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The association of PD-L1 expression status and the PD-1/PD-L1 inhibitor-related toxicity profile in non-small cell lung cancer

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Abstract

Objective While PD-L1 expression serves as a predictive biomarker for programmed cell death 1 and its ligand (PD-1/PD-L1) inhibitor efficacy in patients with non-small cell lung cancer (NSCLC), its association with treatment-related adverse events (TRAEs) has yet to be fully elucidated. This study systematically evaluated the correlation between PD-L1 expression status and TRAEs in patients with NSCLC.

Methods We systematically searched the Cochrane Library, Embase, and PubMed databases from inception to June 30, 2024, to identify prospective clinical trials examining PD-1/PD-L1 inhibitors among NSCLC patients that reported treatment-related toxicity data stratified by PD-L1 expression.

Results Twenty-six prospective trials ($N=5,453$) were analyzed. At the 1%, 25%, and 50% PD-L1 cutoffs, PD-L1-negative patients presented significantly reduced risks of grade 3–4 TRAEs (OR = 0.37, 0.53, 0.41; 95% CI = 0.18–0.77, 0.31–0.90, 0.19–0.97; $P<0.01$, 0.02, 0.04). Similarly, PD-L1-negative patients had significantly reduced risks of AEs leading to treatment discontinuation at the 1% and 25% PD-L1 cutoffs (OR = 0.25, 0.38; 95% CI = 0.08–0.76, 0.16–0.89; $P=0.01$, 0.03) but not at the 50% PD-L1 cutoff (OR 0.28, 95% CI 0.07–1.12, $P=0.07$). Subgroup analyses revealed elevated all-grade TRAEs with the 22C3 immunohistochemistry assay ($P<0.001$), whereas first-line therapy recipients ($P=0.006$) and open-label trial participants ($P=0.002$) presented increased grade 3–4 TRAEs.

Conclusions PD-L1 positivity may predict increased risks of grade 3–4 TRAEs and AEs leading to treatment discontinuation in NSCLC patients receiving PD-1/PD-L1 blockade. Furthermore, PD-L1 expression might be a useful biomarker for toxicity management in patients with NSCLC after PD-1/PD-L1 inhibitor treatment.

Keywords PD-L1 expression, PD-1/PD-L1 inhibitor, Toxicity profile, Non-small cell lung cancer

Background

Non-small cell lung cancer (NSCLC) poses a major public health threat worldwide due to its high incidence and mortality rates [1]. Currently, immune checkpoint inhibitors targeting programmed cell death 1 (PD-1) and its ligand (PD-L1) have become standard therapies for advanced NSCLC patients without actionable driver mutations (such as those in the *EGFR* or *ALK* genes), leading to the widespread adoption of these agents in clinical practice worldwide.

In addition to the efficacy of PD-1/PD-L1 inhibitor treatment, its toxicity profile is one primary concern among patients and is usually a deciding factor for

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clinicians when patients start any treatment in the clinic. PD-1/PD-L1 inhibitors may be correlated with various categories of treatment-related adverse events (TRAEs), including rash, diarrhea, pneumonitis, hypothyroidism, and hepatotoxicity [2]. Moreover, severe toxicities (e.g., grade 3–4 adverse events or adverse events leading to discontinuation) can result in debilitating or fatal outcomes, thereby profoundly impacting patients, families, and society [2, 3]. Furthermore, early detection and intervention are critical for managing these toxicities. Therefore, the identification of predictive biomarkers for PD-1/PD-L1 inhibitor-induced toxicity represents an urgent clinical challenge, as this information would enable precise risk stratification, facilitate personalized treatment optimization, and alleviate the socioeconomic burdens associated with managing TRAEs.

According to the National Comprehensive Cancer Network guidelines and multiple other guidelines (e.g., the European Society for Medical Oncology), treatment options for PD-1/PD-L1 inhibitor-based therapy are dependent on PD-L1 expression, owing to its utility as a biomarker for predicting response [4–6]. However, it remains unclear whether PD-L1 expression is associated with toxicity profiles, as current safety data are not stratified based on PD-L1 status. Moreover, the toxicity profile associated with PD-1/PD-L1 inhibitors is often understated during decision-making for treatment processes [7]. Therefore, we conducted this study to investigate whether PD-L1 expression is a predictive biomarker for the toxicity profile in NSCLC patients receiving PD-1/PD-L1 blockade.

Materials and methods

The current study of toxicity analyses was performed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [8]. The present study was not registered.

Trial search strategy

On June 30, 2024, three independent researchers (Q. Z., H. H. and L-Y.OY.) systematically searched the Cochrane Library, Embase, and PubMed databases without language restrictions, and the results were confirmed by a third investigator (X–Y. H.). Supplementary Table S1 shows the details of the search strategy. We also searched for unpublished/ongoing trials at https://clinicaltrials.gov/and meeting abstracts (World Conference on Lung Cancer, American Association of Cancer Research, etc.) between January 1, 2012, and June 30, 2024. Furthermore, we manually searched the reference lists of the included articles.

Criteria for selection and exclusion

Two independent researchers (Q. Z. and H. H.) screened the studies, and the third investigator (L-Y.OY.) verified it. To reduce the risk of bias, we further excluded studies adopting PD-1/PD-L1 inhibitor-based combination therapy because different combination therapies may contribute substantially to the toxicity profile. The eligibility criteria were established based on the PICO framework., as follows: (1) participants: clinical trials prospectively enrolling NSCLC patients; (2) intervention: PD-1/PD-L1 inhibitor monotherapy; (3) control: none; and (4) outcome: the occurrence of TRAEs (events/incidence and sample size). Hence, non-prospective clinical trials, such as retrospective studies, case reports, and reviews, were excluded. When duplicate trials were identified, researchers retained the trial with the longest follow-up time and/or with the most recent follow-up.

Data extraction and assessment of risk of bias

Two researchers (P.H. and R.Y.) independently retrieved the standardized data, and a third researcher (W-X.W.) confirmed. The following data were extracted from the included studies: study name, study design, study type, tumor stage, line of therapy, median age, male sex (%), PD-1/PD-L1 inhibitor type, sample size (number of participants evaluable for toxicity), immunohistochemistry (IHC) assay, median treatment duration, PD-L1-stained cell type, and PD-L1 expression. The treatment-related toxicity profile (all-grade, grade 3–4, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, and fatal adverse events (FAEs)) was determined by the principal investigator of the original trial. We then extracted the aforementioned treatment-related toxicity profile to conduct the current study. When detailed information regarding TRAEs was not available, we sought to communicate with the corresponding author of the original trial for confirmation and identified the ambiguous interpretation as "not available (NA)". AEs were assessed in accordance with the National Cancer Institute Common Terminology Criteria guidelines.

Two independent researchers (P.H. and R.Y.) used the 9-point Newcastle–Ottawa Scale (NOS) [9] with eight items to assess the study quality in nonrandomized clinical trials. Each trial was classified into three main groups (selection, comparability, and outcomes for cohort studies) [9]. High-quality studies were identified as those with a score of 7 or higher. For randomized clinical trials, the abovementioned two researchers independently appraised each trial using the 7-item Cochrane Collaboration tool [10]. Any discrepancies were settled through discussion or consultation with a third researcher (X–Y. H.).

Statistical analysis

GraphPad Prism software (version 10.1.0; GraphPad Software, San Diego, CA) was used to perform all the statistical analyses, and two-tailed *P* values less than 0.05 were considered statistically significant. Among the different PD-L1 expression levels, the chi-square test or Fisher's exact test (if appropriate) was used to calculate the frequencies of the toxicity profiles. When one (or more) value was zero, 0.5 was added to each value before the odds ratio (OR) and confidence interval (CI) were calculated. In trials examining the same anti-PD-1/PD-L1 drug, we evaluated the toxicity profile for different PD-L1 expression levels to study whether the toxicity was PD-L1 expression dependent. Subgroup analysis was carried out to measure the relationships of the line of therapy (2 or later line vs. first-line), study design (double-blind vs. open-label), clinical phase (phase 3 vs. phase 1/2), and IHC assay type (22 C3 vs. other) with the frequency of toxicity profiles in those trials enrolling the same PD-L1 expression and PD-1/PD-L1 inhibitor.

Results

Search results and major clinical characteristics

As shown in Fig. 1, we screened a total of 16,442 publications via both electronic databases and manual searches. After the initial screening, 133 trials were used for detailed eligibility assessment. Finally, the remaining 26 prospective studies [11–36] were identified for the final toxicity analyses.

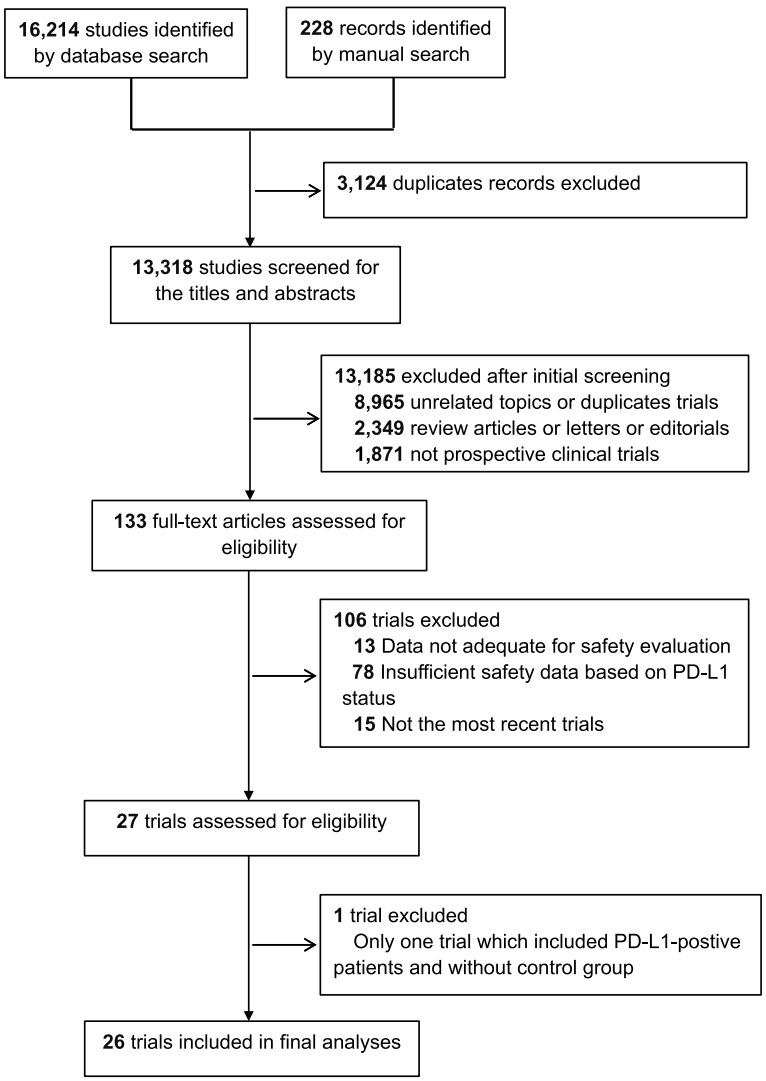

Fig. 1 Flow diagram of the study. Abbreviations: programmed cell death protein ligand-1, PD-L1

Except for three trials [14, 22, 29], all trials were conducted at multiple centers, and the major clinical features are listed in Table 1. Three trials [21, 28, 36] were double-blind trials, and the majority of the trials (23 trials, 88.5%) [11–20, 22–27, 29–35] were open-label. Seventeen trials (65.4%) involved PD-1 inhibitors (fourteen with pembrolizumab [14, 17, 21–23, 25–27, 29, 31–34, 36] and three with nivolumab [11, 12, 30]), and nine trials (34.6%) involved PD-L1 inhibitors (five with durvalumab [16, 18–20, 35] and four with atezolizumab [13, 15, 24, 28]). All trials focused on nonresectable NSCLC patients (one trial [14] with *EGFR*-positive mutations), except one trial [22] that included resectable NSCLC patients (stage II/IIIA). Fifteen trials (57.7%) [12, 14, 20, 21, 24, 26–32, 34–36] were performed in the 1 st-line setting, seven trials (26.9%) [11, 17–19, 23, 25, 33] were performed in the 2- or later-line setting, three trials (11.5%) [13, 15, 16] were performed in the mixed-line setting (first-line and 2- or later-line setting), and the remaining trial [22] was performed in the neoadjuvant setting.

Overall, the total safety population included 5,453 patients with performance statuses between 0 and 2 and with a minimum of one dose of treatment. The number of patients tested for PD-L1 expression ranged from 5–683 per trial, and the median age of all patients enrolled ranged from 59 to 76. The percentage of male patients differed among the trials, varying from 36% to 78.6% of all safety calculations. For the assessment of PD-L1 expression, all the included trials used two different types of staining: three trials assessed PD-L1 expression in tumor and immune cells [13, 15, 24], and 23 trials assessed PD-L1 expression in tumor cells (88.5%). In total, five PD-L1 IHC assays involving 5 different PD-L1 antibodies (28–8, SP142, 73–10, SP263, and 22 C3) were adopted for the estimation of PD-L1 expression, and two studies (7.7%) [25, 35] did not include a detailed PD-L1 IHC assay or PD-L1 antibody (Table 1).

Study quality and risk bias assessment

The methodological quality of the nonrandomized clinical trials is listed in Supplementary Table S2 after one trial [25] with a conference abstract only was excluded. The NOS results revealed that all the trials were considered high-quality, and the average overall score was 7.3 (range 7–8). As summarized in Supplementary Table S3, we did not detect any major flaws in the risk of bias assessment among randomized clinical trials. However, there was generally a high risk of performance and detection bias because most trials were open-label and lacked blinded interventions.

The association between PD-L1 expression status and the frequency of grade 3–4 TRAEs

The overall frequency of grade 3–4 TRAEs was 15.9% (867 of the 5,453 evaluable patients). When a 1% cutoff value was set, patients who were PD-L1-negative had a significantly lower frequency of grade 3–4 TRAEs than did those with PD-L1-positive tumors in the nivolumab cohort (7.5% vs. 18.2%, OR 0.37, 95% CI 0.18–0.77; $P<$ 0.01; Fig. 2A). The frequency of durvalumab-induced grade 3–4 TRAEs was significantly lower in PD-L1-negative patients than in PD-L1-positive patients at the 25% cutoff value (8.8% vs. 15.4%, OR 0.53, 95% CI 0.31–0.90; $P=$ 0.02; Fig. 2B). Among patients receiving pembrolizumab, PD-L1-negative patients (< 50%) also experienced a lower frequency of grade 3–4 TRAEs (9.2% vs. 19.7%, OR 0.41, 95% CI 0.19–0.97, $P=$ 0.04); however, PD-L1-negative (< 1%) patients had a significantly greater frequency of grade 3–4 TRAEs than PD-L1-positive (≥ 1%) patients did (60% vs. 16.2%, OR 7.74, 95% CI 1.57–43.4, $P<$ 0.01; Fig. 2C).

The relationship between PD-L1 expression status and the frequency of AEs leading to discontinuation

AEs leading to discontinuation were reported in 357 of the 5,054 evaluable patients, resulting in an overall incidence of 7.1%. The frequency of AEs leading to discontinuation was lower among patients who were PD-L1-negative (< 1%) than among those who were PD-L1-positive (≥ 1%) in the nivolumab cohort (2.8% vs. 10.6%, OR 0.25, 95% CI 0.08–0.76, $P=$ 0.01; Fig. 3A). Similar results were observed in the durvalumab cohorts for patients who were PD-L1-negative (< 25%) versus PD-L1-positive (≥ 25%) (2.5% vs. 6.4%, OR 0.38, 95% CI 0.16–0.89, $P=$ 0.03; Fig. 3B). Patients who were PD-L1-negative (< 50%) tended to have a lower incidence of AEs leading to discontinuation than those who were PD-L1-positive (≥ 50%) (3.1% vs. 10.1%, OR 0.28, 95% CI 0.07–1.12, $P=$ 0.07; Fig. 3C).

The association between PD-L1 expression status and the frequency of all-grade TRAEs

The pooled frequency of all-grade TRAEs was 66.3% (3,581 of 5,405 evaluable patients). In the nivolumab cohort, the frequency of all-grade TRAEs did not significantly differ between patients with PD-L1 expression < 1% and those with PD-L1 expression ≥ 1% (61.3% vs. 67.8%, OR 0.75, 95% CI 0.49–1.16, $P=$ 0.20; Fig. 4A). Similarly, when a 25% cutoff value was used to define PD-L1 expression, no significant differences were found between the positive and negative groups in the durvalumab cohort (59.1% vs. 61.1%, OR 0.92, 95% CI 0.66–1.28, $P=$ 0.62; Fig. 4B). A similar pattern was found at the

Table 1 The major clinical features of included clinical trials

Study name	Study design	Study type	Tumor stage	Line of therapy	Sample size	Age (years), median (range)	Male (%)	PD-1/PD-L1 inhibitors	MTD	PD-L1 SCT	IHC assay	PD-L1 (%)
CheckMate 057, multi-centre [11]	open 3	RCT	Adv	2 or later	121	61 (37–84)	151 (52)	Nivo 3 mg/kg q2w	6 doses	TC	28–8	> 1
					106			Nivo 3 mg/kg q2w				< 1
CheckMate 026, multi-centre [12]	open 3	RCT	Adv	1 st	267	63 (32–89)	87 (32)	Nivo 3 mg/kg q2w	3.7 months	TC	28–8	> 5
BIRCH, multi-centre [13]	open 2	single-arm	Adv	mix-line	659	64 (28–88)	389 (59)	Atezo 1200 mg q3w	4.2 months	TC and IC	SP142	> 5
NCT02879994, single center [14]	open 2	single-arm	Adv. EGFR +	1 st	11	61 (35–71)	4 (36)	Pembro 200 mg q3w	3.0 months	TC	22 C3	> 1
FIR, multi-centre [15]	open 2	single-arm	Adv	mix-line	137	66 (42–85)	79 (58)	Atezo 1200 mg q3w	2.9 months	TC and IC	SP142	> 5
Study1108, multi-centre [16]	open 1/2	single-arm	Adv	mix-line	165	65 (26–85)	100 (61)	Durva 10 mg/kg q2w	16.3 weeks	TC	SP263	> 25
					120	64 (35–87)	60 (50)	Durva 10 mg/kg q2w	12.0 weeks			< 25
KEYNOTE-025, multicenter [17]	open 1b	single-arm	Adv	2 or later	38	66 (41–78)	26 (68)	Pembro 10 mg/kg q3w	NA	TC	22 C3	> 1
ATLANTIC, multi-centre [18]	open 2	single-arm	Adv	3 or later	68	61 (55–67)	39 (57)	Durva 10 mg/kg q2w	24.1 weeks	TC	SP263	> 90
ARCTIC, multi-center [19]	open 3	RCT	Adv	3 or later	62	63.5(35–79)	42 (68)	Durva 10 mg/kg q2w	21.1 weeks	TC	SP263	> 25
					117	63 (19–83)	73 (62)	Durva 10 mg/kg q2w	16.0 weeks			< 25
MYSTIC, multi-center [20]	open 3	RCT	Adv	1 st	161	64 (32–84)	113 (69)	Durva 20 mg/kg q4w	16.0 weeks	TC	SP263	> 25
KEYNOTE-598, multi-center [21]	blind 3	RCT	Adv	1 st	281	65 (35–85)	191 (67)	Pembro 200 mg q3w	9.7 months	TC	22 C3	> 50
NEOMUN, single center [22]	open 2	single-arm	stage II/IIIA	Neo	10	59 (40–83)	7 (70)	Pembro 200 mg q3w	9.7 months	TC	SP263	> 1
					5	61 (49–67)	4 (80)	Pembro 200 mg q3w				< 1
KEYNOTE-010, multi-centre [23]	open 2/3	RCT	Adv	2 or later	683	63 (56–69)	425 (62)	Pembro 2/10 mg/kg q3w	3.5 months	TC	22 C3	> 1
Impower110, multicenter [24]	open 3	RCT	Adv	1 st	286	64 (30–81)	196 (71)	Atezo 1200 mg q3w	5.3 months	TC and IC	SP142	> 1

Table 1 (continued)

Study name	Study design	Study type	Tumor stage	Line of therapy	Sample size	Age (years), median (range)	Male (%)	PD-1/PD-L1 inhibitors	MTD	PD-L1 SCT	IHC assay	PD-L1 (%)
REPLAY trial,multicenter [25]	open 2	single-arm	Adv	2 or later	55	63.7 (NA)	40 (73)	Pembro 200 mg q3w	5.3 cycles	TC	NA	> 1
KEYNOTE-024, multi-centre [26]	open 3	RCT	Adv	1 st	154	64.5 (33–90)	92 (60)	Pembro 200 mg q3w	7.9 months	TC	22 C3	> 50
CYPRESS 1, multi-center [27]	open 2	RCT	Adv	1 st	48	68 (49–83)	32 (64)	Pembro 200 mg q3w	24.4 weeks	TC	22 C3	> 50
CITYSCAPE, multi-center [28]	blind 2	RCT	Adv	1 st	68	68 (58–73)	48 (71)	Atezo 1200 mg q3w	2.81 months	TC	22 C3	> 1
PEOPLE, single center [29]	open 2	single-arm	Adv	1 st	65	70.9 (64–77)	44 (68)	Pembro 200 mg q3w	NA	TC	22 C3	< 50
CheckMate 227, multi-centre [30]	open 3	RCT	Adv	1 st	391	64 (41–87)	272 (69)	Nivo 240 mg q2w	4.6 months	TC	28–8	> 1
INTR@PID LUNG 037, multicenter [31]	open 3	RCT	Adv	1 st	152	68 (61–75)	116 (76)	Pembro 200 mg q3w	37.6 months	TC	73–10	> 80
KEYNOTE-042, multi-centre [32]	open 3	RCT	Adv	1 st	636	63 (57–69)	450 (71)	Pembro 200 mg q3w	6.75 months	TC	22 C3	> 1
KEYNOTE-033, multicenter [33]	open 3	RCT	Adv	2 or later	213	61 (28–83)	157 (74)	Pembro 2 mg/kg q3w	4.2 months	TC	22 C3	> 1
CTONG1901, multi-center [34]	open 2	RCT	Adv	1 st	14	59 (51–73)	11 (79)	Pembro 200 mg q3w	13 cycles	TC	22 C3	> 50
SAKK 19/17, multi-center [35]	open 2	single-arm	Adv	1 st	48	76 (37–87)	29 (60)	Durva 1500 mg q4w	2.8 months	TC	NA	> 25
LEAP-007, multi-center [36]	blind 3	RCT	Adv	1 st	312	66 (37–87)	224 (71)	Pembro 200 mg q3w	5.5 months	TC	22 C3	> 1

Data are listed as median (range), and *n* (%), unless otherwise stated

Abbreviations: *Adv* Advanced, *Atezo* Atezolizumab, *Durva* Durvalumab, *EGFR* Epidermal growth factor receptor, *IC* Immune cells, *IHC* Immunohistochemistry, *MTD* Median treatment durations, *Nivo* Nivolumab, *Neo* Neoadjuvant therapy, *NA* Not available, *PD-1* Programmed cell death 1, *PD-L1* Programmed death ligand 1, *Pembro* pembrolizumab, *q4w* every 4 weeks, *q3w* every 3 weeks, *q2w* every 2 weeks, *RCT* Randomized clinical trial, *SCT* Staining cell type, *TC* Tumour cells

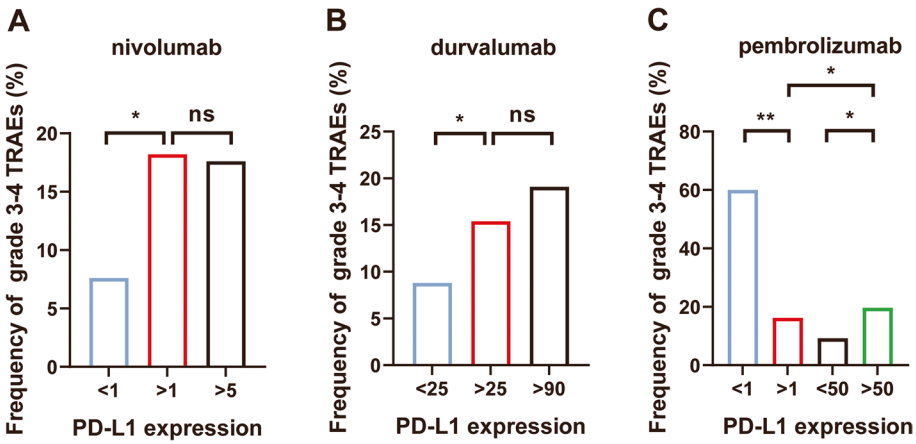

Fig. 2 Overall frequency of grade 3–4 TRAEs according to PD-1/PD-L1 inhibitor type and PD-L1 expression. Abbreviations: AEs, adverse events; FAEs, fatal adverse events; PD-L1, programmed cell death protein ligand-1; SAEs, serious adverse events; TRAEs, treatment-related adverse events. ns indicates nonsignificant differences ($P > 0.05$), * indicates $P < 0.05$, and ** indicates $P < 0.01$

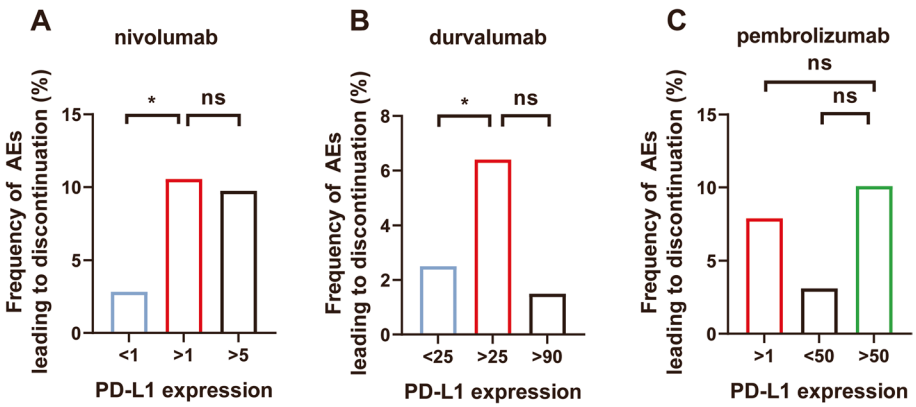

Fig. 3 Overall frequency of TRAEs leading to discontinuation according to PD-1/PD-L1 inhibitor type and PD-L1 expression. Abbreviations: AEs, adverse events; FAEs, fatal adverse events; PD-L1, programmed cell death protein ligand-1; SAEs, serious adverse events; TRAEs, treatment-related adverse events. ns indicates nonsignificant differences ($P > 0.05$), and * indicates $P < 0.05$

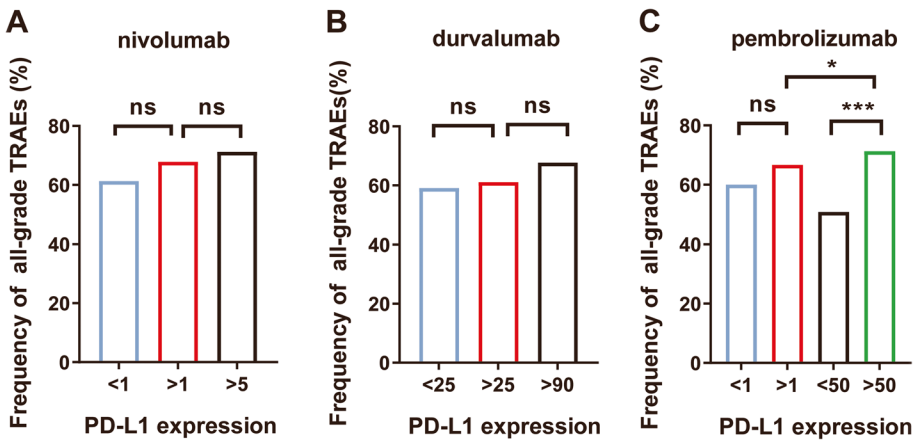

Fig. 4 Overall frequency of all-grade TRAEs according to PD-1/PD-L1 inhibitor type and PD-L1 expression. Abbreviations: AEs, adverse events; FAEs, fatal adverse events; PD-L1, programmed cell death protein ligand-1; TRAEs, treatment-related adverse events. ns indicates nonsignificant differences ($P > 0.05$), * indicates $P < 0.05$, and *** indicates $P < 0.001$

1% cutoff value for the frequency of all-grade TRAEs in the pembrolizumab cohort (60.0% vs. 66.6%, OR 0.75, 95% CI 0.15–4.25, $P = 0.75$); however, a significantly lower frequency of all-grade TRAEs was observed in PD-L1-negative patients at the 50% cutoff value (59.1% vs. 71.3%, OR 0.41, 95% CI 0.24–0.70, $P < 0.001$, Fig. 4C).

The association between PD-L1 expression status and the frequency of SAEs

The frequency of treatment-related SAEs was 10.9% (332 of the 3,034 evaluable patients). No difference was detected among PD-L1-negative patients (< 1%) and PD-L1-positive patients (≥ 1%) in the nivolumab cohort (6.6% vs. 10.2%, OR 0.63, 95% CI 0.27–1.40, $P = 0.26$; Fig. 5A). Additionally, no statistically significant differences were detected in the durvalumab cohort when PD-L1 expression was used at a cutoff value of 25% (4.2% vs. 8.0%, OR 0.51, 95% CI 0.25–1.05; $P = 0.06$; Fig. 5B). However, with a 50% cutoff value, the frequency of pembrolizumab-related SAEs was lower among PD-L1-negative patients than among PD-L1-positive patients (3.1% vs. 16.7%, OR 0.16, 95% CI 0.04–0.60, $P < 0.01$; Fig. 5C).

Relationship between PD-L1 expression status and the frequency of FAEs

The frequency of treatment-related FAEs was 0.81% (44 of the 5453 evaluable patients). The most common FAEs included respiratory distress/failure, including interstitial lung disease, and pneumonitis/pneumonia (50%, 22 of 44 patients). As depicted in Fig. 6A, PD-L1-negative and PD-L1-positive patients had a similar frequency of nivolumab-related FAEs at the 1% cutoff value (0.0% vs. 3.9%, OR 0.96, 95% CI 0.05–20.1; $P = 1.0$). The same result was noted among PD-L1-negative (< 25%) patients and PD-L1-positive (≥ 25%) patients in the durvalumab cohort (0.42% vs. 0.69%, OR 0.61, 95% CI 0.05–4.12, $P =$

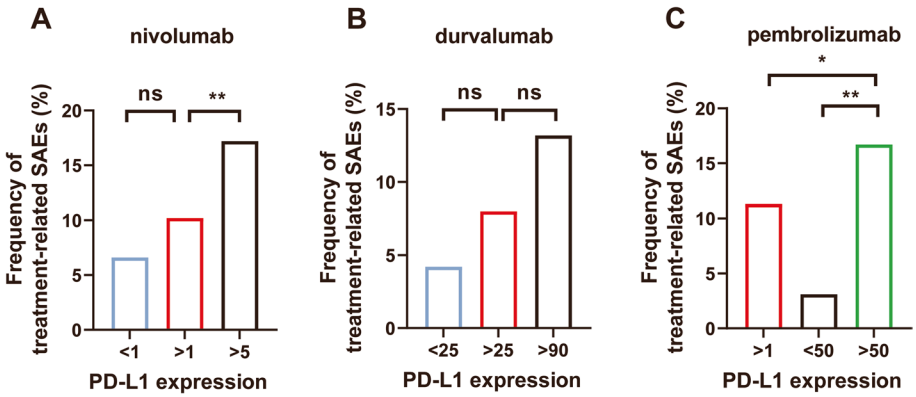

Fig. 5 Overall frequency of treatment-related SAEs according to PD-1/PD-L1 inhibitor type and PD-L1 expression. Abbreviations: AEs, adverse events; FAEs, fatal adverse events; PD-L1, programmed cell death protein ligand-1; TRAEs, treatment-related adverse events. ns indicates nonsignificant differences ($P > 0.05$), and ** indicates $P < 0.01$

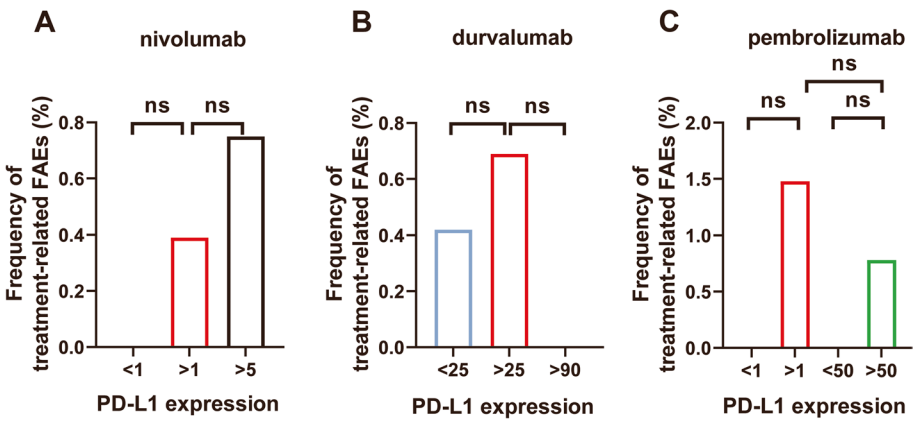

Fig. 6 Overall frequency of treatment-related FAEs according to PD-1/PD-L1 inhibitor type and PD-L1 expression. Abbreviations: AEs, adverse events; FAEs, fatal adverse events; PD-L1, programmed cell death protein ligand-1; TRAEs, treatment-related adverse events. The ns indicates nonsignificant differences ($P > 0.05$)

1.0; Fig. 6B). For patients treated with pembrolizumab, a consistent outcome was detected in PD-L1-negative patients vs. PD-L1-positive patients at the 1% cutoff (0.0% vs. 1.5%, OR 5.95, 95% CI 0.32–110.0, $P = 1.0$) and the 50% cutoff value (0.0% vs. 0.78%, OR 0.88, 95% CI 0.05–16.18, $P = 1.0$, Fig. 6C).

Relationship between PD-L1-positivity and toxicity profile

We further assessed the PD-L1-positive results by performing an assessment of the included trials describing the toxicity profile at cutoff values of 1%, 5%, 25%, 50%, and 90%. However, a consistent PD-L1-dependent pattern between the PD-L1-positive and PD-L1-toxicity profiles was not noted among the different PD-L1 inhibitor types (Figs. 2, 3, 4, 5, 6 and 7).

Subgroup analyses

We further conducted a subgroup analysis to evaluate the associations of line therapy (first-line vs. 2 or later line), study design (open-label vs. double-blind), clinical phase (phase 3 vs. phase 1/2), and IHC assay type (22 C3 vs. other) with the frequency of toxicity profiles. This analysis was performed by including PD-L1 > 1% patients treated with pembrolizumab because of the relatively large sample size available. As shown in Table 2, we did not observe any significant differences in most subgroup analyses. Notably, the 22 C3 IHC assay revealed that patients had a greater frequency of all-grade TRAEs ($P < 0.001$). Compared with patients receiving 2 or later -line therapy, patients receiving first-line therapy experienced a greater frequency of grade 3–4 TRAEs ($P = 0.006$). Moreover, the frequency of grade 3–4 TRAEs was significantly lower in the open-label trials than in the double-blind trials ($P = 0.002$).

Discussion

Identifying risk factors for toxicity profiles is essential for tailoring therapeutic regimens in NSCLC patients [37]. While early-phase pembrolizumab trials and subsequent atezolizumab investigations failed to establish a significant association between PD-L1 expression and immune-related adverse events (irAEs) in NSCLC patients [13, 38], a real-world clinical study of pembrolizumab demonstrated that high PD-L1 expression independently predicts elevated irAE risk [39]. Moreover, the PD-L1 expression level has been demonstrated to be

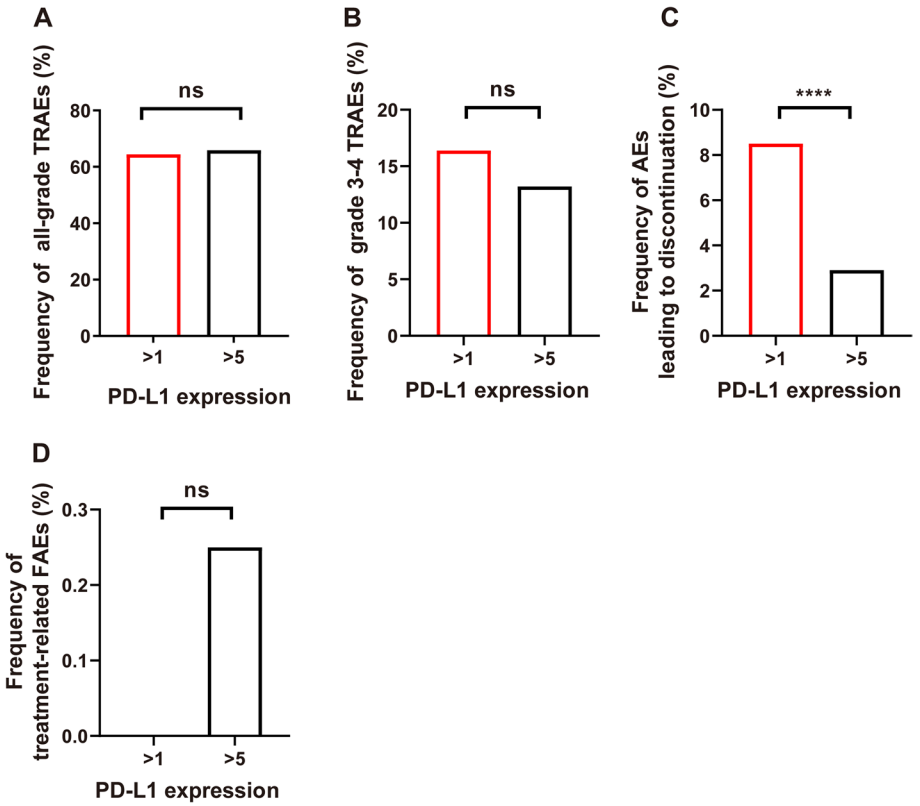

Fig. 7 Dose-dependent results of PD-L1 positivity and toxicity profiles in the atezolizumab cohort. Abbreviations: AEs, adverse events; FAEs, fatal adverse events; PD-L1, programmed cell death protein ligand-1; TRAEs, treatment-related adverse events. ns indicates nonsignificant differences ($P > 0.05$), and **** indicates $P < 0.0001$

Table 2 Subgroup analyses of the frequency of pembrolizumab-related TRAEs

All-grade TRAEs	**Frequency (%)**	**OR and 95%CI**	***P*-value**
line of therapy (first-line vs. 2 or later line)	65.2% (632/969) vs. 67.9% (672/989)	0.88 (0.73–1.07)	0.21
study design (open-label vs. double-blind)	65.9% (1085/1646) vs. 70.2% (219/312)	0.82 (0.63–1.07)	0.15
clinical phase (phase 3 vs. phase 1/2)	67.0% (1236/1844) vs. 59.7% (68/114)	1.38 (0.94–2.03)	0.12
IHC assay type (22 C3 vs. other)	67.3% (1274/1893) vs. 46.2% (30/65)	2.39 (1.46–3.92)	< 0.001
Grade 3–4 TRAEs	**Frequency (%)**	**OR and 95%CI**	***P*-value**
line of therapy (first-line vs. 2 or later line)	18.6% (180/969) vs. 13.9% (138/989)	1.41 (1.11–1.79)	0.006
study design (open-label vs. double-blind)	15.1% (248/1646) vs.22.4 (70/312)	0.61 (0.46–0.82)	0.002
clinical phase (phase 3 vs. phase 1/2)	16.4% (302/1844) vs. 14.0% (16/114)	1.20 (0.69–2.12)	0.6
IHC assay type (22 C3 vs. other)	16.5% (313/1893) vs. 7.7% (5/65)	2.34 (1.01–5.55)	0.06
AEs leading to discontinuation	**Frequency (%)**	**OR and 95%CI**	***P*-value**
line of therapy (first-line vs. 2 or later line)	8.8% (84/959) vs. 7.1% (66/934)	1.26 (0.90–1.76)	0.17
study design (open-label vs. double-blind)	7.9% (125/1581) vs. 8.0% (25/312)	0.99 (0.64–1.55)	0.91
clinical phase (phase 3 vs. phase 1/2)	7.8% (144/1844) vs. 12.2% (6/49)	0.61 (0.27–1.35)	0.28
IHC assay type (22 C3 vs. other)	7.9% (150/1893) vs. NA (NA/65)	NA	NA
Treatment-related SAEs	**Frequency (%)**	**OR and 95%CI**	***P*-value**
line of therapy (first-line vs. 2 or later line)	NA vs.11.3% (77/683)	NA	NA
study design (open-label vs. double-blind)	11.3% (77/683) vs. NA/312	NA	NA
clinical phase (phase 3 vs. phase 1/2)	11.3% (77/683) vs. NA/114	NA	NA
IHC assay type (22 C3 vs. other)	11.3% (77/683) vs. NA/65	NA	NA
Treatment-related FAEs	**Frequency (%)**	**OR and 95%CI**	***P*-value**
line of therapy (first-line vs. 2 or later line)	1.9% (19/969) vs. 1.0 (10/989)	1.96 (0.94–4.03)	0.09
study design (open-label vs. double-blind)	1.4% (23/1646) vs. 1.9% (6/312)	0.72 (0.30–1.69)	0.45
clinical phase (phase 3 vs. phase 1/2)	1.5% (28/1844) vs. 0.9% (1/114)	1.74 (0.30–18.1)	1
IHC assay type (22 C3 vs. other)	1.5% (29/1893) vs. 0% (0/65)	2.07 (0.13–34.29)	0.62

Abbreviations: *CI* Confidence interval, *FAEs* Fatal adverse events, *OR* Odds ratio, *PD-1* Programmed cell death 1, *PD-L1* Programmed cell death ligand 1, *IHC* Immunohistochemistry, *SAEs* Serious adverse events, *TRAEs* Treatment-related adverse events

strongly associated with treatment efficacy, and patients who experience irAEs tend to have a significantly higher objective response rate [37, 40]. This situation indicates that PD-L1 expression may be correlated with irAEs, possibly because 1) high PD-L1 expression reflects a tumor microenvironment with more pronounced baseline immune suppression, which may lead to excessive immune activation after PD-1/PD-L1 blockade and trigger multiple inflammatory responses, and 2) PD-1/PD-L1 inhibitors may lead to stronger immune activation in nontarget organs with high PD-L1 expression through T-cell-mediated bystander effects, resulting in adverse reactions. However, irAEs represent only the immune effect of incorrect stimulation of the immune system on normal tissues, and TRAEs indicate the toxicity profile of therapy (including irAEs and non-irAEs). Overall, the relationship between the PD-L1 expression level and TRAEs is worthy of further exploration.

Our study, which included 26 prospective trials and 5,453 patients, is the first and largest study of the relationship between PD-L1 expression status and TRAEs in patients with NSCLC receiving PD-1/PD-L1 inhibitors. We observed that PD-L1-positive patients presented a greater than twofold increase in the risks of grade 3–4 TRAEs and treatment discontinuation due to AEs at most PD-L1 expression cutoffs. Notably, patients with PD-L1 expression <1% had significantly more grade 3–4 TRAEs in the pembrolizumab cohort, which was contrary to our main findings. The inconsistent effect in the pembrolizumab cohort could be attributed to the small number of patients included ($n = 5$) and the relatively significantly higher incidence of grade 3–4 TRAEs [22]. Moreover, we did not detect a significantly lower frequency of AEs leading to discontinuation in PD-L1-negative patients at the 50% cutoff ($P = 0.07$), which may also have been biased with the small sample size ($n = 65$) included. Although variability in treatment duration may theoretically confound risk assessments of PD-1/PD-L1 inhibitors, our analysis revealed comparable or shorter median treatment durations in the high PD-L1 expression cohort, suggesting that these outcomes reflect intrinsic biological differences rather than differential exposure times. Future studies should be conducted to determine whether PD-L1-high tumors exhibit preexisting T-cell dysfunction that predisposes patients to post-treatment hyperactivation.

In fact, the multidimensional heterogeneity of PD-L1 IHC assays is an important confounding factor in evaluating the association between the expression of PD-L1 and toxicity risk [41, 42]. In our subgroup analysis, a higher frequency of all-grade TRAEs was found in patients in whom the 22 C3 IHC assay was used for PD-L1 expression assessment. A previous study evaluating the comparative performance of four PD-L1 IHC assays (22 C3, 28–8, SP142, and SP263) for detecting PD-L1 expression in tumors revealed different analytical sensitivities; thus, interchanging detection platforms and applying nonstandardized cutoff values may lead to PD-L1 status misclassification in specific patient cohorts [43]. Therefore, multi-institutional efforts to establish harmonized PD-L1 scoring protocols across different IHC platforms are needed.

A lower frequency of grade 3–4 TRAEs among patients enrolled in open-label trials than among those enrolled in double-blind trials may reflect reporting bias in open-label trials. Additionally, patients receiving first-line therapy had a greater frequency of grade 3–4 TRAEs. These patients may have a longer median treatment duration, and previous therapy (i.e., chemotherapy) may result in immune suppression [44]. For the use of PD-1/PD-L1 inhibitors in the treatment of NSCLC patients with certain genetic mutations, no study has compared the differences in safety profiles between PD-L1-negative and PD-L1-positive patients. A phase 2 trial (NCT02879994) [14] in 11 EGFR mutation-positive NSCLC patients receiving pembrolizumab reported TRAEs at rates of 65% (any grade), 9.1% (grade 3–4), and 0% (mortality); while the any-grade TRAE incidence and mortality results aligned with our findings, the incidence of grade 3–4 TRAEs in the previous study was lower than the incidence observed in our cohort (9.1% vs. 15.9%). Further multicenter, randomized phase III trials are needed to confirm this association.

The current study may have several limitations. First, we investigated the summary frequency of TRAEs on the basis of trial-level data rather than individual patient-level data; thus, the generalizability of the results may be limited. Second, patients in real-world clinical practice may experience a greater frequency of TRAEs, as the included clinical trials enrolled only patients with better performance status. Third, caution should be exercised in elucidating the results because subgroup analyses included a small number of patients. With additional evidence available, this topic needs to be further explored in future trials to support our results.

Conclusions

PD-L1-positive patients may suffer a greater frequency of grade 3–4 TRAEs and AEs leading to discontinuation than PD-L1-negative patients with NSCLC treated with PD-L1/PD-L1 inhibitors at most PD-L1 cutoff values. PD-L1 expression might be a useful biomarker for PD-1/PD-L1 inhibitor risk management in patients with NSCLC.

Abbreviations

CI	Confidence interval
EGFR	Epidermal growth factor receptor
FAEs	Fatal adverse events
NSCLC	Non-small cell lung cancer
OR	Odds ratio
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
IHC	Immunohistochemistry
SAEs	Serious adverse events
TRAEs	Treatment-related adverse events

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Conceptualization: X-R. H.; Investigation: Q. Z., H. H., L-Y. OY., R. Y., W-X. W., and P. H.; Formal Analysis and Visualization: Q. Z., H. H., L-Y. OY. and X-R H; Methodology: H. H., and Q. Z.; Writing Original Draft: Q. Z., H. H., L-Y. OY., R. Y., W-X. W., P. H. and X-R H; All authors read and approved the final manuscript.

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Data availability

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate

Ethical approval is not applicable. This study is a study of other research studies.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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