Systematic Review and Meta-Analysis

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Efficacy and safety of PD-1/PD-L1 immune checkpoint inhibitors in treating non-Hodgkin lymphoma

A systematic review and meta-analysis of clinical trials

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Abstract

Background: Immunotherapy with programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) inhibitors has been widely used in the treatment of solid tumors and Hodgkin lymphoma, demonstrating powerful efficacy and good safety. However, there is no systematic review and meta-analysis to fully investigate the efficacy and safety of PD-1/PD-L1 inhibitors in treating non-Hodgkin lymphoma (NHL).

Methods: We searched PubMed, EMBASE, The Cochrane Library, China National Knowledge Infrastructure, Wanfang database, and abstracts of conference proceedings of annual meetings up to January 23, 2022, to identify eligible clinical trials. To evaluate the efficacy of PD-1/PD-L1 inhibitors, objective response rate (ORR), complete response rate (CRR), 1-year overall survival rate, and 1-year progression-free survival rate were analyzed. For safety analysis, we calculated rates of any grade and grade ≥3 treatment-related adverse events.

Results: Overall 22 studies and 1150 participants were enrolled in this meta-analysis. The pooled ORR, CRR, 1-year overall survival, and 1-year progression-free survival rates were 0.43 (95% confidence interval [CI], 0.33–0.54), 0.21 (95% CI, 0.13–0.31), 0.72 (95% CI, 0.58–0.89), and 0.42 (95% CI, 0.29–0.62), respectively. The ORR and CRR in the combination immunochemotherapy subgroup (0.65 and 0.41) were higher than those in the monotherapy (0.27 and 0.09) and combination chemotherapy (0.39 and 0.19) subgroups. This study was registered with PROSPERO (#CRD 42022316805).

Conclusion: Given that there were limited clinical trials and relatively few relevant studies, we conducted this meta-analysis to fully elucidate the efficacy and safety of PD-1/PD-L1 inhibitors in NHL. Our results suggested that PD-1/PD-L1 inhibitors improved outcomes of responses as well as survival rates in NHL patients with tolerable adverse events. More well-designed randomized clinical trials are still needed to further confirm our findings.

Abbreviations: cHL = classical Hodgkin lymphoma, CI = confidence interval, CRR = complete response rate, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, ICIs = immune checkpoint inhibitors, irAEs = immune-related adverse events, mAbs = monoclonal antibodies, MINORS = methodological index for non-randomized studies, NHL = non-Hodgkin lymphoma, ORR = objective response rate, OS = overall survival, PD-1 = programmed cell death protein-1, PD-L1 = programmed cell death ligand-1, PFS = progression-free survival, PMBCL = primary mediastinal B cell lymphoma, RCTs = randomized clinical trials, TRAEs = treatment-related adverse events.

Keywords: efficacy, immune checkpoint inhibitors, meta-analysis, non-Hodgkin lymphoma, PD-1/PD-L1 inhibitors, safety

1. Introduction

Non-Hodgkin lymphoma (NHL) is one of the most common hematological malignant neoplasms, which arises from B, T, and natural killer lymphocytes. The whole world is facing an aggravating disease burden of NHL, with estimated 80,470 new cases in the US in 2022.[1] This constitutes approximately 4.2% of all new cancers both in males and females. There will be an estimated 20,250 deaths from NHL in 2022, and the overall 5-year survival rate is 73.8% for NHL of all races and all stages.[1]

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The authors have no conflicts of interest to disclose.

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

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NHL includes many subtypes, ranging from the more indolent follicular lymphoma (FL) to the more aggressive diffuse large B-cell lymphoma (DLBCL).[2] Although treatment regimens are based on diverse subtypes, chemotherapy is a typical treatment. Unfortunately, many patients had poor responses to frontline chemotherapies or had disease relapse after treatment.

Recent advances in immunotherapy, especially in immune checkpoint inhibitors (ICIs), have revolutionized the treatment of hematological malignancies. Programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) blockades are the most widely studied ICIs. PD-1 is expressed in immune cells while PD-L1 is expressed in tumor cells and antigen-presenting cells. Immunosuppression is one of the most important mechanisms of tumor immune escape. PD-1/PD-L1 inhibitors block the interaction of PD-1 and PD-L1, leading to the cessation of immunosuppression and resurrection of T-cell mediated anti-tumor immune effect.[3]

Since the first PD-1 inhibitor, pembrolizumab was approved for the treatment of unresectable or metastatic melanoma in 2014, the US Food and Drug Administration and the Chinese National Medical Products Administration have approved 7 and 5 PD-1/PD-L1 inhibitors, respectively. In hematological malignancies, PD-1/PD-L1 inhibitors were first used in classical Hodgkin lymphoma (cHL) and achieved impressive efficacy, with a high overall response rate ranging from 69% to 80.4%.[4–6] As for NHL, pembrolizumab, one of the PD-1 inhibitors has also been approved in relapsed or refractory primary mediastinal B cell lymphoma (PMBCL) recently. Here, we conducted a meta-analysis to evaluate the efficacy and safety of PD-1/PD-L1 inhibitors in NHL.

2. Methods

2.1. Literature search

We searched PubMed, EMBASE, The Cochrane Library, China National Knowledge Infrastructure, Wanfang database, and abstracts of conference proceedings of annual meetings (American Society of Clinical Oncology and American Society of Hematology) to identify all the relevant studies up to January 23, 2022. Language is limited to English and Chinese. We used the following search terms: "PD-1 inhibitor" OR "PD-L1 inhibitor" OR "immune checkpoint inhibitor" OR "nivolumab" OR "pembrolizumab" OR "sintilimab" OR "tislelizumab" OR "camrelizumab" OR "penpulimab" OR "toripalimab" OR "cemiplimab" OR "durvalumab" OR "avelumab" OR "atezolizumab" AND "non-Hodgkin lymphoma." Two authors (J.G. and J.Z.) independently screened the literature for eligibility and any disagreements were adjudicated by an experienced investigator. This research followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and a prospective protocol for this study was built on the PROSPERO online platform (#CRD 42022316805).

2.2. Inclusion and exclusion criteria

The inclusion criteria were described as follows: patients in all studies were exclusively diagnosed with NHL, with no restrictions on subtypes or stages; patients were treated with PD-1/PD-L1 inhibitors alone or combined with other therapies; and studies reported any of the following data: objective response rate (ORR), complete response rate (CRR), 1-year overall survival (OS) rate, 1-year progression-free survival (PFS) rate, and rates of any grade and grade ≥3 treatment-related adverse events (TRAEs).

Exclusion criteria: studies were not related to our research topics or not clinical trials; studies with <20 NHL patients or <80% of total participants with NHL were excluded unless data were separately provided for this subgroup; retrospective studies, reviews, basic researches, case reports, editorials, and expert opinions were excluded; and studies with insufficient data after contacting the authors.

2.3. Data extraction and quality assessment

Two authors (JG and ZY) reviewed and independently extracted data from the selected studies. We extracted the first author's name, publication year, ClinicalTrials.gov number, phase, disease, the number of patients, the median age of patients, treatment, median follow-up time, ORR, CRR, 1-year OS rate, 1-year PFS rate, rate of any grade TRAEs, and rate of grade ≥3 TRAEs. The methodological index for non-randomized studies (MINORS) was used to evaluate the quality of all eligible studies. MINORS contained 12 items and the first 8 ones were specifically designed for non-comparative studies. Each item was scored from 0 to 2. Zero indicated that it was not reported, 1 represented that it was reported but inadequately, and 2 represented that it was reported adequately.[7]

2.4. Statistical analysis

The primary outcome for efficacy was ORR. The secondary outcomes included CRR, 1-year OS rate, 1-year PFS rate, rate of any grade TRAEs, and rate of grade ≥3 TRAEs. We presented results after calculating the pooled ORR, CRR, 1-year OS rate, and 1-year PFS rate with 95% confidence interval (CI) to evaluate the efficacy of PD-1/PD-L1 inhibitors in treating NHL. For safety analysis, rates of any grade and grade ≥3 TRAEs with 95% CI were calculated. The Q statistic ($P < .05$ was considered significant) and I^2 statistics were used to estimate the study heterogeneity. $I^2 > 50\%$ and $P < .05$ indicate that significant heterogeneity is observed between studies, a random effects model will be used in the meta-analysis. Otherwise, a fixed effects model will be chosen. Subgroup analyses were performed to find out the possible sources of heterogeneity according to treatment regimens, disease subtypes, studied drugs, different types of ICIs, and the median age of patients, to recognize the optimum treatment regimens for different subtypes of NHL. Sensitivity analyses were conducted to assess the stability of the results. Publication bias was tested through funnel plot asymmetry and Begg's test and Begg test. All the data statistical analyses and plotting were conducted by using the "meta" package in R software 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed P value <.05 was considered statistically significant.

3. Results

3.1. Study selection and quality assessment

A total of 905 studies were identified by our search strategy; 83 studies were removed after duplication; 757 studies were excluded after reading titles and abstracts; and 43 studies were excluded after full-text review according to inclusion and exclusion criteria. Finally, 22 studies[8–29] were enrolled in the meta-analysis. A flowchart of our study selection process was shown in Figure 1. The MINORS score of each included study ranged from 8 to 13, indicating that no study had a low quality (Table 1).

3.2. Characteristics of eligible studies

The characteristics of eligible studies were summarized in Table 2. We included 22 studies and a total of 1150 participants for statistical analysis. The enrolled studies were published from 2013 to 2022 and were all single-arm-designed clinical trials. The median age of the involved patients ranged from 30 to 69 years old. Among these studies, 530 patients in 7 studies were treated with PD-1/PD-L1 inhibitors monotherapy, 321 patients

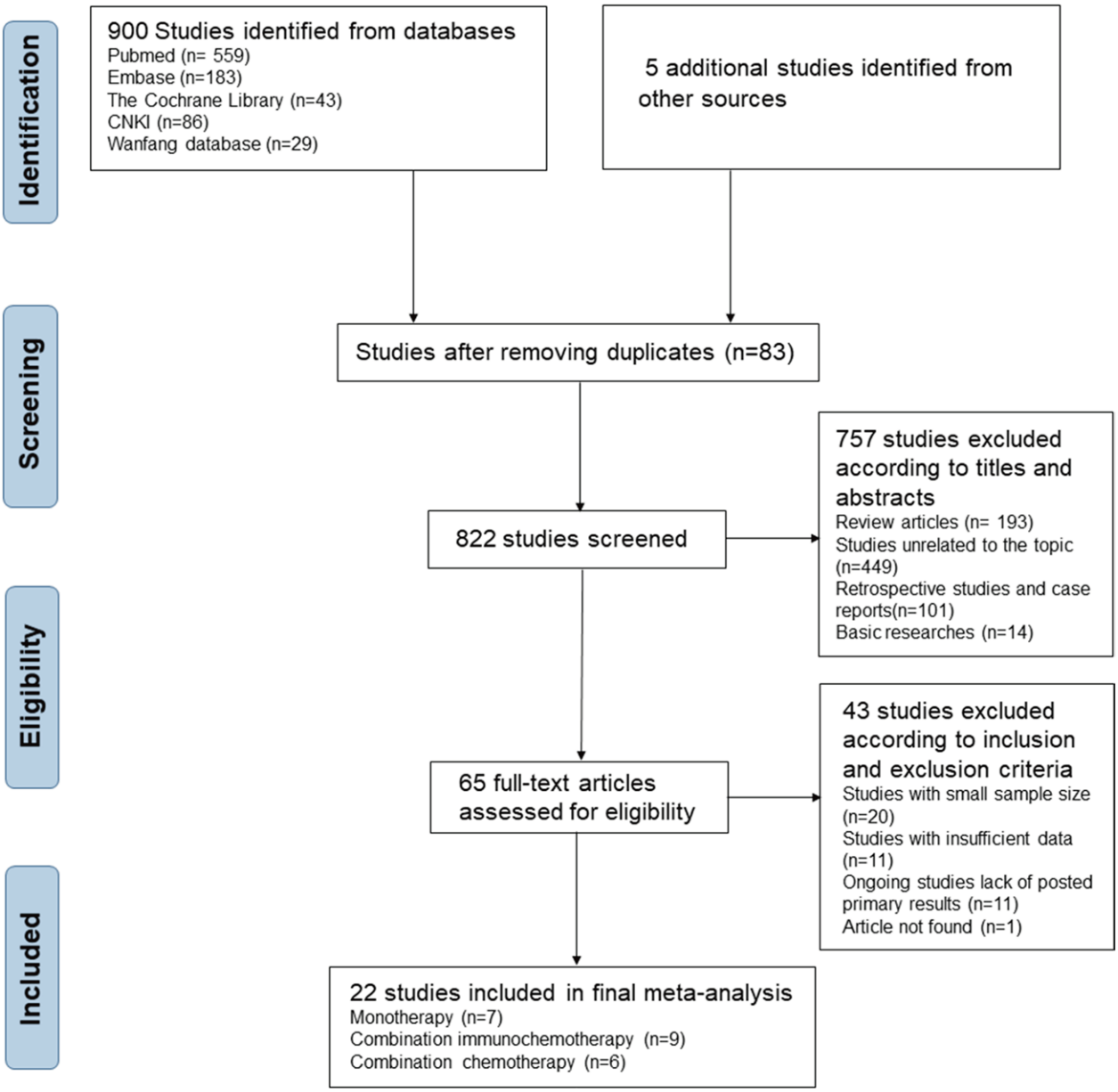

Figure 1. Flowchart of the study selection. CNKI = China National Knowledge Infrastructure.

in 9 studies were treated with PD-1/PD-L1 inhibitors plus immunochemotherapy, and 299 patients in 6 studies were treated with PD-1/PD-L1 inhibitors and chemotherapy. The PD-1/PD-L1 inhibitors used included pidilizumab (n = 2), nivolumab (n = 7), pembrolizumab (n = 2), avelumab (n = 2), geptanolimab (n = 1), atezolizumab (n = 3), tislelizumab (n = 1), durvalumab (n = 2), camrelizumab (n = 1), and sintilimab (n = 1). The studies involved different subtypes of NHL, including 10 trials reporting the treatment of DLBCL, 3 trials reporting the treatment of PMBCL, 2 studies describing therapies of extranodal natural killer /T cell lymphoma, 6 studies describing therapy regimens of FL, and 1 trial reporting results of treating peripheral T-cell lymphoma.

3.3. Efficacy analysis

The pooled ORR, CRR, 1-year-OS rate, and 1-year-PFS rate were the main indicators to evaluate the efficacy of PD-1/PD-L1 inhibitors in treating NHL. A total of 21 studies and 1066 patients[8–18,20–29] were included in the analysis of ORR and CRR, with the pooled ORR and CRR being 0.43 (95% CI, 0.33–0.54) and 0.21 (95% CI, 0.13–0.31), respectively (Fig. 2A and B). Additionally, in 7 included studies, 300 patients[13,16,18–20,22,27] and 244 patients[16,19,20,22,23,27,28] were analyzed to assess the 1-year OS rate and 1-year PFS rate. The pooled 1-year OS and PFS rates were 0.72 (95% CI, 0.58–0.89) and 0.42 (95% CI, 0.29–0.62), indicating overall good efficacy (Fig. 2C and D). However, in terms of the 4 evaluation indicators, significant heterogeneity was observed among the studies (in ORR analysis: $I^2 = 98\%$, $P < .01$; in CRR analysis: $I^2 = 92\%$, $P < .01$; in 1-year OS rate analysis: $I^2 = 84\%$, $P < .01$; in 1-year PFS rate analysis: $I^2 = 80\%$, $P < .01$).

3.4. Safety analysis

The safety of PD-1/PD-L1 inhibitor treatment for NHL was assessed by rates of any grade and grade ≥3 TRAEs. Among all studies, 9 studies were enrolled in the safety analysis. A total of 581 patients[9–11,13,14,22,23,28,29] were in the analysis of any grade TRAEs rate and 604 patients[9–11,13–15,23,27,28] were in the analysis

Table 1

The scores of MINORS.

Reference	Study aim	Patient inclusion	Prospective data collection	Study endpoint	Unbiased endpoint evaluation	Follow-up period	Loss to follow up	Sample size calculation	Total score
Armand P (2013)[8]	2	2	2	2	0	2	2	1	13
Lesokhin AM (2016)[9]	2	2	2	2	0	2	2	0	12
Ansell SM (2019)[10]	2	2	2	2	0	2	2	1	13
Armand P (2019)[11]	2	2	2	2	0	2	2	1	13
Kim SJ (2020)[12]	2	2	2	2	0	2	2	1	13
Armand P (2021)[13]	2	2	2	2	0	2	2	1	13
Shi Y (2021)[14]	2	2	2	2	0	2	2	1	13
Westin JR (2014)[15]	2	2	2	2	0	2	2	1	13
Smykova OG (2019)[16]	2	2	2	2	0	2	2	0	12
Hutchings M (2019)[17]	2	2	2	2	0	0	0	0	8
Hawkes EA (2020)[18]	2	2	2	2	0	2	2	0	12
Davies A (2021)[19]	2	2	2	2	0	0	1	0	9
Hawkes EA (2021)[20]	2	2	2	2	0	2	2	0	12
Palomba ML (2021)[21]	2	2	2	2	0	2	1	0	11
Zinzani PL (2021)[22]	2	2	2	2	0	2	2	0	12
Nowakowski GS (2022)[23]	2	2	2	2	0	2	1	1	12
Younes A (2019)[24]	2	2	2	2	0	2	2	1	13
Tam CS (2019)[25]	2	2	2	2	0	2	1	0	11
Witzig TE (2019)[26]	2	2	2	1	0	2	2	0	11
Herrera AF (2020)[27]	2	2	2	2	0	2	1	1	12
Mei Q (2020)[28]	2	2	2	2	0	2	2	1	13
Huang H (2021)[29]	2	2	2	2	0	2	1	0	11

The items above in MINORS represent a stated aim of the study, the inclusion of consecutive patients, prospective collection of data, endpoint appropriate to the study aim, unbiased evaluation of endpoints, follow-up period appropriate to the major endpoint, loss to follow up not exceeding 5%, and prospective calculation of the sample size.
MINORS = methodological index for non-randomized studies.

of grade ≥3 TRAEs rate. The pooled estimation of any grade TRAEs and grade ≥3 TRAEs rates were 0.75 (95% CI, 0.65–0.83) and 0.29 (95% CI, 0.17–0.40), respectively (Fig. 3A and B). We chose the random effects model to calculate pooled effect sizes of both analyses due to obvious heterogeneity (in the analysis of any grade TRAEs rate: I^2 = 74%, P < .01; in the analysis of grade ≥3 TRAEs rate: I^2 = 94%, P < .01).

3.5. Subgroup analysis

Subgroup analyses were conducted based on their clinical relevance and importance. In terms of therapeutic effects of PD-1/PD-L1 inhibitors, ORR was 0.34, 0.38, 0.58, 0.65, 0.50, and 0.35 for nivolumab, pembrolizumab, pidilizumab, avelumab, durvalumab, and atezolizumab, respectively. However, the pooled ORR almost had no difference between PD-1 inhibitors treatment (0.41, 95% CI, 0.30–0.53) and PD-L1 inhibitors treatment (0.49, 95% CI, 0.27–0.70). Interestingly, CRR was lower in PD-1 inhibitors treatment than in PD-L1 inhibitors treatment (0.16, 95% CI, 0.07–0.26 vs 0.29, 5% CI, 0.10–0.53), whereas 1-year OS and PFS rates were higher in PD-1 inhibitors subgroups (1-year OS rate: 0.79, 95% CI, 0.66–0.96 vs 0.64, 95% CI, 0.41–0.99; 1-year PFS rate: 0.56, 95% CI, 0.43–0.73 vs 0.31, 95% CI, 0.15–0.63) than in the other subgroups. The ORR and CRR in the combination immunochemotherapy subgroups (0.65 and 0.41) were all higher than those in other subgroups with monotherapy (0.27 and 0.09) or combination chemotherapy (0.39 and 0.19), indicating PD-1/PD-L1 inhibitors plus monoclonal antibodies (mAbs) were more effective. In addition, patients <60 years old had a generally better response than those who were >60 years old in analyses of ORR, CRR, 1-year OS, and 1-year PFS rates. Patients with PMBCL had a higher 1-year PFS rate than those with other subtypes of NHL and there was no heterogeneity in the PMBCL subgroup (0.562, I^2 = 0, P = .93).

The risk of any grade TRAEs was higher in the combination immunochemotherapy subgroup than in the monotherapy subgroup and the combination chemotherapy subgroup while the risk of grade ≥3 TRAEs was average among the 3 subgroups. As for age, no significant difference was observed between patients <60 years old and patients >60 years old in analyses of risks of any grade or grade ≥3 TRAEs. Results of subgroup analyses in the meta-analysis are presented in Table S, Supplemental Digital Content, http://links.lww.com/MD/I147.

3.6. Bias analysis and sensitivity analysis

The results of Begg's test and Begg test did not show any evidence of publication bias in the pooled ORR (P = .32) and no publication bias was observed in the funnel plot of ORR. However, potential publication biases were observed in the pooled CRR, 1-year OS rate, 1-year PFS rate, any grade TRAEs rate, and grade ≥3 TRAEs rate (P = .03, P < .01, P < .01, P = .01, and P = .01). Funnel plots of the pooled CRR, 1-year OS rate, 1-year PFS rate, any grade TRAEs rate, and grade ≥3 TRAEs rate also indicated the same results.

Sensitivity analyses were performed to evaluate the stability of the enrolled studies. No change was observed by omitting 1 individual study at a time, indicating stable results of our study.

4. Discussion

Immunotherapies have deeply revolutionized the treatment of lymphoma. PD-1/PD-L1 inhibitors, the emerging ICIs, have been highly effective in treating cHL because Reed Sternberg cells overexpress PD-L1.[30] Additionally, research work has demonstrated that PD-L1 and PD-1 are also upregulated in various lymphoid malignancies including DLBCL, PMBCL, and anaplastic large-cell lymphoma,[31,32] making PD-1/PD-L1 checkpoint blockades promising therapeutic targets. However, the efficacy and safety of PD-1/PD-L1 inhibitor therapy in treating NHL remained poorly understood.

The unique immunoglobulin idiotype on the surface of lymphomas can be combined with different kinds of adjuvants and then be stimulated to elicit robust humoral and cellular responses, making lymphomas ideal targets for rapidly developing

Table 2

The characteristics of included studies.

First author & publication year	ClinicalTrials.gov number	Phase	Disease	No.	Median age (yr, range)	Treatment	Median follow-up time (mo, range)	ORR/CRR/1-year OS rate/1-year PFS rate/TRAEs rate/TRAEs rate (grade ≥3)
Monotherapy								
Armand P 2013[8]	NCT00532259	2	DLBCL	66	57 (19–80)	Pidilizumab (1.5 mg/kg q6w)	16	51%/34%/NR/NR/NR/NR
Lesokhin AM 2016[9]	NCT01592370	1b	Cohort 1: B-NHL	31	65 (23–74)	Nivolumab (1 or 3 mg/kg q2w)	16.65 (0.4–33)	26%/10%/NR/NR/71%/26%
		2	Cohort 2: T-NHL	23	61 (30–81)			17%/0/NR/NR/74%/22%
Ansell SM 2019[10]	NCT02038933	2	Cohort 1: auto-HCT-failed DLBCL	87	62 (24–75)	Nivolumab (3 mg/kg q2w)	9 (0.1–25)	10%/3%/NR/NR/62% (in all patients)/24% (in all patients)
			Cohort 2: auto-HCT-ineligible DLBCL	34	68 (28–86)		6 (0.2–24)	3%/0/NR/NR/–/–
Armand P 2019[11]	NCT01953692	1b	Cohort 1: PMBCL	21	31 (22–62)	Pembrolizumab (10 mg/kg q2w or 200 mg q3w)	29.1	48%/33%/NR/NR/71%/24%
	NCT02576990	2	Cohort 2: PMBCL	53	33 (20–61)	Pembrolizumab (200mg q3w)	12.5	45%/13%/NR/NR/57%/23%
Kim SJ 2020[12]	NCT03439501	2	ENKTL	21	54 (24–78)	Avelumab (10 mg/kg q2w)	15.7	38%/24%/NR/NR/NR/NR
Armand P 2021[13]	NCT02038946	2	FL	92	67 (37–87)	Nivolumab (3 mg/kg q2w)	NR	4%/1%/78%/NR/54%/15%
Shi Y 2021[14]	NCT03502629	2	PTCL	102	52.5 (18–78)	Geptanolimab (3 mg/kg q2w)	4.06 (0.3–22.9)	38%/14%/NR/NR/80%/25%
Combination immunochemotherapy								
Westin JR 2014[15]	NCT00904722	2	FL	30	61 (35–79)	Pidilizumab (3 mg/kg q4w) rituximab (375 mg/m^2 qw)	15·4 (1.8–35)	66%/52%/NR/NR/NR/0
Smykova OG 2019[16]	NCT03259529	1/2	B-NHL	23	NR	A	16 (2–23)	52%/30%/54%/30%/NR/NR
Hutchings M 2019[17]	NCT03533283	1b	B-NHL	38	67 (38–82)	Atezolizumab (1200 mg q3w) glofitamab (0.07–6 mg q3w)	NR	36%/17%/NR/NR/NR/NR
Hawkes EA 2020[18]	NCT03244176	2	DLBCL	28	54 (20–79)	Avelumab (10 mg/kg q2w) rituximab (375 mg/m^2 q2w) R-CHOP	16	89%/89%/89%/NR/NR/NR
Davies A 2021[19]	NCT03422523	2	Arm B: DLBCL	41	NR	Atezolizumab (840 mg q2w) R-Gemox	NR	NR/NR/54%/15%/NR/NR
Hawkes EA 2021[20]	NCT03245021	2	FL	39	54 (28–79)	B	17.5 (7–39)	92%/54%/96%/72%/NR/NR
Palomba ML 2021[21]	NCT02220842	1b	Cohort 1: FL	26	59.5 (41–83)	Atezolizumab (1200 mg q3w)	45	54%/23%/NR/NR/NR/NR
			Cohort 2: DLBCL	23	69 (26–90)	obinutuzumab (1000 mg qw x1, 1000 mg q3w x7)	35.9	17%/4%/NR/NR/NR/NR
Zinzani PL 2021[22]	NCT02581631	1/2	PMBCL	30	35.5	Nivolumab (240 mg q3w) brentuximab vedotin (1.8 mg/kg q3w)	33.7	73%/37%/79%/56%/83%/NR
Nowakowski GS 2022[23]	NCT03003520	2	Arm A: DLBCL	43	62	C	6.2	97%/68%/NR/68%/95%/72%
Combination chemotherapy								
Younes A 2019[24]	NCT02329847	1/2a	Cohort 1: FL	40	62 (52.5–70)	Nivolumab (3 mg/kg q2w) Ibrutinib	19·6 for PFS; 19·2 for OS	33%/10%/NR/NR/NR/NR
			Cohort 2: DLBCL	45	64 (46–74)	(420 mg or 560 mg qd)	18·4 for PFS; 19·6 for OS	36%/16%/NR/NR/NR/NR
Tam CS 2019[25]	NCT02795182	1b	Cohort 1: DLBCL	27	65 (27–80)	Tislelizumab (200 mg q3w) zanubrutinib (160 mg bid)	3 (0.1–28.3)	37%/15%/NR/NR/NR/NR
Witzig TE 2019[26]	NR	1/2	DLBCL	61	67 (30–85)	Pembrolizumab (200 mg/kg q3w) acalabrutinib (100 mg bid)	5.2 (0.4–30.4)	26%/7%/NR/NR/NR/NR
Herrera AF 2020[27]	NCT02401048	1b/2	Cohort 1: DLBCL	34	67 (22–82)	Durvalumab (10 mg/kg q2w)	17.5 (0.2–23.6)	25%/19%/33%/18%/NR/56% (in all patients)
			Cohort 2: FL	27	57 (31–79)	ibrutinib (560 mg qd)	17 (1.8–28.1)	26%/4%/89%/39%/NR/–

(*Continued*)

Table 2

(*Continued*)

First author & publication year	ClinicalTrials.gov number	Phase	Disease	No.	Median age (yr, range)	Treatment	Median follow-up time (mo, range)	ORR/CRR/1-year OS rate/1-year PFS rate/TRAEs rate/TRAEs rate (grade ≥3)
Mei Q 2020[28]	NCT03346642	2	PMBCL	27	30 (18–45)	Camrelizumab (200 mg q3w)	24.8 (3.2–32.4)	74%/56%/NR/56%/93%/33%
Huang H 2021[29]	NCT03820596	1b/2	ENKTL	38	NR	GVD	12.7 (0.9–21.5)	59%/49%/NR/NR/66%/NR

A = nivolumab (1 mg/kg q2w), bendamustine (70 mg/m^2 for 2 d q4w), gemcitabine (700 mg/m^2 on d1, d8, 15), and rituximab (375 mg/m^2 q4w); B = nivolumab (240 mg q2w) plus rituximab (375 mg/m^2 q2w), and nivolumab (480 mg q4w) plus rituximab (375 mg/m^2 q12w) for maintenance; C = durvalumab (1125 mg q3w) plus R-CHOP for induction, and durvalumab (1500 mg q4w) for consolidation; D = sintilimab (200 mg q3w) plus chidamide (phase I: 20 mg–30 mg, biw; phase II recommended dosage).

auto-HCT = autologous hematopoietic cell transplantation, CRR = complete response rate, DLBCL = diffuse large B-cell lymphoma, ENKTL = extranodal natural killer/T cell lymphoma, FL = follicular lymphoma, GVD = gemcitabine, vinorelbine, and peated liposomal doxorubicin, NHL = non-Hodgkin lymphoma, NR = not reported, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PMBCL = primary mediastinal B cell lymphoma, PTCL = peripheral T cell lymphoma, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, R-Gomox = rituximab, gemcitabine, and oxaliplatin, TRAEs = treatment-related adverse events.

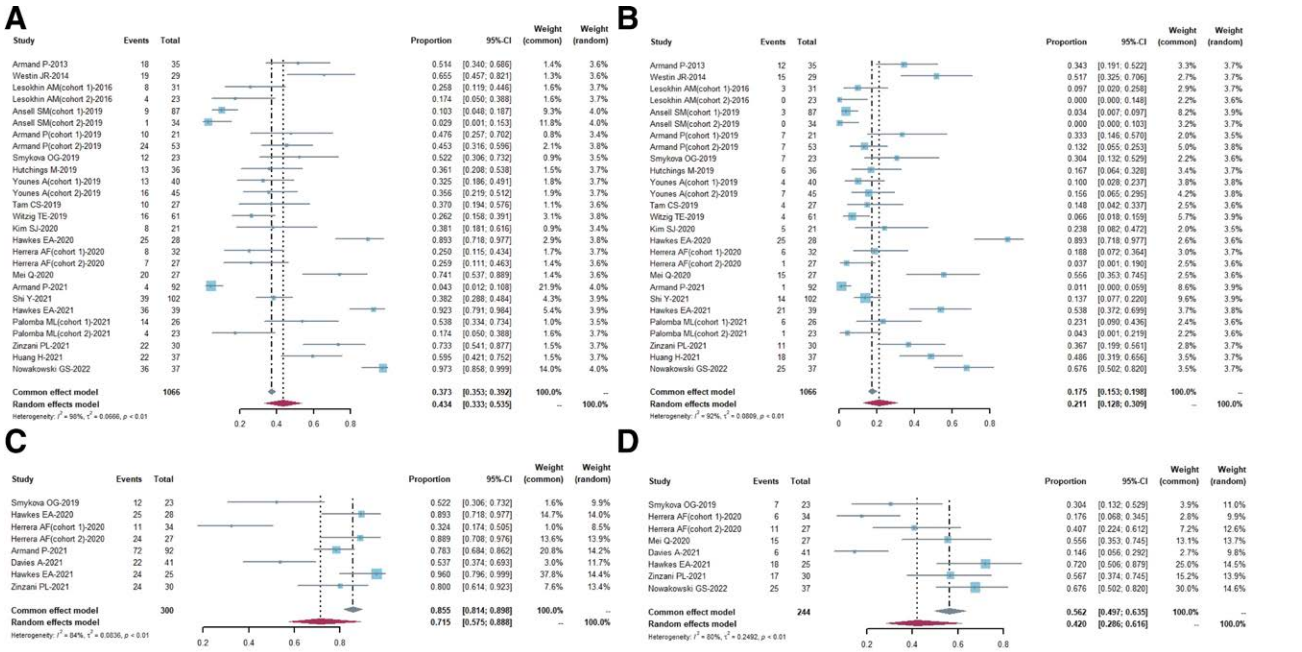

Figure 2. Forest plot of the efficacy of PD-1/PD-L1 inhibitors in treating patients with NHL. (A) Pooled objective response rate (ORR). (B) Pooled complete response rate (CRR). (C) Pooled 1-year overall survival (OS) rate. (D) Pooled 1-year progress-free survival (PFS) rate. The diamonds represent the pooled indexes. The line crossing the square represents the 95% CI. I^2 indicates the level of heterogeneity. *P* shows the significance of differences between the studies. CI = confidence interval, NHL = non-Hodgkin lymphoma, PD-1 = programmed cell death protein-1, PD-L1 = programmed cell death ligand-1.

immunotherapy.[31] The mechanisms of PD-1/PD-L1 overexpression in hematological malignancies are varied, including immune responses to interferon-γ produced by activated T cells, induction via Janus kinase 2 signaling pathways, and Epstein-Barr virus infection.[33,34] In cHL, PD-L1 is upregulated as a result of copy number amplification of chromosome 9p24.1.[30]

We performed an up-to-date meta-analysis involving 22 studies and a total of 1150 participants diagnosed with NHL to evaluate the efficacy and safety of PD-1/PD-L1 inhibitors in treating these patients. In general, the pooled ORR, CRR, and 1-year PFS rates were 0.43 (95% CI, 0.33–0.54), 0.21 (95% CI, 0.13–0.31), and 0.42 (95% CI, 0.29–0.62), respectively. Surprisingly, the pooled 1-year OS rate reached 0.72 (95% CI, 0.58–0.89). In terms of safety, the pooled any grade TRAEs and grade ≥3 TRAEs rates were 0.75 (95% CI, 0.65–0.83) and 0.29 (95% CI, 0.17–0.40), respectively. The results above indicated very promising efficacy and good safety of PD-1/PD-L1 inhibitors in NHL. Significant heterogeneity was observed among the eligible studies. Therefore, subgroup analyses based on treatment regimens, disease subtypes, studied drugs, different types of ICIs, and the median age of patients were performed to investigate the source of heterogeneity. We also conducted bias analyses and sensitivity analyses, revealing robust results of our study.

In our analysis, we found that the PD-1/PD-L1 inhibitor used as a single agent yielded low response rates, which was similar to existing results.[35,36] However, the efficacy of PD-1/PD-L1 inhibitors cooperating with immunochemotherapy was better than PD-1/PD-L1 inhibitors monotherapy or PD-1/PD-L1 inhibitors combined with chemotherapy. Accumulating evidence has indicated that PD-1/PD-L1 blockades together with mAbs produce synergistic anti-tumor activity. Important tumor regression and survival benefits were observed in lung cancer-bearing mice treated with both anti-4-1BB mAb and anti-PD-L1 mAb.[37] Michael J Overman et al conducted a phase 2 trial to investigate the efficacy of the combination therapy of PD-1/PD-L1 inhibitors and cytotoxic T lymphocyte-associated protein 4 mAb in colon cancer. The results showed durable clinical benefits with nivolumab plus ipilimumab relative to nivolumab monotherapy.[38] Another 3-arm trial for patients with untreated metastatic or unresectable melanoma also proved significant survival benefits with a combination

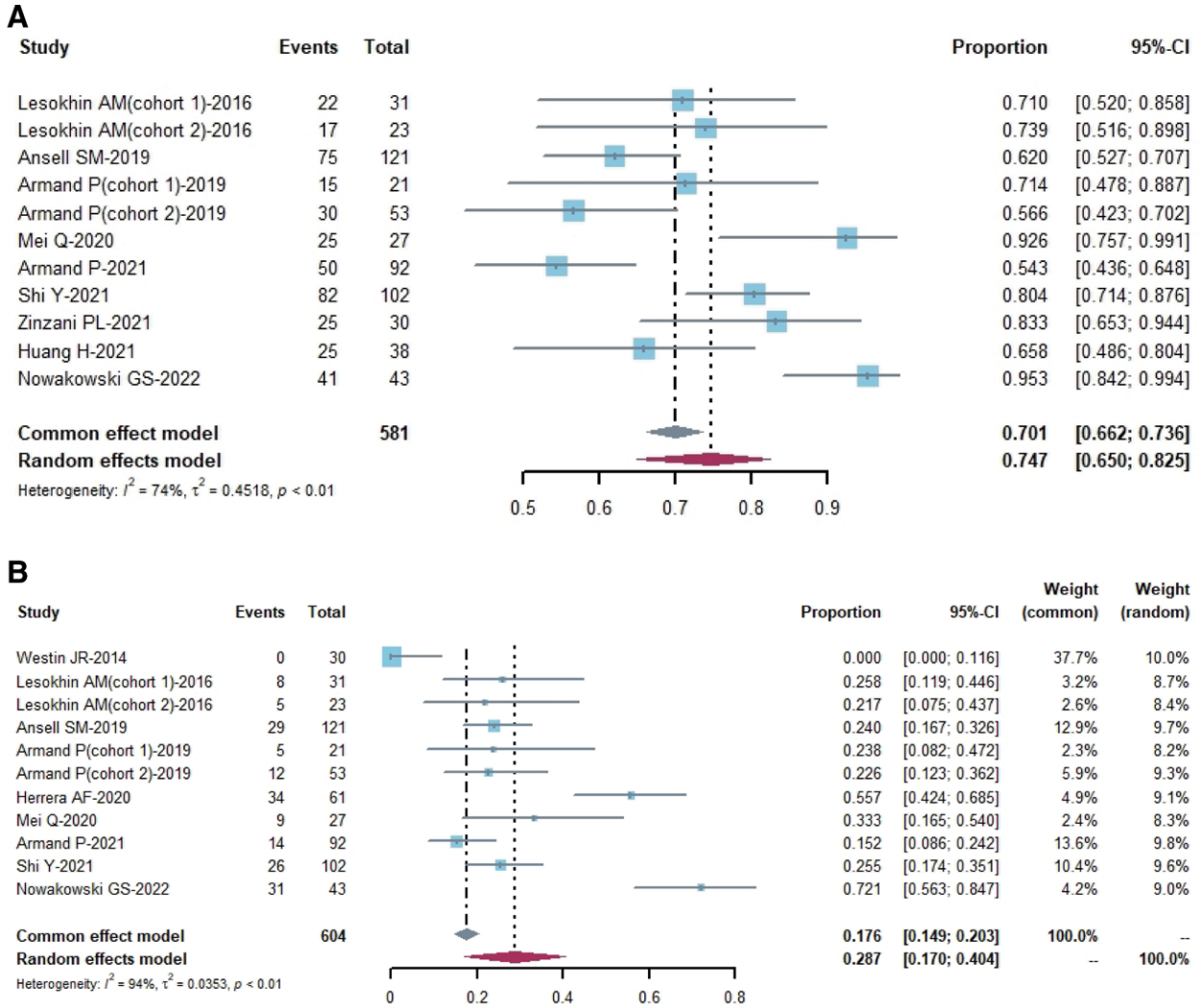

Figure 3. Forest plot of the safety of PD-1/PD-L1 inhibitors in treating patients with NHL. (A) Pooled rate of any grade treatment-related adverse events (TRAEs). (B) Pooled rate of grade ≥3 TRAEs. The diamonds represent the pooled indexes. The line crossing the square represents the 95% CI. I^2 indicates the level of heterogeneity. *P* shows the significance of differences between the studies. CI = confidence interval, NHL = non-Hodgkin lymphoma, PD-1 = programmed cell death protein-1, PD-L1 = programmed cell death ligand-1.

of PD-1 antibody and cytotoxic T lymphocyte-associated protein 4 antibody.[39] Now the combination of nivolumab and ipilimumab is widely administered for the treatment of advanced melanoma and renal cell carcinoma in Japan.[40]

Different from early studies, most patients in the combination immunochemotherapy subgroup received PD-1/PD-L1 inhibitors and CD20 mAbs in our study. Preclinical studies have demonstrated that PD-1 blockades can cooperate with CD20 mAbs by enhancing anti-CD20-mediated B-cell cytotoxicity to improve long-term OS.[41] In addition, CD30 antibody-drug conjugate, brentuximab vedotin as a single agent has been deemed inactive in PMBCL despite the high expression of CD30. Hopefully, the remarkable results of PD-1/PD-L1 inhibitors in tandem with CD30 antibody-drug conjugates make it a promising immunochemotherapy in the treatment of PMBCL.[42]

As is known, NHL is divided into different subtypes depending on pathologic types. Previous studies showed mixed results of PD-1/PD-L1 blockade therapy among various NHL subtypes. It was worth noting that patients with PMBCL had a higher 1-year PFS rate than patients diagnosed with other subtypes of NHL in this meta-analysis.

As we mentioned, PD-1/PD-L1 blockades are highly effective in cHL owing to copy number alterations of 9p24.1 and the genes encoding PD-L1. Gene expression profiling has shown similarities between PMBCL and cHL since they share increased expression of PD-L1.[43] Nevertheless, the PD-L1 expression level in other NHL subtypes is not as high as the one in PMBCL. PD-L1 expression was identified only in 11% of patients with DLBCL, especially in non-germinal center B-cell DLBCL and Epstein-Barr virus-positive DLBCL.[44,45] Neoplastic cells from mantle cell lymphoma, marginal zone lymphoma, and grade 1 to 2 FL were barely PD-1 positive.[46–48] In the future, more randomized clinical trials (RCTs) are expected to assess the efficacy and safety of PD-1/PD-L1 inhibitor therapy in different subtypes of NHL.

Whether there is a huge difference in clinical efficacy between PD-1 inhibitors and PD-L1 inhibitors is worth investigating. Consistent with the favorable survival outcomes of PD-1 antibodies than PD-L1 antibodies,[49,50] survival benefits in treatment regimens containing PD-1 inhibitors than those with PD-L1 inhibitors were also found here. The possible reason is that molecular interactions blocked by these 2 antibodies are not identical. PD-1 inhibitors have a higher binding affinity of PD-1/PD-L1 interaction than PD-L1 inhibitors, which may partly explain the different survival.[51] Although a few studies support better survival benefits in PD-1 inhibitors, others suggest similarities between the patterns of clinical activity in PD-1 and PD-L1 antibodies.[52,53] Besides the mentioned ligands, PD-1

and PD-L1 have additional binding partners.[54] PD-1 inhibitor blocks interactions between PD-1 and both PD-L1 and PD-L2, whereas PD-L1 inhibitor blocks interactions between PD-L1 and both PD-1 and CD80. Both PD-1/PD-L2 and PD-L1/CD80 pathways deliver inhibitory signals by suppressing T cell activation and cytokine production in the tumor microenvironment,[54,55] which illustrates the limitations of PD-1 and PD-L1 inhibitors in immune activation indirectly. Additionally, the difference in therapeutic benefits between the 2 inhibitors was not reported in our analysis. Therefore, more head-to-head studies need to be performed to further compare survival benefits and therapeutic responses of the 2 antibodies directly in the future.

Our results confirmed tolerable adverse events of PD-1/PD-L1 inhibitors in treating NHL. Main adverse events related to anti-PD-1/anti-PD-L1 agents are immune-related, with multiple organs and systems being involved, such as hematology, cardiology, respiratory, ophthalmology, and so on. Although the pooled any grade TRAEs rate reached 0.75, only a few patients had grade ≥3 TRAEs. Yucai Wang et al conducted a meta-analysis including 125 clinical trials and 20,128 patients to explore TRAEs of PD-1/PD-L1 inhibitors in various kinds of malignancies. The results suggested that 66% of 18,610 patients from 106 studies developed at least 1 adverse event of any grade, and 14% of 18,715 patients from 110 studies developed at least 1 adverse event of grade 3 or higher severity in all kinds of tumors, including hematological tumors and other solid tumors, which were similar to our findings.[56] Jun Shao et al also found out that ICI therapy was safer than chemotherapy, especially anti-PD-1 drug in non-small-cell lung cancer.[57] The potential reason for the adverse effects of PD-1/PD-L1 inhibitors is that disinhibition of T-cell function by ICIs can lead to immune-related adverse events (irAEs).[58] Unfortunately, most of the studies enrolled in our meta-analysis only reported TRAEs, making it hard for us to focus on the unique irAEs of PD-1/PD-L1 inhibitors in treating NHL.

Given that there are limited clinical trials and relatively few relevant studies so far, the efficacy and safety of PD-1/PD-L1 inhibitors in NHL are not fully elucidated. Therefore, we conducted this meta-analysis and compared the clinical benefits of PD-1 inhibitors with PD-L1 inhibitors, as well as the efficacy of different PD-1/PD-L1 antibodies-related regimens in NHL. Overall, our findings confirmed the positive results of efficacy and good toleration of PD-1/PD-L1 inhibitors in NHL patients. The results also suggested that PD-1/PD-L1 inhibitors in conjunction with immunochemotherapy had better clinical benefits than PD-1/PD-L1 inhibitors monotherapy or PD-1/PD-L1 inhibitors combined with chemotherapy, which may provide important guidance for treatment selection in patients and clinicians in current clinical practice and future research. Furthermore, our study included 22 clinical trials involving 1150 patients, which provided a more stable and reliable estimation.

There are several potential limitations in our current analysis that need to be taken into account when interpreting the results. Firstly, the exact source of heterogeneity remained unclear even though we produced subgroup analyses depending on possible sources of heterogeneity. Therefore, we chose random effects models in the pooled analyses with the existence of heterogeneity. Secondly, the studies involved in the analyses of 1-year OS and 1-year PFS rates were limited, thereby possibly causing some biases in our results. Thirdly, the safety of PD-1/PD-L1 inhibitors was evaluated by analyzing TRAEs instead of irAEs. There is a chance that safety analysis depending on irAEs is more specific for PD-1/PD-L1 inhibitor therapy. Last but not least, studies in this meta-analysis were all phase 1 or 2 clinical trials, which were prone to have potential performance bias. We hope a larger number of RCTs on PD-1/PD-L1 inhibitors in treating NHL can be conducted soon.

In conclusion, we performed a meta-analysis and contributed to investigating the efficacy and safety of PD-1/PD-L1 inhibitors in NHL. Our results indicated favorable efficacy and tolerable adverse events of PD-1/PD-L1 checkpoint blockades in NHL. These findings are useful for the treatment selection of clinicians and patients in real clinical settings. Furthermore, well-designed and long-term follow-up RCTs are expected to confirm the findings of this meta-analysis.

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Author contributions

JG searched databases, selected studies, extracted and analyzed data, and wrote the first draft of the manuscript. JZ searched databases and selected studies. XZ reviewed the results and provided help for paper writing. ZY took responsibility for data extraction and data analysis. JC contributed to the study design and edited the manuscript. BC was responsible for supervising the data analysis.
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Writing – original draft: Jiaheng Guan.
Writing – review & editing: Xiaoping Zhang, Jian Cheng.
All authors read and approved the final manuscript.

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