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Role of programmed cell death ligand-1 expression on prognostic and overall survival of breast cancer
A systematic review and meta-analysis

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Abstract

Background: Recently, the correlation of immunological checkpoint marker programmed cell death ligand-1 (PD-L1) and the prognosis of various cancers has been a research hotspot. The aim of this study is to examine the prognostic effect of PD-L1 in breast cancer.

Methods: PubMed, EMBASE, Web of Science, the Cochrane Library database were searched for eligible studies and additional hand-searching were reviewed as an augmentation. Pooled hazard ratios (HR) and 95% confidence interval (CI) for overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS)/recurrence-free survival (RFS), and metastasis-free survival (MFS) were estimated using fixed- or random-effect models.

Results: Data from 19 studies involving 12,505 patients were collected. Study quality was assessed according to guidelines for assessing quality in prognostic studies. PD-L1 expression was significantly associated with lymph node metastasis ($P < .001$), high tumor grade ($P < .001$), negative hormone receptor ($P < .001$), human epidermal growth factor receptor 2 (HER2) positivity ($P < .001$), high Ki67 ($P < .001$), and high tumor-infiltrating lymphocytes (TILs) ($P < .001$). PD-L1 expression had no significant impact on CSS (pooled HR 0.83, 95% CI = 0.64–1.09, $P = .19$) or MFS (pooled HR 1.11, 95% CI = 0.62–1.97, $P = .72$), but significantly correlated with shortened OS (pooled HR 1.52, 95% CI = 1.14–2.03, $P = .004$) and DFS (pooled HR 1.31, 95% CI = 1.14–1.51, $P < .000$). Subgroup analysis showed that not PD-L1 RNA expression, but protein expression was associated with shorter survival, in addition, the adverse prognostic effect of PD-L1 expression remained in luminal A, luminal B, and HER2 subtype, not in basal-like or triple-negative subtype.

Conclusions: An elevated PD-L1 expression significantly correlates with high-risk prognostic indicators and decreased survival in patients with breast cancer.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, DFS = disease-free survival, HR = hazard ratios, IHC = immunohistochemical staining, MFS = metastasis-free survival, OS = overall survival, PD-L1 = programmed cell death ligand-1, RFS = recurrence-free survival.

Keywords: breast cancer, meta-analysis, prognosis, programmed cell death ligand-1

1. Introduction

Breast cancer is by far the most common malignant tumor in women worldwide.[1] Advances in diagnosis, chemotherapy, endocrine therapy, and anti-human epidermal growth factor

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receptor 2 (HER2) therapy have significantly improved the survival of patients with breast cancer, but recurrence and metastasis remain the leading cause of breast cancer death.[2] Cancer cells can also maintain an immunosuppressive microenvironment that favors tumor progression by expressing immune inhibitory signals.[3] Interaction between programmed cell death ligand-1 (PD-L1 or CD274) and its receptor PD-1 is a major inhibitory pathway in maintaining an immunosuppressive tumor microenvironment. Interestingly, in recent years, inhibition of the immune checkpoint regulator PD-L1 or PD-1 is a new anticancer therapy.[4,5]

PD-L1 is one of the ligands of PD-1 and is expressed on hematopoietic cells, epithelial cells, and a number of tumor cells, including melanoma, lung, ovarian, and renal cell carcinomas. PD-1 is expressed on tumor-infiltrating CD8^{+} T cells, as well as CD4^{+} T cells, natural killer T cells, B cells, activated monocytes and dendritic cells. PD-L1 expressed on tumor cells bind themselves with PD-1 on the surface of T cells, thereby inhibiting T cells function, losing its killing effect on tumor cells.[6,7] Moreover, upregulation of PD-L1 has been described closely in association with the clinicopathological status of cancer patients.[8,9] Based on these results, targeting the PD-L1/PD-1 pathway to improve antitumor immune response is under investigation in multiple human cancers.[10–12] PD-L1 has been reported not to be expressed in normal breast tissue but to be

increased in nearly half of breast cancer. Some researchers have reported their paper with regards to PD-L1 expression in breast cancer and have raised concerns about the role of PD-L1 as a prognostic factor.[13] However, its prognostic role in breast cancer is still under debate. Study by Qin et al[14] evaluated the PD-L1 expression by immunohistochemical (IHC) staining, and revealed the association of high PD-L1 expression with poor prognosis in patients with breast cancer. This correlation was also validated in several other studies.[15–17] On the contrary, Beckers et al[18] demonstrated that PD-L1 expression improved outcome in triple-negative breast cancer.

Given the discrepancy in PD-L1 assessment assay and relative small sample size of each individual study, we conducted a meta-analysis with newest and largest quantity of relevant publications[13–31] to clearly investigate role of PD-L1 expression on prognostic and overall survival of breast cancer.

2. Materials and methods

Sine this study is a meta-analysis of previously published studies, the ethical approval and patient consent are not required.

2.1. Search strategy

A comprehensive search of PubMed, EMBASE, Web of Science, the Cochrane Library for relevant publications for the period up to June 10, 2017 was conducted. Databases were searched using the following terms, both as text words and Medical Subjects Heading [MeSH] terms: "Breast Neoplasm," "Programmed Cell Death 1 Receptor," and Keywords.

"Breast Cancer," "PD-L1," "B7-H1," "CD274." This search strategy was created by combining the above terms via the Boolean operator "OR" and "AND." In addition, we augmented our computerized literature search by manually reviewing the reference lists of identified studies, relevant reviews, and meta-analyses. We also checked abstracts from the American Cancer Society of Clinical Oncology (ASCO) meetings available at http://meetinglibrary.asco.org for citations. The search criteria were limited to articles published in the English language. When the same population was included in different publications, the most recent study was used for analysis. The literature retrieval was conducted in duplication by 2 independent reviewers (SL and LC).

2.2. Eligibility criteria

To be included in this analysis, studies should meet the following inclusion criteria after the full text were reviewed: they focused on breast cancer; all selected cancer patients were pathologically confirmed; and correlation between PD-L1 and prognosis was described. Articles were excluded from the analyses based on the following criteria: non-English papers; non-human experiments; review articles, meeting abstracts, or case reports; duplicate publication; PD-L1 expressed on other cell (e.g., immune cell and stromal cell), not tumor cell; and insufficient data about hazard ratios (HR) and 95% confidence interval (CI), or the Kaplan–Meier curve could not be extracted.

2.3. Data extraction

Data were extracted from each study by 2 reviewers (SL and LC) independently according to the pre-specified selection criteria. Decisions were compared and disagreements about study

selection were resolved by discussion or by involving a 3rd reviewer (JJ). The following information was extracted from the literatures: author; year of publication; country; number of patients; clinicopathological characteristics of patients; tumor stage; specimen; detection method; detection standard of positive/high PD-L1 expression. Survival data including HR and 95% CI for overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS)/recurrence-free survival (RFS) and metastasis-free survival (MFS) was directly extracted from tables or text of included studies for further pooled analysis.

2.4. Author contact

We sent e-mails to the corresponding authors (or any other author with a contact e-mail address listed on the main manuscript) if we could not get the full text or sufficient data.

2.5. Quality assessment

The quality of the selected articles was assessed according to guidelines for assessing quality in prognostic studies and 6 items relevant to this study were used.[32]

2.6. Data synthesis and statistical analysis

Clinicopathological data were presented as means and proportions, differences between groups were tested with Pearson chi-squared test. Statistical heterogeneity was assessed by means of the Cochran Q and I^2 tests. A probability value of $P < .1$ or $I^2 \geq 50\%$ indicated the existence of significant heterogeneity.[33] When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported using the DerSimonian and Laird method,[34] which considers both within-study and between-study variations. If there was no significant heterogeneity, a fixed-effects model was adopted.

Sensitivity analysis was performed to assess the extent to which the combined estimates might be affected by individual studies, in which the meta-analysis estimates were computed after omission of each study in turn.[35] The potential for publication bias was assessed using the Egger linear regression test and Begg rank correlation test for funnel plot asymmetry.[36,37] P value $<.05$ was considered statistically significant. All P values are 2-tailed. Meta-analysis was performed using Review Manager (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration)[38] and R software (version 3.2.3; R Core Team, Vienna, Austria).[39]

3. Results

3.1. Search results

We identified 1009 publications and the process of study selection is summarized in Fig. 1. After screening, 825 articles were eliminated because they were duplicates, non-human studies, reviews, case reports, meeting abstracts, or studies on other tumors. After reviewing the complete text of 184 records, 165 articles were excluded because 155 records were non-prognosis studies, while 4 articles did not have sufficient data for further analysis, 5 studies evaluated the prognostic role of PD-1 expressed on immune cells, and 1 study about prognostic role of PD-L1 positive immune cell. In total, 19 articles were available for meta-analysis because of their quality and availability of data.[13–31]
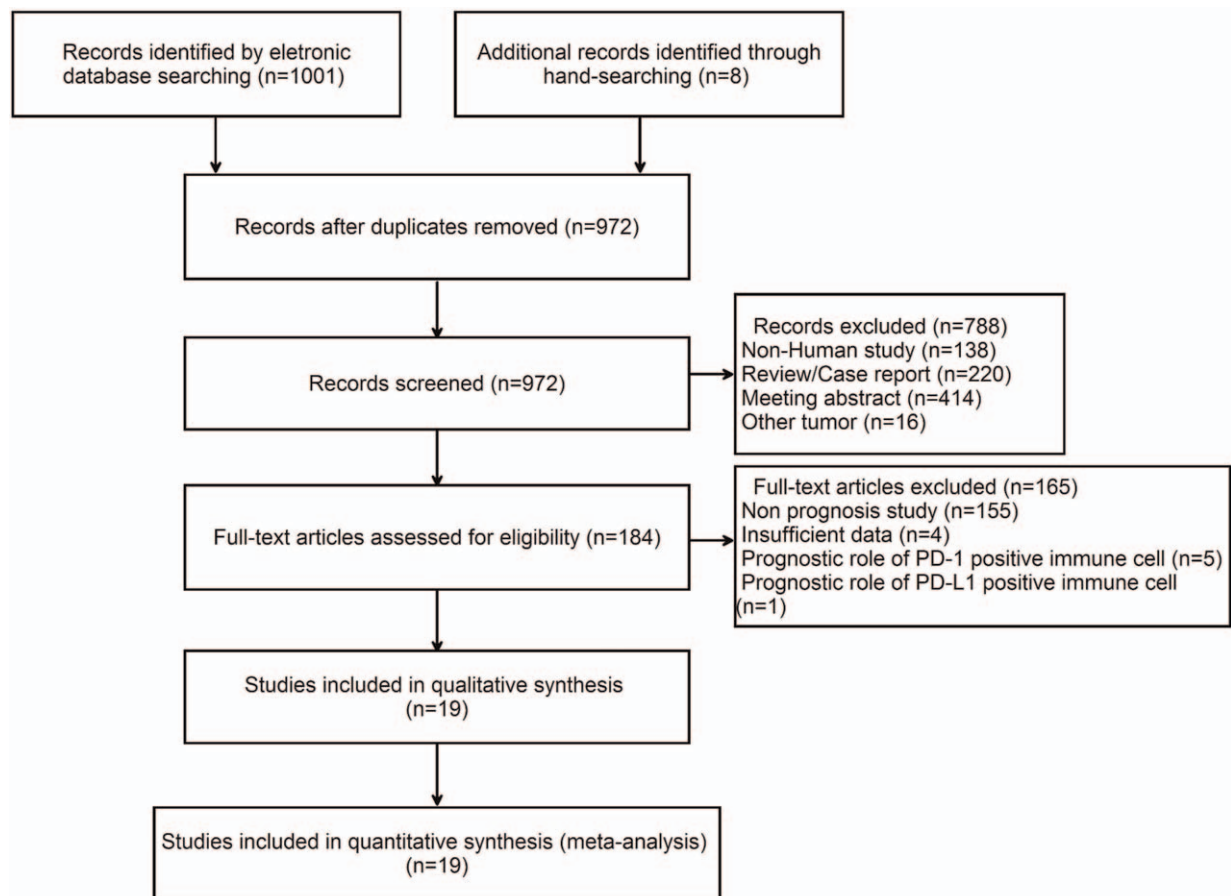
Figure 1. PRISMA flow chart of the literature search.

3.2. Characteristics of the studies and study quality

The main characteristics of 19 eligible studies are presented in Table 1. The publication years ranged from 2014 to 2017, and a total of 12,505 breast cancer patients from Switzerland, USA, Austria, France, Australia, Korea, China, Brazil, Italy, UK, Spain, Canada, and Japan were included. The number of patients in each study ranged from 97 to 5454. Study by Tymoszuk et al[24] contained 2 cohorts and reported separately

Table 1
Main characteristics of the included studies.

| Author	Year	Country	N	Tumor stage	PD-L1 level	Detection method	Blind	PD-L1+ N(%)	Detection standard (positive/high expression)	End point	Follow up, mo
Muenst[13]	2014	Switzerland	650	I–III	Protein	IHC	—	152(23.4%)	H-score ≥100	OS	65 (1–174)
Schalper[19]	2014	USA	636	I–III	RNA	Fluorescent RNAscope assay	—	201(31.6%)	Quantitative fluorescence score of gene DapB mRNA (negative control)	CSS/RFS	139 (3–385)
Tymoszuk (A)[24]	2014	Austria	96	I–IV	RNA	qPCR	—	—	Median of delta Ct expression value	OS/RFS	109.2(1.2–264)
Tymoszuk (B)[24]	2014	France	36	I–IV	RNA	qPCR	—	—	Median of delta Ct expression value	OS/RFS	81.6(7.2–120)
Sabatier[22]	2015	France/UK	5454	I–IV	RNA	Microarrays	—	1076(19.7%)	Tumor/normal breast ratio ≥2	CSS/MFS	7.17 (86/85)
Beckers[18]	2015	Australia	161	I–III	Protein	IHC	—	123(76.4%)	H-score ≥100	OS/CSS	55 (0–213)
Park[28]	2015	Korea	333	I–III	Protein	IHC	Yes	163(48.9%)	H-score ≥2+-3+	OS/DFS	117.6 (4.8–153.6)
Qin[14]	2015	China	870	I–III	Protein	IHC	Yes	189(21.7%)	membrane staining ≥5%	OS/DFS/MFS	98 (17–265)
Bertucci[29]	2015	France	112	III-IV	RNA	microarrays	—	42(37.5%)	Tumor/normal breast ratio ≥2	CSS/MFS	43
Bae[27]	2016	Korea	465	I–III	Protein	IHC	Yes	63(13.5%)	H-score ≥100	OS/DFS	41 (1–158)
Baptista[30]	2016	Brazil	189	I–III	Protein	IHC	Yes	107(56.6%)	Median Allred score	OS/DFS	86.2
Chen[16]	2016	China	309	I–III	Protein	IHC	Yes	153(49.5%)	Median PD-L1 protein density(0.022)	OS/RFS	70
Li[26]	2016	USA	136	I–III	Protein	IHC	—	14(10.3%)	H-score ≥5	OS/DFS	36-144
Li[15]	2016	China	501	I–III	Protein	IHC	—	231(46.1%)	H-score≥100	OS/RFS	64 (1–80)
Okabe[25]	2016	Japan	97	I–III	Protein	IHC	Yes	32(33.0%)	H-score ≥100	OS/DFS	120
Botti[21]	2017	Italy	238	I–IV	Protein	IHC	Yes	77(32.4%)	PD-L1 expression ≥10%	OS/DFS	100
Mori[23]	2017	Japan	248	I–III	Protein	IHC	—	103(41.5%)	PD-L1 expression ≥50%	OS/RFS	68(2–150)
Tsang[17]	2017	China	1091	I–III	Protein	IHC	—	295(27.0%)	Mean immunoscore (staining intensity/ percentage of positive cells)	OS/DFS	63(1–210)
Polonia[31]	2017	Spain	440	I–III	Protein	IHC	—	28 (6.4%)	Membranous/cytoplasmic staining ≥1%	OS	120 (1–120)
Wang[20]	2017	Canada	443	I–III	Protein	IHC	Yes	73(16.5%)	H-score	OS/RFS	87(2–251)
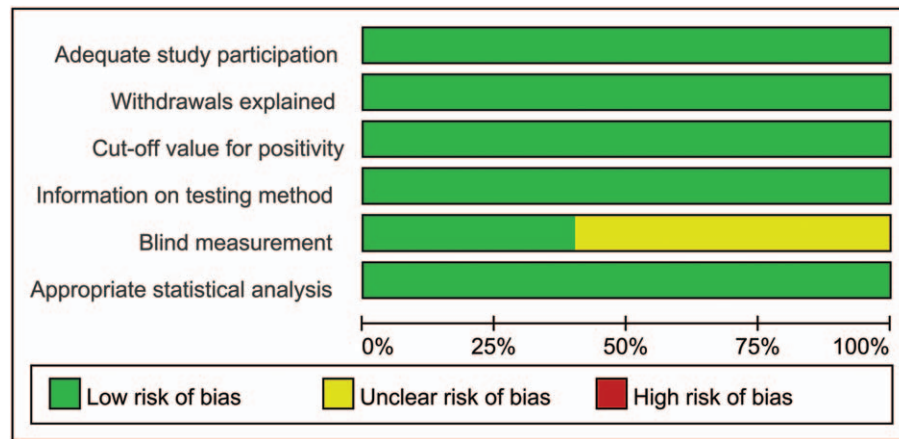
Figure 2. Quality assessment according to guidelines for assessing quality in prognostic studies.

(cohort A and cohort B). The PD-L1 expression levels were measured in protein by IHC in 15 studies and detected in RNA level in 4 studies by microarrays, Fluorescent RNAscope assay, or quantitative Real-Time PCR Experiments. To evaluate PD-L1 positivity in selected studies, different cut-off were used according to various scoring systems including Histo-score system (H-score), quantitative fluorescence (QIF) detection score, PD-L1 expression in tumor/normal breast samples (T/NB ratio), 4-point scale, Allred score, or Immuno-score (staining intensity and percentage of PD-L1 positive tumor cells). PD-L1 positive rate in all studies ranged from 6.4% to 76.4%.

Figure 2 summarized the methodological quality of these 19 included studies assessed by guidelines for assessing quality in prognostic studies with 6 items in assessing potential opportunity for bias. All of these included studies had a representative study participation and scored "low risk"; no loss to follow-up was associated with expression of PD-L1 in any study and all scored "low risk"; they all showed cut-off or scoring systems in evaluating PD-L1 positivity and scored "low risk"; all of 19 studies described information about primary antibody used in IHC or probe in RNA detection and scored "low risk"; blind interpretation were reported in 8 studies[14,16,20,21,25,27,28,30] and scored "low risk," others did not described that and scored "unclear"; all studies conducted survival analyses based on univariate and/or multivariate survival analyses. There is no selective reporting of results and scored "low risk." Results of quality assessment were summarized in Fig. 3.

3.3. PD-L1 expression and clinicopathological features

Correlations between PD-L1 expression and clinicopathological features were analyzed and showed in Table 2. High PD-L1 expression associated with lymph node metastasis[13–20,22,23,25,27,28,30,31] ($P < .001$), high tumor grade[13–20,22,23,25,27,29–31] ($P < .001$), negative hormone receptor[13–20,22,23,25,27–31] ($P < .001$), positive HER2[13,15,17] ($P < .001$), high Ki67[13,14,16,17,22,23,27,28,31] ($P < .001$), and high tumor-infiltrating lymphocytes (TILs)[16–19,23,27,29] ($P < .001$). However, neither T stage[13–15,17,19,20,22,23,25–28,30,31] ($P = .501$) nor patients' age[15,16,19–22,25,27–29] ($P = .500$) was significantly correlated with PD-L1 expression.

3.4. PD-L1 expression and patient survival

We assessed the prognostic value of PD-L1 expression in terms of OS, CSS, DFS/RFS, and MFS. For OS, altogether 16 studies[13–18,20,21,23–28,30,31] (n = 4719) reported OS data. Significant heterogeneity existed among included studies ($I^2 = 67\%$, Cochrane Q $P < .000$). Pooled result by random model revealed PD-L1 expression associated with poor prognosis in term of shortened OS (pooled HR 1.52, 95%CI = 1.14–2.03, $P = .004$) (Fig. 4A). Four studies[18,19,22,29] (n = 3724) focused on CSS and no heterogeneity was existed among these studies ($I^2 = 0\%$, Cochrane Q, $P = .79$). Pooled result by fixed model revealed PD-L1 expression had no impact on CSS (pooled HR 0.83, 95% CI = 0.64–1.09, $P = .19$) (Fig. 4B).

Fourteen studies[14–17,19–21,23–28,30] (n = 4241) provided DFS/RFS data and no significant heterogeneity existed among included studies ($I^2 = 48\%$, Cochrane Q $P = .02$). Pooled result by fixed model showed that PD-L1 overexpression was associated with shorter DFS/RFS in patients with breast cancer than PD-L1 negative expression (pooled HR 1.31, 95% CI = 1.14–1.51, $P < .000$) (Fig. 4C). For MFS, 3 studies[14,22,29] presented MFS data (n = 2035). Significant heterogeneity existed among included studies ($I^2 = 61\%$, Cochrane Q $P = .08$). Pooled result by random model revealed PD-L1 expression had no significant effect on MFS (pooled HR 1.11, 95% CI = 0.62–1.97, $P = .72$) (Fig. 4D).

3.5. Sensitivity and subgroup analysis

Sensitivity analysis was conducted to determine whether the exclusion of each study resulted in a significant difference. We performed the same pooled calculus after omitting each study in turn, and no change was calculated for OS, CSS, DFS, and MFS, indicating that our results were statistically robust. Since different PD-L1 expression level and breast cancer subtypes have been assessed in these included studies and could be potential confounding factors. Subgroup analyses were conducted to evaluate variations in PD-L1 protein/RNA level and intrinsic subtype for breast cancer. In protein-level subgroup, statistical difference was determined for OS, DFS, and MFS, not for CSS, while in RNA-level subgroup, PD-L1 status was not significantly associated with any end point (Table S1, http://links.lww.com/MD/C925). In subgroup analysis by intrinsic subtype, PD-L1

Figure 3. Summary of methodological quality of each included studies on basis of review authors' judgments on 6 items relevant to this review from guidelines for assessing quality in prognostic studies.

Table 2

Associations between PD-L1 expression and clinicopathological features.

Clinical parameters	PD-L1(+) (%)	PD-L1(−) (%)	P value
Age[15,16,19–22,25,27–29]			
Young	634 (28.4)	1601 (71.6)	.500
Old	1260 (25)	3782 (75)	
T stage[13–15,17,19,20,22,23, 25–28,30,31]			.501
T$_1$	947(26.6)	2616(73.4)	
T$_{\geq 2}$	1421(27.2)	3798(72.8)	
Lymph node metastasis[13–20,22, 23,25,27,28,30,31]			<.001*
No	1315(25.7)	3805(74.3)	
Yes	1581(32.4)	3298(67.6)	
Grade[13–20,22,23,25,27,29–31]			<.001*
G$_{1/2}$	1105(20.5)	4291(79.5)	
G$_3$	1380(29.9)	3239(70.1)	
ER status[13–20,22,23,25,27–31]			<.001*
Positive	1620(22.3)	5655(77.7)	
Negative	1246(34.4)	2371(65.6)	
PR status[14–17,20,22,27,29–31]			<.001*
Positive	961(18.6)	4211(81.4)	
Negative	1282(28.0)	3301(72.0)	
HER2 status[13,15,17]			<.001*
Positive	479(30.4)	1098(69.6)	
Negative	2295(24.8)	6956(75.2)	
Ki67 status[13,14,16,17,22,23,27,28,31]			<.001*
High	1315(28.7)	3261(71.3)	
Low	896(17.7)	4177(82.3)	
TIL[16–19,23,27,29]			<.001*
High	383(39.1)	597(60.9)	
Low	446(31.9)	954(68.1)	

ER = estrogen receptor, PR = progesterone receptor, T = tumor, TIL = tumor infiltrating lymphocyte.
* Statistical significant.

associated with longer CSS and MFS in basal-like subtype (Table S2, http://links.lww.com/MD/C925).

3.6. Publication bias

Begg and Egger tests did not reveal publication bias affecting the hazard ratios for OS, CSS, DFS, and MFS. The *P* values for these tests were present in Table S3, http://links.lww.com/MD/C925.

4. Discussion

A growing body of evidence suggests that the PD-L1/PD-1 pathway plays a key role in tumor immune escape. The correlations between PD-L1 expressions and different tumors have been studied by many researches.[6,40,41] PD-L1 expression was also investigated as an indicator of survival for breast cancer in numerous studies,[42,43] however, the results were inconsistent and conflicting. A study of 870 patients reported patients with high PD-L1 expression had decreased DFS, MFS, and OS compared with those with no PD-L1 expression, indicating that PD-L1 expression is an indicator of poor prognosis in breast cancer patients.[14] Conversely, a study of 636 stage I–III breast carcinomas showed that PD-L1 mRNA expression is related to improved RFS.[19] Several other studies reported no significant difference between the locoregional recurrence or survival of patients with high PD-L1 expression and patients with no PD-L1 expression.[21,23,28] These conflicting results warrant further

expression was associated with shorten OS and/or DFS in luminal A subtype, luminal B (HER2$^-$ and HER2$^+$) subtype and HER2 subtype. Of note, neither OS nor DFS was associated with PD-L1 expression in basal-like subtype or triple-negative subtype. For CSS and MFS, only one study showed PD-L1 expression was
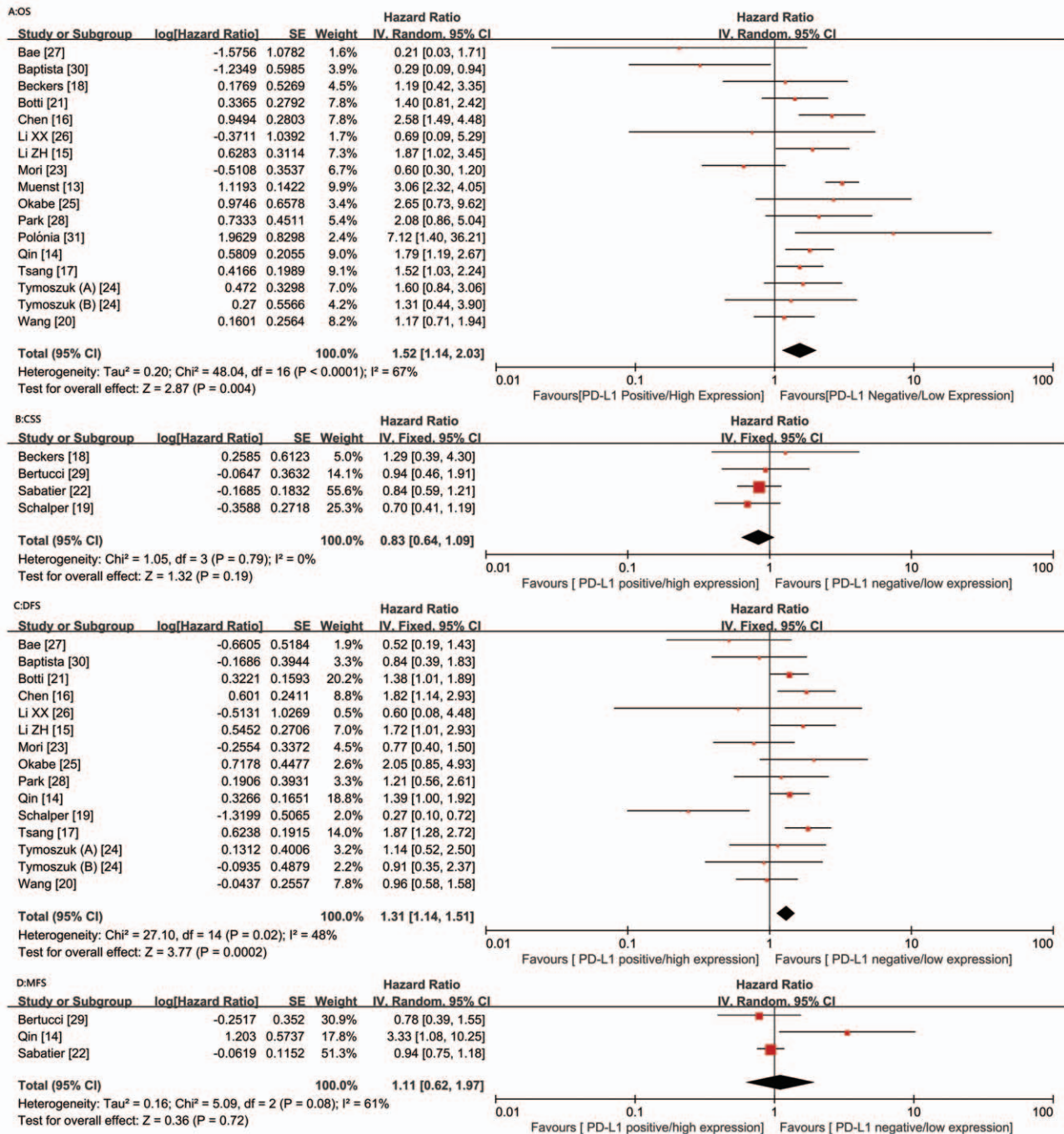
Figure 4. Forest plots of hazard ratios for survival based on PD-L1 expression. A, OS. B, CSS. C, DFS. D, MFS. CI = confidence interval, CSS = cancer-specific survival, DFS = disease-free survival, IV = inverse variance, MFS = metastasis-free survival, OS = overall survival.

exploration. To arrive at a reasonable conclusion, we searched and performed this meta-analysis including 19 studies with a total of 12,505 patients. The present meta-analysis provided strong evidence that PD-L1 expression on tumors is significantly associated with worse OS (HR 1.52, 95% CI = 1.14–2.03, P = .004) and DFS (HR 1.31, 95% CI = 1.14–1.51, P = .0002) in breast cancer, while no effect on CSS (HR 0.83, 95% CI = 0.64–1.09, P = .19) or MFS (HR 1.11, 95% CI = 0.62–1.97, P = .72). Maybe less studies focusing on CSS and MFS is the reason and the effect of PD-L1 on CSS or MFS is a subject of ongoing

investigation. Further subgroup analyses by intrinsic subtype confirmed that the adverse prognostic effect of PD-L1 expression remained in luminal A, luminal B, and HER2 subtype, not in basal-like or triple-negative subtype.

In addition, when the clinicopathological features were considered, high PD-L1 expression was associated with lymph node involved, high tumor grade, negative hormone receptor, positive HER2, high Ki67, and the presence of TILs. The finding that PD-L1 expression is associated with the above high-risk prognostic factors in breast cancer could indicate that activation

of the PD-L1/PD-1 pathway may help these tumors evade antitumor immune response, these tumor cells even consequently proliferate and spread more rapidly. These results might strengthen the sensitivity and specificity of PD-L1 in predicting the clinical survival of breast cancer.

To evade from the immune system's monitoring, tumor cells in microenvironment can modulate PD-L1 expression via 2 major pathways, the extracellular pathway and the intracellular signaling pathway. The former is induced by IFNγ production from TILs and subsequent IFNGRs/JAK/STAT signaling in tumor cells,[44–46] this pathway depends on the presence of TILs.[47] The latter does not depend on the presence of the TILs and multiple mechanisms can lead to PD-L1 expression, including chromosomal amplification,[48] activating mutation in epidermal growth factor receptor,[49] or activation of the phosphoinositide 3-kinases/protein kinase B/mammalian target of rapamycin pathway.[47,50] PD-L1 expressed on tumor cells bind themselves with PD-1 on the surface of T cells, thereby inhibiting T cells function, losing its killing effect on tumor cells.[51] This reveals that antitumor immunity is elicited against many solid tumors, it is also affected by immunosuppressive factors. PD-L1 not only induces tumorigenesis and invasiveness, but also makes tumor cells less susceptible to specific CD8^{+} T cells.[5] Results from these preclinical in vivo models make breast cancer an attractive candidate for immunotherapies targeted against this molecule. In addition, results from subgroup analysis by PD-L1 expression level showed that high PD-L1 protein expression was associated with shorter survival, but high PD-L1 RNA expression did not have any impact on survival.

Tumoral PD-L1 expression is of considerable clinical interest due to the recent development of PD-L1/PD-1 blocking antibodies. A number of antibodies directed against PD-L1 (atezolizumab, avelumab, durvalumab) or PD-1 (nivolumab, pembrolizumab) are currently under clinical investigation.[52] The early phase I clinical studies targeting PD-L1/PD-1 pathway with monoclonal antibodies have received substantial attention. Emens presented effect of atezolizumab in a phase I trial in patients with metastatic triple-negative breast cancer (TNBC). Among 21 patients, 3 patients had partial remission and 2 patients had complete remission. Overall, the 24-week PFS rate was 33%.[53] In another phase I b trial with avelumab for 168 patients with metastatic or locally advanced breast cancer, Heery et al[54] presented that 9 patients responded to treatment (1 complete response and 8 partial responses). In the phase I trial KEYNOTE-12, pembrolizumab has been used to determine whether it is effective in the treatment of breast cancer. 58.6% of patients screened positive for PD-L1 and the overall response rate was 18.5%.[55] Currently, there are ongoing phase II (KEYNOTE-86, NCT02447003) and phase III clinical trials (KEYNOTE-119, NCT02555657) that will evaluate pembrolizumab as a monotreatment for TNBC while other phase I–III studies investigate the combination of pembrolizumab with chemotherapy. Furthermore, the anti-PD-L1 durvalumab (MEDI4736) and the anti-PD-1 nivolumab (BMS-936558/MDX-1106) are under investigation in breast cancer.[52] However, these findings are also consistent with the viewpoint that over-expression of PD-L1 indicates a poor prognosis and therapeutic blockade of the PD-L1/PD-1 pathway might be a valid treatment approach in breast cancer.

Despite our efforts in performing a comprehensive and accurate analysis, yet several limitations should be taken into account when interpreting results. Firstly, the analysis was limited to articles published in English. Secondly, a majority of the selected studies measured PD-L1 expression by IHC, the variable detection antibodies, tissue preparation, processing variability might account for the high variability in PD-L1 positive rate reported by different authors. Finally, the techniques and cut-off values for evaluating PD-L1 expression were different among the included studies, which might have caused some of the heterogeneity. A standardized methodology should be set up to improve consistency and reproducibility in the measurement of PD-L1 for future studies.

5. Conclusions

In summary, the current evidence shows that an elevated PD-L1 expression is a negative prognostic factor in breast cancer. More multicenter studies with larger sample size are warranted to present more reliable results of the clinical relevance and precise molecular explanation for the abnormal expression of PD-L1 in the future.

Author contributions

Conceptualization: Shichao Li.
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Investigation: Li Chen.
Methodology: Shichao Li.
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Resources: Li Chen.
Software: Shichao Li.
Validation: Jun Jiang.
Visualization: Jun Jiang.
Writing – original draft: Shichao Li.
Writing – review & editing: Jun Jiang.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30.

[2] Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784–92.

[3] Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015;33:1974–82.

[4] Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455–65.

[5] Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293–7.

[6] Meng X, Huang Z, Teng F, et al. Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. Cancer Treat Rev 2015;41:868–76.

[7] Schutz F, Stefanovic S, Mayer L, et al. PD-1/PD-L1 pathway in breast cancer. Oncol Res Treat 2017;40:294–7.

[8] Mittendorf EA, Philips AV, Meric-Bernstam F, et al. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res 2014;2:361–70.

[9] Gatalica Z, Snyder C, Maney T, et al. Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. Cancer Epidemiol Biomarkers Prev 2014;23:2965–70.

[10] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.

[11] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13.

[12] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123–35.

[13] Muenst S, Schaerli AR, Gao F, et al. Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. Breast Cancer Res Treat 2014;146:15–24.

[14] Qin T, Zeng YD, Qin G, et al. High PD-L1 expression was associated with poor prognosis in 870 Chinese patients with breast cancer. Oncotarget 2015;6:33972–81.

[15] Li Z, Dong P, Ren M, et al. PD-L1 expression is associated with tumor FOXP3(+) regulatory T-cell infiltration of breast cancer and poor prognosis of patient. J Cancer 2016;7:784–93.

[16] Chen S, Wang RX, Liu Y, et al. PD-L1 expression of the residual tumor serves as a prognostic marker in local advanced breast cancer after neoadjuvant chemotherapy. Int J Cancer 2017;140:1384–95.

[17] Tsang JY, Au WL, Lo KY, et al. PD-L1 expression and tumor infiltrating PD-1+ lymphocytes associated with outcome in HER2+ breast cancer patients. Breast Cancer Res Treat 2017;162:19–30.

[18] Beckers RK, Selinger CI, Vilain R, et al. Programmed death ligand 1 expression in triple-negative breast cancer is associated with tumour-infiltrating lymphocytes and improved outcome. Histopathology 2016;69:25–34.

[19] Schalper KA, Velcheti V, Carvajal D, et al. In situ tumor PD-L1 mRNA expression is associated with increased TILs and better outcome in breast carcinomas. Clin Cancer Res 2014;20:2773–82.

[20] Wang ZQ, Milne K, Derocher H, et al. PD-L1 and intratumoral immune response in breast cancer. Oncotarget 2017;8:51641–51.

[21] Botti G, Collina F, Scognamiglio G, et al. Programmed death Ligand 1 (PD-L1) tumor expression is associated with a better prognosis and diabetic disease in triple negative breast cancer patients. Int J Mol Sci 2017;18:pii: E459.

[22] Sabatier R, Finetti P, Mamessier E, et al. Prognostic and predictive value of PDL1 expression in breast cancer. Oncotarget 2015;6:5449–64.

[23] Mori H, Kubo M, Yamaguchi R, et al. The combination of PD-L1 expression and decreased tumor-infiltrating lymphocytes is associated with a poor prognosis in triple-negative breast cancer. Oncotarget 2017;8:15584–92.

[24] Tymoszuk P, Charoentong P, Hackl H, et al. High STAT1 mRNA levels but not its tyrosine phosphorylation are associated with macrophage infiltration and bad prognosis in breast cancer. BMC Cancer 2014;14:257.

[25] Okabe M, Toh U, Iwakuma N, et al. Predictive factors of the tumor immunological microenvironment for long-term follow-up in early stage breast cancer. Cancer Sci 2017;108:81–90.

[26] Li X, Wetherilt CS, Krishnamurti U, et al. Stromal PD-L1 expression is associated with better disease-free survival in triple-negative breast cancer. Am J Clin Pathol 2016;146:496–502.

[27] Bae SB, Cho HD, Oh MH, et al. Expression of programmed death receptor ligand 1 with high tumor-infiltrating lymphocytes is associated with better prognosis in breast cancer. J Breast Cancer 2016;19:242–51.

[28] Park IH, Kong SY, Ro JY, et al. Prognostic implications of tumor-infiltrating lymphocytes in association with programmed death Ligand 1 expression in early-stage breast cancer. Clin Breast Cancer 2016;16:51–8.

[29] Bertucci F, Finetti P, Colpaert C, et al. PDL1 expression in inflammatory breast cancer is frequent and predicts for the pathological response to chemotherapy. Oncotarget 2015;6:13506–19.

[30] Baptista MZ, Sarian LO, Derchain SF, et al. Prognostic significance of PD-L1 and PD-L2 in breast cancer. Hum Pathol 2016;47:78–84.

[31] Polonia A, Pinto R, Cameselle-Teijeiro JF, et al. Prognostic value of stromal tumour infiltrating lymphocytes and programmed cell death-ligand 1 expression in breast cancer. J Clin Pathol 2017;70:860–7.

[32] Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427–37.

[33] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[34] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[35] Tobias A. Assessing the influence of a single study in the meta-analysis estimate. Stat Tech Bull 1999;8:15–7.

[36] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[37] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[38] Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.

[39] R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; 2015. Available at: https://www.R-project.org. Accessed 10 December 2015.

[40] Gentzler R, Hall R, Kunk PR, et al. Beyond melanoma: inhibiting the PD-1/PD-L1 pathway in solid tumors. Immunotherapy 2016;8:583–600.

[41] Chen J, Jiang CC, Jin L, et al. Regulation of PD-L1: a novel role of pro-survival signalling in cancer. Ann Oncol 2016;27:409–16.

[42] Dawood S, Rugo HS. Targeting the host immune system: PD-1 and PD-L1 antibodies and breast cancer. Curr Opin Support Palliat Care 2016;10:336–42.

[43] Vonderheide RH, Domchek SM, Clark AS. Immunotherapy for breast cancer: what are we missing? Clin Cancer Res 2017;23:2640–6.

[44] Schalper KA. PD-L1 expression and tumor-infiltrating lymphocytes: revisiting the antitumor immune response potential in breast cancer. Oncoimmunology 2014;3:e29288.

[45] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252–64.

[46] Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 2015;27:450–61.

[47] Lastwika KJ, Wilson W3rd, Li QK, et al. Control of PD-L1 expression by oncogenic activation of the AKT-mTOR pathway in non-small cell lung cancer. Cancer Res 2016;76:227–38.

[48] Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010;116:3268–77.

[49] Rech AJ, Vonderheide RH. Dynamic interplay of oncogenes and T cells induces PD-L1 in the tumor microenvironment. Cancer Discov 2013;3:1330–2.

[50] Crane CA, Panner A, Murray JC, et al. PI(3) kinase is associated with a mechanism of immunoresistance in breast and prostate cancer. Oncogene 2009;28:306–12.

[51] Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

[52] Hartkopf AD, Taran FA, Wallwiener M, et al. PD-1 and PD-L1 immune checkpoint blockade to treat breast cancer. Breast Care (Basel) 2016;11:385–90.

[53] Emens LA, Braiteh FS, Cassier P, et al. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer. Annual Meeting of the American Association for Cancer Research 2015; abstr 2859.

[54] Heery CR, O'Sullivan-Coyne G, Madan RA, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol 2017;18:587–98.

[55] Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. J Clin Oncol 2016;34:2460–7.