

Meta-Analysis

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The potential prognostic and predictive roles of programmed cell death protein 1 expressed by tumor-infiltrating lymphocytes in solid tumors: a meta-analysis

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Abstract

Aim: Several previous studies have evaluated the potential role of programmed cell death protein 1 (PD-1) expressed by tumor-infiltrating lymphocytes (TILs) in various solid tumors and performed its prognosis role in patients' survival with inconsistent results. This study aims to further systematically evaluate the association of PD-1 by TILs with clinicopathological parameters and clinical outcomes in solid tumor patients.

Methods: A comprehensive search was conducted in PubMed, Embase, Web of Science, CNKI and Wanfang databases for relevant studies. The potential prognostic and predictive roles of PD-1 were assessed by pooled hazard ratio (HR), odds ratio (OR) and 95% confidence intervals (CI). A total of 1863 patients were selected for in-depth analysis.

Results: The results demonstrated that PD-1 by TILs was correlated to overall survival for ovarian cancer (HR = 0.40, 95% CI: 0.26-0.61, $P < 0.00001$). Higher PD-1 expression was associated with lymph node metastasis (OR = 2.55, 95% CI: 1.22-5.29, $P = 0.01$) and tumor grade (OR = 3.08, 95% CI: 2.07-4.57, $P < 0.00001$).

Conclusion: The prognostic role of PD-1 by TILs is variant in different tumor types, which highlights the role of PD-1 by TILs as a potential predictive and prognostic biomarker and the development of strategies against the PD-L1/PD-1 axis would be a promising therapeutic target for some solid tumors.



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Keywords: Programmed cell death protein 1, meta-analysis, solid tumors, prognosis

INTRODUCTION

Programmed cell death protein 1 (PD-1), a member of the CD28 receptor family, is expressed by activated lymphocytes and inhibits their proliferation functions after binding to PD-1 ligands such as PD-L1^[1]. The interactions with PD-1/PD-L1 signaling has been shown to improve clinical outcome and restore functional T-cell responses in several cancers^[2].

Although PD-1 has generated increasing interest as a target for immune modulation in cancers, the prognostic values of PD-1 expressed by tumor-infiltrating lymphocytes (TILs) in solid tumors were still unclear^[3]. Several previous studies have reported the PD-1 by TILs is more than a predictive biomarker but as a worse prognosis marker in multiple solid tumors such as gastric cancer^[4], non-small cell lung cancer (NSCLC)^[5], renal cell cancer^[6] and nasopharyngeal cancer^[7]. Another studies showed that PD-1 expression is associated with favorable survival in breast cancer^[8], glioblastoma^[9], metastatic melanoma^[10], ovarian cancer^[11] and primary human papillomavirus-positive head and neck cancers^[12]. Furthermore, one study displayed that the positive expression of PD-1 expression is not correlated with overall survival (OS) for esophageal squamous cell carcinoma (ESCC)^[13]. The different of tissue samples, detection methods and evaluation criterions might be partly responsible for the inconsistent results.

And with the development of PD-L1/PD-1 targeted therapy, some predictive and prognostic biomarkers are crucial to be identified for the option of individualized anti-PD-1 targeted treatment^[14]. Therefore, we conducted this meta-analysis to comprehensively evaluate the prognostic value of PD-1 by TILs in solid tumors, which will further facilitate the development of PD-L1/PD-1 immune check-point targeted therapy and identify novel strategies targeting PD-1.

METHODS

Publication searching

The eligible studies published in PubMed, Embase, Web of Science, CNKI and Wanfang databases were searched using the following keywords: “programmed cell death 1 receptor” or “PD-1” or “programmed death 1” or “CD279 antigen” and “cancer” or “tumor” or “neoplasm” or “carcinoma” and “prognosis” or “outcome” or “survival”. In addition, we also manually screened the reference lists derived from randomized controlled trials and systematic review to avoid omitting related publications. The search language was limited to English and Chinese.

Inclusion and exclusion criteria

Inclusion criteria for this meta-analysis are: (1) full text available; (2) study focus on the association of PD-1 with clinicopathological parameters and OS; (3) cohort study, cross-sectional study or case-control study; (4) sufficient data or higher dots per inch of K-M survival curves. In addition, the exclusion criteria are as follows: (1) cell or animal studies; (2) case reports or review; (3) conference abstracts or comments; (4) repeated articles.

Data extraction and quality assessment

Two investigators (Liu RZ and Ku JW) independently extracted the data from the relevant studies. The disagreements were resolved by consensus. The extracted data are as follows: first author name, publication year, patient source, cancer type, number of patients, detection method, clinicopathological parameters, effect size, hazard ratio (HR) and 95% confidence intervals (CI). The quality of eligible studies were assessed through the Newcastle-Ottawa scale (NOS) method^[15]. Study with NOS scores above to 6 point were usually considered to be higher quality.

Table 1. Features of included studies

Authors	Year	Country	Cancer type	No. of patients	PD-1(+) patients	Clinicopathological parameters	Effect size	HR, 95% CI	NOS score
Badoual <i>et al.</i> ^[12]	2013	France	HNSCC	64	31/33(++/+)	NR	OS	Yes	7
Feng <i>et al.</i> ^[13]	2016	China	ESCC	88	45	B, C, D, E, G	OS	Yes	6
Zheng <i>et al.</i> ^[22]	2016	China	NSCLC	42	15/27(++/+)	B, H, I	OS	NR	7
Shen <i>et al.</i> ^[23]	2017	China	Pancreatic cancer	94	47/47(++/+)	A, B, C, D, E, G	OS	Yes	7
Harter <i>et al.</i> ^[24]	2015	Germany	NSCLC	62	18/44(++/+)	NR	OS	NR	6
Webb <i>et al.</i> ^[25]	2015	Canada	Ovarian cancer	195	75	NR	OS	Yes	6
Duchnowska <i>et al.</i> ^[27]	2016	Poland	Breast cancer	84	17	NR	OS	Yes	6
Chen <i>et al.</i> ^[28]	2016	China	ESCC	349	117	A, B, C, D, E, F	OS	Yes	7
Muenst <i>et al.</i> ^[29]	2013	USA	Breast cancer	660	104	C, D, E, G	OS	Yes	6
Sun <i>et al.</i> ^[30]	2015	China	ESCC	225	69	A, B, C, D	OS	Yes	6

HNSCC: head and neck squamous cell carcinoma; NSCLC: non-small cell lung cancer; ESCC: esophageal squamous cell carcinoma; NR: not reported; A: age; B: gender; C: tumor invasion depth; D: lymph node metastasis; E: tumor stage; F: tumor location; G: tumor grade; H: histology type; I: treatment method; OS: overall survival; HR: hazard ratios; CI: confidence interval; NOS: Newcastle-Ottawa scale

Statistical analysis

All statistical analysis were conducted using the RevMan5.2 and STATA version 12.0 (STATA Corporation, College Station, TX, USA). HR and 95% CI were combined to assess the survival impact of PD-1 in solid tumors. For studies that offered only Kaplan-Meier curves, Engauge Digitizer (version 4.1) was performed to extract the survival data and calculate the estimated HRs and 95% CIs according to Tierney's method^[16]. Additionally, pooled odds ratio (OR) and 95% CI were used to determine the association of PD-1 and clinicopathological features.

Heterogeneity is assessed using Cochrane's *Q* test and *I*² measurement (no heterogeneity, *I*² = 0%-25%; low heterogeneity, 25%-50%; moderate heterogeneity, 50%-75%; high heterogeneity, 75%-100%)^[17]. *P* < 0.1 or *I*² > 50% indicate a significant heterogeneity. Random effects model was initially applied to combine the estimates of effect^[18]. Otherwise, a fixed effects model was utilized^[19]. Sensitivity analysis was used to illustrate any significant heterogeneity among studies. Begg's^[20] and Egger's test^[21] were deemed to explain publication bias with *P* value of less than 0.05.

RESULTS

Characteristics of included studies

A total of 701 studies were identified by electronic search and 388 studies were excluded because of duplication. After reading the titles and abstracts, 221 studies were excluded and 92 possible full text studies were carefully reviewed. Finally, 10 manuscripts containing 12 retrospective cohort studies were included for quantitative analysis in the meta-analysis [Figure 1]. The patients were diagnosed with various solid cancers including: ESCC, NSCLC, hepatocellular carcinoma, pancreatic cancer, breast cancer and ovarian cancer. The features of included studies were presented in Table 1.

To detect the expression of PD-1 by TILs, all studies used immunohistochemistry, except for 2 studies^[22,23], which used quantitative immunofluorescence, but the proportion of PD-1 expression was consistent with the others in that study. The detailed methodologies used to detect PD-1 are summarized in Table 2. Furthermore, 2 cohorts of patients were reported by Harter *et al.*^[24] and Webb *et al.*^[25], respectively. PD-1 by TILs was assessed and the survival curves were reported independently, so they have been statistically analyzed as 4 individual studies.

PD-1 by TILs and overall analysis

A total of 12 studies with 1863 patients were enrolled in survival analysis. Seven studies with data on PD-1 positive expression and OS in solid tumors. There are 2 studies provided OS for breast cancer (2 cohort

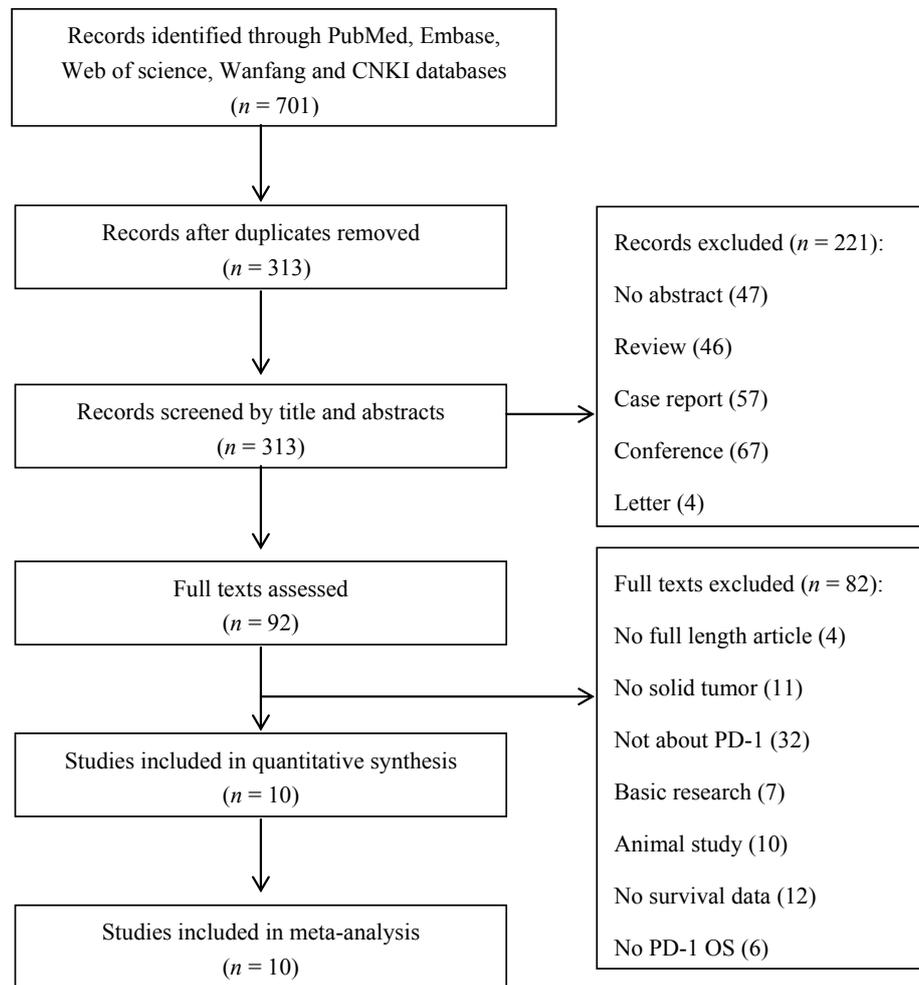


Figure 1. Flow diagram for selection of studies. PD-1: programmed cell death protein 1; OS: overall survival

Table 2. Evaluation of human PD-1 by immunohistochemistry

Authors	Detection method	Antibody clone	Antibody dilution	Antibody source	Cutoff value
Badoual <i>et al.</i> ^[12]	IHC	CT-011	1:100	CureTech LTD	NR
Feng <i>et al.</i> ^[13]	IHC	NR	NR	NR	NR
Zheng <i>et al.</i> ^[22]	IFC	NR	NR	BioLegend	> 12.27% of cells
Shen <i>et al.</i> ^[23]	IFC	AB52587	1:200	Abcam	NR
Harter <i>et al.</i> ^[24]	IHC	NAT-105	1:50	Abcam	Total score > 1 ^a
Webb <i>et al.</i> ^[25]	IHC	NAT-105	1:200	Biocare Medical	NR
Duchnowska <i>et al.</i> ^[27]	IHC	NBP1-88104	1:100	Novus	Total score > 1 ^b
Chen <i>et al.</i> ^[28]	IHC	NAT105	1:100	Abcam	Total score > 1 ^b
Muenst <i>et al.</i> ^[29]	IHC	MRQ-22	1:50	Rocklin	NR
Sun <i>et al.</i> ^[30]	IHC	MRQ-22	1:100	Abcam	Total score > 1 ^b

^aAll samples were scored according to the frequency of positive cells related to all cells (as percentage) on the stained TMA core: frequency 0-1% score 0; 1%-10% score 1; 10%-25% score 2; 25%-50% score 3; > 50% score 4; additionally we multiplied the frequency score with the intensity of staining (1 weak staining, 2 moderate staining, 3 strong staining). ^bTotal score was calculated by adding a score of staining percentage to another score of staining intensity. The area of staining was scored as 0 (no tumor cells stained), 1 (< 25% of cells stained), 2 (≥ 25% of cells stained). Staining intensity was graded as 0 (no staining), 1 (weak staining), 2 (moderate staining), 3 (strong staining). PD-1: programmed cell death protein 1; IHC: immunohistochemistry; IFC: immunofluorescence; NR: not reported

studies in the same one paper), 3 studies for ESCC and 2 studies for ovarian cancer. A random effect model was used to calculate the pooled HR and 95% CI due to the high heterogeneity ($P < 0.0001$, $I^2 = 83\%$). The results showed that PD-1 expression was not associated with patients OS (HR = 0.86, 95% CI: 0.56-1.31, $P = 0.47$)

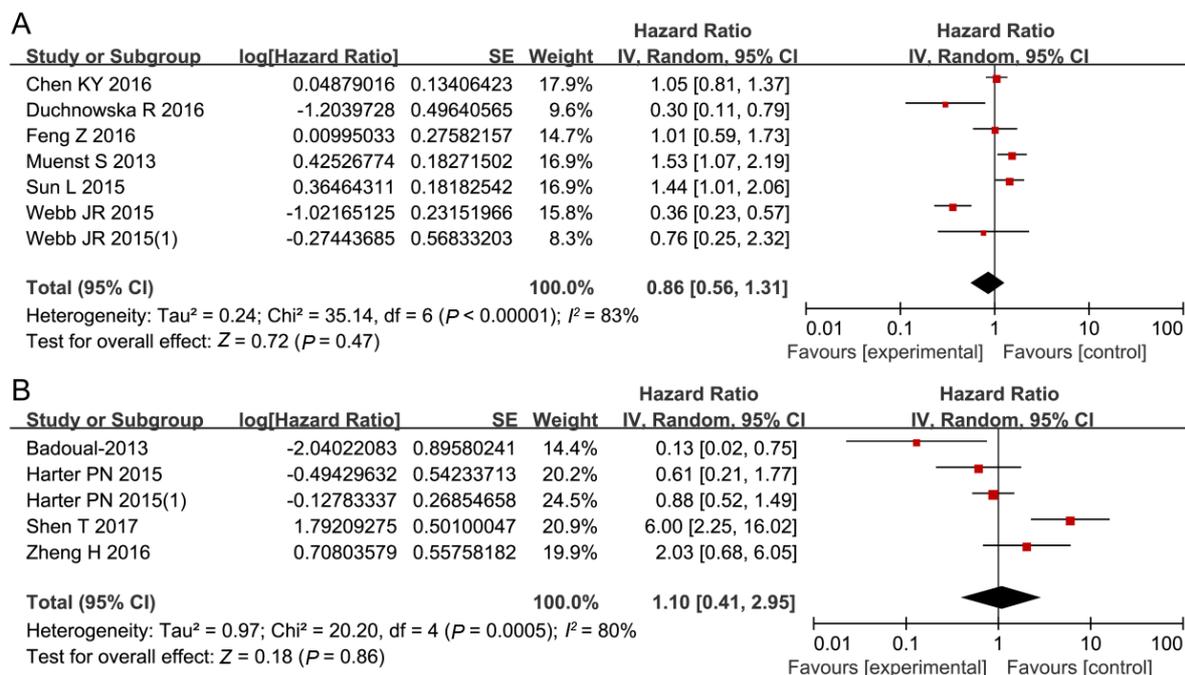


Figure 2. Forest plots of PD-1 expression and OS in solid tumor patients. The squares and horizontal lines correspond to the study-specific HR and 95% CI. The area of the square reflects the study-specific weight. The diamonds represents the pooled OR and 95% CI. The solid vertical line is at the null value (HR = 1). The associations between positive or negative expression of PD-1 (A) and strong or moderate positive expression of PD-1 (B) with OS are shown. PD-1: programmed cell death protein 1; OS: overall survival; HR: hazard ratio; OR: odds ratio; CI: confidence interval

[Figure 2A]. Another 5 studies provided data on PD-1 high or low expression and OS. There are 2 studies provided OS for NSCLC, 1 study for head and neck squamous cell carcinoma, 1 study for pancreatic cancer and 1 study for melanoma. The pooled HR was 1.10 (95% CI: 0.41-2.95, *P* = 0.65) in solid tumor patients with high heterogeneity (*I*² = 80%, *P* = 0.0005) [Figure 2B].

PD-1 by TILs and subgroup analysis

We also conducted subgroup meta-analysis to explore the possible source of heterogeneity. In the subgroup analysis stratified by patients source, pooled HR estimate for OS was 1.15 (95% CI: 0.94-1.40, *P* = 0.16) for Asian patients with low heterogeneity (*I*² = 10%, *P* = 0.33) [Figure 3A], and 0.61 (95% CI: 0.24-1.56, *P* = 0.30) for non-Asian patients with high heterogeneity (*I*² = 89%, *P* < 0.0001) [Figure 3B]. In the stratified analysis by cancer type, there are 2 studies provided OS for breast cancer, 3 studies for ESCC and 2 studies for ovarian cancer. There was no significant association between PD-1 expression and patients OS of breast cancer (HR = 0.72, 95% CI: 0.15-3.55, *P* = 0.69) [Figure 4A] and ESCC (HR = 1.15, 95% CI: 0.94-1.40, *P* = 0.16) [Figure 4B]. With no significant heterogeneity (*P* = 0.22, *I*² = 33%), a fixed-effects model was conducted to evaluate their relationship for ovarian cancer. The results found that PD-1 expression was statistically significantly associated with patients OS (HR = 0.40, 95% CI: 0.26-0.61, *P* < 0.00001) [Figure 4C].

PD-1 by TILs and clinicopathological parameters

The average positive expression rates of PD-1 by TILs were 31.35% in all of the studies. There were the higher PD-1 overexpression in NSCLC, ESCC and pancreatic cancer, with accounting for 35.71%, 61.23% and 50.01%, respectively. And PD-1 expression levels in melanoma, breast cancer and ovarian cancer ranged from 8.59% to 22.97%.

Four studies including 1209 tissue samples investigated the association of PD-1 overexpression with status of lymph node. With significant heterogeneity (*P* = 0.0008, *I*² = 82%), a random-effects model showed a

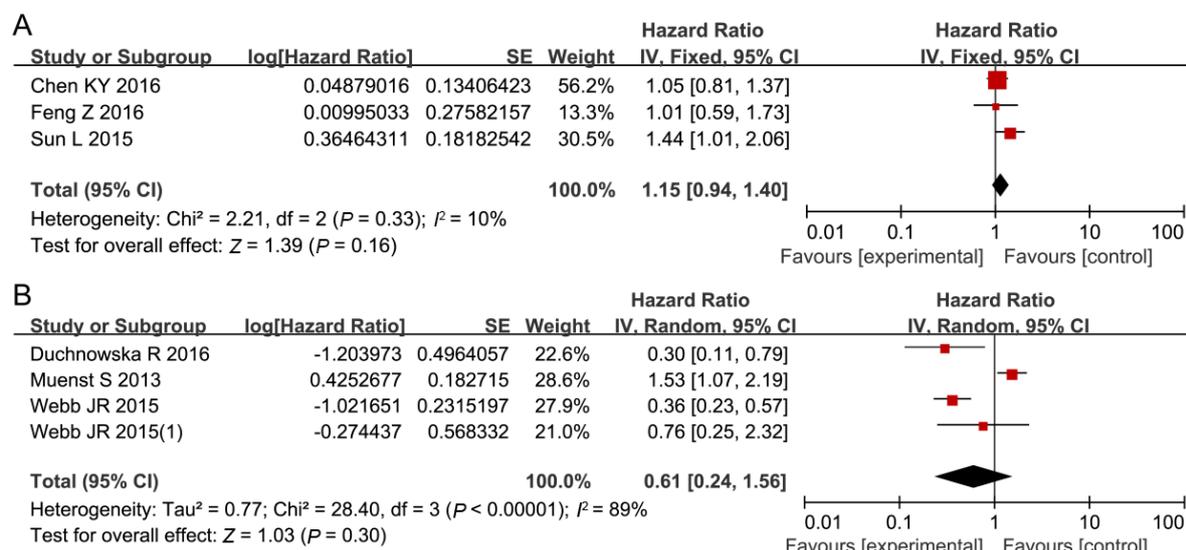


Figure 3. Forest plots for subgroup meta-analysis by patient source. The relationships between PD-1 overexpression and OS in Asia patients (A) and in non-Asia patients (B) are shown. PD-1: programmed cell death protein 1; OS: overall survival; CI: confidence interval

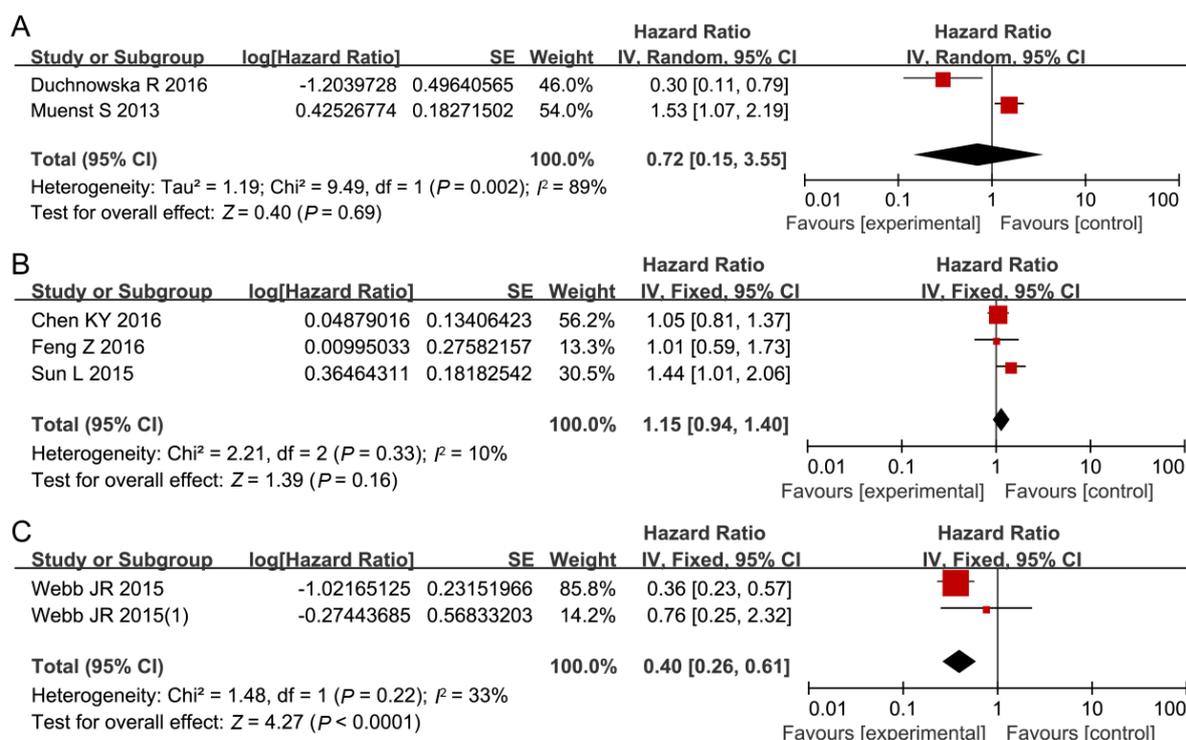


Figure 4. Forest plots for subgroup meta-analysis stratified by cancer type. The relationships between PD-1 expression and OS in breast cancer (A), ESCC (B) and ovarian cancer (C) are shown. PD-1: programmed cell death protein 1; OS: overall survival; ESCC: esophageal squamous cell carcinoma; CI: confidence interval

significant difference between lymph node metastasis group (35.0%) and lymph node non-metastasis group (21.4%) ($\text{OR} = 2.55$, 95% CI: 1.22-2.59, $P = 0.01$) [Figure 5A]; 3 studies reported the relationship of PD-1 overexpression with tumor grade. With no significant heterogeneity ($P = 0.92$, $I^2 = 0\%$), a fixed-effects model was used in the study. The results revealed a significant difference between 274 grade 3/4 tissues (28.1%) and

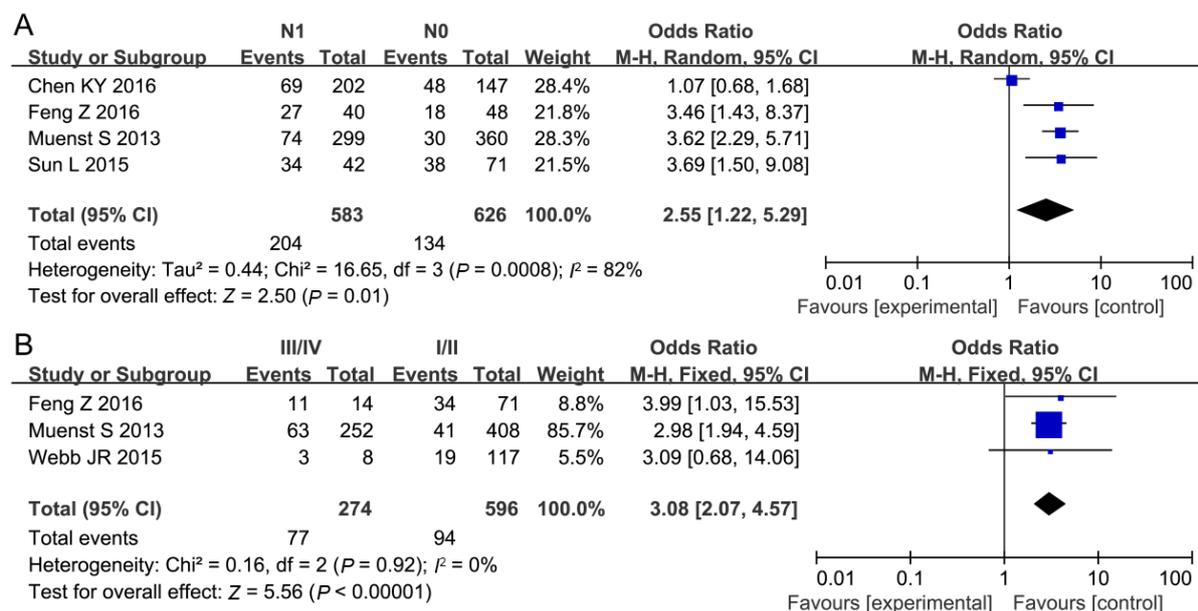


Figure 5. Forest plots of PD-1 expression and the clinical pathological parameters of patients with solid tumors. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the square reflects the study-specific weight. The diamonds represents the pooled OR and 95% CI. The solid vertical line is at the null value (OR = 1). The associations of PD-1 expression with lymph node status (A) and tumor grade (B) are shown. PD-1: programmed cell death protein 1; OR: odds ratio; CI: confidence interval

Table 3. Associations of PD-1 expression and clinical features

Variables	No. of study	OR (95% CI)	Z, P (OR)	Heterogeneity (I ² , P bias)	Publication bias (Egger test) (t, P)	Pooling model
Age (years): ≤ 65 vs. > 65	2	1.20 (0.48-3.02)	0.39, 0.70	73%, 0.06	-	Random
Gender: male vs. female	3	0.96 (0.78-1.18)	0.36, 0.72	0%, 0.81	0.42, 0.748	Fixed
T: T3/T4 vs. T1/T2	4	1.17 (0.61-2.24)	0.48, 0.64	91%, 0.000	0.57, 0.627	Random
Lymph node metastasis: yes vs. no	4	2.55 (1.22-5.59)	2.05, 0.01*	82%, 0.0008	1.09, 0.389	Random
Tumor grade: 3/4 vs. 1/2	3	3.08 (2.07-4.57)	5.56, < 0.0001*	0%, 0.92	0.12, 0.923	Fixed
TNM stage: III/IV vs. I/II	4	1.04 (0.71-1.54)	0.21, 0.84	0%, 0.93	3.38, 0.077	Fixed

*Statistical significance. PD-1: programmed cell death protein 1; OR: odds ratio; CI: confidence interval

596 grade 1/2 tissues (15.8%) (OR = 3.08, 95% CI: 2.07-4.57, P < 0.00001) [Figure 5B]. We did not find the significant association of PD-1 with age, TNM stage or tumor invasion depth in solid tumor [Table 3].

Publication bias

Begg’s and Egger’s test were applied to evaluate the publication bias of the included studies. No obvious asymmetry was presented through the visual assessment of the Begg’s funnel plots [Figure 6]. Furthermore, the formal evaluation of Egger’s test also failed to find the significant bias (P = 0.723).

Sensitivity analysis

Sensitivity analysis was conducted to justify the influence of individual study on the synthetic results of OS. The pooled HR was not significantly influenced after omitting any singly study for the effect of PD-1 expression on OS in our study [Figure 7].

DISCUSSION

PD-1, as one of the co-inhibitory receptors, plays an important role in cancer immunity equilibrium and immunity escape stages^[26]. In the present study, we comprehensively assessed the association of PD-1

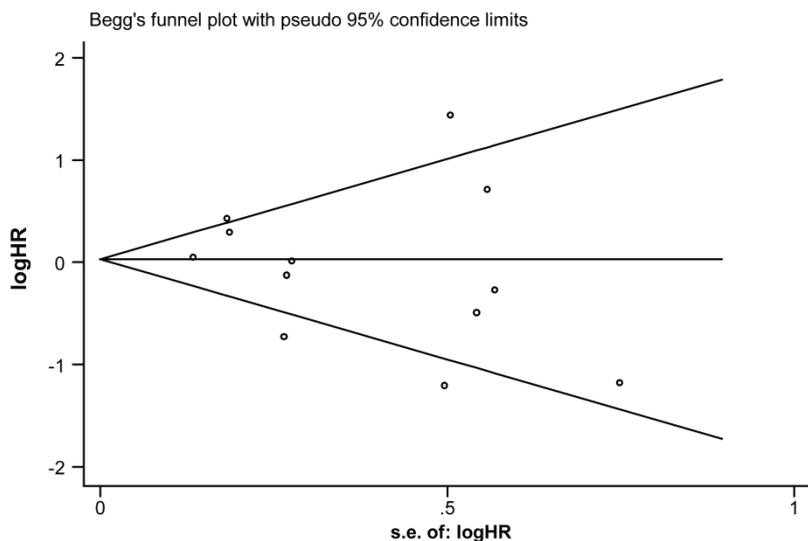


Figure 6. Begg's funnel plot for publication bias analysis. HR: hazard ratio

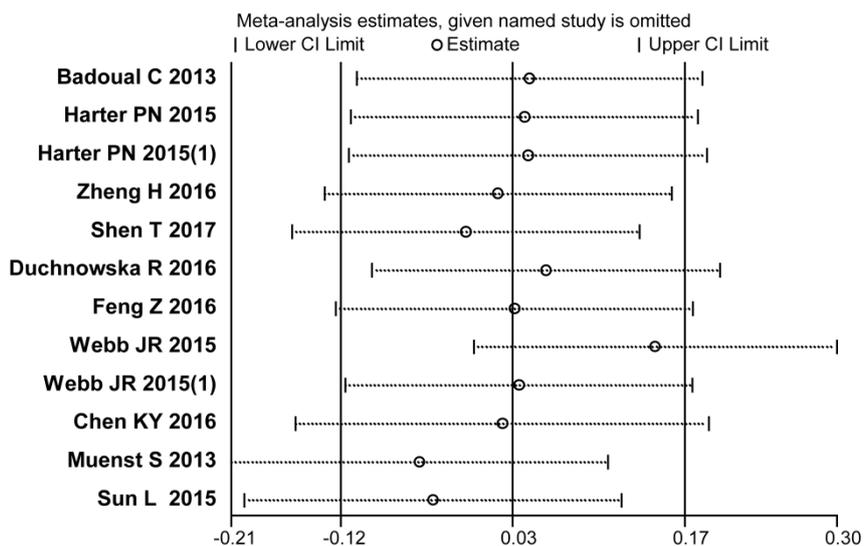


Figure 7. Sensitivity analysis of the meta-analysis. CI: confidence interval

expressed by TILs with OS in solid tumor and revealed that the prognostic role of PD-1 by TILs is variant in different solid tumor types. This study included 10 eligible publications with 12 cohort studies and a total of 1863 patients. To the best of our knowledge, this is the first systematic assessment of the association of PD-1 by TILs with OS in solid tumor.

With respect to the tumor type, when we performed the subgroup meta-analysis stratified by tumor types, ovarian cancer was correlated with better survival for patients with high PD-1 levels rather than other solid tumor. Although PD-1 by TILs was not associated with OS for all of included studies in the meta-analysis^[12,13,22-30]. However, the results of studies using different clone to PD-1 antibodies were controversy in breast cancer^[27,29] [Supplementary Figure 1] in our meta-analysis. One recent study reported the opposite results using variant PD-L1 antibodies in melanoma and lung cancer^[14]. The difference of antibody clones, limited specificity, or distinct IHC protocols used may be partly explain the contradictory results^[31]. Further studies are urgent to clarify the impact of antibodies on the results of studies.

Another important finding in the present study is that patients with lymph node metastasis and tumor grade 3/4 have higher PD-1 by TILs than patients with non-lymph node metastasis and 1/2 tumor grade. It is known that tumor grade and lymph node metastasis are usually major barriers to cancer treatment. And patients developed lymph node metastasis and tumor grade 3/4 have lower survival rates. To a certain extent, PD-1 by TILs may be contributed to the immunosuppression to aggravate the tumor growth and carcinogenesis, and further negatively affecting patients' survival. One study in clinical trials showed that PD-1-positive tumors tend to be more responsive to anti-PD-1 or anti-PD-L1 therapies^[32]. It is reasonable to suggest that patients with lymph node metastasis and tumor grade 3/4 seem to be more sensitive to anti-PD-1 or anti-PD-L1 antibodies-based therapies.

Besides, PD-L1 expression state is another key point of PD-1/PD-L1-mediated tumor immune escape. In tumor tissues, PD-1 was mainly expressed by TILs, and PD-L1 was detected by both tumor cells and TILs^[33]. PD-1 by TILs was significantly correlated with PD-L1 expressed by tumor cells^[34,35]. Furthermore, the findings that PD-L1-positive TILs in cancer provides a suitable microenvironment for the development of tumor growth and treatment resistance, which was known to be mediated by the induction of activated IL-6 signaling^[36,37]. Although immunotherapy using recombinant antibodies and vaccines, such as the therapies targeting PD-L1/PD-1, have been linked with prognosis and treatment response for a few solid tumors including a number of GI malignancies^[38,39], the expression of PD-L1 by CIK cells, TILs, and tumor cells within the tumor microenvironment remains to be elucidated.

Although the quality assessment of included studies is higher, there are still some limitations in the study. First of all, the quality of included studies is with selection bias due to the deletion of some unqualified literatures. Secondly, the screening of language is only English and Chinese and could not represent the whole population. Thirdly, the research objects are mainly cancerous tissues and the potential role of PD-1 in blood specimen remains unclear. Finally, the sample size in some of studies is small and further studies with larger sample size are still needed.

In conclusion, this meta-analysis demonstrates that PD-1 expressed by TILs is associated with lymph node metastasis and tumor grade in solid tumor. And more importantly, the prognostic role of PD-1 is variant in different solid tumors, which assumed that PD-1 by TILs seems to be a potential predictive biomarker and the development of strategies against the PD-L1/PD-1 axis would be a promising therapeutic target for some solid tumors.

DECLARATIONS

Acknowledgments

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Authors' contributions

Conception and design: Zhang DY, Liu RZ, Ku JW, Ma YH, Yi YJ

Manuscript writing: Zhang DY, Liu RZ, Ku JW, Ma YH

Manuscripts review and editing: Zhang DY

Data source and availability

Data are searched in PubMed, Embase, Web of Science, CNKI and Wanfang databases.

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Conflicts of interest

All authors declare no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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REFERENCES

1. Dong H, Strome SE, Salomao DR, Tamura J, Hirano F, Flie DB, Roche PC, Lu J, Zhu G, Tamada K, Lennon VA, Celis E, Chen L. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002;8:793-800.
2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252-64.
3. Lu P, Youngblood BA, Austin JW, Mohammed AU, Butler R, Ahmed R, Boss JM. Blimp-1 represses CD8 T cell expression of PD-1 using a feed-forward transcriptional circuit during acute viral infection. *J Exp Med* 2014;211:515-27.
4. Qing Y, Li Q, Ren T, Xia W, Peng Y, Liu GL, Luo H, Yang YX, Dai XY, Zhou SF, Wang D. Upregulation of PD-L1 and APE1 is associated with tumorigenesis and poor prognosis of gastric cancer. *Drug Des Devel Ther* 2015;9:901-9.
5. Anagnostou VK, Brahmer JR. Cancer immunotherapy: a future paradigm shift in the treatment of non-small cell lung cancer. *Clin Cancer Res* 2015;21:976-84.
6. Xu F, Xu L, Wang Q, An G, Feng G, Liu F. Clinicopathological and prognostic value of programmed death ligand-1 (PD-L1) in renal cell carcinoma: a meta-analysis. *Int J Clin Exp Med* 2015;8:14595-603.
7. Hsu MC, Hsiao JR, Chang KC, Wu YH, Su IJ, Jin YT. Increase of programmed death-1-expressing intratumoral CD8 T cells predicts a poor prognosis for nasopharyngeal carcinoma. *Mod Pathol* 2010;23:1393-403.
8. Baptista MZ, Sarian LO, Derchain SF, Pinto GA, Vassallo J. Prognostic significance of PD-L1 and PD-L2 in breast cancer. *Hum Pathol* 2016;47:78-84.
9. Liu Y, Carlsson R, Ambjorn M, Hasan M, Badn W, Darabi A, Siesjo P. PD-L1 expression by neurons nearby tumors indicates better prognosis in glioblastoma patients. *J Neurosci* 2013;33:14231-45.
10. Thierauf J, Veit JA, Affolter A, Bergmann C, Grunow J, Laban S, Lennerz JK, Grunmuller L, Mauch C, Plinkert P.K, Hess J, Hoffmann TK. Identification and clinical relevance of PD-L1 expression in primary mucosal malignant melanoma of the head and neck. *Melanoma Res* 2015;25:503-9.
11. Darb-Esfahani S, Kunze CA, Kulbe H, Sehouli J, Wienert S, Lindner J, Budczies J, Bockmayr M, Dietel M, Denkert C, Braicu I, Jöhrens K. Prognostic impact of programmed celldeath-1 (PD-1) and PD-ligand 1 (PD-L1) expression in cancer cells and tumor-infiltrating lymphocytes in ovarian high grade serous carcinoma. *Oncotarget* 2016;7:1486-99.
12. Badoual C, Hans S, Merillon N, Ravel P, Benhamouda N, Levionnoks E, Besnier N, Gev A, Pere H, Tran T, Guerin CL, Chauvat A, Dransart E, Alanio C, Albert S, Bruneval P, Gridman WH, Lenoire FM, Oudard S, Johannes L, Olive D, Brasnu D, Tartour E. PD-1-expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV-associated head and neck cancer. *Cancer Res* 2013;73:128-38.
13. Feng Z, Xiang LL, Hai TW, Zuo PW, Bao LH, Hai FZ, Xiao LW, Li L. Programmed cell death 1 expression in esophageal squamous cell carcinoma and association with clinical characteristics. *Indian J Cancer* 2015;52:176-8.
14. Wu P, Wu D, Li LJ, Chai Y, Huang J. PD-L1 and survival in solid tumors: a meta analysis. *PLoS One* 2016;10:e0131403.
15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-5.
16. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;7:16-24.
17. Higgins JP, Thompson SG, Deeks JJ, Altaman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
19. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.
20. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.
21. Egger M, Davey SG, Schneider M. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
22. Zheng H, Liu X, Zhang JH, Shawn JR, Matthias W, Kong YX, Zhu LL, Zhu JJ, Monika J, Chandra PB. Expression of PD-1 on CD4+ T cells in peripheral blood associates with poor clinical outcome in non-small cell lung cancer. *Oncotarget* 2016;7:56233-40.
23. Shen T, Zhou L, Shen H, Shi C, Jia S, Ding G, Cao L. Prognostic value of programmed cell death protein 1 expression on CD8+ T lymphocytes in pancreatic cancer. *Sci Rep* 2017;7:7848-58.

24. Harter PN, Bernatz S, Scholz A, Zeiner PS, Zinke J, Kiyose M, Blasel S, Beschoner R, Senft C, Bender B, Ronellenfitsch MW, Wikman H, Glatzel M, Meinhardt M, Juratli TA, Steinbach JP, Plate KH, Wischhusen J, Weide B, Mittelbronn M. Distribution and prognostic relevance of tumor-infiltrating lymphocytes (TILs) and PD-1/PD-L1 immune checkpoints in human brain metastases. *Oncotarget* 2015;6:40836-49.
25. Webb JR, Milne K, Nelson BH. PD-1 and CD103 are widely coexpressed on prognostically favorable intraepithelial CD8 T cells in human ovarian cancer. *Cancer Immunol Res* 2015;3:926-35.
26. Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases-elimination, equilibrium and escape. *Curr Opin Immunol* 2014;27:16-25.
27. Duchnowska R, Peksa R, Radecka B, Trojanwski T, Jarosz B, Olszewski WP, Och W, Kozłowski W, Kowalczyk A, Loi S, Biernat W, Jassem J; Polish Brain Metastasis Consortium. Immune response in breast cancer brain metastases and their microenvironment: the role of the PD-1/PD-L axis. *Breast Cancer Res* 2016;18:43-51.
28. Chen KY, Cheng GP, Zhang FR, Zhang N, Li D, Jin JY, Wu JZ, Ying LS, Mao WM, Su D. Prognostic significance of programmed death-1 and programmed death-ligand 1 expression in patients with esophageal squamous cell carcinoma. *Oncotarget* 2016;7:30772-80.
29. Muenst S, Soysal SD, Gao F, Obermann EC, Oertli D, Gillanders WE. The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer. *Breast Cancer Res Treat* 2013;139:667-76.
30. Sun L, Liu AL, Ku JW, Wei Y, Liu S, Zhang DY. Programmed death 1 expression on tumor tissues correlates with prognosis in esophageal squamous cell carcinoma patients. *Clin J Exp Surg* 2015;32:1817-9.
31. Xu H, Lin G, Huang C, Zhu W, Miao Q, Fan X, Wu B, Zheng X, Lin X, Jiang K, Hu D, Li C. Assessment of concordance between 22C3 and SP142 immunohistochemistry assays regarding PD-L1 expression in non-small cell lung cancer. *Sci Rep* 2017;7:16956-7034.
32. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014;515:563-7.
33. He Y, Rozeboom L, Rivard CJ, Ellison K, Dziadziszko R, Yu H, Zhou C, Hirsch FR. PD-1, PD-L1 protein expression in non-small cell lung cancer and their relationship with tumor-infiltrating lymphocyte. *Med Sci Monit* 2017;23:1208-16.
34. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, Higuchi T, Yagi H, Takakura K, Honjo T, Fujii S. Programmed cell death 1 ligand1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci U S A* 2007;104:3360-5.
35. Nakano O, Sato M, Naito Y, Orikasa S, Aizawa M, Suzuki Y, Shintaku I, Nagura H, Ohtani H. Proliferative activity of intratumoral CD8(+)T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. *Cancer Res* 2001;61:5132-6.
36. D'Angelo SP, Shoushtari AN, Agaram NP, Kuk D, Qin LX, Carvajal RD, Dickson MA, Gounder M, Keohan ML, Schwartz GK. Prevalence of tumor-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment. *Hum Pathol* 2015;46:357-65.
37. Dai C, Lin F, Geng R, Ge X, Tang W, Chang J, Wu Z, Liu X, Lin Y, Zhang Z, Li J. Implication of combined PD-L1/PD-1 blockade with cytokine-induced killer cells as a synergistic immunotherapy for gastrointestinal cancer. *Oncotarget* 2016;7:10332-44.
38. Abdel RO. PD-L1 expression and outcome of advanced melanoma patients treated with anti-PD-1/PD-L1 agents: a meta-analysis. *Immunotherapy* 2016;8:1081-9.
39. Abdel RO. Correlation between PD-L1 expression and outcome of NSCLC patients treated with antiPD-1/PD-L1 agents: a meta-analysis. *Crit Rev Oncol Hematol* 2016;101:75-85.