ORIGINAL ARTICLE

The prognostic value of programmed cell death ligand 1 expression in non-Hodgkin lymphoma: a meta-analysis

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ABSTRACT

Objective: Although the prognostic value of programmed cell death-ligand 1 (PD-L1) expression in non-Hodgkin lymphoma (NHL) has been evaluated in many studies, the results remain controversial. To investigate the prognostic role of PD-L1 expression and the association between PD-L1 expression and clinicopathological features of NHL, we performed a meta-analysis.

Methods: The PubMed, EMBASE, and Cochrane Library databases were searched up to November 30, 2017. The hazard ratio (HR), 95% confidence interval (CI), and odds ratios (OR) with 95% CIs were combined to evaluate the association of PD-L1 expression with overall survival (OS) and clinicopathological features. Review manager 5.3 and STATA 12.0 were used in this meta-analysis.

Results: A total of 2,005 patients across nine studies were enrolled in our meta-analysis, and the pooled results showed that high PD-L1 expression was associated with a poor prognosis (HR=2.04, 95% CI: 1.18–3.54, P=0.01). In the subgroup analysis according to histology types, pooled results demonstrated that an increased PD-L1 expression was an unfavorable prognostic factor for diffuse large B-cell lymphoma (HR=1.92, 95% CI: 1.06–3.48, P=0.03) but not for natural killer/T-cell lymphoma (HR=2.41, 95% CI: 0.47–12.22, P=0.29). Pooled ORs indicated that PD-L1 expression was higher in NHL with international prognostic indices of ≥3. However, PD-L1 expression had no correlation with gender, age, disease stage, lactate dehydrogenase level, B symptoms, and germinal center B-cell-like lymphoma.

Conclusions: High PD-L1 expression was a poor prognostic biomarker in patients with NHL. Because of our limited sample size, high-quality studies with larger sample sizes are needed to validate our results.

KEYWORDS Meta-analysis; non-Hodgkin lymphoma (NHL); programmed cell death ligand 1 (PD-L1); prognosis

Introduction

The incidence of non-Hodgkin lymphoma (NHL) has been steadily increasing over the past few decades. Approximately 85%–90% of NHLs are of B-cell origin, while the remaining NHLs originate from T cells and natural killer (NK) cells[1]. At present, the Ann Arbor staging system and the International Prognostic Index (IPI) are predominantly used to predict NHL prognosis[2]. However, prognosis varies among patients with similar pathological types of NHL and who have received the same treatments. Therefore, it is necessary to

identify personalized biomarkers that are able to not only accurately predict prognosis but also serve as therapeutic targets to improve the survival of patients.

The B7-CD28 family of costimulatory molecules plays key roles in T-cell activation and tolerance. Programmed cell death-ligand 1 [PD-L1; also known as cluster of differentiation 274 (CD274)] and PD-L2 (also known as CD273) are important B7 family members. Studies have found that PD-L1 and PD-L2 interact with the programmed cell death protein 1 (PD-1) receptor, thereby transmitting negative regulatory signals to induce apoptosis and immune incompetence of tumor antigen-specific T cells and promote tumor immune evasion[3]. In addition, PD-L1 cell-intrinsic signaling protects cancer cells from interferon (IFN) cytotoxicity and accelerates tumor progression[4].

Clinical trials show that anti-PD-1 antibodies relieve the inhibitory effect of tumors on T cells by blocking PD-1/PD-L1 complex formation, thereby activating the tumor-killing

effect of immune effector cells in patients with tumors[5]. Our previous study showed that PD-L1 overexpression correlated with poor prognosis in breast cancer[6], gastric cancer[7], and lung cancer[8]. However, the relationship between PD-L1 expression and NHL is controversial. Studies have also found that patients with PD-L1 expression may benefit from anti-PD-1/PD-L1 treatment[9]. Therefore, a complete understanding of the relationship among PD-L1 expression, NHL prognosis, and identification of patient populations with high PD-L1 expression levels is of great significance for predicting the prognosis of NHL and screening for individuals who can potentially benefit from inhibition of the PD-L1/PD-L1 pathway.

To address the above described question, we conducted a meta-analysis to assess the relationship between PD-L1 expression and prognosis and determine the relationships between PD-L1 expression and clinicopathological features.

Materials and methods

Search strategy

We conducted an electronic search for published articles in the PubMed, Embase, and Cochrane databases from January 1999 to November 2017. The key terms included the following keywords: (PD-L1 OR B7-H1 OR CD274 OR programmed cell death 1 ligand 1 protein) AND (lymphoma OR Non-Hodgkin Lymphoma OR Lymphoma, Non-Hodgkins). To explore other potentially eligible studies, we also reviewed references of the eligible articles.

Literature selection criteria

Inclusion criteria
The studies that met the following criteria were included: (1) NHL was histologically diagnosed, (2) PD-L1 expression was measured in NHL tissue by immunohistochemistry staining, (3) the correlation of PD-L1 expression with overall survival (OS) and clinicopathological features was investigated, (4) studies were published in English. When different studies included the same patient population, only the most recent article or the most complete article was included in the present meta-analysis.

Data extraction
Two investigators independently extracted the relevant data, and a third investigator resolved any controversies. The following data were extracted: first author, publication year, patient source, tumor type, patient sample size, stage,

evaluation method, PD-L1-positive expression rate, outcome, clinicopathological parameters and hazard ratio (HR) and 95% confidence interval (CI) values for OS. If the HRs and its 95% CI were not reported in eligible studies, we extracted the HR from Kaplan-Meier curves, using the Engauge-Digitizer 4.1 software. Two investigators independently conducted quality assessments of all studies using the Newcastle–Ottawa scale (NOS), and any discrepancies were resolved by discussion. The maximum NOS score is nine points, and studies that received a score of six or higher were considered high-quality studies.

Statistical analysis

The HR and 95% CI values were used to assess the relationship between PD-L1 expression and survival, while odds ratio (OR) and 95% CI values were used to determine the relationships between PD-L1 expression and clinical parameters. The heterogeneity of the studies was evaluated using χ^2 test and I^2 analysis. A P value of < 0.1 or an I^2 value of $> 50\%$ indicated the presence of heterogeneity between studies. The random-effects model was employed when heterogeneity was present. If there was no heterogeneity, the fixed-effect model was applied. Subgroup analysis was employed to identify the sources of heterogeneity. Publication bias was assessed using the Egger's and Begg's tests. Review Manager 5.3 (Revman, the Cochrane Collaboration; Oxford, England) and STATA version 12.0 (Stata Corporation; College Station, TX, USA) were used in the present study. P values of < 0.05 indicated statistically significant differences.

Results

Search results and study characteristics

In the present study, a total of 973 records were identified by the primary search strategy. After screening study titles and abstracts, 944 records were excluded because they were duplicate studies or not related to NHL. Twenty-nine potentially eligible studies were further reviewed in full text. Finally, nine studies meeting the inclusion criteria were included in the present study. The study inclusion flowchart is shown in **Figure 1**.

The details of the eligible studies are shown in **Table 1**. Nine studies including 2, 005 patients were measured in our meta-analysis. The number of patients with NHL ranged from 73 to 1, 253 in each study. Three studies were conducted in China, two in Japan, two in Korea, one in the
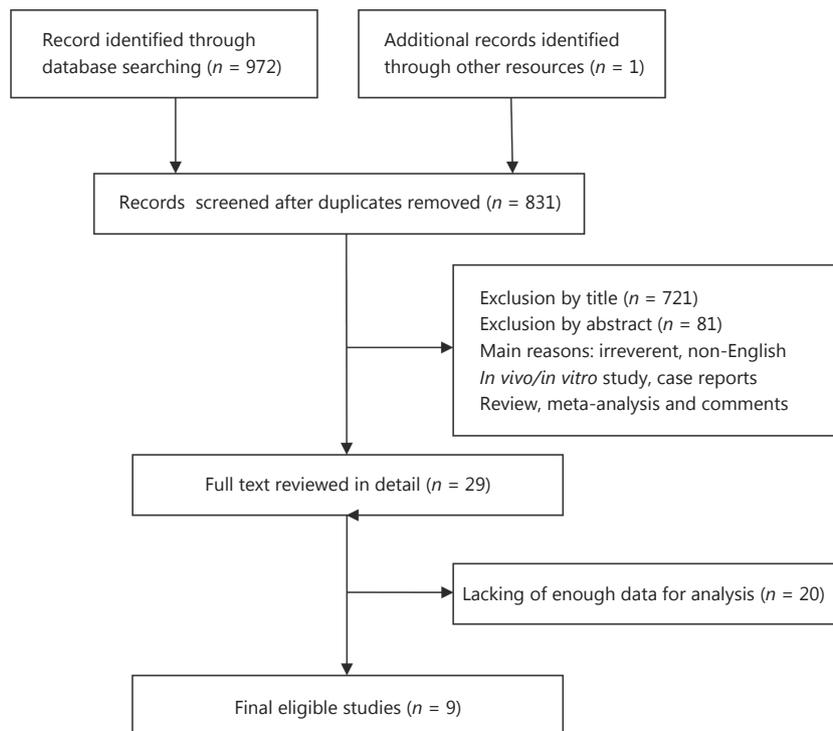
Figure 1 Flow chart of study selection.

USA, and one in Germany. According to NHL subtypes, diffuse large B-cell lymphoma (DLBCL) was evaluated in five studies, NK/T-cell lymphoma (NKTCL) in three, and adult T-cell leukemia/lymphoma (ATLL) in one. Eligible study quality, as assessed by NOS, ranged from six to eight. Therefore, the studies were considered to be of a relatively high quality.

Prognostic factors for overall survival

We investigated the prognostic value of PD-L1 expression in NHL. All of the nine studies evaluated the association between PD-L1 expression and OS. The pooled HR for OS showed that PD-L1 positive expression was associated with poorer prognosis, compared to PD-L1 negative NHL (HR = 2.04, 95% CI: 1.18–3.54, $P = 0.01$) (**Figure 2**). A random-effects model was used because statistically significant heterogeneity was found among the studies ($P < 0.001$, $I^2 = 71\%$). We conducted a subgroup analysis according to histology types, which suggested that PD-L1 positive expression is an indicator of a poor prognosis for patients with DLBCL (HR = 1.92, 95% CI: 1.06–3.48, $P = 0.03$) (**Figure 3**) but not for those with NKTCL (HR = 2.41, 95% CI: 0.47–12.22, $P = 0.29$) (**Figure 4**).

Correlation of PD-L1 expression with clinicopathological characteristics

Gender

We evaluated the correlation between PD-L1 expression and gender across a panel of 395 patients from four studies. Of the 217 male patients, 62 (28.6%) were PD-L1 expression positive, and 36 (20.2%) of the 178 female patients were PD-L1 expression positive. Since the studies were not significantly heterogeneous ($P=0.95$, $I^2=0\%$), we used the fixed-effect model for the pooled analysis. The pooled OR indicated no significant correlation between PD-L1 expression and sex (OR = 1.55; 95% CI: 0.92–2.60, $P = 0.10$) (**Figure 5A**).

Age

The association of PD-L1 expression with age was evaluated in four studies, across a total of 359 patients. Of the 184 older patients (> 60 years), 33 (17.9%) were PD-L1 positive, and 55 (31.4%) of the 175 younger patients (≤ 60 years) were PD-L1 positive. Since the studies were not significantly heterogeneous ($P = 0.74$, $I^2 = 0\%$), we used the fixed-effect model for the pooled analysis. The results showed that PD-L1

Table 1 Characteristics of the studies included in the meta-analysis

Author	Year	Country	Tumor type	No. of patients	Stage	Detection methods	Cutoff-value	PD-L1 positive	Outcome	HR estimation	Prognostic value	Quality score
Kiyasu et al.[15]	2015	Japan	DLBCL	1,253	I–IV	IHC	30%	37% (461/1253)	OS	HR	Poor	6
Bi et al.[16]	2016	China	NKTCL	77	I–II	IHC	38%	33.8% (26/77)	OS	HR	Poor	8
Dong et al.[17]	2016	China	DLBCL	100	I–IV	IHC	5%	54% (54/100)	OS	HR	Poor	8
Kim et al.[20]	2016	Korea	NKTCL	73	I–IV	IHC	10%	61.6% (45/73)	OS	HR	Good	7
Kwon et al.[21]	2016	Korea	DLBCL	126	I–IV	IHC	10%	61.1% (77/126)	OS	HR	NR	6
Miyoshi et al.[22]	2016	Japan	ATLL	135	I–IV	IHC	50%	7% (10/135)	OS	HR	Good	6
Xing et al.[18]	2016	USA	DLBCL	86	I–IV	IHC	30%	16% (14/86)	OS	HR	Poor	6
Fang et al.[19]	2017	China	DLBCL	76	I–IV	IHC	10%	26.3%% (20/76)	OS	HR	Poor	6
Jo et al.[23]	2017	Germany	ENKTL	79	I–III	IHC	5%	79.7% (63/79)	OS	K-M	NR	7

DLBCL: diffuse large B-cell lymphoma, NKTCL: natural killer/T-cell lymphoma, ATLL: adult T-cell leukemia/lymphoma, ENKTL: extranodal NK/T-cell lymphoma, IHC: immunohistochemistry, OS: overall survival, HR: hazard ratio, K-M: Kaplan–Meier curve, NR: not relevant.
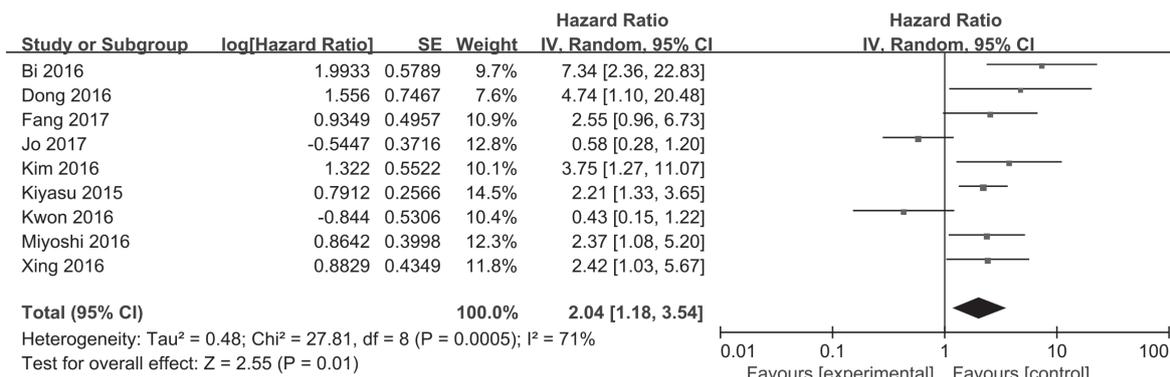

Study or Subgroup	**log[Hazard Ratio]**	**SE**	**Weight**	**Hazard Ratio IV, Random, 95% CI**
Bi 2016	1.9933	0.5789	9.7%	7.34 [2.36, 22.83]
Dong 2016	1.556	0.7467	7.6%	4.74 [1.10, 20.48]
Fang 2017	0.9349	0.4957	10.9%	2.55 [0.96, 6.73]
Jo 2017	-0.5447	0.3716	12.8%	0.58 [0.28, 1.20]
Kim 2016	1.322	0.5522	10.1%	3.75 [1.27, 11.07]
Kiyasu 2015	0.7912	0.2566	14.5%	2.21 [1.33, 3.65]
Kwon 2016	-0.844	0.5306	10.4%	0.43 [0.15, 1.22]
Miyoshi 2016	0.8642	0.3998	12.3%	2.37 [1.08, 5.20]
Xing 2016	0.8829	0.4349	11.8%	2.42 [1.03, 5.67]
Total (95% CI)			100.0%	2.04 [1.18, 3.54]

Heterogeneity: Tau² = 0.48; Chi² = 27.81, df = 8 (P = 0.0005); I² = 71%
Test for overall effect: Z = 2.55 (P = 0.01)

Figure 2 Forest plot describing the association between PD-L1 expression and OS of patients with NHL.

expression had no clear correlation with age (OR = 0.59; 95% CI = 0.34–1.03, $P = 0.06$) (**Figure 5B**).

Ann Arbor stage

Four studies, including a total of 444 patients, evaluated the relationship between PD-L1 expression and Ann Arbor stage. Of the 212 patients with stage III-IV NHL, 91 (42.9%) were PD-L1 expression positive. Ninety-seven patients (41.8%) were PD-L1 expression positive among the 232 patients with stage I-II NHL. Since the studies were not significantly

heterogeneous ($P = 0.65$, $I^2 = 0\%$), we used the fixed-effect model for the pooled analysis. The pooled OR indicated that no significant association was found between PD-L1 expression and Ann Arbor stage (OR = 1.19; 95% CI: 0.76–1.87, $P = 0.44$) (**Figure 5C**).

IPI score

Five studies, including 640 patients, analyzed the correlation of PD-L1 expression with IPI score. Of 267 patients with IPI scores ≥3, 75 (28.1%) were PD-L1 positive, and 108 (29%) of
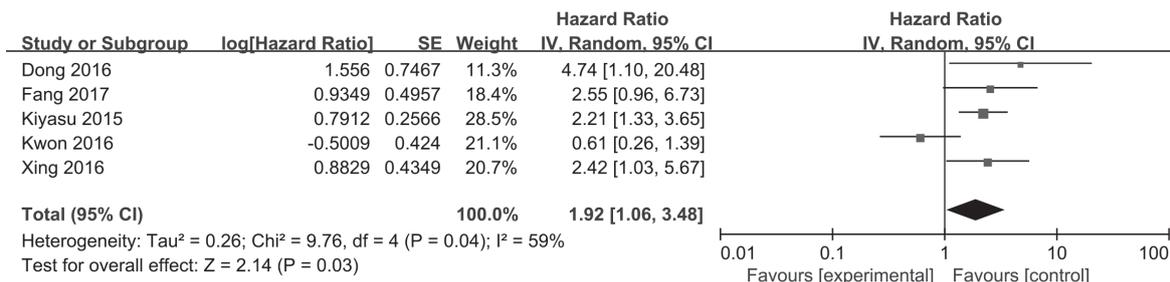
| | | | | Hazard Ratio | Hazard Ratio |
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Dong 2016	1.556	0.7467	11.3%	4.74 [1.10, 20.48]	
Fang 2017	0.9349	0.4957	18.4%	2.55 [0.96, 6.73]	
Kiyasu 2015	0.7912	0.2566	28.5%	2.21 [1.33, 3.65]	
Kwon 2016	-0.5009	0.424	21.1%	0.61 [0.26, 1.39]	
Xing 2016	0.8829	0.4349	20.7%	2.42 [1.03, 5.67]	
Total (95% CI)			100.0%	1.92 [1.06, 3.48]	

Heterogeneity: Tau² = 0.26; Chi² = 9.76, df = 4 (P = 0.04); I² = 59%
Test for overall effect: Z = 2.14 (P = 0.03)

0.01   0.1   1   10   100
Favours [experimental]   Favours [control]

Figure 3 Forest plot describing the association between PD-L1 expression and OS of patients with DLBCL.

| | | | | Hazard Ratio | Hazard Ratio |
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bi 2016	1.9933	0.5789	32.1%	7.34 [2.36, 22.83]	
Jo 2017	-0.5447	0.3716	35.3%	0.58 [0.28, 1.20]	
Kim 2016	1.322	0.5522	32.6%	3.75 [1.27, 11.07]	
Total (95% CI)			100.0%	2.41 [0.47, 12.22]	

Heterogeneity: Tau² = 1.81; Chi² = 16.76, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 1.06 (P = 0.29)

0.01   0.1   1   10   100
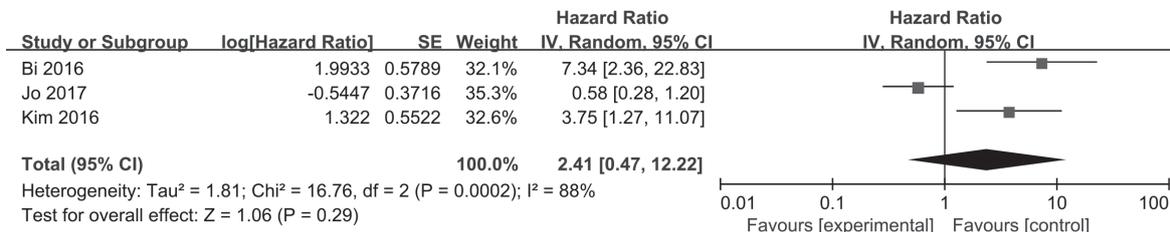Favours [experimental]   Favours [control]

Figure 4 Forest plot describing the association between PD-L1 expression and OS of patients with NKTCL.

the 373 patients with IPI scores of <3 were PD-L1 positive. Since the studies were not significantly heterogeneous ($P = 0.27$, $I^2 = 22\%$), we used the fixed-effect model for the pooled analysis. PD-L1 positive expression was found to be significantly associated with IPI score (OR = 1.59, 95% CI: 1.03–2.45, $P = 0.04$) (**Figure 5D**).

Serum LDH

The relationship between PD-L1 expression and LDH level was analyzed in five studies, which included 360 patients. Sixty-two (31%) patients were PD-L1 expression positive out of the 200 patients with elevated LDH, and 68 (42.5%) of the 160 patients with normal LDH levels were PD-L1 expression positive. Since the studies were not significantly heterogeneous ($P = 0.11$, $I^2 = 48\%$), we used the fixed-effect model for the pooled analysis. Increased PD-L1 expression was not found to be significantly associated with LDH level (OR = 0.68, 95% CI: 0.40–1.16, $P = 0.16$) (**Figure 5E**).

B symptoms

Four studies with a total of 328 patients analyzed the relationship between PD-L1 expression and B symptoms. Positive PD-L1 expression was found in 34 (36.6%) out of 93 patients with positive B symptoms, while 46 (19.6%) out of 235 patients with negative B symptoms were PD-L1 expression positive. Since the studies were significantly

heterogeneous ($P=0.02$, $I^2=70\%$), we used a random-effect model for the pooled analysis. No significant relationship was detected between PD-L1 expression and B symptoms (OR=1.84, 95% CI: 0.57–5.93, $P=0.31$) (**Figure 5F**).

Choi classification

Two studies containing 1, 353 patients evaluated the correlation of PD-L1 expression with Choi classification. Of the 501 patients with germinal center B-cell-like (GCB) NHL, 38 (7.6%) were PD-L1 expression positive, and 148 (17.4%) of 852 patients with non-GCB NHL were PD-L1 positive. Since the studies were not significantly heterogeneous ($P = 0.65$, $I^2 = 0\%$), we used the fixed-effect model for the pooled analysis. The combined OR for the GCB group versus the non-GCB group was 0.33 (95% CI: 0.22–0.49, $P<0.001$) (**Figure 5G**).

Publication bias and sensitivity analysis.

Begg's and Egger's tests were conducted to evaluate the publication bias in the literature. No evident asymmetry among these studies was present. The P values for these tests were 0.175 and 0.580, respectively (**Figure 6**). In addition, a sensitivity analysis was conducted to evaluate the stability of the present study, by sequentially removing one study. The results were not influenced by any individual study, suggesting that the results of this study are credible.
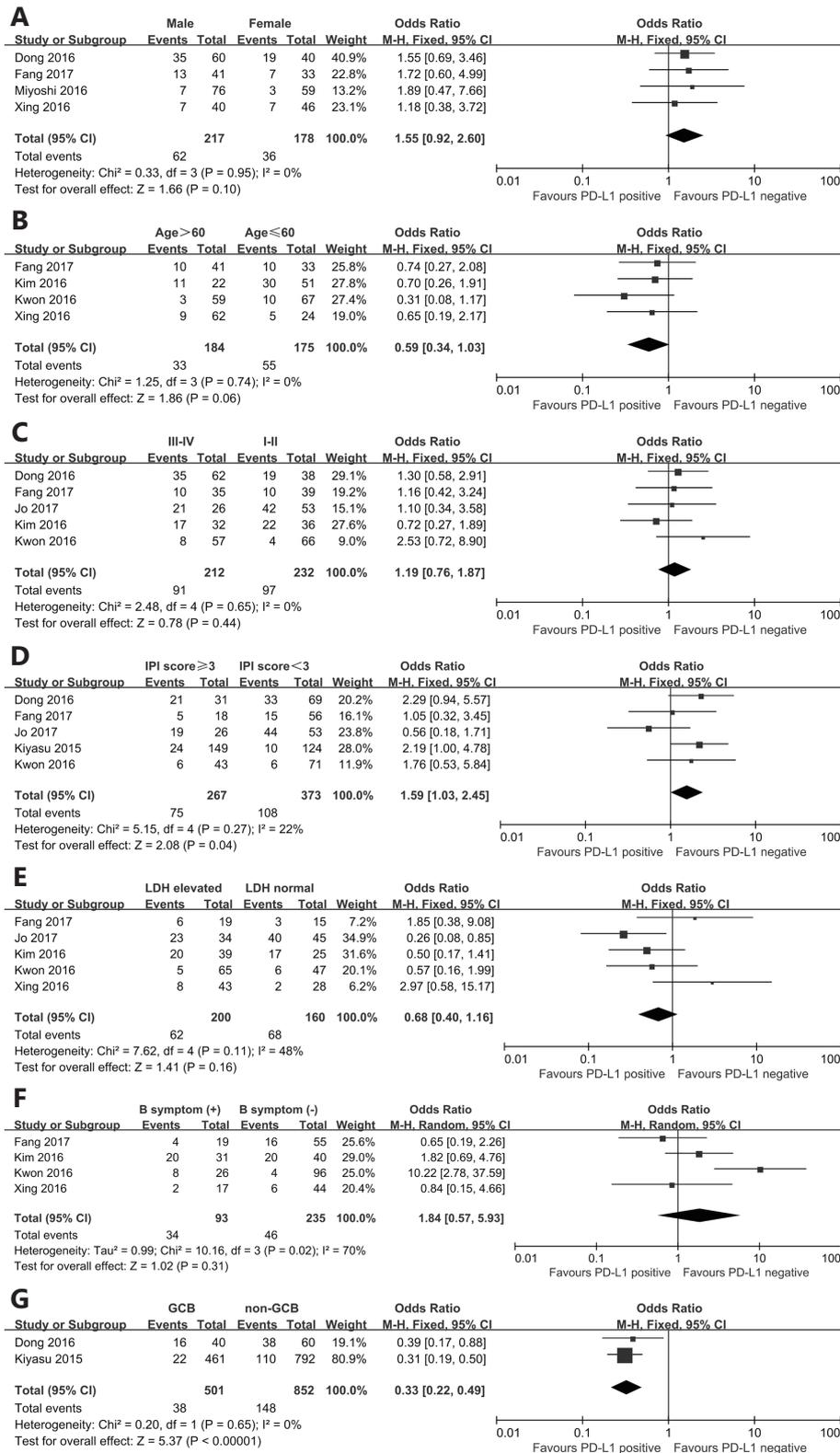
Figure 5 Forest plots for the association between PD-L1 expression and clinicopathological features. (A) Gender. (B) Age. (C) Ann Arbor Stage. (D) IPI score. (E) Serum LDH. (F) B symptom. (G) Choi classification.
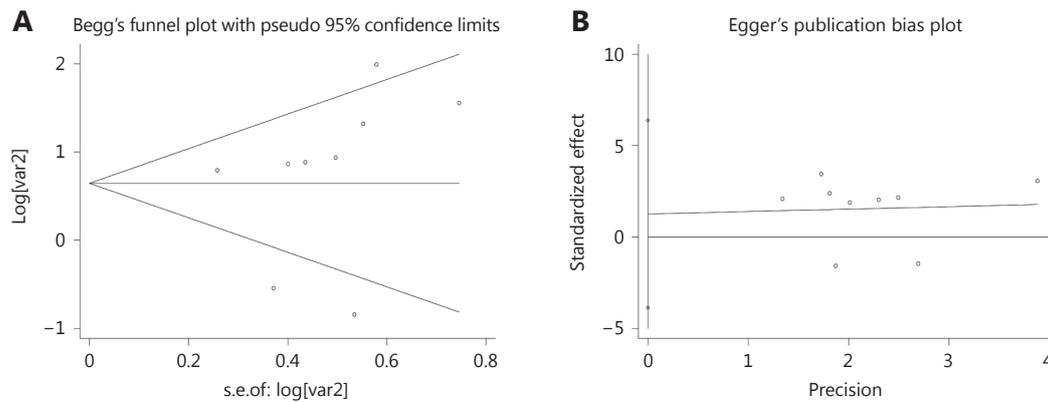
Figure 6 Egger's and Begg's funnel plot with 95% confdence intervals for OS publication bias testing. (A) Begg's funnel plot with 95 % confidence intervals for OS publication bias testing. (B) Egger's funnel plot with 95 % confidence intervals for OS publication bias testing.

Discussion

PD-L1 is expressed in a variety of human tumors such as non-small cell lung cancer[10], breast cancer[11], colon cancer[12], gastric cancer[13], and hepatocellular carcinoma[14]. The clinical significance of PD-L1/PD-1 expression in NHL has received increasing attention. At present, the relationship between the expression of PD-L1 and the prognosis of patients with NHL remains controversial. Some studies have proposed that positive PD-L1 expression correlates with a poor prognosis[15-19], while other studies have shown that positive PD-L1 expression does not correlate with prognosis or correlates with a good prognosis[20-23].

In the present study, a meta-analysis was applied for the first time to systematically analyze the relationship between PD-L1 expression and the prognosis of patients with NHL. The results showed that PD-L1 expression correlated with poor prognosis in patients with NHL. Different subtypes of NHL display distinct clinical characteristics and biological behaviors. To reduce heterogeneity between studies, grouping was performed based on NHL pathological subtypes. The subgroup analysis showed that PD-L1 expression correlated with poor prognosis in DLBCL. However, no correlation was detected between PD-L1 expression and the prognosis of patients with NK/T-cell lymphoma.

The results of the present study are consistent with those of Kiyasu et al[15]. The study conducted by Kiyasu et al. included a total of 1,253 patients with DLBCL, among whom 461 (37%) had positive PD-L1 expression. Compared to the patients with negative without PD-L1 expression, patients with positive PD-L1 expression showed poorer prognosis. The study conducted by Dong et al.[17] included 100 patients with DLBCL, among whom 48 (48%) had positive PD-L1

expression. This study also showed that positive PD-L1 expression correlated with poor prognosis in patients with DLBCL. In addition, this study found that PD-L1 predicted the prognosis of DLBCL more effectively when combined with p-AKT. However, the study conducted by Kwon et al. showed that there was no correlation between positive PD-L1 expression and prognosis, while positive PD-1 expression and tumor-infiltrating lymphocytes correlated with a good prognosis[13]. The following reasons might account for the contradictory results: (1) different antibodies were used in the above studies for examining PD-L1 protein expression, (2) the criteria that were employed by the studies to define positive PD-L1 expression were inconsistent, (3) the clinical stages of the included patients and the intervening factors varied among the studies, and (4) the different sampling times affected PD-L1 detection. Therefore, establishment of a unified platform for detecting PD-L1 and standardized criteria for defining positive PD-L1 expression are of great significance to future PD-L1 examinations. In addition, our results showed that PD-L1 expression did not associate with OS in NKTCL. Because of the limited number of cases, high-quality studies with larger homogeneous populations are needed to determine the role of PD-L1 expression in NKTCL.

Tumor immunotherapy has become the main treatment approach for various tumors, among which PD-1/PD-L1 inhibitor-based therapies are most commonly used. Previous studies have found that inhibitors of the PD-1/PD-L1 pathway exhibit high efficacy in the treatment of recurrent and refractory NHL, and upregulated PD-L1 expression positively correlates with the efficacy of PD-1/PD-L1 pathway inhibitors in Hodgkin lymphoma and NHL[24]. Upregulation of PD-L1 expression is mainly achieved through intracellular and extracellular mechanisms. The intracellular mechanism mainly involves the regulation of PD-L1 expression at the

transcriptional and translational levels through various intracellular signaling pathways. For example, the mechanistic target of rapamycin/AKT and nuclear factor kappa B signaling pathways have been demonstrated to play important roles in regulating PD-L1 expression in a variety of tumors. Structural variations (SVs) in the 3′-untranslated region of the PD-L1 gene also affect PD-L1 expression. Under certain circumstances, such SVs cause open reading frame rearrangements of the PD-L1 gene, ultimately resulting in the elevation of PD-L1 protein expression.

To further verify the findings, researchers have employed the clustered regularly interspaced palindromic repeats (CRISPR)/CRISPR-associated nuclease 9 gene-editing technique to destroy SVs in mouse models. SV elimination impeded the increase in PD-L1 protein expression[25]. The extracellular mechanism mainly involves various proinflammatory factors and cytokines that are secreted by the tumor microenvironment, among which IFN gamma (IFN-γ) plays a particularly important role[26]. In clinical practice, the patient populations who may potentially benefit from targeted immunotherapy can be screened out by analyzing the relationship between PD-L1 overexpression and clinical parameters. The results of the present study show that PD-L1 expression correlated with IPI. A higher rate of positive PD-L1 expression was detected when IPI was ≥3. However, PD-L1 expression was not related to sex, age, tumor stage, LDH, or B symptoms. DLBCL is the most common NHL subtype and is divided into GCB and non-GCB subtypes based on the tumor origin[27]. Our study found that PD-L1 expression was higher in GCB DLBCL compared to non-GCB DLBCL. Clarification of the relationships between PD-L1 expression and clinical parameters may allow the identification of beneficiaries at the clinical level.

To our knowledge, this is the first meta-analysis to analyze the relationship of PD-L1 expression with prognosis and clinical parameters in NHL. Our study included a large number of samples, which imparts a high statistical power. Therefore, the results of the present study are more stable and accurate than those of previous individual studies. However, we acknowledge that the present study had certain limitations. First, only two studies that focused on NKTCL were included in our meta-analysis. Therefore, combining the results of the included studies resulted in a relatively low statistical power. A larger sample size is needed to confirm the findings of our meta-analysis. Second, without individual patient data, certain data on the relationships between clinical parameters and PD-L1 could not be combined. Third, the included studies used different PD-L1 antibodies and cutoff values, which might have affected the stability of

the results. Finally, only English-language articles were included in our analysis. Therefore, a potential publication bias might arise.

In conclusion, despite the limitations described above, our meta-analysis is the first report to focus on the prognostic significance of PD-L1 expression in patients with NHL. The results of the present study demonstrate that positive PD-L1 expression is a prognostic predictor of NHL. Additionally, the present study found that higher IPI values were associated with higher PD-L1 expression, demonstrating that patients with a high IPI may be prime candidates for PD-1/PD-L1 inhibitor therapy. In the future, multicenter, large-sample studies need to be performed to further confirm the relationship between PD-L1 and NHL.

Acknowledgements

Conflict of interest statement

No potential conflicts of interest are disclosed.

References

1. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. Lancet. 2012; 380: 848-57.
2. Horwitz SM, Zelenetz AD, Gordon LI, Wierda WG, Abramson JS, Advani RH, et al. NCCN guidelines insights: Non-Hodgkin's lymphomas, version 3.2016. J Natl Compr Canc Netw. 2016; 14: 1067-79.
3. Liu BS, Song YP, Liu DL. Recent development in clinical applications of PD-1 and PD-L1 antibodies for cancer immunotherapy. J Hematol Oncol. 2017; 10: 174
4. Gato-Cañas M, Zuazo M, Arasanz H, Ibañez-Vea M, Lorenzo L, Fernandez-Hinojal G, et al. PDL1 Signals through conserved sequence motifs to overcome interferon-mediated cytotoxicity. Cell Rep. 2017; 20: 1818-29.
5. Zinzani PL, Ribrag V, Moskowitz CH, Michot JM, Kuruvilla J, Balakumaran A, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood. 2017; 130: 267-70.
6. Zhang MH, Sun HB, Zhao S, Wang Y, Pu HH, Wang Y, et al. Expression of PD-L1 and prognosis in breast cancer: a meta-analysis. Oncotarget. 2017; 8: 31347-54.

7. Zhang MH, Dong YD, Liu HT, Wang Y, Zhao S, Xuan QJ, et al. The clinicopathological and prognostic significance of PD-L1 expression in gastric cancer: a meta-analysis of 10 studies with 1, 901 patients. Sci Rep. 2016; 6: 37933

8. Zhang MH, Li GL, Wang YB, Wang Y, Zhao S, Haihong P, et al. PD-L1 expression in lung cancer and its correlation with driver mutations: a meta-analysis. Sci Rep. 2017; 7: 10255

9. Yuasa T, Masuda H, Yamamoto S, Numao N, Yonese J. Biomarkers to predict prognosis and response to checkpoint inhibitors. Int J Clin Oncol. 2017; 22: 629-34.

10. Li D, Zhu X, Wang H, Li N. Association between PD-L1 expression and driven gene status in NSCLC: A meta-analysis. Eur J Surg Oncol. 2017; 43: 1372-9.

11. Kim HM, Lee J, Koo JS. Clinicopathological and prognostic significance of programmed death ligand-1 expression in breast cancer: a meta-analysis. BMC Cancer. 2017; 17: 690

12. Koganemaru S, Inoshita N, Miura Y, Miyama Y, Fukui Y, Ozaki Y, et al. Prognostic value of programmed death-ligand 1 expression in patients with stage III colorectal cancer. Cancer Sci. 2017; 108: 853-8.

13. Kwon MJ, Kim KC, Nam ES, Cho SJ, Park HR, Min SK, et al. Programmed death ligand-1 and MET co-expression is a poor prognostic factor in gastric cancers after resection. Oncotarget. 2017; 8: 82399-414.

14. Sideras K, Biermann K, Verheij J, Takkenberg BR, Mancham S, Hansen BE, et al. PD-L1, Galectin-9 and CD8^{+} tumor-infiltrating lymphocytes are associated with survival in hepatocellular carcinoma. OncoImmunology. 2017; 6: e1273309

15. Kiyasu J, Miyoshi H, Hirata A, Arakawa F, Ichikawa A, Niino D, et al. Expression of programmed cell death ligand 1 is associated with poor overall survival in patients with diffuse large B-cell lymphoma. Blood. 2015; 126: 2193-201.

16. Bi XW, Wang H, Zhang WW, Wang JH, Liu WJ, Xia ZJ, et al. PD-L1 is upregulated by EBV-driven LMP1 through NF-κB pathway and correlates with poor prognosis in natural killer/T-cell lymphoma. J Hematol Oncol. 2016; 9: 109

17. Dong L, Lv HJ, Li W, Song Z, Li LF, Zhou SY, et al. Co-expression of PD-L1 and p-AKT is associated with poor prognosis in diffuse large B-cell lymphoma via PD-1/PD-L1 axis activating intracellular AKT/mTOR pathway in tumor cells. Oncotarget. 2016; 7: 33350-62.

18. Xing W, Dresser K, Zhang R, Evens AM, Yu HB, Woda BA, et al. PD-L1 expression in EBV-negative diffuse large B-cell lymphoma: clinicopathologic features and prognostic implications. Oncotarget. 2016; 7: 59976-86.

19. Fang X, Xiu B, Yang ZZ, Qiu WZ, Zhang L, Zhang SX, et al. The expression and clinical relevance of PD-1, PD-L1, and TP63 in patients with diffuse large B-cell lymphoma. Medicine. 2017; 96: e6398

20. Kim WY, Jung HY, Nam SJ, Kim TM, Heo DS, Kim CW, et al. Expression of programmed cell death ligand 1(PD-L1) in advanced stage EBV-associated extranodal NK/T cell lymphoma is associated with better prognosis. Virchows Arch. 2016; 469: 581-90.

21. Kwon D, Kim S, Kim PJ, Go H, Nam SJ, Paik JH, et al. Clinicopathological analysis of programmed cell death 1 and programmed cell death ligand 1 expression in the tumour microenvironments of diffuse large B cell lymphomas. Histopathology. 2016; 68: 1079-89.

22. Miyoshi H, Kiyasu J, Kato T, Yoshida N, Shimono J, Yokoyama S, et al. PD-L1 expression on neoplastic or stromal cells is respectively a poor or good prognostic factor for adult T-cell leukemia/lymphoma. Blood. 2016; 128: 1374-81.

23. Jo JC, Kim M, Choi Y, Kim HJ, Kim JE, Chae SW, et al. Expression of programmed cell death 1 and programmed cell death ligand 1 in extranodal NK/T-cell lymphoma, nasal type. Ann Hematol. 2017; 96: 25-31.

24. Merryman RW, Armand P, Wright KT, Rodig SJ. Checkpoint blockade in Hodgkin and non-Hodgkin lymphoma. Blood Adv. 2017; 1: 2643-54.

25. Kataoka K, Shiraishi Y, Takeda Y, Sakata S, Matsumoto M, Nagano S, et al. Aberrant *PD-L1* expression through 3'-UTR disruption in multiple cancers. Nature. 2016; 534: 402-6.

26. Abiko K, Matsumura N, Hamanishi J, Horikawa N, Murakami R, Yamaguchi K, et al. IFN-γ from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer. Br J Cancer. 2015; 112: 1501-9.

27. Li SY, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. Pathology. 2018; 50: 74-87.