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REVIEW

# Prognostic and clinicopathological value of PD-L1 expression in primary breast cancer: a meta-analysis

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## Abstract

**Purpose** To evaluate the association between PD-L1 expression (PD-L1+) and clinicopathological characteristics and effect on prognosis in primary breast cancer (PBC).

**Methods** A systematic search of the PubMed, Web of Science, and Embase databases was conducted in November 2018. Studies detecting PD-L1 using immunohistochemistry, and concerning its prognostic or clinicopathological significance in PBC were included. The HR with 95% CI for survival, and the events for clinicopathological features were pooled.

**Results** Forty-seven studies were included, with a total of 14,367 PBC patients. PD-L1+ tumor cells (TCs) were associated with ductal carcinomas, large tumor size, histological Grade 3 tumors, high Ki-67, ER and PR negative, and triple-negative breast cancer; and also, related to high tumor-infiltrating lymphocytes (TILs) and PD-1 expression. PD-L1+ TCs were significantly associated with shorter disease-free survival (DFS, HR = 1.43, 95% CI 1.21–1.70, $P < 0.0001$) and overall survival (OS, HR = 1.58, 95% CI 1.14–2.20, $P = 0.006$). And the HRs of PD-L1+ TCs on DFS and OS were higher (1.48 and 1.70, respectively) and homogeneous when using whole tissue section, compared with tumor microarrays. However, PD-L1+ TILs related to better DFS (HR = 0.45, 95% CI 0.28–0.73, $P = 0.001$) and OS (HR = 0.41, 95% CI 0.27–0.63, $P < 0.0001$).

**Conclusion** PD-L1 expression on TCs associates with high-risk clinicopathological parameters and poor prognosis in PBC patients, while PD-L1+ TILs may relate to a better survival. Comprehensive assessment of TCs and TILs is required when evaluating the clinical relevance of PD-L1 expression in future studies.

**Keywords** Primary breast cancer · PD-L1 · Immunohistochemistry · Prognosis · Meta-analysis

## Introduction

Immunotherapy with checkpoint inhibitors has shown unprecedented efficacy in treating multiple immunogenic tumors, such as non-small cell lung cancer (NSCLC) and malignant melanoma, and is rapidly changing the clinical practice of medical oncology [1]. One of the immune checkpoint molecules, programmed death-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is expressed on various tumor cells, activated B cells and T cells, dendritic cells, and macrophages [2]. The binding of PD-L1 to its receptor, programmed death 1 (PD-1), could regulate T-cell activity and maintain immune tolerance of self-antigens [3]. Similar to self-antigen recognition, upregulation of PD-L1 could also mediate the immune escape of tumor cells (TCs). It has been reported that the expression of PD-L1 not only related to the response of immune checkpoint therapy but also signified a poor prognosis in many cancer types, such as NSCLC, melanoma, and renal cell carcinoma [1, 4–6].

Breast cancer (BC) was traditionally considered as an immune-inert tumor, as extensive research on the prognostic value of immune cells in primary breast cancer (PBC) in the 1980–1990s did not identify any prognostic factors [7]. However, the number of studies on the prevalence of PD-L1 in BC has grown rapidly in the past 3 years, especially in aggressive subtypes as triple-negative breast cancer (TNBC) [8, 9]. The reason for this increase is the potential

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of immunotherapy with anti-PD-1 and anti-PD-L1 compounds as general novel approaches to manage BC. As of September, 2018, up to 208 trials (285 trials with any form of immunotherapy) open to BC patients are assessing drugs targeting PD-1 and PD-L1, either as monotherapy or in combination with other regimens [10]. Therefore, it is of interest to explore the clinical relevance of PD-L1 expression in BC. This subject is a matter of debate, both as to the predictive role of PD-L1 for the efficacy of PD-1/PD-L1 blockade therapy, but also its value as a prognostic marker.

With regard to PD-L1 as a predictive marker of immunotherapy, the data for BC are still limited. And the PD-L1 expression on both TCs and tumor-infiltrating lymphocytes (TILs) did not guarantee response and vice versa, as reported in series of clinical trials [11–13]. As to PD-L1 as a prognostic factor, however, many studies have found that PD-L1 expression on TCs related to multiple indicators for unfavorable prognosis, such as high tumor grade, ER and PR negative, and TNBC subtype, and also, PD-L1 expression indicated a shorter survival [14, 15]. Several meta-analyses in 2016, based on limited number of studies, also validated this relationship that high PD-L1 expression by immunohistochemistry (IHC) related to worse prognosis [16–18]. However, results that no association with prognosis or even a reverse relationship have also been reported in recent studies [19, 20]. Moreover, PD-L1 expression on TILs was also found to be correlated with the survival of BC patients, but have failed to reach consensus [20, 21]. And a recent meta-analysis reported a positive association between PD-L1 expression on TILs and a more favorable cancer prognosis, which seemed to conflict with PD-L1 expression on TCs [22].

Given the relatively limited sample size of prior meta-analyses and the discrepancy in prognostic value of PD-L1 expression, we performed an up-to-date meta-analysis to investigate PD-L1 expression in PBC patients and its association with clinicopathological features and clinical outcomes. Our findings may help determine whether PD-L1 expression could be a useful prognostic factor.

## Methods

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [23]. Since this study analyzed the data from previously published studies, ethical approval and informed consent were not required.

### Search strategy and selection of studies

A comprehensive search of the Medline/PubMed, Web of Science, and EMBASE databases was performed on November 28, 2018, for relevant studies, covering a time period from 2003 until 2018. We employed the following search terms and Boolean operators: (PD-L1 OR B7-H1 OR CD274 OR "programmed cell death 1 ligand 1″ OR "PD-L1 costimulatory protein" OR "B7 homolog 1" OR "B7-H1 antigen" OR "CD274 antigen") AND ("breast cancer" OR "breast neoplasms" OR "breast tumor" OR "breast carcinoma" OR "cancer of breast" OR "human mammary neoplasm" OR "human mammary carcinoma"). Studies that met all of the following criteria were included: (1) included patients with histologically confirmed primary breast cancer; (2) expression of PD-L1 was detected by IHC; (3) investigated the correlation between PD-L1, clinicopathological parameters, or prognosis. Studies were excluded if they met any of the following criteria: (1) review articles, conference abstracts, or non-English papers; (2) evaluated PD-L1 at mRNA levels, or using methods other than IHC; (3) patients in which underwent immunotherapy; (4) non-human experiments; (5) duplicate publications.

Two authors reviewed the primary search outcomes independently. Titles and abstracts were reviewed initially to assess their feasibility of inclusion. When duplicates were identified using EndNote software (version X7) or manual screening, only the most complete article was analyzed. Full texts review was performed subsequently based on the inclusion criteria, and the reference list of the articles of interest was reviewed to identify the additional eligible trial. Any disagreements were resolved by discussion.

### Data extraction and quality assessment

Data extraction was conducted by two authors according to the pre-designed data extraction form. The following data were extracted: first author, publication year, country, sample size, format of pathological sections, IHC evaluation methods, antibodies for PD-L1 detection, staining sites, cut-off values, PD-L1 positivity, and clinical outcomes. Both the PD-L1 positive and high expression in the individual study were considered as PD-L1+ group, while the other as PD-L1− group. Pathologic complete response (pCR), disease-free survival (DFS), recurrence-free survival (RFS), and overall survival (OS) were evaluated as patient outcomes. For the clinicopathological features, number of events were extracted, whereas hazard ratio (HR) and 95% confidence interval (CI) were extracted for survival data. When survival data were not available in the articles, data were requested by contacting with the first or corresponding authors.

Quality assessment of the included studies was performed strictly by two independent authors using the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort studies [24]. The NOS consists of three key categories, including selection, comparability, and outcome. One point was added

when there was enough support information for an item. Notably, a maximum score of two points in comparability dimension was added if the two cohorts were comparable for age and neoadjuvant chemotherapy (NAC) condition before tissue biopsy or surgery. Any disagreements between authors were resolved by consensus. The maximum possible score of NOS is 9 points, and studies that obtained at least 6 points were considered to be of high quality.

### Statistical analysis

Review Manager (RevMan) version 5.3.5 (Cochrane Collaboration, Oxford, UK) and Stata SE12.0 (Stata Corporation, College Station, TX, USA) were used to perform meta-analysis for data from each study. The association between PD-L1 expression and prognosis was chosen as primary end points. Pooled HR and its 95% CI were generated using the inverse variance method to evaluate survival data, while risk ratio (RR) with 95% CI was calculated using the Mantel–Haenszel method to determine the association between PD-L1 expression and clinicopathological parameters. Forest plots were used to present the pooled results. Heterogeneity across studies was evaluated using both the Q statistic (Chi-square test) and Higgins $I^2$ index. An $I^2$ value of $>50\%$ was indicative of significant heterogeneity. In this case, subgroup analysis and sensitivity analysis were carried out to find the potential cause of heterogeneity, and a random-effects model was used. Otherwise, a fix-effect model was taken. Egger's and Begg's test were performed to assess the potential publication bias. All tests were two-sided, and $P$ values of $<0.05$ were considered statistically significant.

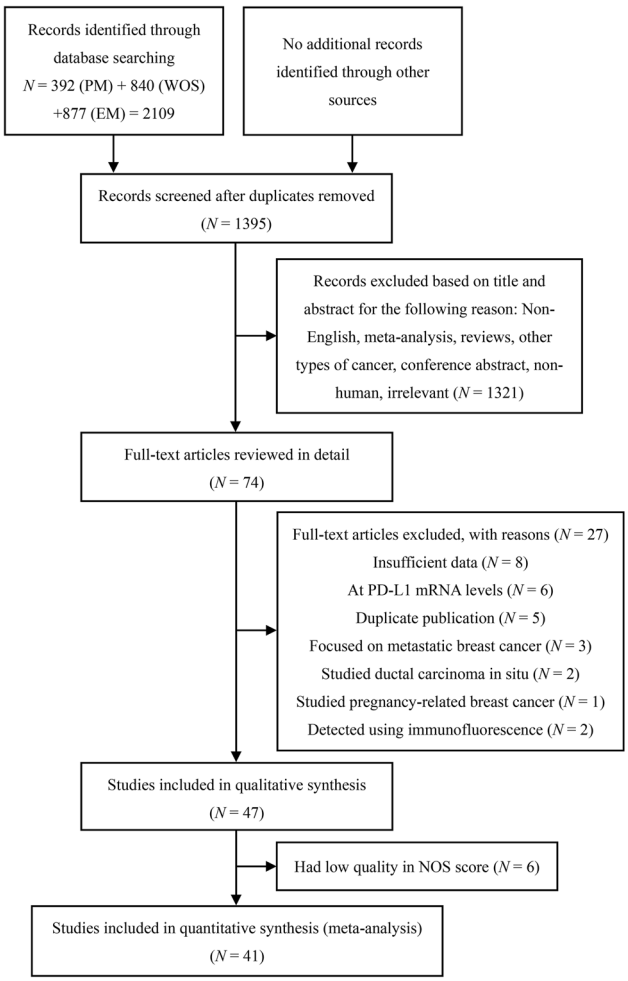


**Fig. 1** Flowchart of study selection. *PM* PubMed, *WOS* web of science, *EM* embase, *NOS* Newcastle–Ottawa Quality Assessment Scale

## Results

### Search results and study characteristics

The search was completed on November 28, 2018. And the detailed flow diagram of screening process is presented in Fig. 1. A total of 2109 records were initially identified by the electronic search. After screening the titles and abstracts, we excluded 2035 studies that were duplicates or irrelevant. After reviewing 74 full-text articles in detail, we determined that 47 studies met our inclusion criteria [14, 15, 19–21, 25–66]. No additional studies were obtained through checking the reference lists of these articles.

The quality of included studies, as assessed by NOS score, ranged from 3 to 9 (Table 1 and Table S1). We excluded six studies with relatively low quality (<6) because of the incomparability of baseline information between the PD-L1+ and PD-L1− cohorts and the insufficient data for outcome assessment [25–30]. Otherwise, two studies obtained high scores in the selection and comparability categories but without survival data were included to evaluate the association between PD-L1 expression and clinicopathological parameters [31, 32]. Thus, a total of 41 trials were analyzed in the final meta-analysis.

The characteristics of the included studies are presented in Table 1. The publication years of these studies ranged from 2006 to 2018, and most of them (91.8%) were published between 2016 and 2018. A total of 14,367 patients were enrolled in the studies, with the sample sizes of individual study ranged from 22 to 3916. All of the included studies retrospectively focused on PBC patients, among which, 21 studies only contained certain molecular subtypes (15 TNBC [20, 21, 26, 28, 30, 33–41, 43], 4 HER2-enriched [42, 44–46], and 2 inflammatory breast cancer [47, 49]). Expression of PD-L1 was assessed using tissue microarrays (TMA, 20 studies [15, 19, 21, 25, 27, 32–34, 37, 42, 44, 45, 48–52, 54]), whole tissue section (WTS, 17 studies [14, 29–31, 36, 38, 39, 43, 53, 55–62]), or core needle biopsy (CNB, 10 studies [26, 28, 35, 41, 46, 47,

**Table 1** Characteristics of the studies included in our analysis

| Study/year | Study type | Country | Cohort | No. of patients | Median age (range) | Follow-up time (months) | Outcomes | NOS Score |
|---|---|---|---|---|---|---|---|---|
| Ghebeh et al. 2006 | RC | Saudi Arabia | PBC | 44 | 45 | NA | NA | 6 |
| Muenst et al. 2014 | RC | Switzerland | PBC | 650 | 64 (27–101) | 65 (1–174) | OS | 6 |
| Ali et al. 2015 | RC | UK | PBC | 3916 | NA | NA | DFS | 4 |
| Qin et al. 2015 | RC | China | PBC | 870 | 47 (21–84) | 98 (17–265) | DFS OS | 8 |
| Bae et al. 2016 | RC | Korea | PBC | 465 | 52.3 (24–81) | 41 (1–158) | DFS OS | 8 |
| Baptista et al. 2016 | RC | Brazil | PBC | 189 | 60 | 86.2 | DFS OS | 7 |
| Beckers et al. 2016 | RC | Australia | PBC (TNBC) | 161 | 57 (28–89) | 55 (0–213) | OS BCSS | 7 |
| Cimino-Mathews et al. 2016 | RC | USA | PBC | 43 | 54 | NA | OS | 6 |
| Guo et al. 2016 | RC | China | PBC (TNBC) | 183 | NA | 76.4 | BCSS | 9 |
| Li Z et al. 2016 | RC | China | PBC | 501 | 64 (1–80) | 53 (29–83) | RFS OS | 8 |
| Li X et al. 2016 | RC | USA | PBC (TNBC) | 136 | NA | NA | DFS OS | 6 |
| Park et al. 2016 | RC | Korea | PBC | 316 | 47 (28–78) | 118 (5–154) | DFS OS | 8 |
| Sun et al. 2016 | RC | Korea | PBC (TNBC) | 218 | NA | NA | DFS OS | 6 |
| Botti et al. 2017 | RC | Italy | PBC (TNBC) | 238 | 57 (24–93) | 60 | DFS OS | 6 |
| Buisseret et al. 2017 | RC | Belgium | PBC | 125 | NA | NA | NA | 5 |
| Cerbelli et al. 2017 | RC | Italy | PBC (TNBC) | 54 | 50 (28–75) | NA | pCR | 6 |
| Chen et al. 2017 | RC | China | PBC | 309 | 49 | 70 | RFS OS | 8 |
| Dill et al. 2017 | RC | USA | PBC | 245 | NA | NA | NA | 5 |
| Joneja et al. 2017 | RC | USA | PBC (MBC) | 297 | NA | NA | NA | 3 |
| Kim et al. 2017 | RC | Korea | PBC (HER2+) | 167 | 52.6 (23–85) | 39 (1–58) | DFS OS | 8 |
| Kitano et al. 2017 | RC | Japan | PBC | 166 | 54 (23–76) | 115 (4–202) | DFS OS pCR | 8 |
| Lou et al. 2017 | RC | China | PBC | 64 | NA | NA | NA | 6 |
| Mori et al. 2017 | RC | Japan | PBC (TNBC) | 248 | 60 (30–89) | 68 (2–150) | RFS OS | 7 |
| Okabe et al. 2017 | RC | Japan | PBC | 97 | 58 (27–84) | 127.3 | DFS OS | 8 |
| Polónia et al. 2017 | RC | Spain | PBC | 435 | 60 (28–92) | 120 (1–120) | DFS OS | 8 |
| Thompson et al. 2017 | RC | USA | PBC | 47 | 59 (34–87) | 52 (0–167) | NA | 5 |
| Tsang et al. 2017 | RC | China | PBC | 1091 | 54.5 (22–94) | 63 (1–210) | DFS OS | 7 |
| Wang et al. 2017 | RC | Canada | PBC | 443 | NA | 87 (2–251) | RFS OS | 8 |
| Adams et al. 2018 | RC | USA | PBC (TNBC) | 128 | 55.5 | NA | OS | 6 |
| Arias-Pulido et al. 2018 | RC | USA | PBC (IBC) | 221 | NA | NA | RFS BCSS pCR | 6 |
| Asano et al. 2018 | RC | Japan | PBC | 177 | NA | 40.8 (1–72) | DFS OS pCR | 9 |
| Barrett et al. 2018 | RC | USA | PBC (TNBC) | 54 | NA | NA | DFS OS | 5 |
| Choi et al. 2018 | RC | Korea | PBC (TNBC) | 117 | 50 (24–79) | 53 (4–135) | RFS OS | 7 |
| He et al.2018 | RC | USA | PBC (IBC) | 68 | 48 (23–75) | 45 (3–210) | OS | 8 |

**Table 1** (continued)

| Study/year | Study type | Country | Cohort | No. of patients | Median age (range) | Follow-up time (months) | Outcomes | NOS Score |
|---|---|---|---|---|---|---|---|---|
| Hou et al. 2018 (Cohort A) | RC | USA | PBC (HER2+) | 123 | 56 (30–76) | NA | pCR | 6 |
| Hou et al. 2018 (Cohort B) | RC | USA | PBC (HER2+) | 216 | 53 (27–88) | 73 (7–162) | OS | 9 |
| Lee et al. 2018 | RC | Korea | PBC (TNBC) | 34 | 51 (14–86) | NA | DFS | 4 |
| Li M et al. 2018 | RC | China | PBC (TNBC) | 101 | 51 (27–74) | 49 (11–94) | DFS OS | 8 |
| Li F et al. 2018 | RC | China | PBC | 112 | NA | NA | NA | 6 |
| Li Y et al. 2018 | RC | USA | PBC (HER2+) | 191 | 52 (25–86) | NA | RFS OS | 9 |
| McLemore et al. 2018 | RC | USA | PBC | 76 | 50.9 (26–77) | NA | pCR | 7 |
| Pelekanou et al. 2018 | RC | USA | PBC | 120 | 51.5 (22–75) | NA | DFS OS pCR | 6 |
| Ren et al. 2018 | RC | China | PBC (TNBC) | 195 | 50.8 (24–90) | NA | DFS OS | 8 |
| Sobral-Leite et al. 2018 | RC | Netherlands | PBC | 410 | NA | NA | DFS BCSS | 7 |
| Tomioka et al. 2018 | RC | Japan | PBC (TNBC) | 22 | NA | NA | DFS OS pCR | 4 |
| Wang et al. 2018 | RC | China | PBC (TNBC) | 148 | 49 (27–69) | 66.5 (5–91) | DFS pCR | 7 |
| Zhou et al. 2018 | RC | China | PBC | 136 | 54 (30–84) | 45.3 (2–NA) | DFS | 9 |

*NOS* Newcastle–Ottawa Scale, *RC* retrospective cohort, *PBC* primary breast cancer, *TNBC* triple-negative breast cancer, *MBC* metaplastic breast cancer, *IBC* inflammatory breast cancer, *HER2+* HER2-enriched, *DFS* disease-free survival, *OS* overall survival, *RFS* recurrence-free survival, *BCSS* breast cancer-specific survival, *pCR* pathologic complete response, *NA* not available

63–66]). All studies detected PD-L1 using IHC, but at least 16 different antibodies were used, among which clone SP142 was used most commonly in 11 studies [21, 27–29, 32, 33, 35, 47, 50, 54, 64], followed by clone E1L3N (9 studies [19, 20, 25, 31, 38, 39, 42, 43, 58]), clone 28-8 (4 studies [34, 44, 49, 59]), and clone SP263 (4 studies [26, 40, 45, 46]) (Table 2). Twenty-nine studies considered membranous staining as PD-L1+ [21, 25–32, 34, 35, 37–50, 53, 58, 64, 66], whereas others reported cytoplasmic only (three studies [59, 61, 62]) or both membranous and cytoplasmic staining (15 studies [14, 15, 19, 20, 33, 36, 51, 52, 54–57, 60, 63, 65]) could be considered as positive expression. Different cut-off values for the percentage of PD-L1+ cells were utilized in 28 studies, ranging from 1 to 50%, while 18 studies used composite scores of staining intensity and percentage of positive cells. Most studies (41 of 47 studies) evaluated PD-L1 expression on TCs, with the rates of PD-L1+ ranging from 1.7 to 64%, while the others considered that staining in both TCs and TILs as PD-L1+ [28, 31, 36, 41, 54, 64]. Additionally, the expression of PD-L1 on TILs reported in 21 studies was relatively higher than those in TCs, with the positive rates varying from 1.07 to 93% [14, 20, 21, 25–27, 32–34, 38–40, 42–48, 58, 66].

## PD-L1+ TCs and clinicopathological parameters

In the present study, associations between PD-L1+ TCs and clinicopathological characteristics were analyzed, as summarized in Table 3. The summary RR for PD-L1+ versus PD-L1− group was 1.05 (95% CI 1.00–1.09, $P = 0.03$) for ductal carcinomas, 1.07 (95% CI 1.00–1.15, $P = 0.05$) for large tumor size, 1.44 (95% CI 1.28–1.63, $P < 0.00001$) for histological Grade 3 tumors, 1.56 (95% CI 1.20–2.02, $P = 0.0009$) for ER negative, 1.40 (95% CI 1.11–1.76, $P = 0.004$) for PR negative, 1.24 (95% CI 1.05–1.45, $P = 0.01$) for high Ki-67, and 1.70 (95% CI 1.29–2.23, $P = 0.0001$) for TNBC subtype. In addition, PD-L1+ was significantly associated with the present of TILs (RR = 2.16, 95% CI 1.64–2.84, $P < 0.00001$) and PD-1 expression (RR = 4.29, 95% CI 1.70–10.86, $P = 0.002$). However, we did not find any correlation with patient age, lymph node metastasis, lymphovascular invasion, HER2 positive as well as HER2-enriched subtype. Most variables were analyzed using a random-effects model because of the significant heterogeneity among studies, while a fix-effect model was used for patient age ($I^2 = 41\%$, $P_{\text{heterogeneity}} = 0.03$) and histological type ($I^2 = 42\%$, $P_{\text{heterogeneity}} = 0.07$) because of their low heterogeneity.

**Table 2** Detection methods of the PD-L1 expression in the included studies

| Study/year | Format of sampling | IHC evaluation method | Antibody | | | | Cut-off | Staining sites | Positive cell (TCs/TILs) | PD-L1 positive (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Company | Source | Type | Clone | | | | |
| Ghebeh et al. 2006 | WTS | Percentage | eBioscience | Mouse | MAB | MIH1 | ≥ 5% | M & C | TCs, TILs | 34, 41 |
| Muenst et al. 2014 | TMA | H-score | Abcam | Rabbit | PAB | NA | ≥ 100 scores | M & C | TCs | 23.4 |
| Ali et al. 2015 | TMA | Percentage | CST | Rabbit | MAB | E1L3N | > 1% | Membrane | TCs, TILs | 1.7, 6 |
| Qin et al. 2015 | WTS | Percentage | CST | Rabbit | NA | NA | ≥ 5% | Membrane | TCs | 21.7 |
| Bae et al. 2016 | TMA | H-score | CST | Rabbit | MAB | E1L3N | ≥ 100 scores | M & C | TCs | 13.5 |
| Baptista et al. 2016 | TMA | Allred score | Abcam | Rabbit | PAB | NA | Median | M & C | TCs | 56.6 |
| Beckers et al. 2016 | TMA | Percentage | CST | Rabbit | MAB | E1L3N | ≥ 1% | M & C | TCs, TILs | 64, 93 |
| Cimino-Mathews et al. 2016 | TMA | Percentage | NA | Mouse | MAB | 5H1 | ≥ 5% | Membrane | TCs, TILs | 21, 53 |
| Guo et al. 2016 | TMA | I & P | Ventana | Rabbit | MAB | SP142 | 3+ & ≥ 10% | M & C | TCs, TILs | 8.7, 4.9 |
| Li Z et al. 2016 | WTS | H-score | Abcam | Rabbit | PAB | NA | ≥ 100 scores | M & C | TCs | 46.1 |
| Li X et al. 2016 | WTS | H-score | CST | Rabbit | MAB | E1L3N | > 0 scores | Membrane | TCs, TILs | 21, 40 |
| Park et al. 2016 | WTS | H-score | Abcam | Rabbit | PAB | NA | 3+ | M & C | TCs | 51.6 |
| Sun et al. 2016 | TMA | Percentage | Abcam | Rabbit | MAB | 28-8 | ≥ 5% | Membrane | TCs, TILs | 12.4, 36.7 |
| Botti et al. 2017 | TMA | Percentage | Ventana | Rabbit | MAB | SP142 | ≥ 10% | Membrane | TCs, TILs | 35.2, 42.8 |
| Buisseret et al. 2017 | WTS | Percentage | CST | Rabbit | MAB | E1L3N | ≥ 1% | Membrane | TCs + TILs | 23.6 |
| Cerbelli et al. 2017 | Biopsy | Percentage | Ventana | Rabbit | MAB | SP142 | ≥ 1% | Membrane | TCs | 35 |
| Chen et al. 2017 | WTS | Density | Abcam | Rabbit | MAB | 28-8 | Median | Cytoplasm | TCs | 49.5 |
| Dill et al. 2017 | TMA | Percentage | Ventana | Rabbit | MAB | SP142 | ≥ 1%, >5% | Membrane | TCs, TILs | 12.2, 29 |
| Joneja et al. 2017 | WTS | I & P | Ventana | Rabbit | MAB | SP142 | 2+ & ≥ 5% | Membrane | TCs | 45.8 versus 7.9 |
| Kim et al. 2017 | TMA | Allred score | CST | Rabbit | MAB | E1L3N | Mean | Membrane | TCs, TILs | 48.5, 30.5 |
| Kitano et al. 2017 | Biopsy | Percentage | ProScience | Rabbit | PAB | NA | ≥ 1% | M & C | TCs | 37.3 |
| Lou et al. 2017 | WTS | IHC score | NA | NA | NA | NA | ≥ 3 scores | Cytoplasm | TCs | 37.5 |
| Mori et al. 2017 | WTS | Percentage | CST | Rabbit | MAB | E1L3N | ≥ 1%, ≥ 5% | Membrane | TCs, TILs | 41.5, 52.0 |
| Okabe et al. 2017 | WTS | H-score | Abcam | Rabbit | MAB | EPR1161(2) | ≥ 100 scores | M & C | TCs | 33 |
| Polónia et al. 2017 | TMA | Percentage | Ventana | Rabbit | MAB | SP142 | ≥ 1% | M & C | TCs + TILs | 6.4 |
| Thompson et al. 2017 | TMA | Percentage | Ventana | Rabbit | MAB | SP142 | > 5% | Membrane | TCs, TILs | 17, 29 |
| Tsang et al. 2017 | TMA | Immunoscore | Novus | NA | PAB | NA | ≥ 30 scores | M & C | TCs | 27 |
| Wang et al. 2017 | TMA | H-score | Ventana | Rabbit | MAB | SP142 | Upper quartile | Membrane | TCs | 16.5 |
| Adams et al. 2018 | TMA | Percentage | CST | NA | NA | NA | > 10% | Membrane | TCs | 48.4 |
| Arias-Pulido et al. 2018 | Biopsy | Percentage | Ventana | Rabbit | MAB | SP142 | ≥ 5% | Membrane | TCs, TILs | 8.1, 66.1 |
| Asano et al. 2018 | Biopsy | Percentage | MBL | Mouse | MAB | 27A2 | ≥ 10% | M & C | TCs | 23.7 |
| Barrett et al. 2018 | WTS | IHC score | MRL | Mouse | MAB | 22C3 | ≥ 4 scores | Membrane | TCs | 37 |
| Choi et al. 2018 | WTS | Percentage | EMD Millipore | NA | NA | NA | ≥ 5% | M & C | TCs + TILs | 83 |
| He et al.2018 | TMA | Percentage | Abcam | Rabbit | MAB | 28-8 | > 1% | Membrane | TCs | 36.8 |

**Table 2** (continued)

| Study/year | Format of sampling | IHC evaluation method | Antibody | | | | Cut-off | Staining sites | Positive cell (TCs/TILs) | PD-L1 positive (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Company | Source | Type | Clone | | | | |
| Hou et al. 2018 (Cohort A) | Biopsy | Percentage | Ventana | Rabbit | MAB | SP263 | ≥ 1%, ≥ 10% | Membrane | TCs, TILs | 17.1, 54.5 |
| Hou et al. 2018 (Cohort B) | TMA | Percentage | Ventana | Rabbit | MAB | SP263 | ≥ 1% | Membrane | TCs, TILs | 5.6, 12 |
| Lee et al. 2018 | Biopsy | H-score | Ventana | Rabbit | MAB | SP263 | ≥ 5 | Membrane | TCs, TILs | 44.1, 61.8 |
| Li M et al. 2018 | WTS | Percentage | CST | Rabbit | MAB | E1L3N | ≥ 5% | Membrane | TCs, TILs | 25.7, 30.7 |
| Li F et al. 2018 | WTS | IHC score | Abcam | Rabbit | PAB | NA | ≥ 3 scores | Cytoplasm | TCs | 19.6 |
| Li Y et al. 2018 | TMA | Percentage | Abcam | Rabbit | MAB | 28-8 | ≥ 1% | Membrane | TCs, TILs | 25.7, NA |
| McLemore et al. 2018 | Biopsy | Percentage | Ventana | Rabbit | MAB | SP142 | > 1% | Membrane | TCs + TILs | 35.5 |
| Pelekanou et al. 2018 | Biopsy | Percentage | MRL | Mouse | MAB | 22C3 | ≥ 1% | Membrane | TCs, TILs | 19.2, 39.2 |
| Ren et al. 2018 | TMA | Percentage | Ventana | Rabbit | MAB | SP263 | ≥ 25% | Membrane | TCs, TILs | 6.7 31.3 |
| Sobral-Leite et al. 2018 | WTS | Percentage | CST | Rabbit | MAB | E1L3N | ≥ 1%, ≥ 5% | Membrane | TCs, TILs | 25.9, 54.1 |
| Tomioka et al. 2018 | Biopsy | Percentage | Ventana | Rabbit | MAB | SP142 | ≥ 50% | Membrane | TCs + TILs | 22.7 |
| Wang et al. 2018 | Biopsy | H-score | Abcam | Rabbit | MAB | EPR19759 | ≥ 100 scores | Membrane | TCs + TILs | 32.4 |
| Zhou et al. 2018 | WTS | I & P | Abcam | Rabbit | MAB | EPR19759 | ≥ 2+/> 10% | M & C | TCs | 33.1 |

*PD-L1* programmed death-ligand 1, *TCs* tumor cells, *TILs* tumor-infiltrating lymphocytes, *WTS* whole tissue section, *TMA* tissue microarray, *I & P* intensity and percentage, *MAB* monoclonal antibody, *PAB* polyclonal antibody, *M & C* membrane and cytoplasm, *NA* not available

**Table 3** Association between PD-L1 expression and clinicopathological features

| Clinicopathological parameter | Number, studies | No. of patients | Overall RR | 95% CI | Heterogeneity | | | Significance (*P* value) |
|---|---|---|---|---|---|---|---|---|
| | | | | | $\chi^2$ | $I^2$ (%) | *P* | |
| Patient age < 50 | 19 [14, 19, 21, 31, 33, 39, 40, 43, 49, 50, 55–57, 59–63, 65] | 3820 | 1.03 | 0.94–1.12 | 30.65 | 41 | 0.03 | 0.56 |
| Tumor size ≥ 2 cm | 25 [14, 15, 19, 21, 31, 36, 39, 40, 43–45, 50–63] | 7177 | 1.07 | 1.00–1.15 | 64.87 | 61 | < 0.0001 | **0.05** |
| Invasive ductal carcinomas | 10 [19, 21, 31–33, 40, 45, 46, 49, 58] | 2371 | 1.05 | 1.00–1.09 | 17.23 | 42 | 0.07 | **0.03** |
| Histologic Grade 3 tumors | 29 [14, 15, 19, 21, 31–33, 36, 39, 40, 42–46, 48–55, 57–61, 65] | 8109 | 1.44 | 1.28–1.63 | 240.34 | 88 | < 0.00001 | < **0.00001** |
| Lymph node metastasis | 30 [14, 15, 19, 21, 31, 33, 34, 36, 39, 40, 42, 44–46, 49–63, 65] | 8421 | 1.04 | 0.96–1.12 | 63.4 | 53 | 0.0004 | 0.32 |
| Lymphovascular invasion | 8 [31, 33, 42, 45, 49, 52, 53, 59] | 2874 | 1.06 | 0.85–1.33 | 17.07 | 59 | 0.02 | 0.59 |
| ER negative | 18 [14, 15, 19, 31, 45–47, 49–55, 57–60] | 6446 | 1.56 | 1.20–2.02 | 223.88 | 92 | < 0.00001 | **0.0009** |
| PR negative | 16 [14, 19, 31, 45–47, 49–55, 58–60] | 5546 | 1.4 | 1.11–1.76 | 216.62 | 93 | < 0.00001 | **0.004** |
| HER2 positive | 17 [14, 15, 19, 31, 47, 49, 51–60, 63] | 5676 | 1.11 | 0.91–1.37 | 37.47 | 57 | 0.002 | 0.3 |
| High Ki-67 | 13 [15, 19, 21, 31, 36, 40, 52–54, 56, 59, 60, 63] | 4818 | 1.24 | 1.05–1.45 | 160.18 | 93 | < 0.00001 | **0.01** |
| TNBC subtype | 19 [15, 19, 31, 32, 47–50, 52–55, 57–60, 63–65] | 6428 | 1.76 | 1.33–2.34 | 168.49 | 89 | < 0.00001 | **0.0001** |
| HER2+ subtype | 14 [15, 19, 31, 32, 48, 50, 52, 54, 55, 58–60, 64, 65] | 4998 | 1.21 | 0.88–1.66 | 36.16 | 64 | 0.0006 | 0.23 |
| High TIL | 14 [14, 19, 31, 36, 40, 42, 43, 47, 48, 52, 55, 58, 59, 65] | 3640 | 2.16 | 1.64–2.84 | 162.54 | 91 | < 0.00001 | < **0.00001** |
| PD-1 positivity | 7 [15, 31, 40, 45, 60, 63, 65] | 1633 | 4.29 | 1.70–10.81 | 152.16 | 96 | < 0.00001 | **0.002** |

*PD-L1* programmed death-ligand 1, *RR* risk ratio, *95% CI* 95 % confidence interval, *TNBC* triple-negative breast cancer, *HER2+* HER2-enriched, *TIL* tumor-infiltrating lymphocytes, *PD-1* programmed death 1

*P* values in bold are statistically significant

## PD-L1+ TCs and clinical outcomes

A total of 33 studies evaluated the relationship between PD-L1+ TCs and patients' survival, among which, HR and their 95% CIs were only obtained in 14 studies for DFS (4349 patients [19, 38, 41–43, 51–53, 56–60, 63]), 17 for OS (5890 patients [15, 19, 20, 36–39, 43, 49–53, 55–57, 59]), and five for RFS (1500 patients [36, 39, 44, 50, 55]) (Table 1). For DFS, the meta-analysis showed that PD-L1+ was significantly associated with shorter DFS in PBC patients than those in the PD-L1− group (HR = 1.43, 95% CI 1.21–1.70, $P < 0.0001$) (Fig. 2a). The heterogeneity among the included studies was low ($I^2 = 40\%$, $P_{\text{heterogeneity}} = 0.07$), therefore, a fix-effect model was used for the analysis. Similarly, the pooled result by random-effects model also indicated that PBC patients with PD-L1+ TCs had shorter OS (HR = 1.58, 95% CI 1.14–2.20, $P = 0.006$), although high heterogeneity existed among included studies ($I^2 = 76\%$, $P_{\text{heterogeneity}} < 0.00001$) (Fig. 2b). For RFS, however, the pooled result revealed no relationship between

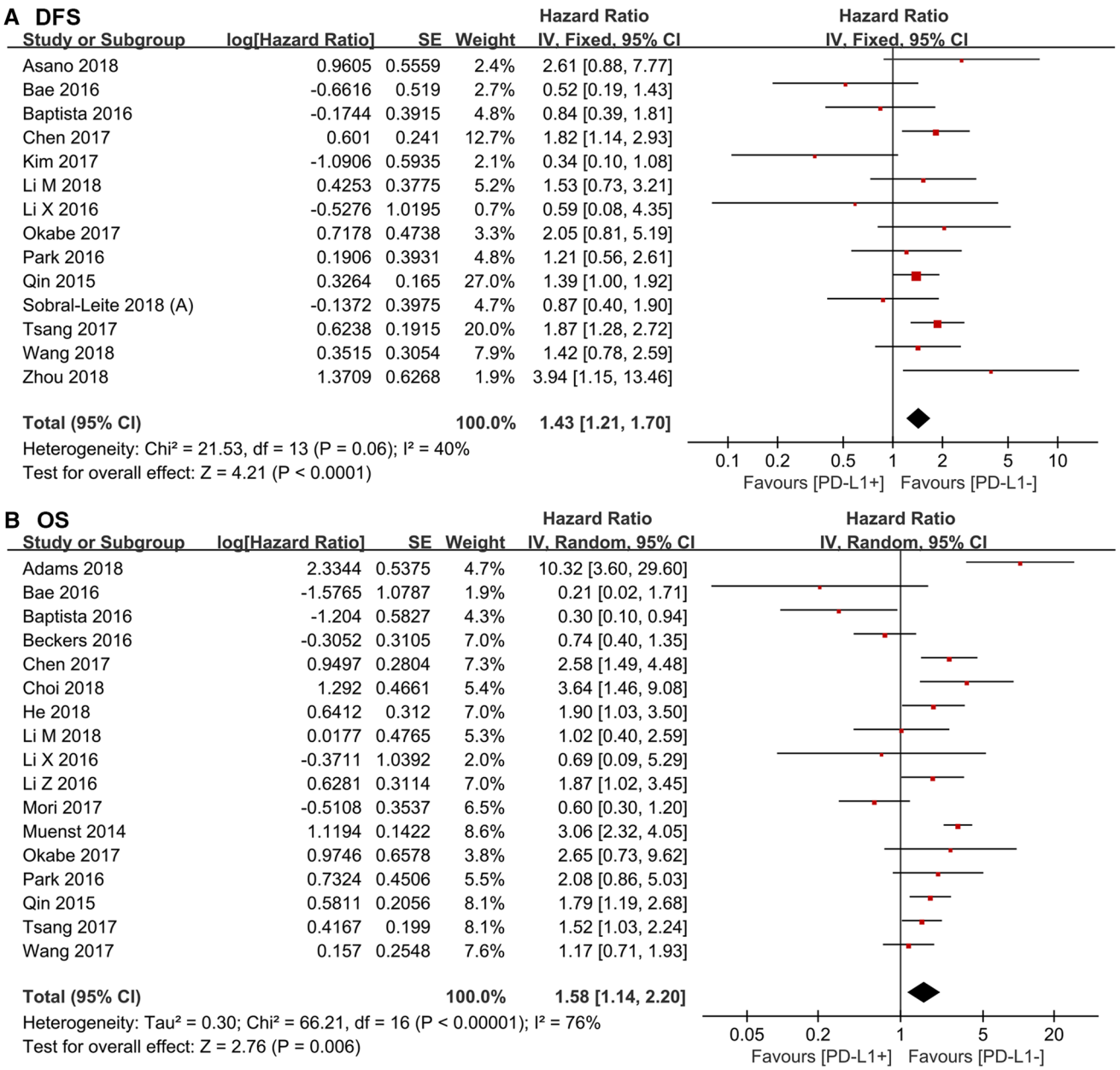


**Fig. 2** Meta-analyses of PD-L1+ tumor cells and **a** disease-free survival (DFS); and **b** overall survival (OS)

PD-L1+ and RFS (HR = 1.08, 95% CI 0.63–1.84, $P = 0.78$), and a significant heterogeneity was detected ($I^2 = 70\%$, $P_{\text{heterogeneity}} = 0.01$) (Fig. S1a).

In addition to the survival data, total events of pCR were obtained in eight studies (1085 patients [35, 41, 46, 47, 63–66]), comprising patients who underwent NAC treatment. Upon pooling the results of these studies, we observed that PD-L1+ TCs marginally increased the rate of pCR (RR = 1.64, 95% CI 0.99–2.73, $P = 0.05$), but with a significant heterogeneity ($I^2 = 79\%$, $P_{\text{heterogeneity}} < 0.0001$) (Fig. 3).

Owing to the difference of PD-L1 detection methods in the individual studies, subgroup analyses were performed to evaluate whether these factors could contribute to the heterogeneity. As shown in Fig. 4a, the summary HR of PD-L1+ TCs increased to 1.47 (95% CI 1.20–1.80, $P = 0.0002$) for poor DFS in those studies using WTS slides for IHC staining, with no evidence of heterogeneity ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.46$) [38, 43, 53, 56–60]. However, the relationship was not observed in those using TMA (HR = 1.29, 95% CI 0.95–1.76, $P = 0.10$, $I^2 = 77\%$) or CNB (HR = 1.64, 95% CI 0.97–2.77, $P = 0.07$, $I^2 = 0\%$). Also for OS, an increased risk of mortality for PD-L1+ patients was observed in the WTS subgroup (HR = 1.70, 95% CI 1.18–2.45, $P = 0.004$, $I^2 = 51\%$) (Fig. 4b) [36, 38, 39, 43,

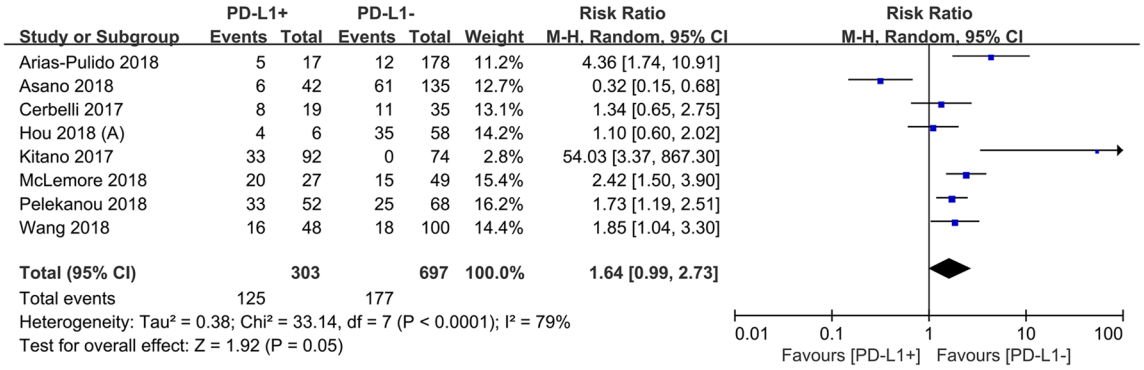


**Fig. 3** Meta-analysis of PD-L1+ tumor cells and pathological complete response

53, 55–57, 59], while there was only a trend of shorter RFS (HR = 1.49, 95% CI 0.82–2.73, $P = 0.19$, $I^2 = 60\%$) (Fig. S1b). We also conducted subgroup analyses according to different types of antibody (Fig. S2), sites of IHC staining considered as PD-L1+ (Fig. S3), and cut-off points (Fig. S4), and found that the adoption of different antibodies and cut-off points had potential contributions to the heterogeneity among included studies.

### PD-L1+ TILs and patients' survival

Relationships between PD-L1+ TILs and patient' survival were also reported, including DFS (8 studies [21, 26, 34, 38, 40, 42, 43, 58]), RFS (3 studies [39, 44, 47]), OS (11 studies [20, 21, 34, 38–40, 42–45, 48]), and breast cancer-specific survival (BCSS) (3 studies [33, 47, 58]). Four studies reported the positive relationships between the presence of PD-L1 in TILs and longer DFS [26, 38] or RFS [44, 47], while three studies showed a significant association with OS [20, 34] or BCSS [58]. The others, however, did not find any correlation between PD-L1+ TILs and patients' survival. The results of DFS/RFS or OS/BCSS were pooled together in the meta-analysis because of the small sample size. Interestingly, pooled results indicated that breast cancer with PD-L1+ TILs had a significantly longer DFS (HR = 0.45, 95% CI 0.28–0.73, $P = 0.001$), with no heterogeneity within included studies ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.53$) (Fig. 5a) [34, 38, 39, 58]. Similar results were also observed for OS in that PD-L1+ TILs had a significant improvement of OS (HR = 0.41, 95% CI 0.27–0.63, $P < 0.001$), with a low heterogeneity ($I^2 = 14\%$, $P_{\text{heterogeneity}} = 0.32$) (Fig. 5b) [20, 34, 38, 39, 58].

### Sensitivity analyses

Sensitivity analysis, in which studies were omitted one at a time, was performed to assess whether the pooled results could be influenced by any individual study. As presented in Fig. S5, no single study significantly affected the pooled results, while the mortality risk of PD-L1+ TCs decreased to 1.49 (95% CI 1.08–2.07, $P = 0.02$) after removal of the study by Muenst et al. [15], though PD-L1 expression in TCs still had a significant impact on OS.

### Publication bias

The results from Begg's and Egger's test did not indicate any publication bias affecting the HR of DFS and OS in the included studies. The *P* values for these tests were 0.443, 0.242 for DFS, and 0.711, 0.158 for OS, respectively (Fig. 6).

## Discussion

Especially in recent years, the clinical relevance of PD-L1 expression in BC, not only its prognostic value but the treatment efficacy of PD-1/PD-L1 blocking immunotherapy, has caught the attention of scientists [8]. Among the emerging PD-L1 blockade regimens, which have been approved by the U.S. Food and Drug Administration (FDA), atezolizumab (Genentech/Roche) plus nab-paclitaxel combination therapy have proven efficacy in treatment-naïve metastatic TNBC patients with PD-L1+ TILs [11]. However, despite the large number of well-described studies published in these years, the relationship between PD-L1 expression and prognosis in PBC patients remains inconsistent and conflicting. Moreover, several meta-analyses conducted in 2016, suggested that PD-L1+ TCs in PBC were associated with multiple high-risk factors and poor survival, only a few studies with different PD-L1 detection methods were included [16–18]. Further exploration is imperative to validate these conflicting results. Therefore, we conducted this meta-analysis based on 47 studies with a cohort of 14367 PBC patients. Our results provide strong evidence that PD-L1+ TCs is significantly

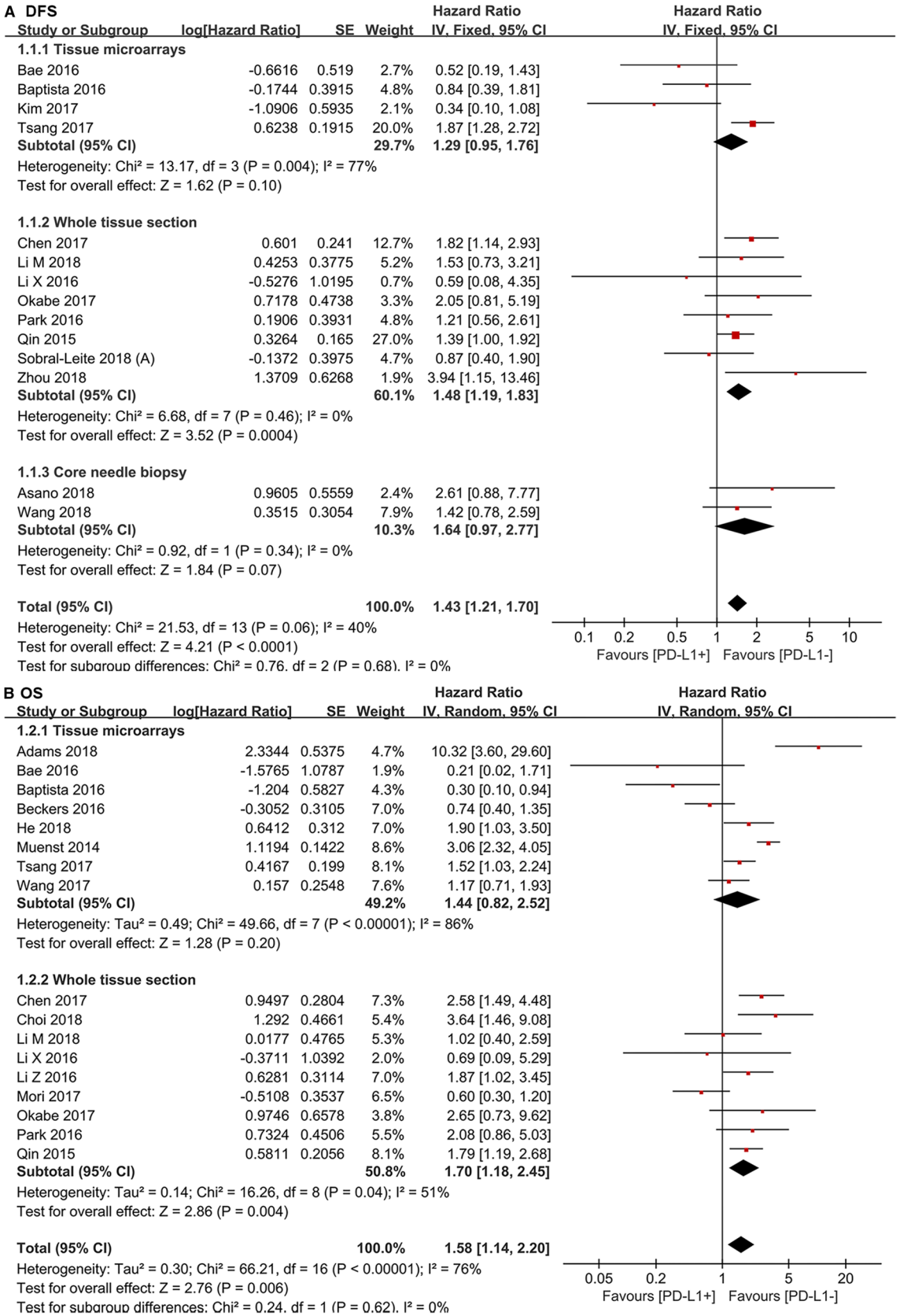


**Fig. 4** Subgroup meta-analyses of PD-L1+ tumor cells and **a** disease-free survival (DFS); and **b** overall survival (OS) by format of pathological sections

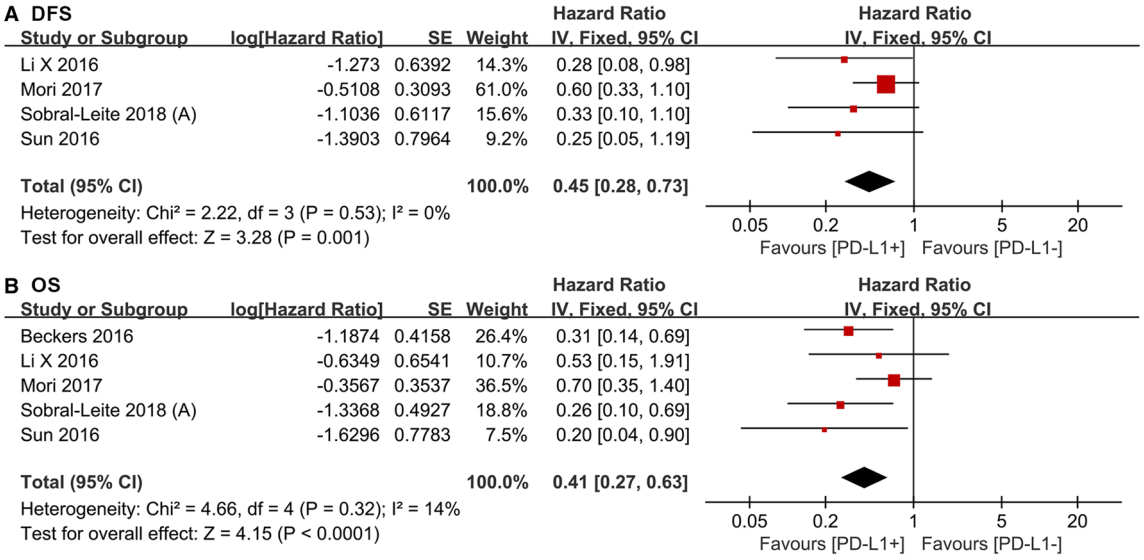


**Fig. 5** Meta-analyses of PD-L1+ tumor-infiltrating lymphocytes and **a** disease-free survival (DFS); and **b** overall survival (OS)

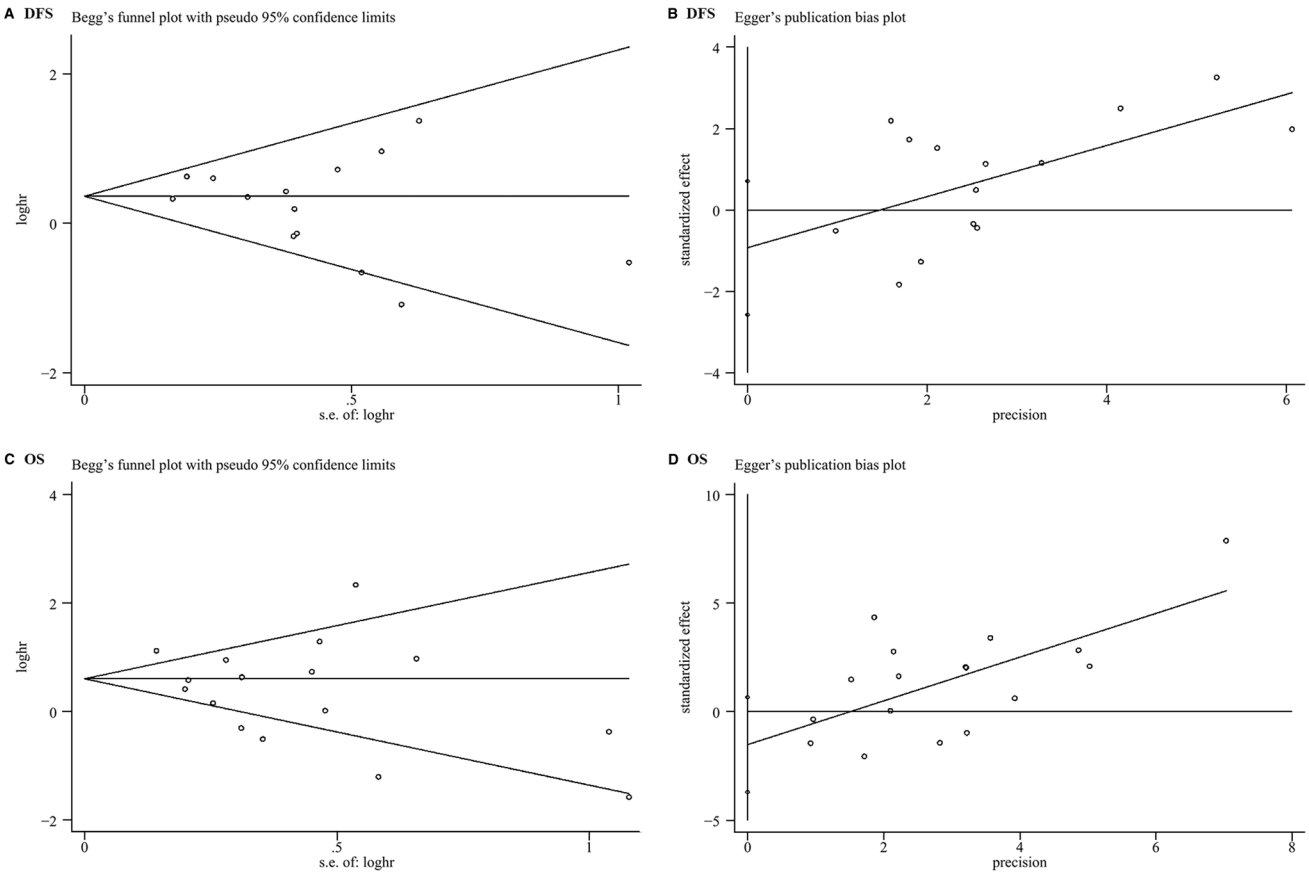


**Fig. 6** Begg's and Egger's publication bias plot of **a**, **b** disease-free survival (DFS); and **c**, **d** overall survival (OS)

associated with shorter DFS (HR = 1.43, 95% CI 1.21–1.70) and OS (HR = 1.58, 95% CI 1.14–2.20) in PBC patients.

Our findings regarding the adverse effects of PD-L1+ TCs are consistent with those of prior studies. The study by Guo et al. [18], which included 5 studies with 2061 PBC patients, demonstrated that patients with PD-L1+ TCs had a higher rate of 10-year mortality risk (MR, 46.8% vs. 21.1%) after surgery and that the pooled RR of MR was 1.64 (95% CI 1.12–2.34). Further results from other meta-analyses also observed associations between PD-L1+ TCs and shorter OS, but the results regarding DFS were not significant [17, 67]. However, in a recent meta-analysis, Kim et al. [68] revealed that PD-L1+ TCs was correlated with higher histological grade, lymph node metastasis, and poorer DFS, rather than OS. The existence of these conflicting results may be attributed to the limited number of included studies, in which changes of some included studies could influence the pooled results. In the present study, survival data were summarized from at least 14 individual studies, and stable results in the sensitivity analysis strengthen the relationship between PD-L1+ TCs and poor prognosis in PBC, though the association with RFS was not predominant owing to the fewer studies included.

These results support the notion that PBC with PD-L1+ TCs may be more aggressive, and relates to multiple high-risk clinicopathological factors that indicated a poor prognosis, as shown by previous studies and our meta-analysis [15, 53]. In the present study, several unfavorable prognostic factors, including high histological grade, Ki-67 index, ER and PR negative, and large tumor size ($P = 0.05$), were positively correlated with PD-L1+ TCs. In addition, aggressive BC subtype (TNBC) also had high rate of PD-L1+ TCs. As demonstrated by Mittendorf et al. [69], activation of the PD-1/PD-L1 pathway in breast cancer could inhibit T-cell proliferation, promote immune cell apoptosis, and may help these tumors evade anti-cancer immune responses. These tumor cells, consequently, proliferate and invade more rapidly. However, the association between PD-L1+ TCs and lymph node involvement was not found in our study, based on 30 individual studies with 8421 PBC patients, which differed from several prior meta-analyses [17, 18, 68].

Indeed, several included studies in our review showed reverse results that PD-L1+ TCs were favorable prognostic variables, suggesting that some unidentified variables might influence the prognostic values of PD-L1+ TCs [42, 44, 51]. A previous report found that PD-L1+ TCs correlated with better DFS and OS in univariate analysis, despite its association with high-risk clinicopathological features, such as high histological grade, Ki-67, ER and PR negative, and HER2 positive [19]. However, only the presence of elevated TILs proved to be independently associated with longer survival in multivariate analysis. Also, in the recent study by Mori et al. [39], an interaction between PD-L1 expression and TILs was identified, and both RFS and OS of the PD-L1+ patients differed significantly in the context of presence or absence of TIL. Hence, the activity and subtypes of TILs should be considered in future studies when evaluating the clinical value of PD-L1.

According to the subgroup analyses, the lack of standardization for detection of PD-L1 could also explain the discrepant results among included studies. Nearly half of the studies used TMAs to perform the IHC staining, which usually contained limited tissue, not taken close enough to the invasive tumor front, where PD-L1 was more frequently detected [20, 22, 38, 58, 70]. Hence, a recent comparison between TMAs and WTS in 118 PBC patients revealed a high false-negative rate of 49% for TMA approach, owing to the heterogeneous distribution of PD-L1 expression [58]. In our study, heterogeneity among included studies was the highest when using TMAs to investigate PD-L1+ TCs, which indicated that detection of PD-L1 using WTS should be recommended in clinical practice. Additionally, regarding which antibodies were used, which cut-off values were defined, and which sites of staining (cytoplasmic or only membranous) were considered positive, variations were also considerable in our review. These diversities in methodology could influence the proportion of PD-L1 positive and also, the prognostic value of PD-L1in PBC patients.

We also investigated PD-L1+ TCs in pre-treatment CNB as a predictive marker in patients receiving NAC treatment. While only one study by Asano et al. [63] found PD-L1 expression to be associated with worse rates of pCR, seven studies showed opposite results or had a trend of benefit from NAC [35, 41, 46, 47, 64–66]. The pooled result revealed a positive relationship with higher rates of pCR ($P = 0.05$), which was in conflict with those for survival data in our review. It was reported that the PD-L1 expression within biopsy materials obtained from one PBC patient varied significantly among fields of view, as a consequence of intratumoral heterogeneity [71]. Also, the limited number of the included studies may inevitably induce some bias and generate conflicting results. Nevertheless, the results regarding the effect of PD-L1+ TCs on pCR and survival were consistent in individual studies and required further investigation.

Although the expression of PD-L1 occurs more frequently in TILs rather than TCs in many studies, its prognostic value has not been well documented. In our meta-analysis, PD-L1+ TILs were found to be associated with decreased risk of disease recurrence and death, which was quite different from those for PD-L1+ TCs. Our results supported the prior meta-analysis, which contained a diversity of cancer types, indicating that PD-L1+ TILs were associated with better prognosis especially in the BC subgroup [22]. These inconsistent results might be explained by distinct mechanisms between PD-L1+ TCs and TILs (Fig. 7) [72]. As demonstrated in prior studies,

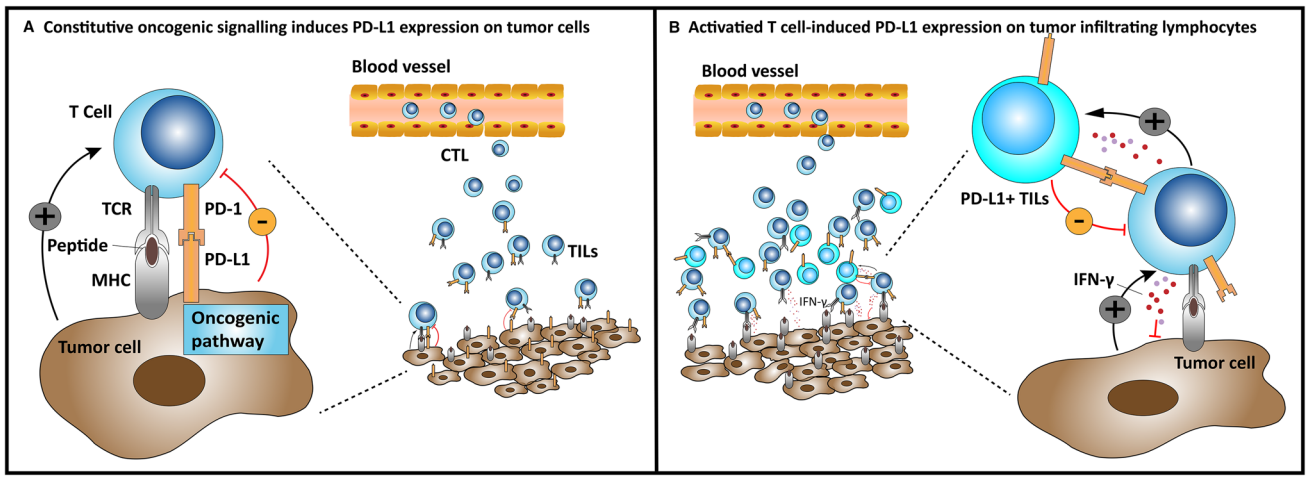


**Fig. 7** General mechanisms of PD-L1 expression on tumor cells (TCs) and tumor-infiltrating lymphocytes (TILs). **a** In some tumors, intrinsic oncogenic signaling can upregulate PD-L1 expression on TCs, and inhibit the recognition and elimination of cytotoxic T cell (CTL). **b** In some tumor microenvironment, PD-L1 is not constitutively expressed by TCs, but rather, it can be expressed on TILs in response to inflammatory signals that are produced by an active anti-tumor immune response. PD-L1+ TILs in this setting may equilibrate the activities of CTL and protect normal cells from the immune attack. *MHC* major histocompatibility complex, *TCR* T-cell receptor, *IFNγ* interferon-γ

PD-L1 expression on TCs were driven mainly through tumor-intrinsic mechanisms, including oncogenic signaling pathway activation or HIF1-α induction by hypoxia [73–75], whereas PD-L1+ TILs could be regulated via adaptive mechanisms, and then reflected a pre-existing immunity [72]. In other words, PD-L1+ TILs are related to activated and increased levels of TILs, reflecting an active anti-cancer immunity that are equilibrated by the PD-L1/PD-1 pathway. Hence, this relationship could explain why blocking PD-L1 using atezolizumab in TNBC patients with PD-L1+ TILs showed favorable outcomes, not TCs [11]. Collectively, these findings highlighted the importance of comprehensive evaluation of PD-L1 expression on both TCs and TILs.

We made an effort to conduct a comprehensive review for the clinical relevance of PD-L1 expression, but several limitations should be taken into account when interpreting our results. First, non-English articles, low-quality or certain studies with negative results that may not have been published, were not included in our meta-analysis, which may have induced some publication bias. Second, survival data were unavailable in some studies with negative results, though great effort was made to contact with corresponding authors. Finally, PD-L1 expression was assessed using different pathological sections, antibodies, and cut-off points, which may cause some of the heterogeneity. Despite these limitations, the funnel plots and sensitive analysis demonstrated that our results were credible.

## Conclusions

With the aim of evaluating the prognostic value of PD-L1 expression in PBC patients, this study presents an overview of the clinicopathological features and patients' survival. Based on our results, PD-L1+ TCs associates with large tumor size, histologic Grade 3 tumors, high Ki-67, ER and PR negative, TNBC subtype, and shorter survival time. However, our exploratory analysis reveals that PD-L1+ TILs may serve as a novel indicator for favorable prognosis. A comprehensive understanding of the biological function of PD-L1+ on both TCs and TILs will be helpful, as this may provide a more scientific foundation for establishing a unified detection approach. This study may be an essential supplement when using PD-L1 to predict the clinical outcomes of PBC patients.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** Not applicable (no informed consent required).

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