Research article

Prognostic and Clinicopathological Significance of Programmed Death-Ligand 1 in Osteosarcoma: a Meta-Analysis

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Abstract

Background: Programmed cell death-ligand 1 (PD-L1) was reported to be associated with survival outcomes in patients with osteosarcoma, but the results were controversial. This study aimed to evaluate the prognostic value of PD-L1 in osteosarcoma.

Methods: The pooled HR and 95%CI were calculated to measure the prognostic role of PD-L1 for overall survival (OS) and disease-free survival (DFS). The odds ratio (OR) and 95%CI were used to evaluate the correlation of PD-L1 and clinicopathological features. Publication bias was measured using Begg's funnel plots.

Results: A total of 9 studies with 538 patients were included in this meta-analysis. The pooled results were HR=1.78, 95%CI=1.36-2.32, p<0.001 for OS and HR=1.24, 95%CI=0.31-5.07, p=0.761 for DFS. PD-L1 was significantly associated with metastasis (OR=8.51, 95%CI=4.3-16.86, p<0.001).

Conclusion: PD-L1 might be a potential prognostic marker in patients with osteosarcoma.

Keywords: meta-analysis; PD-L1; osteosarcoma; prognosis

INTRODUCTION

Osteosarcoma is the most common cancer type of bone originating sarcoma and mainly occurs in adolescents and young adults [1]. Osteosarcoma accounts for approximately 20% of all primary bone tumors [2]. The treatment strategies of osteosarcoma vary in different stages. Surgical resection is the main treatment method for primary tumor and distant metastasis often occurred after surgery. About 40% of osteosarcoma patients are in advanced stage at first diagnosis[3]. Only two-thirds of patients of localized stage are expected to be cured. Novel prognostic markers for osteosarcoma patients are needed to guide clinical management.

As an important mechanism for immune activation and suppression, the programmed cell death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) pathway attractive much attention [4]. PD-L1 is expressed in specific tumors and T and B cells, macrophages [5]. The combination of PD-L1 and PD-1 leads to the suppression of the proliferation and effective responses of T cells [5]. Previous studies showed the prognostic significance of PD-L1 in various solid tumors including colorectal cancer [6], breast cancer [7], prostate cancer [8], hepatocellular carcinoma [9], and ovarian carcinoma [10]. Recent studies also investigated the prognostic value of PD-L1 in osteosarcoma [11-15], whereas the results are inconsistent. Therefore, I performed a meta-analysis to clarify the prognostic and clinical significance of PD-L1 in patients with osteosarcoma.

MATERIALS AND METHODS

Search strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[16]. The ethical approval is not required because all patients are anonymous, and data were collected from the published literature. The databased of PubMed and Web of Science were searched using the following search strategy: ("Programmed Cell Death Ligand 1" or "Programmed Death Ligand 1" or "PDL1" or "B7-H1" or "CD274") and ("osteosarcoma" or "osteogenic sarcoma"). The last search was updated to May 2019. Moreover, the reference lists were also checked for potentially relevant studies.

Selection criteria

The inclusion criteria for eligible studies were as follows: 1) the diagnosis of osteosarcoma was histologically confirmed; 2) the expression of PD-L1 was detected by immunohistochemistry (IHC) or reverse-transcriptase PCR (RT-PCR); 3) PD-L1 was divided as high and low groups; 4) the relationship of PD-L1 and survival and/

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or clinical factors were investigated, and the relevant data were provided or hazard ratio (HR) and 95% confidence intervals (CIs) and be calculated [17]; 5) published in English.

Studies were excluded by the following criteria: 1) reviews, meeting abstract, case reports, or letters; 2) duplicated or overlapping studies; 3) animal studies.

Data extraction and quality assessment

The following information were extracted from eligible studies according to a standardized data-collection protocol: name of the first author, year of publication, study location, sample size, ethnicity, detection method, survival endpoints, HRs and 95%CIs for overall survival (OS) and disease-free survival (DFS). Quality assessment was conducted by using Newcastle-Ottawa Scale (NOS)

[18]. The maximum score of NOS is 9 points and studies scoring greater than six considered to be of high quality.

Statistical analysis

The pooled HR and 95%CI were calculated to measure the prognostic role of PD-L1 for OS and DFS. Statistical heterogeneity among studies was evaluated by Cochran Q test [19] and I2 statistic [20]. I2 >50% or P<0.10 was considered as significant heterogeneity, and the random-effect model was used, otherwise, a fixed-effect model was applied. The odds ratio (OR) and 95%CI were used to evaluate the correlation of PD-L1 and clinicopathological features. Subgroup analysis was performed for further investigation. Publication bias was measured using Begg's funnel plots [21]. The statistical analysis was conducted using Stata version 12.0 (Stata Corporation; Col-

Figure 1. Flow diagram of literature search and selection.
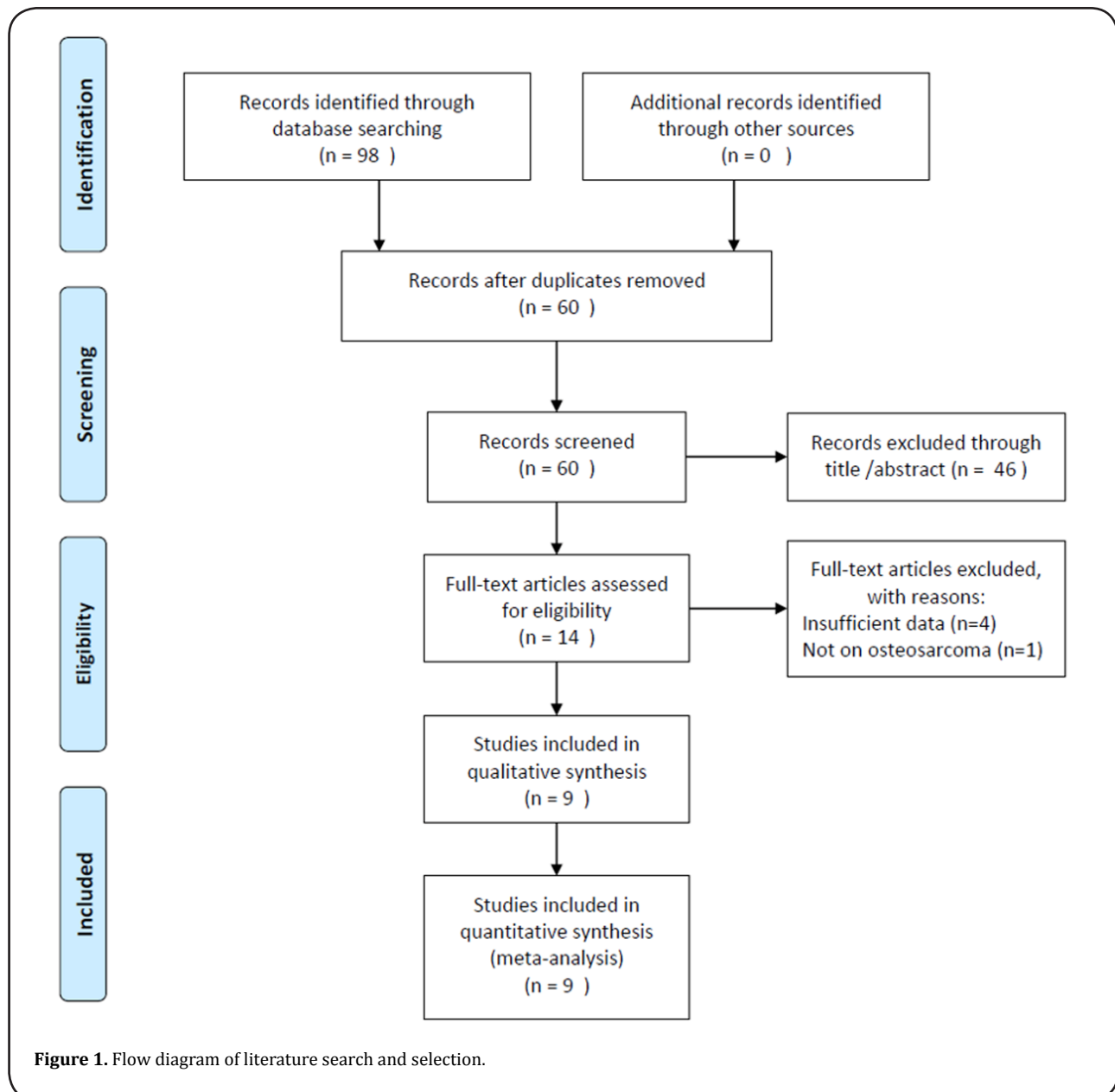
Table 1: Main characteristics of included studies.

Author	Year	Country	Ethnicity	No. of Patients	Detection method	Survival outcomes	NOS score
Jacson K	2014	USA	Caucasian	37	RT-PCR	OS	7
Pratistha	2016	USA	Caucasian	41	IHC	DFS	8
Diego	2017	Brazil	Caucasian	13	IHC	OS	6
Liao	2017	USA	Caucasian	72	IHC	OS, DFS	6
Emanuela	2017	Italy	Caucasian	129	IHC	OS	7
Yang	2018	China	Asian	65	IHC	NA	6
Zhang	2018	China	Asian	93	IHC	OS	7
Liu	2019	China	Asian	69	IHC	OS, DFS	6
Kazushige	2019	Japan	Asian	19	RT-PCR	OS	8

OS: overall survival, **DFS:** disease-free survival, **NOS:** Newcastle-Ottawa Scale, **IHC:** immunohistochemistry, **RT-PCR:** reverse-transcriptase PCR.

lege Station, TX, USA). A P value < 0.05 was considered as statistically significant.

RESULTS

Literature selection and characteristics

A total of 98 studies were identified through initial literature search. After duplicate studies were excluded, 60 records were examined by title and/or abstract. The 46 studies were removed by title and/or abstract screening and 14 studies remained for full-text assessment. After full-text inspection, 6 studies were excluded because of insufficient data (n=5) or not on osteosarcoma (n=1). At last, 9 studies [11-15,22-25] were included in this meta-analysis. The selection process is shown in Figure 1. The included studies published from 2014 to 2019. Three studies were conducted in USA [11,12,14], three in

**Table 2: Pooled HRs and 95% CIs for OS and DFS according to subgroup.**

| Characteristics	No. of Studies	Effects model	Ethnicity	HR (95%CI)	P	Heterogeneity I2(%)	Ph
OS							
Overall	7	Fixed		1.78(1.36-2.32)	<0.001	0	0.574
Ethnicity							
Caucasian	4	Fixed		2.17(1.47-3.2)	<0.001	0	0.869
Asian	3	Fixed		1.48(1.02-2.14)	0.039	4.8	0.35
Sample size							
<50	3	Fixed		1.86(1.03-3.37)	0.039	0	0.831
≥50	4	Fixed		1.75(1.3-2.37)	<0.001	31.3	0.225
NOS score							
>6	5	Fixed		1.95(1.36-2.79)	<0.001	0	0.918
≤6	2	Random		1.52(0.73-3.18)	0.265	68.9	0.073
DFS							
Overall	3	Random		1.24(0.31-5.07)	0.761	91.2	<0.001
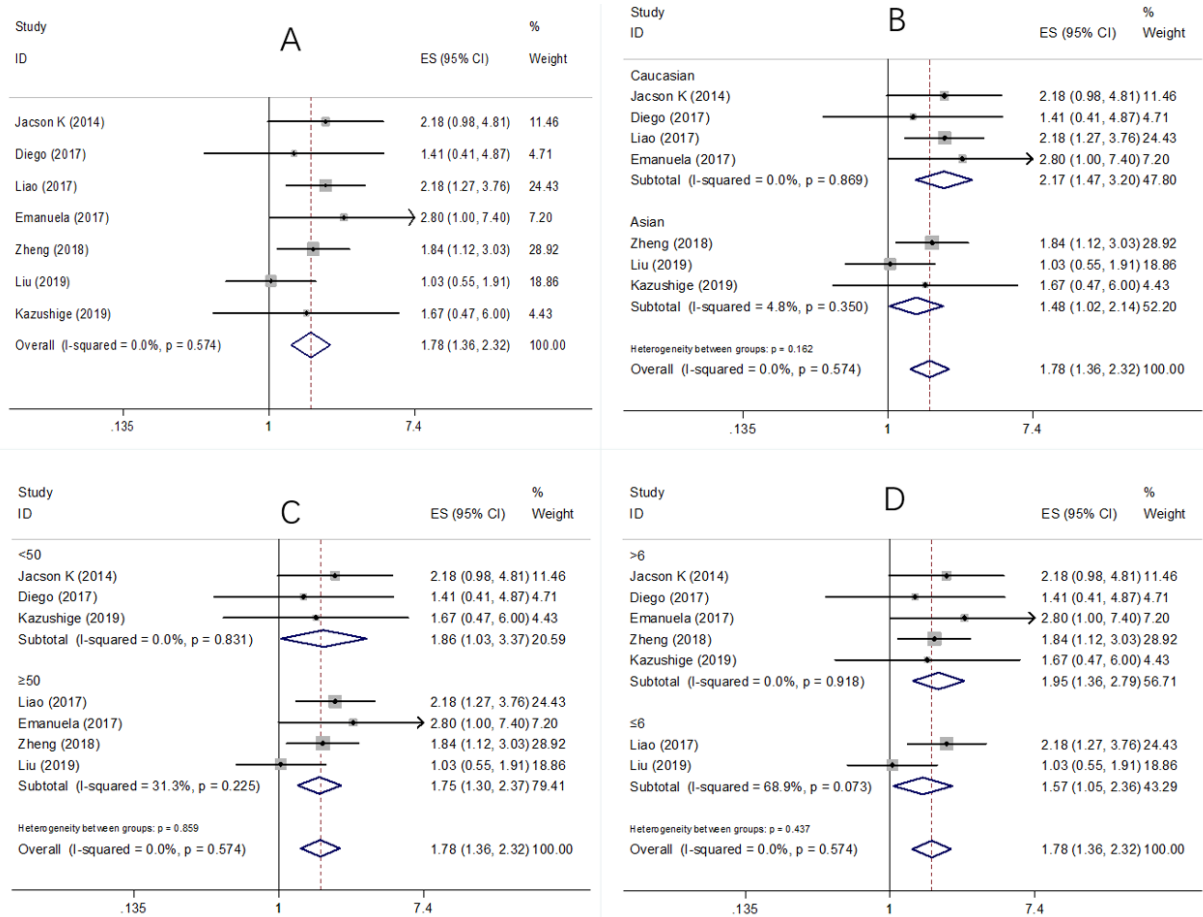
Figure 2. Forest plot of HRs for the association between PD-L1 expression and overall survival (OS) in osteosarcoma patients. **(A)** all patients; **(B)** subgroup analysis by ethnicity; **(C)** subgroup analysis by sample size; **(D)** subgroup analysis by NOS score.

China [22-24], and one in Brazil [13], Italy [15] and Japan [25], respectively. The total sample size was 538, ranging from 13 to 129. All studies were retrospective studies and published in English. The NOS score ranged from 6 to 8, indicating that all eligible studies were of high quality. The main characteristics of included studies were shown
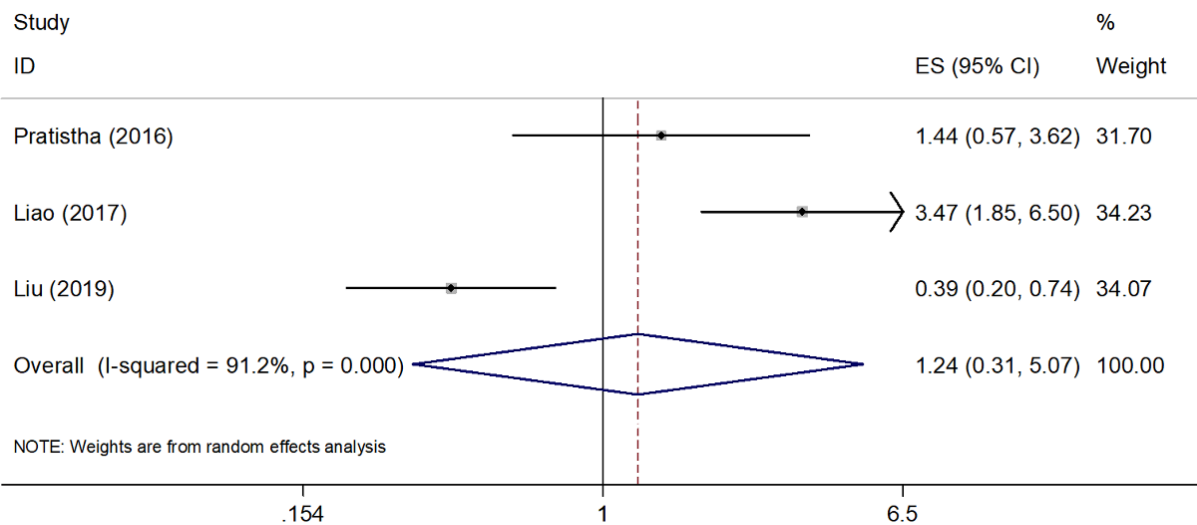
Figure 3. Forest plot of HR for the association between PD-L1 expression and disease-free survival (DFS) in osteosarcoma patients.
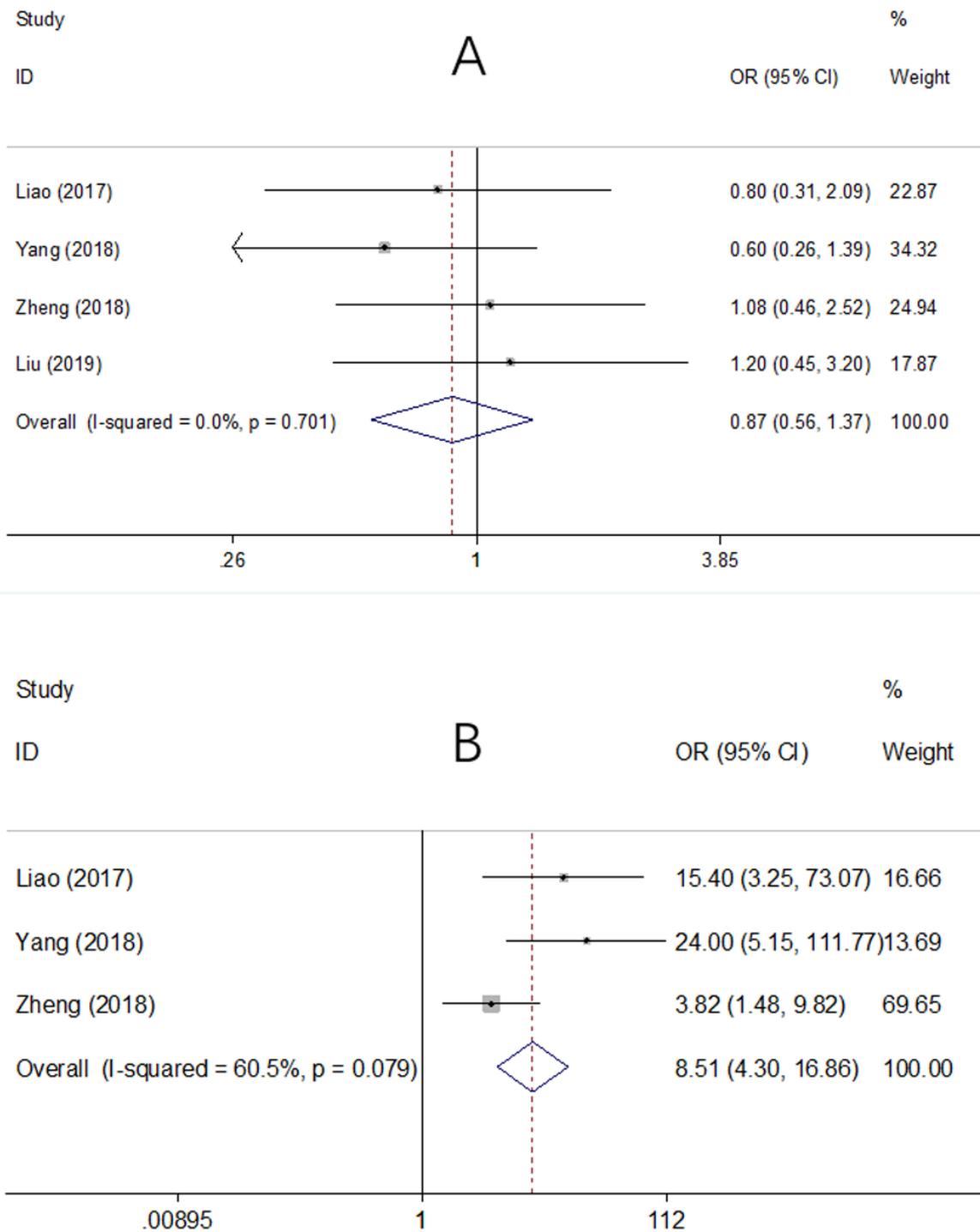
Figure 4. Forest plots of ORs for the association between PD-L1 expression and **(A)** gender (male vs female) and **(B)** metastasis (present vs absent).

in Table 1.

PD-L1 and OS, DFS

Seven studies [11,13-15,23-25] provided the data on PD-L1 and OS in osteosarcoma. The pooled results were: HR=1.78, 95%CI=1.36-2.32, p<0.001, showing that high PD-L1 expression associated with poorer OS (Table 2, Figure 2). To further investigate the relationship of PD-L1 and OS, subgroup analysis by ethnicity, sample size, and NOS score were conducted. The results showed that PD-L1 remained a significant prognostic marker regardless of ethnicity: Caucasians (HR=2.17, 95%CI=1.47-3.2, p<0.001) or Asians (HR=1.48, 95%CI=1.02-2.14, p=0.039), sample size: for n<50 (HR=1.86, 95%CI=1.03-3.37, p=0.039)
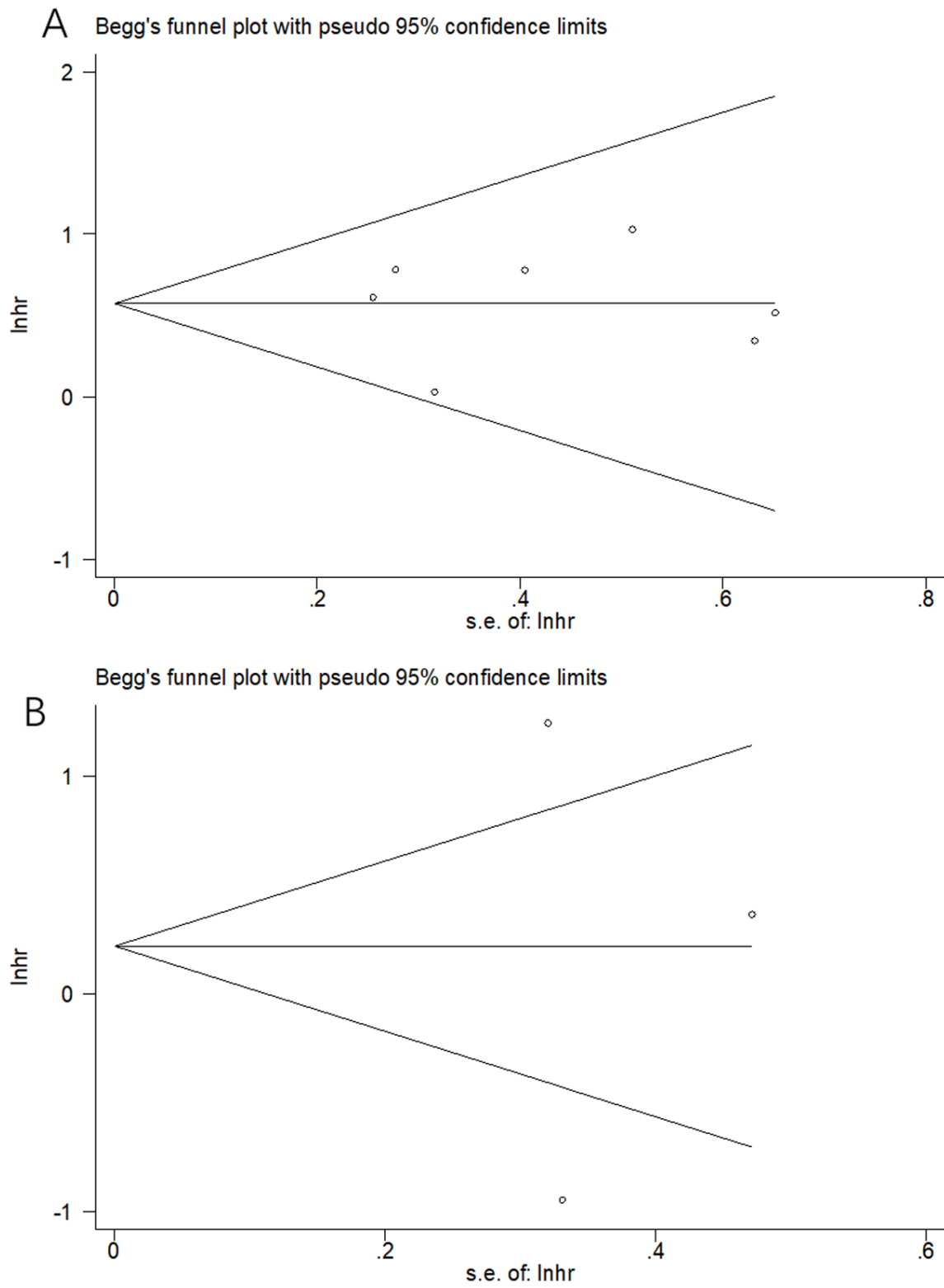
Figure 5. Funnel plots evaluating possible publication bias for **(A)** OS and **(B)** DFS.

and n≥50 (HR=1.75, 95%CI=1.3-2.37, p<0.001). However, PD-L1 had non-significant prognostic value for studies with NOS score ≤6 (HR=1.52, 95%CI=0.73-3.18, p=0.265) (Table 2 and Figure 2). Three studies [12,14,24] investigated the correlation of PD-L1 and DFS in osteo-

sarcoma patients. The combined results were: HR=1.24, 95%CI=0.31-5.07, p=0.761 (Table 2; Figure 3).

PD-L1 and clinicopathological factors

Four studies [14,22-24] presented the data on PD-L1 and

clinicopathological factors including gender (male vs female) and metastasis (present vs absent). As shown in Figure 4, the pooled data were: OR=0.87, 95%CI=0.56-1.37, p=0.556 for gender (male vs female), and OR=8.51, 95%CI=4.3-16.86, p<0.001 for metastasis (present vs absent).

Publication bias

Funnel plots was used to evaluate publication bias. The funnel plots of the studies were symmetrical (Figure 5), showing no significant publication bias.

DISCUSSION

The prognostic and clinical significance of PD-L1 in osteosarcoma were comprehensively analyzed based on data from 9 eligible studies. The aggregated results suggested that elevated PD-L1 expression predicted worse OS and DFS, irrespective of ethnicity and sample size. Furthermore, PD-L1 high expression was also correlated to positive metastasis status. Taken together, this study demonstrated that PD-L1 was a potentially prognostic marker for poor survival and tendency to metastasis in osteosarcoma.

PD-1 and its ligand PD-L1 are often overexpressed in tumor microenvironment, the biding of PD-1 and PD-L1 can induce T cell apoptosis and IL-10 expression to negatively regulate the immune responses and result in immunosuppression [26]. The application of anti-PD-L1 antibodies also showed promising effects in different solid tumors [27-29]. Previous studies also showed the prognostic value of PD-L1 in diffuse large B-cell lymphoma [4], glioma [30], head and neck cancer [31], and non-small cell lung cancer [32]. Li's study showed that positive expression of PD-L1 could serve as a good predictor for poor prognosis of Asian patients with head and neck cancer [31]. The results were in line with our study. Moreover, our data also showed the positive correlation of PD-L1 and metastasis in osteosarcoma. The finding may have clinical implications for osteosarcoma treatment.

Several limitations of the study should be acknowledged. First, the sample size was relatively small. Only 538 patients were included, which may influence the robustness of the statistical results. Second, all included studies were retrospective design. Third, only two clinical factors were investigated, which may ignore correlation of PD-L1 and other clinical characteristics.

In conclusion, this study demonstrated that PD-L1 high expression was associated with poor survival outcomes and positive metastasis status. PD-L1 expression is a significant adverse independent prognostic factor in osteosarcoma. However, due to several limitations, more prospective large-cohort studies are needed to verify these findings.

COMPETING INTERESTS

The author reports no conflicts of interest in this work.

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