are not yet mature among all included RCTs, and only three RCTs presented OS data by PD-L1 status of patients. The pooled OS favored neoadjuvant ICI + CT in the PD-L1 ≥ 1% population (hazard ratio [HR], 0.45; 95% CI, 0.31–0.65; $p < 0.0001$), but not in the PD-L1 < 1% population (HR, 0.89; 95% CI, 0.66–1.19; $p = 0.43$). Conclusions: Compared with neoadjuvant CT alone, neoadjuvant ICI + CT significantly enhanced pCR and EFS for patients with resectable NSCLC regardless of the expression of PD-L1. It seems that only patients with PD-L1 positive tumors may achieve a better OS, but it's currently inconclusive due to immature data, so future research with long-term follow-up is still needed.

Keywords PD-L1, Immune checkpoint inhibitor, Complete pathological response, Event-free survival, Overall survival, Non-small cell lung cancer

Abbreviations

ICI	Immune checkpoint inhibitor
PD-L1	Programmed cell death 1 ligand 1
PD-1	Programmed cell death 1
NSCLC	Non-small-cell lung cancer
pCR	Complete pathological response
EFS	Event-free survival
OS	Overall survival
RCT	Randomized controlled trial
EGFR	Epidermal growth factor receptor
ALK	Anaplastic lymphoma kinase

Lung cancer is the most common malignant tumor and the leading cancer killer worldwide, which seriously threatens the health of humans[1]. Long term smoking, environmental pollution, occupational exposure, and family history are high-risk factors for the onset of lung cancer[2]. Due to atypical early symptoms, most patients

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are diagnosed with advanced or metastatic diseases, and only a small number of patients have the opportunity for direct surgery[3]. Non-small-cell lung cancer (NSCLC) is the most common pathological type of lung cancer, and surgery is the main treatment for early-stage NSCLC, but only a quarter of patients have resectable diseases at the time of diagnosis[4,5]. To improve the resection rate and survival for resectable patients, neoadjuvant CT followed by surgery with or without adjuvant therapy is a commonly used treatment mode in clinical practice. However, approximately 30–55% of patients will still experience recurrence after surgery[6]. Therefore, further exploration of more effective neoadjuvant strategies is urgently needed.

With the development of immunotherapy, immune checkpoint inhibitors (ICIs) play a huge role in the treatment of various solid tumors, including lung cancer[7]. A large number of clinical studies have confirmed that ICI-based regimens can improve the survival of patients in either neoadjuvant, adjuvant, or metastatic setting for lung cancer[8–10]. Evidence has shown that the efficacy of immunotherapy is not ideal for NSCLC patients who had driver gene mutations (such as epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] mutations), so immunotherapy was not recommended for these patients[11,12]. Except patients with driver gene mutations, other patients are generally sensitive to ICI therapies. Thus, exploring prognostic factors for predicting outcomes for patients treated with ICI-based regimens is currently a great interest. Among various biomarkers, PD-L1 is a widely recognized prognostic predictor for ICI treatments[13]. Many clinical trials found that patients with high expression of PD-L1 had better efficacy than those with low PD-L1 expression[14,15], but there were also studies reporting that the expression of PD-L1 was not related to prognosis of NSCLC[16]. A study by Goulart et al. found that the correlation between PD-L1 expression (PD-L1 tumor proportion score $< 1\%$, 1-49%, and $\geq 50\%$) and patient prognosis was unstable in patients with metastatic NSCLC[17]. They found that when evaluating subgroups through PD-L1 expression, the correlation ranged from weak to moderate.

Until now, it has been unclear whether PD-L1 can predict long-term outcomes for NSCLC patients treated with neoadjuvant ICI + CT. The aim of this study is to assess the predictive value of PD-L1 expression in long-term outcomes for patients with resectable NSCLC treated with neoadjuvant ICI combined with CT.

Methods

Screening of literatures

We searched several databases including PubMed, Embase, and cochrane central register of controlled trials [CENTRAL] for relevant clinical trials from inception to March 2024. The keywords for the search strategy are as follows: "Immunotherapy or immune checkpoint inhibitor or pembrolizumab or nivolumab OR cemiplimab OR camrelizumab OR sinilimab OR toripalimab OR tislelizumab OR spartalizumab OR pidilizumab OR atezolizumab or avelumab or tremolumab or durvalumab or OR sugemalimab" and "non small cell lung cancer OR NSCLC OR lung adenocarcinoma OR adenocarcinoma of the lung OR lung squamous cell carcinoma OR squamous cell carcinoma of the lung". We also manually searched relevant references to identify other relevant studies. Only published articles of RCTs reporting experimental data related to neoadjuvant ICI + chemotherapy (CT) versus neoadjuvant CT alone in patients with resectable NSCLC were included. Non-publication literatures, and papers published in languages other than English were not eligible for inclusion. Besides, we excluded clinical trials investigating the use of radiation therapy, molecular targeted therapy, or immunotherapy monotherapy in neoadjuvant setting. Studies that only included NSCLC patients with EGFR or ALK mutations were also excluded. Two independent reviewers (HJF and LPH) screened the literatures based on inclusion and exclusion criteria. Firstly, by reading the titles and abstracts, literatures that were identified as not relevant or published repeatedly were excluded. Secondly, further screening was conducted by reading the abstracts and full texts to exclude literatures that did not meet the inclusion criteria or met the exclusion criteria. Finally, reviewers extracted data from the final included literatures, including study name, author details, publication year, tumor stage, sample size, age, gender, PD-L1 status of patients, treatment regimens, and study outcomes. In the process of literature screening, disagreements were resolved by a third reviewer (MDC).

Data extraction

The available pooled outcomes in this analysis were complete pathological response (pCR), event-free survival (EFS) and overall survival (OS). Other outcomes such as surgical rate, major pathological response (MPR), and R0/R1 resection rates were not available when evaluating subgroups by PD-L1 expression. Two independent reviewers (LP and WHL) extracted data on study name, author details, publication year, tumor stage, sample size, age, gender, PD-L1 status of patients, and neoadjuvant treatment regimen. Clinical outcomes including pCR, EFS, and OS were extracted in detail for further analysis.

Quality assessment

Two independent reviewers (LXJ and HSX) assessed the risk of bias of the included RCTs using the Cochrane risk of bias tool[18], which includes seven items: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biases. Based on the above seven items, the judgments on the risk of bias were classified into three levels: "high risk," "unclear risk," and "low risk". We used funnel plots to evaluate publication bias for the included studies. Disagreements were resolved by a third reviewer (MDC).

Statistical analysis

We conducted meta-analysis of included RCTs using the statistical software of Review Manager 5.4. The outcomes of EFS and OS were pooled as hazard ratios (HRs) with 95% confidence interval (CI), while outcome of complete pathological response was pooled as risk ratio (RR) with its 95% CI. Heterogeneity between studies was evaluated based on the I-squared (I^2) test when conduting meta-analysis. When $I^2 > 50\%$, the heterogeneity

was assessed as high, and then a random-effects model was applied; Otherwise, a fixed-effects model was chosen. If P-value is less than 0.05, it is considered statistically significant.

Results

Search results

Through initial search, 2062 articles were returned. After further screening and removal of duplicate studies, eight RCTs (AEGEAN[19], CheckMate-816[20], KEYNOTE-671[21], NADIM II[22], Neotorch[23], RATIONALE-315[24], TD-FOREKNOW[25], CheckMate 77T[26]) with a total of 3,404 patients met the inclusion criteria. The prisma diagram of the screening process is shown in Fig. 1. Across RCTs, all patients were diagnosed with NSCLC and received neoadjuvant ICI + CT in the study group and neoadjuvant CT alone in the control group. These studies were published between 2022 and 2024. Among these eight RCTs, five programmed cell death 1 (PD-1)

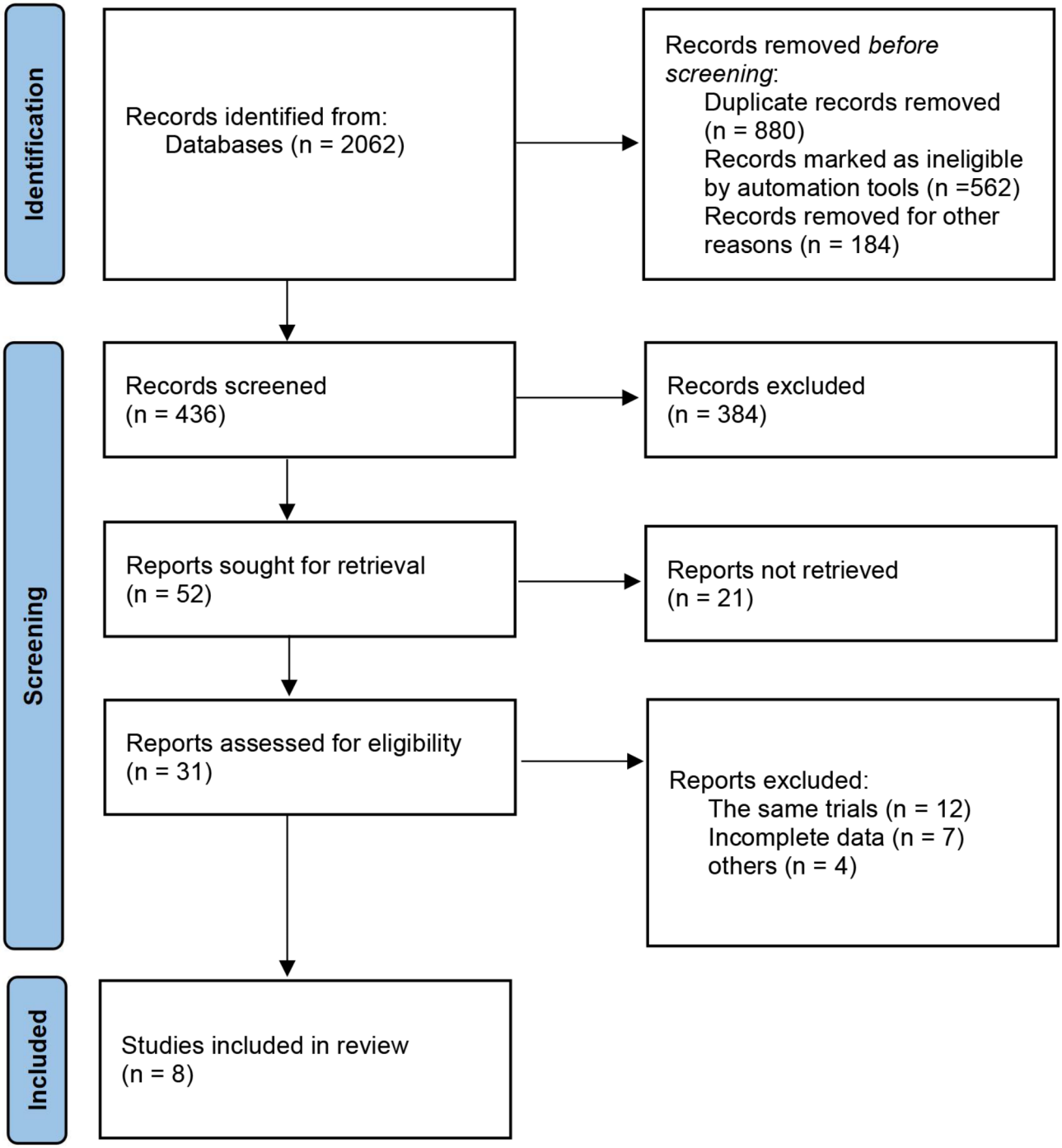

Fig. 1. PRISMA flow chart of study screening.

antibodies (nivolumab, pembrolizumab, toripalimab, camrelizumab, and tislelizumab) and one PD-L1 antibody (durvalumab) were included. The basic characteristics of the included studies and the PD-L1 expression status of patients are shown in Table 1.

Outcome of pCR

Across the eight RCTs, five studies (AEGEAN[19], CheckMate-816[20], NADIM II[22], RATIONALE-315[24], and TD-FOREKNOW[25]) evaluated the pCR data based on PD-L1 expression of patients. The analysis showed that the pooled pCR favored neoadjuvant ICI + CT over neoadjuvant CT in either tumor PD-L1 < 1% (RR, 4.32; 95% CI, 2.52–7.42; $p < 0.0001$; $I^2 = 0\%$), ≥ 1% (RR, 8.78; 95% CI, 4.88–15.78; $p < 0.0001$; $I^2 = 0\%$), 1-49% (RR, 4.33; 95% CI, 2.05–9.17; $p < 0.0001$; $I^2 = 21\%$), or ≥ 50% (RR, 6.85; 95% CI, 3.21–14.62; $p < 0.0001$; $I^2 = 0\%$) population (Fig. 2).

Outcome of EFS

The EFS data for the PD-L1 subgroups can be extracted from six studies (AEGEAN[19], CheckMate-816[20], KEYNOTE-671[21], NADIM II[22], Neotorch[23], and CheckMate 77T[26]). The analysis showed that neoadjuvant ICI + CT was associated with significantly improved EFS compared with neoadjuvant CT in either PD-L1 < 1%(HR, 0.68; 95% CI, 0.56–0.83; $p < 0.0001$; $I^2 = 0\%$), ≥ 1% (HR, 0.44; 95% CI, 0.35–0.56; $p < 0.0001$; $I^2 = 16\%$), 1-49% (HR, 0.56; 95% CI, 0.45–0.70; 0.35–0.56; $p < 0.0001$; $I^2 = 43\%$), or ≥ 50% (HR, 0.40; 95% CI, 0.30–0.51; $p < 0.0001$; $I^2 = 24\%$) population (Fig. 3).

Outcome of OS

The OS data of included trials was immature. There were only three studies (CheckMate-816[20], KEYNOTE-671[21], and NADIM II[22]) presented OS data for the PD-L1 subgroups (The OS data by PD-L1 status of the CheckMate-816 and KEYNOTE-671 studies are available in the reports of the European Society of Medical Oncology [ESMO] Congress 2023–2024 Abstracts[27,28]). The analysis showed that neoadjuvant ICI + CT was associated with significantly improved OS compared with neoadjuvant CT in the PD-L1 ≥ 1% (HR, 0.45; 95% CI, 0.31–0.65; $p < 0.0001$; $I^2 = 52\%$) population. However, there was no significant difference (HR, 0.89; 95% CI, 0.66–1.19; $p = 0.43$; $I^2 = 0\%$) in OS between the two groups in patients with tumor PD-L1 < 1% (Fig. 4) .

Study	Phase	Stage	Sample size		Age, Median (Range)	Male, *n* (%)	PD-L1 expression			Neoadjuvant treatment regimen
			Arms	*N*			Tumor cell < 1%	Tumor cell 1 to 49%	Tumor cell ≥ 50%	
Heymach 2023[19](AEGEAN)	3	Stage IIA to IIIB NSCLC	Study	366	65 (30–88)	252 (68.9)	122 (33.3)	135 (36.9)	109 (29.8)	Durvalumab + carboplatin and paclitaxel
			Control	374	65 (39–85)	278 (74.3)	125 (33.4)	142 (38.0)	107 (28.6)	Carboplatin + paclitaxel
Forde 2022[20](CheckMate-816)	3	Stage IB to IIIA NSCLC	Study	179	64 (41–82)	128 (71.5)	78 (43.6)	51 (28.5)	38 (21.2)	Nivolumab + platinum-doublet chemotherapy
			Control	179	65 (34–84)	127 (70.9)	77 (43.0)	47 (26.3)	42 (23.5)	Platinum-doublet chemotherapy
Wakelee 2023[21](KEYNOTE-671)	3	Stage II to IIIB NSCLC	Study	397	63 (26–83)	279 (70.3)	138 (34.8)	127 (32.0)	132 (33.2)	Pembrolizumab + platinum-doublet chemotherapy
			Control	400	64 (35–81)	284 (71.0)	151 (37.8)	115 (28.8)	134 (33.5)	Platinum-doublet chemotherapy
Provencio 2023[22](NADIM II)	2	Stage IIIA or IIIB NSCLC	Study	57	63.4 (NA)	36 (63.2)	20 (35.1)	19 (33.3)	18 (31.6)	Nivolumab plus platinum-based chemotherapy
			Control	46	63.1 (NA)	34 (73.9)	10 (21.7)	23 (50.0)	13 (28.3)	Platinum-doublet chemotherapy
Lu 2024[23](Neotorch)	3	Stage II or III NSCLC	Study	202	62 (56–65)	181 (89.6)	51 (25.3)	69 (34.2)	64 (31.7)	Toripalimab + platinum based chemotherapy
			Control	202	61 (56–65)	189 (93.6)	54 (26.7)	68 (33.7)	64 (31.7)	Platinum-based chemotherapy
Yue 2024[24](RATIONALE-315)	3	Stage II to IIIA NSCLC	Study	226	62 (30–80)	205 (90.7)	89 (39.4)	NR	NR	Tislelizumab + platinum-based chemotherapy
			Control	227	63 (36–78)	205 (90.3)	84 (37.0)	NR	NR	Platinum-based chemotherapy
Lei 2023[25](TD-FOREKNOW)	2	Stage IIIA or IIIB NSCLC	Study	43	61 (54–65)	34 (79.1)	7 (16.3)	NR	NR	Camrelizumab + platinum-based chemotherapy
			Control	45	61 (54–65)	40 (88.9)	8 (17.8)	NR	NR	Platinum-based chemotherapy
Cascone 2024[26](CheckMate 77T)	3	Stage IIA to IIIB NSCLC	Study	229	66 (NA)	167 (72.9)	93 (40.6)	83 (36.2)	45 (19.7)	Nivolumab + platinum-doublet chemotherapy
			Control	232	66 (NA)	160 (69.0)	93 (40.1)	76 (32.8)	52 (22.4)	Platinum-doublet chemotherapy

Table 1. The characteristics of RCT studies. NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death 1 ligand 1; NR, not reported; NA, not available; RCT, randomized controlled trial.

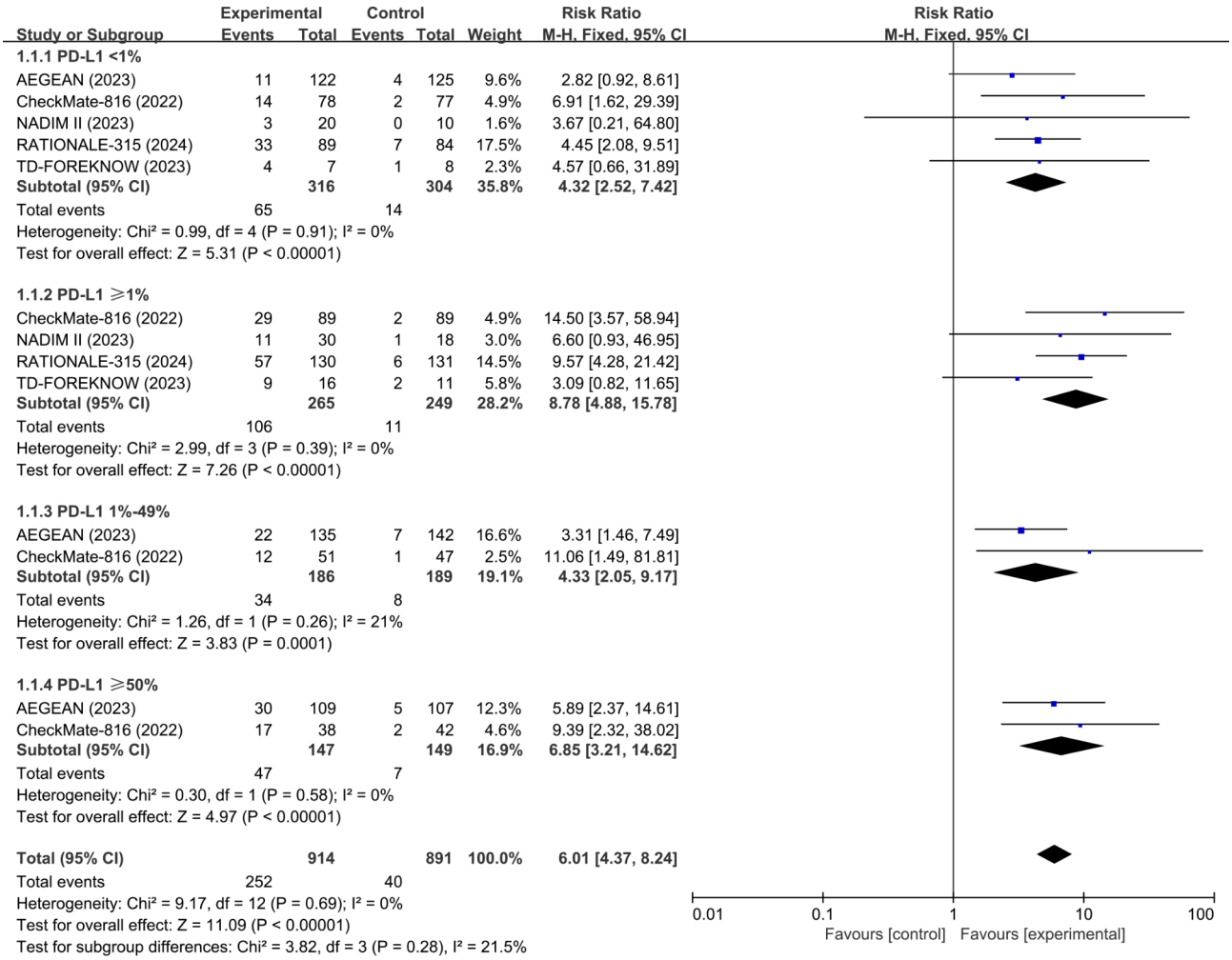

Fig. 2. Pooled risk ratios of pCR among RCTs. pCR, complete pathological response; RCTs, randomized controlled trials.

Quality of the included RCTs

As shown in Fig. 5, the quality of each included RCT was assessed as high, suggesting there was a low risk of bias in this analysis. The funnel plots for EFS and OS were symmetrical, suggesting no publication bias (Fig. 6).

Discussion

For more than a decade, immunotherapy has been applied to the treatment of various cancers, including lung cancer, and ICI-based regimens have completely changed the treatment pattern of NSCLC[29,30]. Thus, exploring sensitive predictive factors for efficacy of ICI treatments is very important for clinical physicians to choose the best beneficial population and appropriate ICI strategies. Although the predictive value of PD-L1 may vary in different cancers or different ICI strategies, PD-L1, as the most important predictive factor for ICI-based therapies, has always been of great concern.

To our knowledge, this is the first meta-analysis of RCTs to comprehensively and systematically evaluate the correlation between PD-L1 expression and its prognostic value in patients with NSCLC undergoing preoperative neoadjuvant immunochemotherapy. Before our study, a research by Deng et al. found that patients with PD-L1 expression ≥ 1% who received neoadjuvant immunotherapy before surgery for NSCLC was associated with a higher rate of MPR and pCR compared with those with PD-L1 expression < 1%[31]. In our study, we found that regardless of PD-L1 expression, pCR and EFS of neoadjuvant immunochemotherapy were superior to those of neoadjuvant CT alone. We also observed a phenomenon that patients with higher PD-L1 expression had lower HR values for EFS, indicating that patients with higher PD-L1 expression might have a lower risk of disease progression. These results were consistent with those by Banna et al., who reported that NSCLC patients who had PD-L1 negative tumors were at higher risk of relapse than those with low or high PD-L1 tumors when treated with neoadjuvant chemo-immunotherapy[32]. Furthermore, in terms of OS, we found that only patients with PD-L1 positive tumors achieved significant OS benefit, whereas in PD-L1 negative patients, no better OS was observed. Despite the immaturity of OS data, these results may indicate that PD-L1 can be used as an valuable prognostic factor for predictiving outcomes for patients with resectable NSCLC treated with

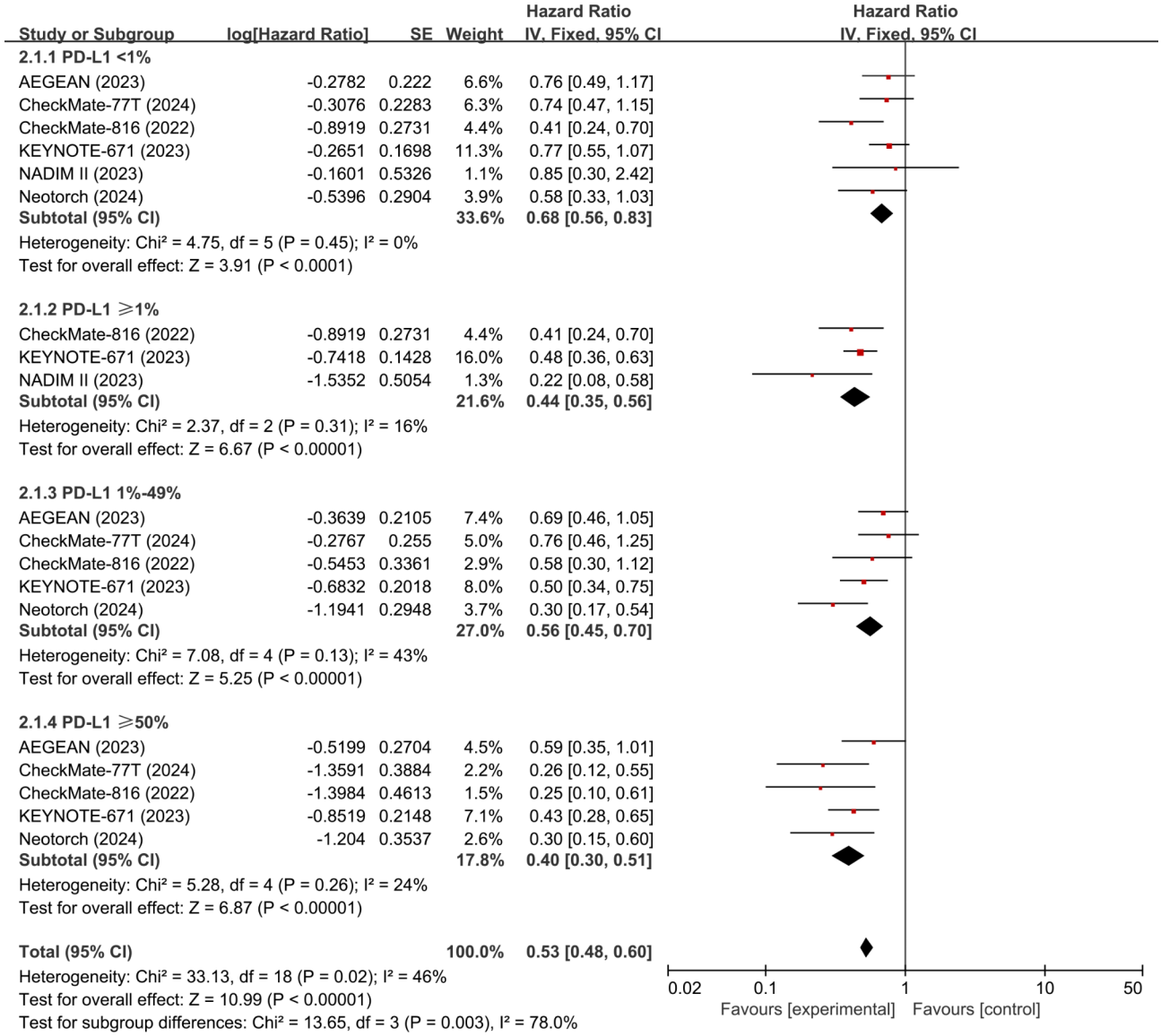

Fig. 3. Pooled hazard ratios of EFS among RCTs. EFS, event-free survival; RCTs, randomized controlled trials.

preoperative immunochemotherapy. Due to the valuable predictive value of PD-L1, our results recommend PD-L1 detection in clinical practice before choosing ICI immunotherapy so as to better predict outcomes of patients.

It is worth noting that the results of our analysis were similar to those of studies on metastatic NSCLC. In the KEYNOTE-189 trial[33], pembrolizumab plus chemotherapy was associated with significantly improved OS and progression free survival (PFS) compared with chemotherapy alone in either PD-L1 < 1%, ≥ 1%, 1-49%, or ≥ 50% subgroup, and the higher PD-L1 expression, the longer median OS seems to achieve. In the Impower150 trial[34], atezolizumab in combination with chemotherapy and bevacizumab resulting in significantly longer PFS and OS in metastatic non-squamous NSCLC, regardless of PD-L1 expression. In addition, similar results were also observed in the studies of IMpower130[35], IMpower132[36], and KEYNOTE-407[37]. Among these trials, we found a commonality that when immunotherapy combined with chemotherapy, the efficacy of their combination therapy is likely to have a synergistic effect, and patients with high PD-L1 expression would have a greater trend of OS benefit.

Another concern is that evidence has shown that the expression and prognostic value of PD-L1 in primary lung and metastatic lesions are highly inconsistent. A recent research reported that the expression of PD-L1 varies at different biopsy sites, and PD-L1 has different predictive value for the benefits of ICIs in NSCLC[38]. The researchers found a significant correlation between PD-L1 and biopsy site ($p = 0.004$). PD-L1 expression was high in adrenal, liver, and lymph node metastases, while PD-L1 expression was low in bone and brain metastases. Higher PD-L1 levels in primary lung lesions and distant metastatic specimens were associated with higher tumor response, longer PFS, and OS. However, PD-L1 in lymph node specimens was not correlated with response or survival rate. Another study reported that PD-L1 negative was more common in primary lung lesion compared to metastatic samples. The distribution of PD-L1 expression (PD-L1 expression was high in

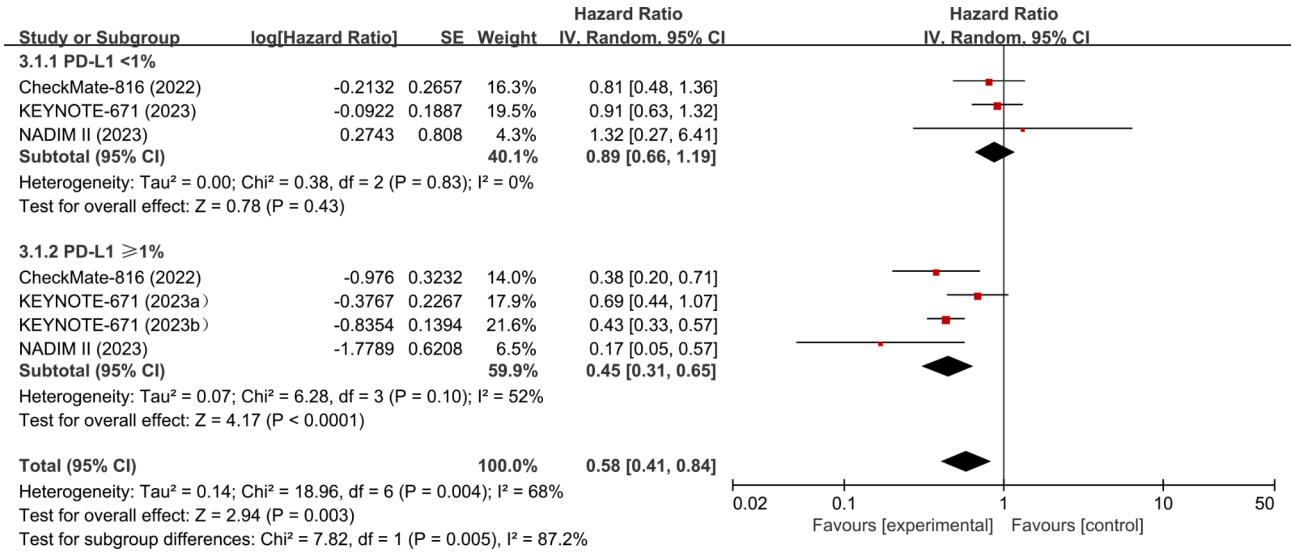

Fig. 4. Pooled hazard ratios of OS among RCTs. OS, overall survival; RCTs, randomized controlled trials. [a]PD-L1 group: 1–49%;[b]PD-L1 group: 50% or higher.

lymph nodes but was predominantly negative in bones) and the predictive ability of PD-L1 expression for tumor response to immunotherapy varies by organ[39]. We believe that this is a great concern that physicians should pay close attention to. When selecting tumor specimens for PD-L1 detection in clinical practice, it would be better to choose the same tissue specimens with high prognostic value (such as lung rather than bone specimens). In our study, because the included patients were all newly diagnosed NSCLC without distant metastasis, the samples tested for PD-L1 were relatively consistent, avoiding research bias caused by PD-L1 testing on different tumor specimens.

Our study has the following main limitations. First, only published RCTs were included in this analysis. Other valuable sources, such as grey literatures and clinical trials on-course were excluded, which may lead to a possibility of selective bias. Besides, our study focused on a comprehensive meta-analysis of outcomes for patients but lacked a systematic literature review process. Second, the number of included RCTs is relatively small, and some RCTs were studies with small sample sizes, which lead to a heterogeneity when analyzing outcomes by PD-L1 subgroups. Third, among the six included ICIs, five were PD-1 antibodies, while only one was PD-L1 antibody. Thus, in-depth analysis cannot be conducted to distinguish whether the prognostic value of PD-L1 expression varies among different types of ICI drugs. Fourth, due to limited data, besides the outcomes of pCR, EFS, and OS, other outcomes such as surgical rate, major pathological response, and R0/R1 resection rates were not feasible when analyzing by PD-L1 subgroups. Finally, the OS data of included studies was not mature, and only three studies provided OS data of PD-L1 subgroups, which have had a great impact on the analysis of OS outcome, so further investigations with longer follow-up time are needed.

Conclusions

This meta-analysis suggested that regardless of PD-L1 expression, neoadjuvant ICI + CT resulted in better pCR and EFS in resectable NSCLC than neoadjuvant CT alone. In terms of OS, it seems that patients with PD-L1 negative tumors had no more OS benefit, and only patients with PD-L1 positive tumors might achieve a significant transformation from EFS benefit to OS benefit; however, the analysis of OS results is currently inconclusive due to immature data. Our research findings support PD-L1 was a valuable biomarker for predicting outcomes of NSCLC patients in this setting. Due to the immature OS data, further in-depth research is necessary.

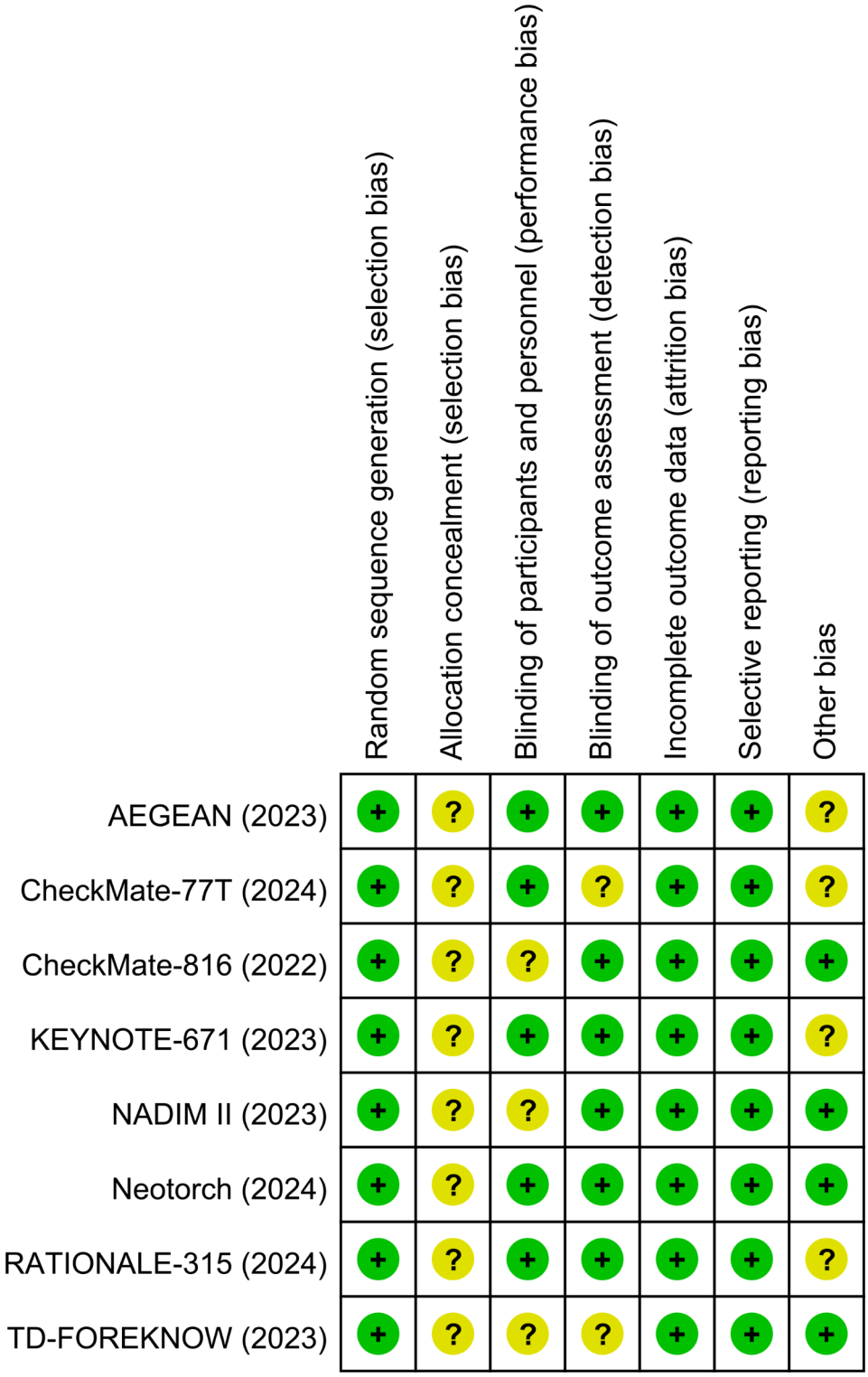

Fig. 5. The assessment of quality of RCTs. RCTs, randomized controlled trials.

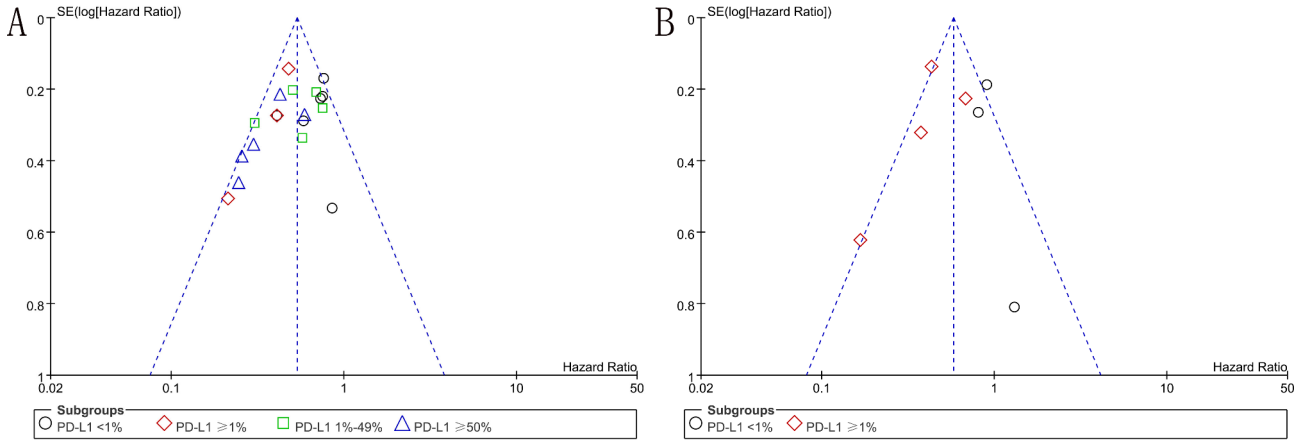

Fig. 6. The funnel plots for EFS and OS. **A**, The funnel plot for EFS; **B**, The funnel plot for OS. EFS, event-free survival; OS, overall survival.

Data availability

Data is provided within the manuscript.

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Author contributions

Study design and writing: MDC and HJF; Data collection and selection: LP and WHL; Statistical analysis: LPH and HJF; Risk of bias assessment: HSX and XLJ; All authors approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

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