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Clinicopathological and Prognostic Value of Programmed Death Ligand-1 (PD-L1) In Breast Cancer: A Meta-Analysis

Qi Xue*and Guochao Zhang

Department of Thoracic Surgery, Cancer Hospital of Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China

Abstract

Background: The association of immunological checkpoint marker programmed death ligand-1 (PD-L1) and the prognosis of various malignancies has been widely observed, recently. However, the association between PD-L1 expression and breast cancer patients' survival remains controversial. Thus, we performed this study to assess the clinical value of PD-L1.

Methods: We searched the electronic databases for eligible literature. Medline/PubMed, EMBASE, the Cochrane Library databases and Grey literature were searched up to 30 March 2016 for the association between PD-L1 expression and breast cancer prognosis. Hazard ratios (HRs) for overall survival (OS) with 95% confidence intervals (CIs) according to the expression status of PD-L1 were calculated from the included studies. Moreover, the odds ratio (OR) was also analyzed to evaluate the association between the clinicopathological parameters of participants and PD-L1 expression.

Results: 10 studies were included in the meta-analysis while 7 for clinical pathological features and PD-L1. We found that elevated PD-L1 had no significant association with breast cancer patients' survival. However, increased PD-L1 was found to be significantly associated with histological grade (OR=1.86, 95% CI: 1.38-2.51; $P_{heterogenecity}$=0.0196), ER (OR=0.36, 95% CI: 0.17-0.75; $P_{heterogenecity}$=0.000), PR (OR=0.31, 95% CI: 0.11-0.86; $P_{heterogenecity}$=0.000) in breast cancer.

Conclusion: We currently can't draw a valid conclusion that PD-L1 status is a predictor of prognosis for patients with breast cancer. Then we should deeply explore the mechanism related to PD-L1 with immune escape and antitumor immune response. Further, develop an evaluation standard for PD-L1 expression which can exactly give the prediction of whether PD-L1 can trigger immune escape or antitumor response. What's more conduct the researches on different molecular subtype. So that make clear whether the PD-L1 related drugs can be used clinically for the very type of breast cancer patients.

Keywords: PD-L1; Breast cancer; Prognosis; Meta-analysis; Clinicopathological features

Introduction

Breast cancer is the most common malignant tumor in women around the world [1]. Although recent advances in surgery and adjuvant therapies have improved the prognosis, however, the overall prognosis for metastatic breast cancer patients remains poor. These days, scientists find the development and prognosis of malignant tumors are closely related to host immune functions. In tumor lesion the immune environment is composed of tumor cells, immune cells, cytokines, and stromal cells [2]. We called the immune cells tumor invasive lymphocytes (TIL). The role of healthy immune system in controlling the progression of malignant disease is well established. So the immune escape along with cancer is the major cause of cancer progression [3]. This is considered being connected by PD-L1 (programmed death ligand 1).

PD-L1 is an important immune checkpoint that mediates tumor-induced immune suppression. PD-L1 expression has been observed in various malignancies. Moreover, several meta-analyses have proved that PD-L1 overexpression indicates a poor prognosis for patients with non-small cell lung cancer and gastrointestinal tract cancer [4-6]. However, the association between PD-L1 expression and the breast cancer survival of patients remains controversial. PD-L1 usually expressed on tumor cells while, PD-1 (programmed death 1) mostly expressed on tumor-infiltrating lymphocytes [7]. Scientists have conducted some researches on PD-L1 and breast cancer, they found PD-L1 expression is associated with poor clinical and pathological features of breast cancer [8-15]. The main mechanism is reported that PD-L1 inhibit the proliferation of activated T-cells and induce the apoptosis of T-cells to form and maintain an immunosuppressive microenvironment since PD-L1 can recognize and bind the PD-1 on tumor-infiltrating lymphocytes [16]. However, last year, some researchers found PD-L1 expression was significantly associated with better OS (p=0.04) in breast cancer patients, including analyzing mRNA expression and using DNA microarray [17,18]. Thus, someone thought PD-L1 expression is considered a positive prognostic biomarker in breast cancer.

Now the prognostic role of PD-L1 in breast cancer is still under debate and requires further comprehensive study to clarify. Thus, we performed a meta-analysis by incorporating all available evidence to reveal the prognostic value of PD-L1 in breast cancer. Meanwhile, analyze the relationship of PD-L1 and the clinical pathological features.

***Corresponding author:** Qi Xue, Department of Thoracic Surgery, Cancer Hospital of Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China, Tel: 008618801038718; E-mail: 799692578@qq.com

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Materials and Methods

Literature search strategy

Two authors of us independently searched for published abstracts and articles. The searched international databases include PubMed, the Cochrane Library databases, EMBASE and Grey literature up to 30 March 2016. The key terms are "PD-L1", "B7-H1", "CD274", "B7 homolog 1" or "programmed death ligand-1" and "breast cancer" and "survival" or "prognosis". We all manually reviewed relevant manuscripts, conference summaries and reference lists and reviews.

Our institutions Ethics Committee have exempted our study from Institutional Review Board approval as our study involves exclusively preexisting anonymous data. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement for reporting systematic reviews recommended by the Cochrane Collaboration was followed for conducting this meta-analysis.

Selection criteria

Studies met the following criteria were eligible for the meta-analysis of PD-L1 expression and breast cancer prognosis, PD-L1 expression and clinicopathological features: (1) data from breast cancer patients; (2) all of the patients were pathologically confirmed; (3) correlation between PD-L1, clinicopathological features and prognosis was described. Articles were excluded from the analyses according to the following criteria: (1) non-English papers; (2) non-human experiments; (3) review articles, case reports or letters; (4) duplicate publication; (5) insufficient data to report the risk ratios (RR) and 95% confidence interval (95% CI).

Data extraction

All data were extracted by two independent reviewers (ZGC&XQ). The quality of the selected articles was assessed according to the Newcastle-Ottawa Scale (NOS) [19]. Data tables were generated to extract all relevant data from texts, tables and figures, including: author, year of publication, country, patient number, cancer type, specimen, detection method, analysis method, the cut-off value, risk ratio, duration of follow-up as well as positive rates of PD-L1 overexpression. OS data were extracted in the form of hazard ratios (HRs) with the corresponding 95% confidence interval (CI). The data collection and assessment of methodological quality followed the quality of reporting of meta-analyses (QUORUM) and the Cochrane Collaboration guidelines (http://www.cochrane.de). All investigators discussed and resolved all discrepancies in the extracted data. All of the eligible studies were of high quality.

Statistical analysis

We performed heterogeneity test among different studies using Q test and I2 statistic. The fixed effect model with Mantel and Haenszel method was used to do the Meta analysis, when the P value of Q test>0.05 and the I2<50%. Otherwise, the random effect model with DerSimonian and Laird method was adopted [20,21]. The pooled hazard ratio (HR) and its 95% confidence interval (CI) were estimated to evaluate the prognosis difference of PD-L1+ group and PD-L1- group. The pooled risk ratio (RR) and its 95% confidence interval (CI) were estimated to evaluate the clinicopathological difference of PD-L1+ group and PD-L1- group. We used funnel plot and Egger's test, as well as Begg's test to assess the publication bias. The P values are two-sided. The significance level was set to be 5%. The statistical analysis was finished using STATA 13.0 (StataCorp, College Station, Texas, USA).

Results

Search results

192 manuscripts were selected according to the search strategy. From the title and abstract review, 182 of the articles were excluded due to non-English papers, non-human experiments, non-breast cancer related studies, non-prognostic researches or non-original articles (e.g. review, letter, case report). Finally, a total of 10 studies were included in the main meta-analysis of PD-L1 and survival, while, 7 for clinical pathological features and PD-L1.

Study selection and characteristics

All features of the 10 eligible studies are listed in Table 1 [8-15,17-18]. Clinical pathological feature use 7 studies from them listed in Table 2. The publication years of the eligible studies ranged from 2014 to 2015. The number of patients in each study ranged from 192 to 5454. The quality of the enrolled studies varied from 5 to 8, with a mean of 7. The clinicopathological features including tumor size, nodal statues, histological grade and (estrogen receptor/progestogen receptor/human epidermal growth factor receptor) ER/PR/HER-2 statues. PD-L1 expression levels were measured in tumor tissue. In addition, tissue immunochemistry staining (IHC) for PD-L1 expression was utilized in 8 studies. The remaining two study applied mRNA technology to detect PD-L1 expression (Table 1). In all studies, none of the patients received neo-adjuvant radio- or chemo-therapy prior to surgery.

Main results

Since the researches use different index for survival (OS/OSS/DFS/MFS/RFS), as shown in Table 3, we divided them into 4 groups. However, we found that elevated PD-L1 had no significant association with breast cancer patients' survival (Figures 1a-1d).

However, in the analysis of the clinical pathological feature, we can see the relationship between elevated PD-L1 and clinicopathological parameters in Table 4. In breast cancer, increased PD-L1 was found to

Author	Year	N	Evaluation	HR	LCI	UCI	Outcome
Qin	2015	870	IHC	1.788	1.195	2.674	OS
Baptista	2015	192	IHC	0.3	0.09	0.94	OS
Park	2015	333	IHC	2.08	0.86	5.04	OS
Muenst	2014	650	IHC	3.063	2.318	4.047	OS
Sabatier	2014	5454	DNA microarray	0.52	0.35	0.77	OSS
Qin	2015	870	IHC	1.386	1.003	1.916	DFS
Baptista	2015	192	IHC	0.84	0.39	1.83	DFS
Park	2015	333	IHC	1.21	0.56	2.62	DFS
Schalper	2014	398 (YTMA201)	QIF	0.268	0.099	0.721	RFS
Sabatier	2014	5454	DNA microarray	0.55	0.38	0.79	MFS

Table 1: The basic information for each study [13,15117].

Study	Author	Detection Method	Year
1	Schalper (398(YTMA201))	QIF	2014
2	Qin	IHC	2015
3	Baptista	IHC	2015
4	Park	IHC	2015
5	Cimino-Mathews	IHC	2015
6	Muenst	IHC	2014
7	Sabatier	DNA microarray	2014

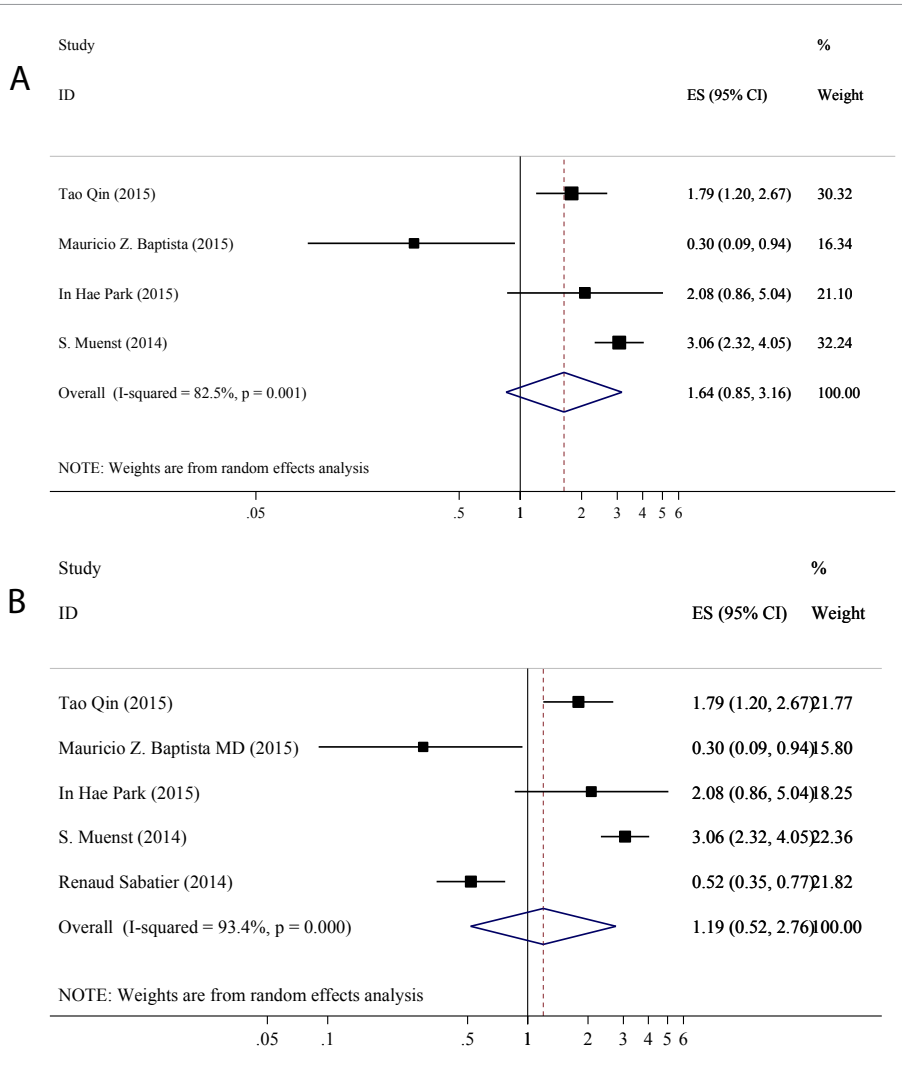
Table 2: Clinical pathological feature studies [13,15,17].

Index	TYPE	Meta-analysis					Heterogeneity test			Model	Publication bias (P value)	
		HR	95%CI		z value	P value	I^2	Q value	P value		Begg's test	Egger's test
A	**OS**	1.640	0.852	3.160	1.48	0.139	82.5%	17.14	0.001	Random	0.308	0.187
B	**OS+OSS**	1.194	0.517	2.757	0.42	0.677	93.4%	60.42	<0.001	Random	0.806	0.439
C	**DFS**	1.276	0.966	1.686	1.72	0.086	0.0%	1.39	0.498	Fixed	0.296	0.370
D	**DFS+MFS+RFS**	0.776	0.444	1.353	0.90	0.371	80.1%	20.08	<0.001	Random	0.462	0.566

Table 3: The result of meta-analysis.

VAR	Meta-analysis					Heterogeneity test			Model	Publication bias (P value)	
	OR	95%CI		z value	P value	I^2	Q value	P value		Begg's test	Egger's test
AGE	0.91	0.78	1.06	1.24	0.2160	41.63	1.71	0.1906	Fixed	1.0000	NA
TumorSize	1.33	0.92	1.92	1.49	0.1356	75.42	20.35	0.0011	Random	0.7071	0.9632
Nodal	1.37	0.98	1.91	1.82	0.0687	80.26	25.32	0.0001	Random	0.2597	0.3878
Histologic	1.86	1.38	2.51	4.05	**0.0001**	62.78	13.43	0.0196	Random	1.0000	0.3907
ER	0.36	0.17	0.75	2.73	**0.0064**	95.39	86.72	0.0000	Random	0.4624	0.7512
PR	0.31	0.11	0.86	2.25	**0.0243**	96.36	55.00	0.0000	Random	1.0000	0.6890
HER-2	1.22	0.85	1.73	1.08	0.2822	60.96	12.81	0.0253	Random	0.7071	0.7838
Ki67	1.16	0.51	2.68	0.36	0.7221	95.16	62.01	0.0000	Random	1.0000	0.2353
Luminal	1.39	0.74	2.62	1.02	0.3061	81.67	10.91	0.0043	Random	1.0000	0.6900

Table 4: The result of meta-analysis.



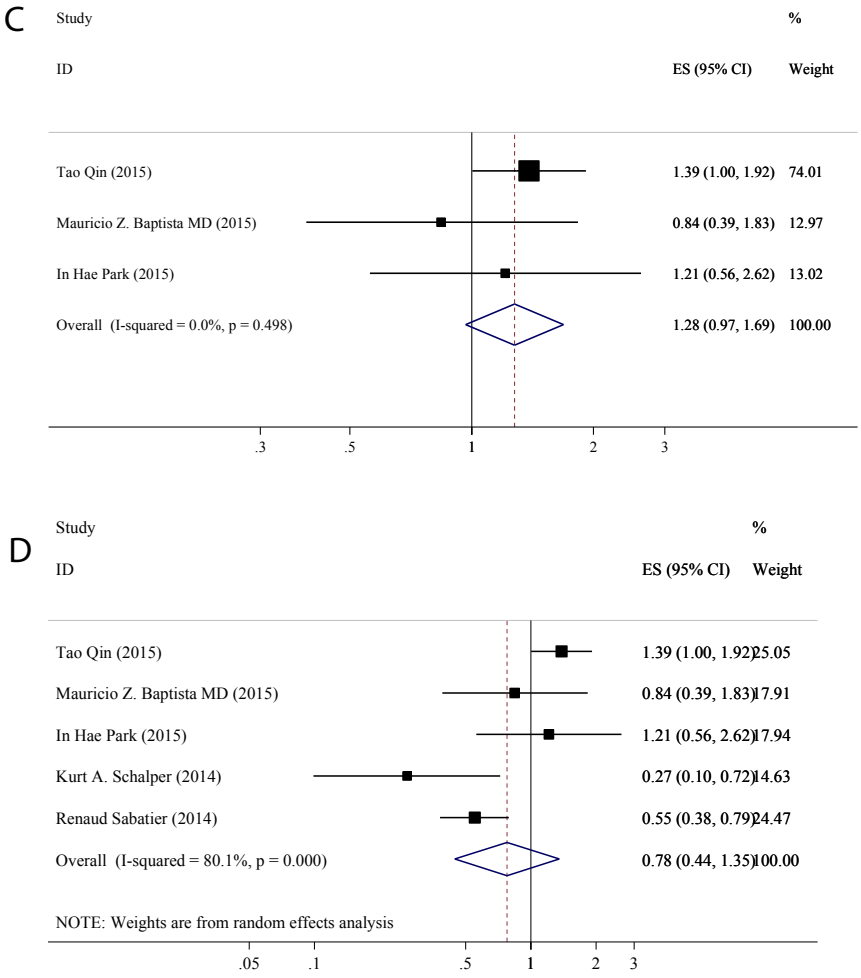


Figure 1: Analysis of PD-L1positive versus PD-L1 negative on tumor cells of breast cancer patients in terms of survival (OS/OS+OSS/DFS/DFS+MFS+RFS).

be significantly associated with histological grade (OR=1.86, 95% CI: 1.38-2.51; $P_{heterogeneity}$=0.0196) (Table 4 and Figure 2a), ER (OR=0.36, 95% CI: 0.17-0.75; $P_{heterogeneity}$=0.000) (Figure 2b), PR (OR=0.31, 95% CI: 0.11-0.86; $P_{heterogeneity}$=0.000) (Figure 2c). No significant relationship was detected between PD-L1 overexpression and other clinical characteristics in breast cancer due to limited studies.

Publication bias

The Begg's funnel plot did not show any evidence of obvious asymmetry. Then, the Egger's linear regression was performed and publication bias was not detected either (Tables 3 and 4).

Discussion

Recently studies suggest that determination of PD-L1 status on tumor cells could help select patients for novel anti- PD-1/PD-L1 therapies [22]. However, the association of the expression of PD-L1 and breast cancer patients' prognosis remains unclear, including the exact relationship between PD-L1 and clinicopathological features. Thus, a meta-analysis incorporating all available data from correlative studies is a reasonable method by which to address these questions. Our study show PD-L1 had no significant association with breast cancer patients' survival. However, the prognosis of many other carcinomas, including non-small-cell lung cancer, gastrointestinal tract cancer, melanoma, show association with PD-L1. We think there must be some reasons, listed below, except for the heterogeneity.

First, in evaluation and criteria for PD-L1 expression we could see that studies using IHC evaluation show PD-L1 related to poor prognosis, however, researches using mRNA evaluation show PD-L1 related to better prognosis. These two techniques have their own drawbacks. For IHC, the accurate determination of PD-L1 protein levels in the tumor samples through IHC is limited by the reliable antibodies, absence of validated assays and interpretative uncertainties for example, the cut-off value. While, the mRNA evaluation includes the case that PD-L1 didn't express on the cell surface. So which technique will be used for PD-L1 expression determination need more research? Anyway, so far, most of the researches for PD-L1 and breast cancer are done by IHC.

Second, the different cut-off value of PD-L1 show different PD-L1 rate and relationship with clinical pathological features. Since IHC evaluation methods and cut-off values were not consistent for breast cancer, the comparison gives a completely opposite result. Why the different evaluation and criteria can give the opposite result? This may be an explanation of the mechanism. PD-L1 related immune escape was considered the reason for breast cancer poor prognosis. However, for the survival benefit of PD-L1+ carcinoma breast cancer patients, the explanation could be the presence

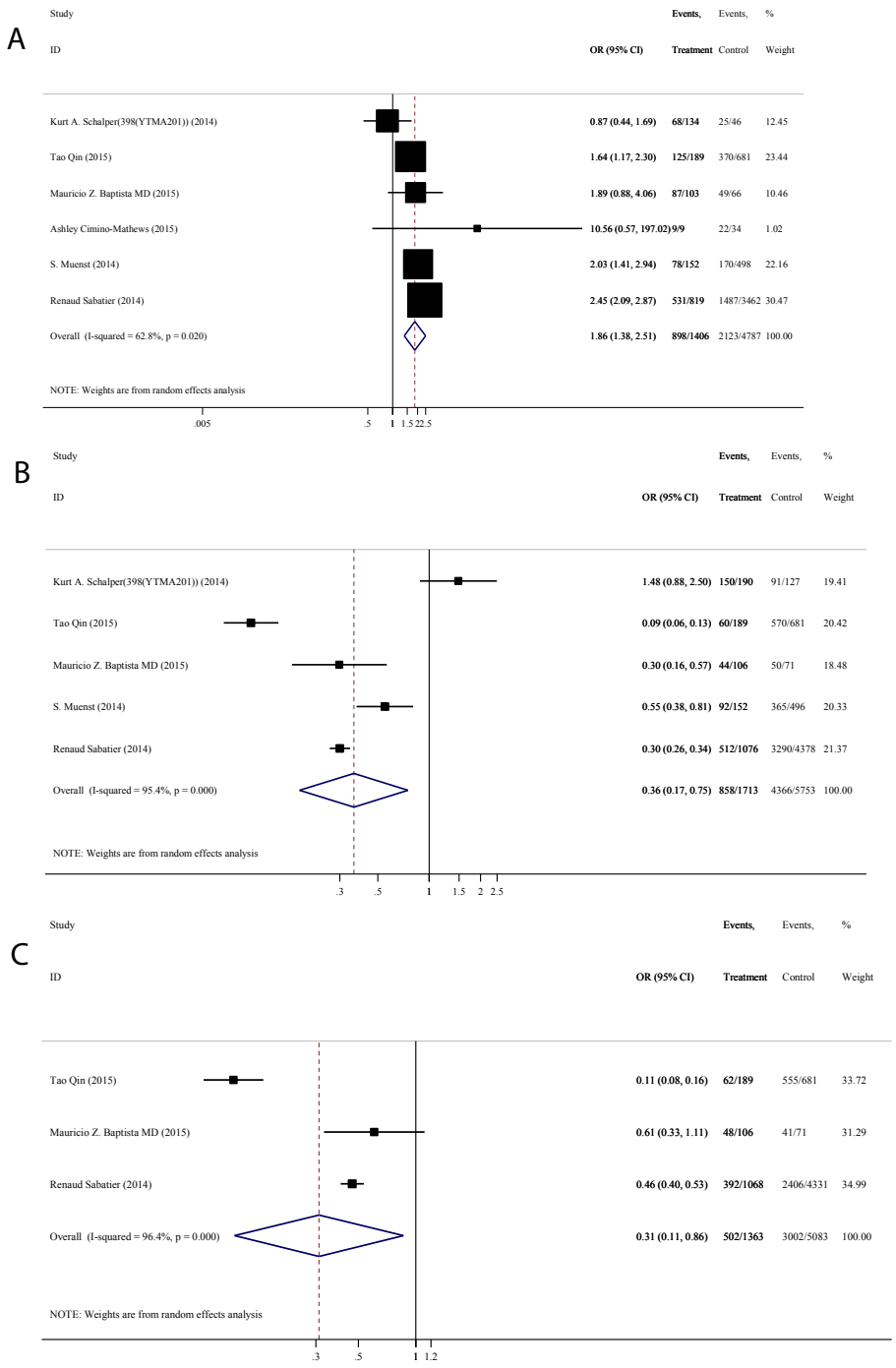


Figure 2: Analysis of PD-L1positive versus PD-L1 negative on tumor cells of breast cancer patients in terms of histological grade/ER/PR.

of a strong antitumor immune response triggered by PD-L1 up regulation [14]. One research show that PD-L1 expression of tumor cells was due to the activation of CD8-positive T cells. Then, the CD8-positive T cells release several cytokines. Through this way, the PD-L1 expression in tumor cells was up regulated by the immune system [18]. From this point, whether PD-L1 can give a poor or better prognosis, whether PD-L1 can trigger immune escape or antitumor immune response due to the PD-L1 expression rate. And a standard PD-L1 cut-off value is essential in PD-L1 expression determination.

Third, different patient subtypes (ER/PR+, HER2+ or TNBC) receive different treatments, which by themselves have different prognosis. However, there is lack of researches on PD-L1 of different subtypes and breast cancer prognosis. We need more researches on correlates of prognosis within a particular subgroup, as illustrated by Klinke [23]. As PD-L1 expression correlates with an on-going anti-tumor immune response, these different molecular subtypes also have a different propensity to engage anti-tumor immunity. For instance, HER2+ overexpression has been reported to down regulate components of the MHC class I antigen-presentation [24].

While, increased PD-L1 was found to be significantly associated with histological grade, ER and PR the histological grade association can be a clue for the relationship between PD-L1 and immune escape, which is the essence of PD-L1. While, we need further more investigation to verify relationship between ER, PR and PD-L1 and their interaction more specific studies on molecular subtype and PD-L1 will made the target therapy more specific.

Conclusion

Despite some trends observed, we currently cannot draw a valid conclusion that PD-L1 status is a predictor of prognosis for patients with breast cancer. We should deeply explore the mechanism related to PD-L1 expression rate, immune escape and antitumor immune response. Further, develop an evaluation standard for PD-L1 expression which can exactly give the prediction of whether PD-L1 can trigger immune escape or antitumor response. What's more conduct the researches on different molecular subtype. So that make clear whether the PD-L1 related drugs can be used clinically for the very type of breast cancer patients. And not only PD-L1 antibodies but also PD-L1 analogue.

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