Original Article

Expression and prognostic value of PD-L1 and PD-L2 in ovarian cancer

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Background: In the present study, we aimed to investigate the expression and prognostic value of co-stimulatory molecules, programmed death ligand-1 (PD-L1) and PD-L2, in ovarian cancer (OC).

Methods: Immunohistochemical (IHC) staining was used to assess the expressions of PD-L1 and PD-L2 in 77 cases of OC, and 10 cases of benign ovarian cyst were employed as negative controls. Moreover, χ^2 test was used to analyze the correlation between the PD-L1/PD-L2 expression and clinicopathological parameters. Kaplan-Meier method was used to compare the effects of PD-L1/PD-L2 expression level on the overall survival (OS) of OC patients.

Results: PD-L1 and PD-L2 were mainly expressed on membrane and in cytoplasm of OC cells. The high-expression rate of PD-L1 and PD-L2 in OC tissues was 44.16% (34/77) and 22.08% (17/77), respectively. The expression of PD-L1 in OC cells was significantly correlated with FIGO stage (P=0.026), while its expression was not significantly correlated with other clinicopathological parameters. There was no significant correlation between PD-L2 and any clinicopathological parameters. Kaplan-Meier survival analysis showed that the OS of high PD-L1 expression group was significantly shorter compared with the low PD-L1 expression group (HR =2.689, 95% CI: 1.400–5.163). Patients with high PD-L2 expression also exhibited significantly shorter OS (HR =2.204, 95% CI: 1.037–4.682). Multivariable analysis displayed that high expression of PD-L1 (HR =2.275, 95% CI: 1.120–4.169), high expression of PD-L2 (HR =2.314, 95% CI: 1.136–4.714) and FIGO stage (HR =11.229, 95% CI: 1.373–91.865) were independent prognostic factors of OC. When negative expressions of both PD-L1 and PD-L2 were used as a combined prognostic factor, the OS was significantly prolonged (HR =3.396, 95% CI: 1.858–6.029). According to our previous studies, patients with negative PD-L1 expression and high T-bet$^+$ TIL infiltration have higher OS than other patients. Patients with positive PD-L1 expression and low T-bet$^+$ TIL infiltration exhibit the shortest OS. Collectively, our findings provided the basis for PD-1/PD-L1 or PD-1/PD-L2 blockade therapy for OC patients.

Conclusions: Co-stimulatory molecules, PD-L1 and PD-L2, were highly expressed in OC tissues, and their expression levels were correlated with FIGO stage, age and prognosis. These results suggested that PD-L1 and PD-L2 were involved in the occurrence and development of malignant OC, indicating their potential value in clinical diagnosis and prognosis of OC.

Keywords: Co-stimulatory molecule; programmed death ligand-1 (PD-L1); programmed death ligand-2 (PD-L2); T-bet; ovarian cancer (OC)

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Introduction

More than 75% of newly diagnosed cases of ovarian cancer (OC) have reached advanced stage due to limited screening methods and atypical clinical symptoms, and the 5-year survival rate of these patients is less than 30% (1). Beforehand detection and early diagnosis are particularly important for overall survival (OS) of cancer patients. With the development of tumor immunotherapy, co-stimulatory signals have gradually become a hot research field, among which the B7 family plays an important role in T cell activation and anti-tumor immune response. Studies have shown that the expressions of programmed death ligand-1 (PD-L1) and PD-L2 can be detected in a variety of tumor tissues, and their expressions are significantly up-regulated in tumor tissues, such as cervical squamous cell carcinoma, breast cancer, liver cancer and so on (2), providing an important foundation for studying mechanisms underlying the OC. In the present study, we assessed the expressions of PD-L1 and PD-L2 in the tumor tissues of OC patients, analyzed the relationship between the expressions of PD-L1 and PD-L2, evaluated the relationship between their expressions and clinical characteristics, and discussed the prognostic value of PD-L1 and PD-L2 for OC patients.

Methods

General information

A total of 81 paraffin-embedded tissue specimens were obtained from OC patients who underwent surgery in the Third Affiliated Hospital of Soochow University from 2006 to 2012, while only 77 samples were used in the final experiment due to the destruction of experimental process and the loss of follow-up. Informed consent was gained before sample collection. This research was approved by the medical ethics committee of the Third Affiliated Hospital of Soochow University (No. 2015042). Attached is the ethical review form. The follow-up period ended in September 2015. None of the patients received chemotherapy or radiotherapy before surgery, and the patients ranged in age from 27 to 74 years, with an average age of 54.06±9.98 years. There were 53 cases of high-grade serous adenocarcinoma and 24 cases of other types of OC. In addition, 16 cases were in FIGO stage I + II, and 61 cases were in III + IV stage. In terms of tumor differentiation, 50 cases showed poor differentiation, 24 cases exhibited moderate differentiation, three cases displayed undefined differentiation, and 70 cases were found to have distant metastasis. Surgical specimens were collected from primary tumor lesions. Moreover, 10 cases of ovarian cyst were employed as negative controls.

Main experimental instruments and reagents

The pathological tissue blanching apparatus and PDG-1500 type fume hood were purchased from Changzhou Zhongwei Electronic Instrument Co., Ltd., and the DM2500 optical microscope and image acquisition system were obtained from LEICA, Germany. Murine monoclonal antibody against human PD-L1 was supplied by Novus Biotech (1:800). Mouse monoclonal antibody against human PD-L2 was provided by R&D Systems (1:150).

Immunohistochemical (IHC) staining

IHC staining was carried out according to the EnVision™ method. Briefly, paraffin-embedded sections were roasted at 90 ℃ for 1 h, then dewaxed and hydrated according to routine methods. Sections were soaked in hydrogen peroxide at room temperature for 30 min, blocked with serum at 37 ℃ for 30 min, rinsed with PBS, and incubated with primary antibody against PD-L1 (1:800) or PD-L2 (1:150) at 4 ℃ overnight. Subsequently, sections were rinsed with PBS and then incubated with rat universal rabbit secondary antibody at 37 ℃ for 30 min, followed by DAB coloration and hematoxylin counterstaining. Finally, the sections were dehydrated in a gradient series of ethanol, dried and sealed by neutral rubber. The tissue cores with clear tissue structure and uniform staining were selected for quantitative analysis.

Standards of data interpretation

Positive staining of PD-L1 and PD-L2 on cancer cells was judged according to Al-Shibli *et al.* (3). The staining results were blindly evaluated by the two independent

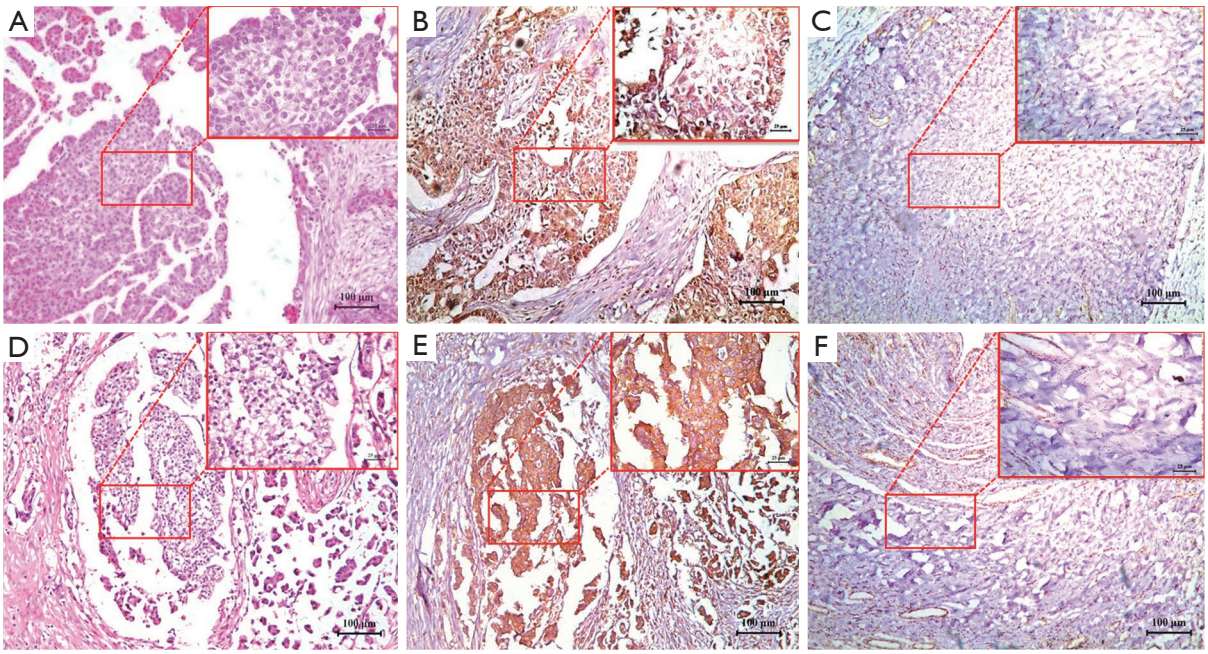

Figure 1 IHC staining for PD-L1 and PD-L2 in OC specimens. Expressions of PD-L1 and PD-L2 in OC and ovarian cyst tissues (A: HE staining of the cancer; B: positive PD-L1 in cancer tissue; C: negative PD-L1 in ovarian cyst group; D: HE staining of cancer tissue; E: positive PD-L2 in cancer tissue; F: negative PD-L2 in ovarian cyst group). IHC, immunohistochemical; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; OC, ovarian cancer.

pathologists of the Third Affiliated Hospital of Soochow University under double-blind conditions using the H-score method. Positive staining was observed with brownish yellow particles in the cytoplasm or on the cell membrane. H-score = (percentage of weakly pigmented tumor cells ×1) + (percentage of moderately colored tumor cells ×2) + (percentage of strongly pigmented tumor cells ×3). The averages of H-score data were taken into statistics.

Statistical analyses

Statistical analysis was performed using SPSS23 and Graphpad Prism 6. Quantitative data were expressed as means ± standard deviation, and the data of cell counts were expressed as adoption rates. The χ^2 test and Fisher's exact probability method were used for comparison between different groups. Kaplan-Meier method and log-rank test were used for survival analysis. Multivariate Cox proportional hazards model was used to analyze correlations between the PD-L1/PD-L2 expression and clinicopathological parameters, such as FIGO stage, age, differentiation, metastasis, histological type and tumor volume.

Results

IHC staining of PD-L1 and PD-L2 in OC tissues

IHC analysis showed that the positive expressions of PD-L1 and PD-L2 were mainly detected on the membrane or in the cytoplasm of OC cells. The high-expression rate of PD-L1 was 44.16% (34/77) in 77 cases of OC, while eight cases of ovarian cyst in the control group exhibited low expression of PD-L1. The high-expression rate of PD-L2 in 77 cases of OC was 22.08% (17/77), while 10 cases of ovarian cyst in the control group displayed low expression of PD-L2 (*Figure 1*).

Relationship between the PD-L1/PD-L2 expression in OC and clinicopathological parameters

The expression of PD-L1 in OC cells was significantly correlated with the FIGO stage (P=0.026), but it was not correlated with other clinicopathological parameters of patients, such as age, histological type, cell grade, tumor diameter, CA125 level and tumor metastasis (P>0.05). The expression of PD-L2 in OC cells was not significantly correlated with the FIGO stage, histological type, cell

Table 1 Relationship between the PD-L1/PD-L2 expression and clinicopathological parameters in OC

Variable	Number	PD-L1				PD-L2			
		High	Low	χ^2	P	High	Low	χ^2	P
Age (years)				3.769	0.052				
<60	52	19	33			12	40	0.093	0.761
≥60	25	15	10			5	20		
Histological type				0.088	0.767			–	0.240
Serous	53	24	29			14	39		
Others	24	10	14			3	21		
Cellular grade				0.036	0.850			0.092	0.762
Middle to well	24	10	14			5	19		
Poor	50	22	28			12	38		
FIGO stage				–	0.026			–	1.000
I + II	16	3	13			3	13		
III + IV	61	31	30			14	47		
Tumor size (cm)				0.027	0.870			1.084	0.298
<10	32	14	18			5	27		
≥10	43	18	25			11	32		
Metastasis				–	0.455			–	0.646
Yes	70	32	38			15	55		
No	7	2	5			2	5		

PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; OC, ovarian cancer.

grading, tumor diameter and tumor metastasis (P>0.05, *Table 1*).

Relationship between the PD-L1/PD-L2 expression and the prognosis of OC

Kaplan-Meier survival analysis showed that the OS in the high-expression group of PD-L1 was significantly shorter compared with its lower-expression group (log-rank χ^2=12.25, P=0.0005, HR =2.689, 95% CI: 1.400–5.163; *Figure 2A*). The OS in the high-expression group of PD-L2 was significantly shortened (log-rank χ^2=6.552, P=0.0105, HR =2.204, 95% CI: 1.037–4.682; *Figure 2B*). Multivariate Cox proportional hazards model showed that high expression of PD-L1 (HR =2.275, 95% CI: 1.120–4.169, P=0.023), high expression of PD-L2 (HR =2.314, 95% CI: 1.136–4.714, P=0.021) and FIGO stage (HR =11.229, 95% CI: 1.373–91.865, P=0.024) were independent risk prognostic factors of OS for OC patients (*Table 2*). Survival analysis using combination of PD-L1 and PD-L2 data showed that when PD-L1 and PD-L2 expressions were both negative in OC tissue, the OS was significantly longer compared with other expressions, and their HR value was higher than that of PD-L1 and PD-L2 alone. In comparison, OS was significantly lower, and HR was higher than any other combined methods (HR =3.396, 95% CI: 1.858–6.029, P<0.0001; *Figures 3,4*). On the basis of the four joint schemes in *Figure 3*, *Figure 4* showed the comparison between one scheme and the other three as a whole.

Relationship between the expressions of PD-L1 and T-bet and the prognosis of OC

Our previous study (4) has shown that significant T-bet$^+$ TIL infiltration can be observed in cancer nests and cancer

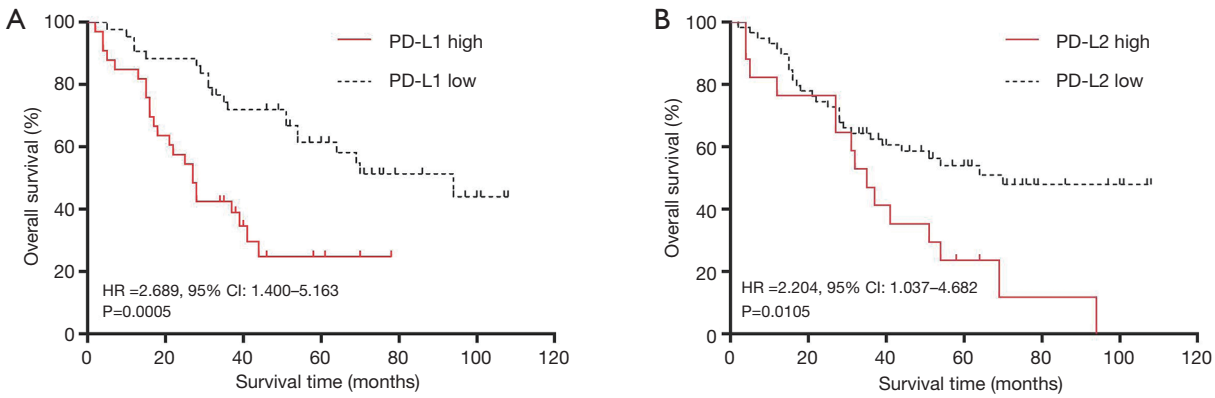

Figure 2 Survival curves of OC patients with different expression levels of PD-L1 and PD-L2. OS in the high PD-L1 expression group was significantly shorter than that in its low expression group (A), and similar trend was observed for PD-L2 (B). PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; OC, ovarian cancer; OS, overall survival.

Table 2 Prognostic effects of OC in multivariate Cox regression analysis

Variable	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age, years (<60/≥60)	1.625	0.875–3.020	0.124	1.801	0.884–3.669	0.105
Histological type (serous/others)	1.125	0.602–2.105	0.712	1.497	0.693–3.235	0.305
Cellular grade (poor/middle to well)	1.843	0.905–3.754	0.092	1.511	0.704–3.246	0.290
FIGO stage (I/II/III/IV)	6.019	1.839–19.704	0.003	11.229	1.373–91.865	0.024
Tumor size, cm (<10/≥10)	0.862	0.469–1.586	0.634	0.578	0.285–1.174	0.130
Metastasis (yes/no)	3.032	0.728–12.623	0.127	0.345	0.027–4.385	0.412
Tumor site (unilateral/bilateral)	1.059	0.580–1.933	0.853	2.062	0.955–4.464	0.065
PD-L1 expression (low/high)	3.032	1.620–5.677	0.001	2.275	1.120–4.619	0.023
PD-L2 expression (low/high)	2.135	1.140–3.996	0.018	2.314	1.136–4.714	0.021

OC, ovarian cancer.

matrix of OC, and patients with high infiltration have better prognosis than those with low T-bet$^+$ TIL infiltration. In the cancer nests, the mean OS of patients with T-bet$^+$ TIL hyperinfiltration was 71.4 months, while it was 49.8 months in patients with low infiltration (P=0.09) (*Figure 5A*). In the cancer matrix, the OS of the two groups was 61.9 and 32.5 months, respectively (P=0.015, *Figure 5B*). The combined data analysis of PD-L1 and T-bet$^+$ TILs in cancer nest revealed that patients with negative PD-L1 expression and T-bet$^+$ TIL hyperinfiltration had better OS than others (P=0.001), while patients with positive PD-L1 expression and low infiltration of T-bet$^+$ TIL had the shortest OS. A similar result was found using combined data analysis of PD-L1 and T-bet$^+$ TILs in cancer stroma. There was no significant difference in the data analysis of PD-L2 and T-bet$^+$ TILs (P>0.05).

Discussion

Previous studies have shown that PD-L1 is expressed in many tumor cells, including gastric cancer, esophageal cancer, lung cancer, breast cancer and so on, and its expression is related to the prognosis of cancer patients (5,6). After PD-L1 neutralizing antibody is used to block PD-L1, cancer immune-escape ability of non-small cell lung cancer (NSCLC) tolerated by radiotherapy resistance

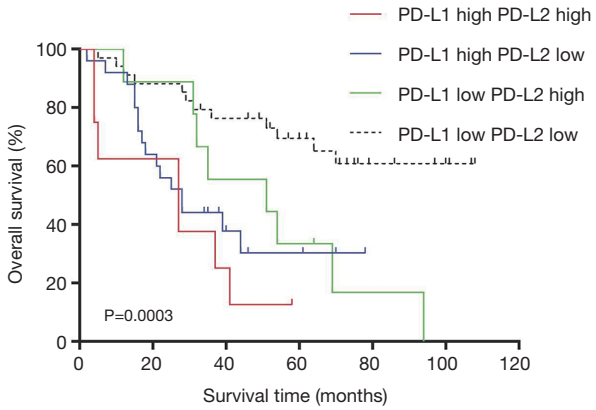

Figure 3 Combined analysis of survival curves of different expression levels of PD-L1 and PD-L2. OS in the group of high PD-L1 expression and high PD-L2 expression, group of high PD-L1 expression and low PD-L2 expression, group of low PD-L1 expression and high PD-L2 expression, and group of low PD-L1 expression and low PD-L2 expression was significantly different. PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; OS, overall survival.

is significantly reversed (7). Head and neck squamous cell carcinoma cells abnormally express PD-L2, which is associated with recurrent or metastatic disease (8). This may be attributed to the apoptosis of T cells in the tumor microenvironment, anti-tumor immunity is inhibited, and lymph node metastasis of the tumor is promoted. OC is an immunogenic tumor (9-11). Qu *et al.* (12) have shown that PD-L1 expressed in OC cells in different degrees, which was related to the differentiation of cancer cells. The expression of PD-L1 in mononuclear cells in ascites or peripheral blood in OC patients was significantly higher than that in benign/borderline lesions (13). However, the predictive role of PD-L1 expression in cancer remains unclear. Few studies have reported the expression of PD-L2 in OC. Our study is the first time to reveal both the expression of PD-L1 and PD-L2 in OC and their combined expression analysis. Although studies have indicated that some drugs, such as Bevacizumab and Olaparib, can improve its prognosis, especially for OC with BRCA mutation (14), the overall prognosis still remains poor for

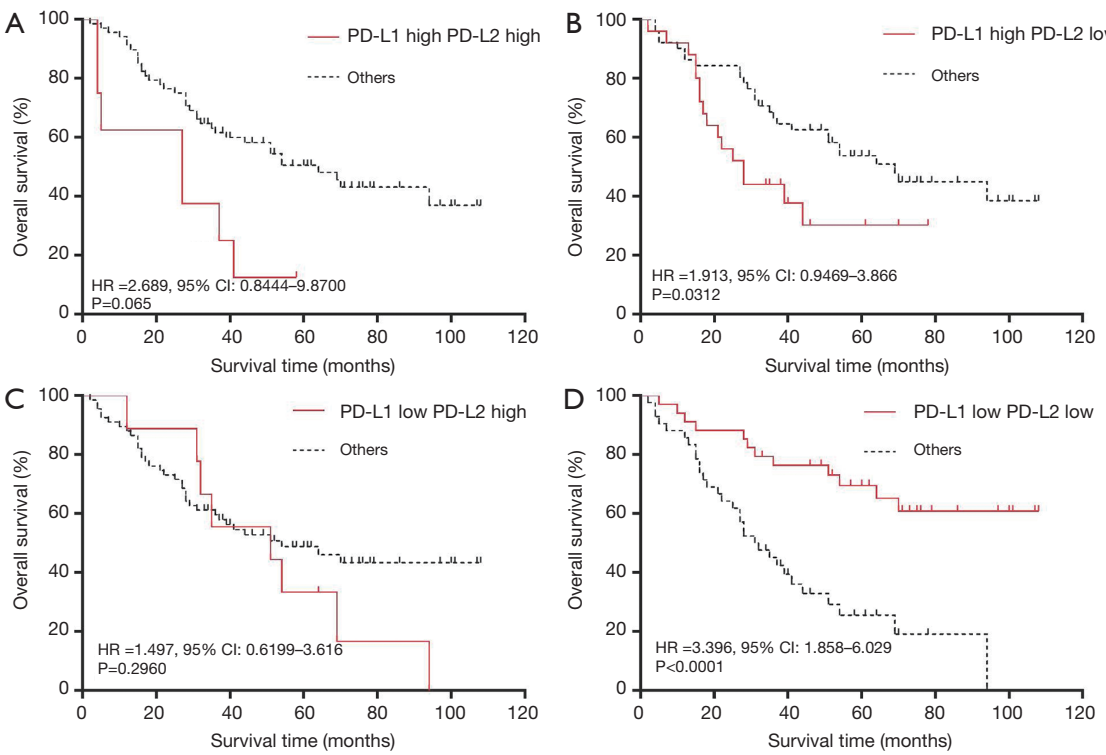

Figure 4 Comparison of survival curves of the combined PD-L1 and PD-L2 expressions. The combined method of PD-L1 low and PD-L2 low had better prognostic predictive value than any other combined methods. *Figure 4* compared one joint scheme with the other three joint schemes as a whole on the basis of *Figure3*. PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2.

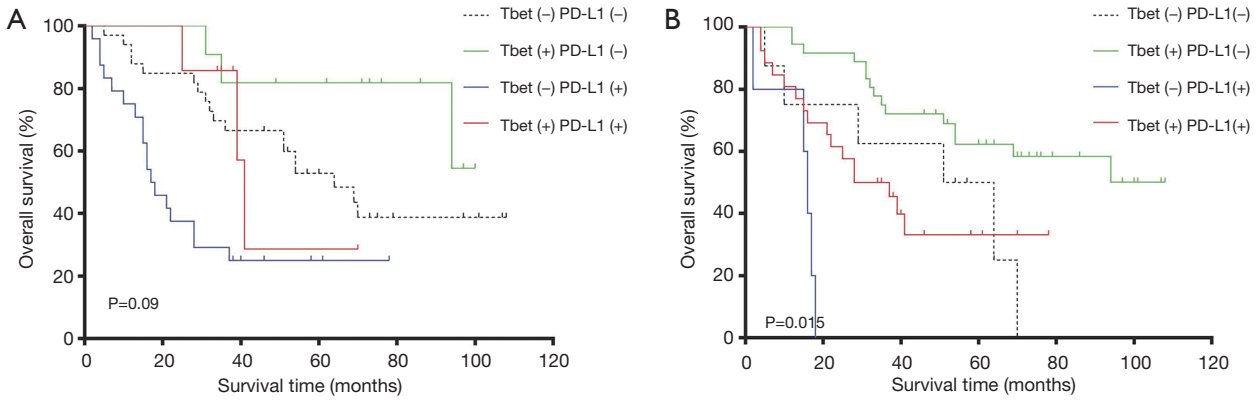

Figure 5 Survival curve of combined solution with different expression levels of PD-L1 and T-bet. (A) It shows the OS in combined solution with different expression levels of PD-L1 and T-bet in OC nest; (B) it shows that in OC nest. PD-L1, programmed death ligand-1; OC, ovarian cancer; OS, overall survival.

the recurrent OC (15,16).

PD-L1 and PD-L2 are up-regulated in a variety of tumor cells, leading to reduced anti-tumor immune response. As important cell cycle checkpoints, the PD-1/PD-L1 and PD-1/PD-L2 pathways play a specific antigen-dependent negative regulatory role and are potential targets of drug intervention in the body and anti-tumor immunotherapy (17). Therefore, the effect of PD-L1/PD-L2 can be blocked by a specific anti-PD-L1/PD-L2 monoclonal antibody or its soluble inhibitory factor, thereby enhancing the function of cytotoxic T lymphocytes in killing tumor cells (18,19). The gene encoding PD-L1/PD-L2 can also be introduced into a viral vector, and an antigen-specific viral vector-based vaccine can be designed to perform immunological intervention therapy on the tumor (20).

In this study, we found that PD-L1 and PD-L2 were highly expressed in OC tissues, showing a positive rate of 43.04% and 22.22%, respectively. The expressions of PD-L1 and PD-L2 were significantly associated with FIGO stage of OC. Survival analysis showed that the prognosis of OC patients in the high-expression group of PD-L1/PD-L2 was inferior to that of the lower-expression group. Survival analysis using combined data of PD-L1 and PD-L2 showed that when PD-L1 and PD-L2 expressions were both negative in OC tissues, the OS was significantly longer compared with other expressions, and their HR value was higher than that of PD-L1 and PD-L2 alone, indicating that its predictive value was better compared with the individual analysis. T-bet is an important transcription factor that regulates the differentiation and function of $CD4^+$ Th1 cells and $CD8^+$ CTLs. The expression of T-bet in TILs, such as OC, gastric cancer and hepatocellular carcinoma, is closely related to the stage and prognosis of the tumor (21,22). Hamanishi *et al.* have observed a significant negative correlation between $CD8^+$ T lymphocyte counts in ovarian epithelial cells and PD-L1 expression in tumor cells (23). As an important transcription factor regulating the development, differentiation and function of $CD8^+$ T cells, T-bet can enhance the effect of $CD8^+$ T cells and inhibit the expression of CD127, playing a fundamental role in the anti-tumor immune response (24,25). The OS of OC patients with negative PD-L1 expression and T-bet^+ TIL hyperinfiltration was significantly longer than that of other groups.

It is well-known that innate immune resistance and adaptive immune resistance, as two general mechanisms, have been emerged for the regulation of PD-L1 by tumor cells (26). The adaptive change in PD-L1 expression would be expected to correlate with local TILs, indicating that focal PD-L1 expression is largely limited to the tumor-stroma interface (27,28). Some studies have indicated that lack of tumor PD-L1 expression in combination with higher score of intraepithelial $CD8^+$ TILs predicts better survival in high-grade serous OC (HGSOC) patients (29,30). It also shows a similar pattern in PD-L2 (31). The combination of PD-L1 expression and intraepithelial $CD8^+$ TILs would have more promising prognostic and predictive potential than either one alone (32,33). Till now, the efficacy of PD-1/PD-L1 blockade therapy in OC remains rather low compared with other tumors, such as NSCLC and melanoma. It is necessary to further investigate the correlation between PD-$L1^+$ and PD-$L2^+$ lymphocyte

subgroups and the patients' prognosis in future study.

Collectively, we showed that the combined expression level of PD-L1 and PD-L2 was an important predictor of prognosis in OC patients. Moreover, the combined data analysis of PD-L1 and T-bet was of great value in evaluating the prognosis of OC patients. Furthermore, the relationship between PD-L2$^+$ and CD8$^+$ T lymphocytes as well as mechanism of regulatory T cells and PD-L1 needs to be further investigated.

Acknowledgments

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.01.09). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research was approved by the medical ethics committee of the Third Affiliated Hospital of Soochow University (No. 2015042) and written informed consent was obtained from all patients.

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