REVIEW

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Analysis of PD-L1 Expression in Breast Cancer: A Systematic Review and Meta-Analysis in Asian Population

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Abstract

Objective: This study aimed to investigate the level of *PD-L1* protein expression in patients with BCs who were of Asian descent. **Methods:** Three databases were conducted on this article up to August 10th, 2022. The reference lists of the publications were examined for further studies, and in cases of duplicates, a study with a larger sample size was added. In survival analysis, the hazard ratio (HR) was applied to the circumstances characterized by the frequency of occurrences, and for the clinicopathological characteristic, the best-adjusted odds ratio (OR) with a 95% confidence interval (CI) was employed. The Newcastle-Ottawa Scale (NOS) was utilized to evaluate selection criteria, comparison, and exposure to establish the quality of the technique in the under-consideration studies. The Z test determined the association analysis of OS, DFS, and clinicopathological characteristics with *PD-L1* expression. **Result:** All eight trials for OS and six for DFS were considered, with 4.111 and 3.071 participants, respectively. Overexpression of *PD-L1* was linked to a reduced OS compared to individuals with undetectable expression (HR= 1.58, 95% CI 1.04–2.40; P=0.03). We analyzed clinicopathological features, and it elevated in individuals with histological grade III (OR=2.39, 95% CI 1.26-4.54; P=0.008) and positive node (OR=0.68, 95% CI 0.48-0.97; P<0.05). **Conclusion:** Overexpression of *PD-L1* was associated with a shorter OS in BCs patients. High *PDL1* was higher in persons with nodal positivity and histological grade III.

Keywords: Breast cancer- PD-L1- prognostic- biomarker

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Introduction

Breast cancer (BCs) is the leading invasive tumor in women commonly. In 2020, it was anticipated that approximately 2.3 million women would receive their first BCs diagnosis. Asia accounted for over half (45.4%!) of all BCs diagnoses (Sung et al., 2021; Lim et al., 2022). The peak of BCs in Asian populations is also relatively experienced at a younger age (40-50 years) compared to non-Asian populations (60-70 years) (Green and Raina, 2008; Leong et al., 2010). Additionally, the M/I ratio of patients with BCs in Asia is far higher than in the rest of the world (0.28). It exceeds the global average and ranks second globally (WHO, 2021). It demonstrates the poor prognosis of BCs patients in the Asian area compared to those in other regions. Several variables contribute to this occurrence, but the immunological link outside of BCs is a topic that is infrequently studied.

One immunological route affecting BCs prognosis is the expression of programmed death-ligand 1 (*PD-L1*). *PD-L1* is an immunological checkpoint in maintaining the normal control of T cell activity and preventing autoimmunity (Hänninen et al., 2021). Nevertheless, the upregulation of *PD-L1* and a number of other proteins decreases the efficacy of immune surveillance and raises the survival probability of cancer cells (Cha et al., 2019).

Since antibodies that target PD-1 or *PD-L1* are the most promising immunotherapeutic options currently available, it is interesting to explore the influence that *PD-L1* has on methods for treating BCs. The significance of *PD-L1* as a prognosis marker and its usefulness as a therapy goal for the success of immune checkpoint suppression are two topics that have been the subject of heated debate. *PD-L1* expression has been shown to have a substantial association with a positive prognosis in some investigations, and this correlation has been used as a prognostic marker (Ali et al., 2015; Bae et al., 2016; Baptista et al., 2016; Beckers et al., 2016), leading to the hypothesis that *PD-L1* expression indicates an efficient immune system against to tumor cells. Nonetheless, a

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reverse connection has also been discovered in a few investigations. In addition, several additional tumor microenvironment (TME) cells, including macrophages, dendritic cells, and fibroblasts, generate *PD-L1*, suppressing anti-tumor immunity. It is a significant determinant of cancer occurrence (Schildberg et al., 2016; Zou et al., 2016).

PD-L1 detection can be used to predict how effectively cancer cells would react to immunotherapy targeting *PD-L1* and its receptor PD-1, which had been adopted for several other tumors. Additionally, *PD-L1* expression can predict clinicopathological BCs features linked with patient prognosis (Javed et al., 2017; Alves, Paredes and Schmitt, 2019).

Previous research has shown that elevated levels of *PD-L1* are linked to a poorer prognosis for BCs patient outcomes (Cirqueira et al., 2021). This poor prognosis is consistent with poor clinicopathological characteristics such as the presence of negative estrogen, progesterone receptor status, lymph node metastases, and high histological grade (Alves, Paredes and Schmitt, 2019). However, to date, there has been no study that summarizes the findings of *PD-L1* expression in Asian populations, considering that the BCs population in Asia is one with the worst outcomes. As a result, this study aimed to explore the expression of the *PD-L1* protein in patients with Asian BCs.

Materials and Methods

Study design and eligibility criteria

A systematic review conducted by the PRISMA (Moher et al., 2009) was completed on three different databases, including PubMed, ScienceDirect, and the Cochrane Library, up until August 10th, 2022. The included papers should: (1) clinical research published in peer-reviewed publications that investigated *PD-L1*; (2) research given information on *PD-L1* as well as clinical and pathological status; and (3) studies with computation data for the calculation of HRs and 95% CIs for OS and DFS; and (4) full-text article. This review's protocol was filed with the International Prospective Register of Systematic Reviews (PROSPERO), with the registration number CRD42023391913, and the paper was produced in accordance with PRISMA principles.

Search strategy and data extraction

We used the following keywords, and a search was conducted on all English-language publications: ("*PD-L1*" OR "B7H1" OR "CD-274") AND ("breast cancer" OR "breast tumor" OR "ca mammae" OR "breast neoplasms"). The reference lists of the published works were looked at for potential new lines of inquiry, and in cases of duplicates, a study with a larger sample size was added. Each research yielded the following information: (1) initial name and year of the author publication; (2) the nation and number of patients; (3) age, median (range) of the sample; (4) IHC method; (5) *PD-L1* antibody; (6) *PD-L1* positive sample; (7) Follow-up, median and range. Three reviewers performed independently the study selection, quality rating, and data extraction. By reaching a consensus, the fourth and fifth reviewers resolved the dispute between the first three.

We separated survival variables into OS and DFS, as well as clinicopathological characteristics into age, grading histology, tumor size, lymph node, ER status, PR status, *HER2* status, *Ki67* Index, staging, chemotherapy, and radiation (Table 2).

Quality assessment

The Newcastle-Ottawa Scale, commonly termed NOS, was applied to assess sample selection, comparison, and exposure to establish the quality of the technique in the under consideration studies (Stang, 2010). Using the findings of the NOS calculation, we could divide the articles' overall quality into two categories: moderate (4-6) and high (7-9). No letters to the editor, comments, case reports, case series, or reviews were included in this publication.

Statistical analysis

In survival analysis, the hazard ratio (HR) was used to conditions characterized by the probability of occurrences, whereas the best-adjusted odds ratio (OR) with a 95% confidence interval (CI) was employed for clinicopathological characteristics. The Egger test analyzed publication bias, and a $p<0.05$ indicated the probability bias of publication. The Q test was used to investigate whether or not there was any heterogeneity across the studies, and if it was discovered, the random effect model was applied ($p<0.10$). Using data from trials for which no specific result was provided, we pooled analyses in Figure 4 to reduce misclassification of exposure and to control for publication bias. Pooled of the survival was calculated using random-effects models and clinicopathological characteristics are both random and fixed models (Figure 4). The Z testing was used for the analysis of *PD-L1* expression and clinical and pathological status for OS and DFS. A summary of the statistical study was provided in the form of a forest plot. We utilized Review Manager 5.3 from Revman Cochrane in London, United Kingdom, during the investigation.

Results

Study eligibility results

The databases yielded a total of 1.013 publications, of which 952 were eliminated due to irrelevant studies. Article eligibility was determined for 23 articles, and 9 papers were eliminated because they did not match the eligibility requirements (Figure 1). Six research from China, four from South Korea, two from Japan, one from Hongkong, and one from Saudi Arabia comprised the final 14 publications included in this manuscript (Table 1).

Table 1 displays the features of the studies that have been listed. These studies' sample sizes ranged from 44 to 1.091 patients. There were a total of 4.929 participants participating in the trials. Five retrospective studies were determined to be suitable for the analysis. In the above investigations, *PD-L1* positive rates varied from 13.7% to 57.0%. The HRs and 95% confidence intervals were derived directly from the source papers. All studies

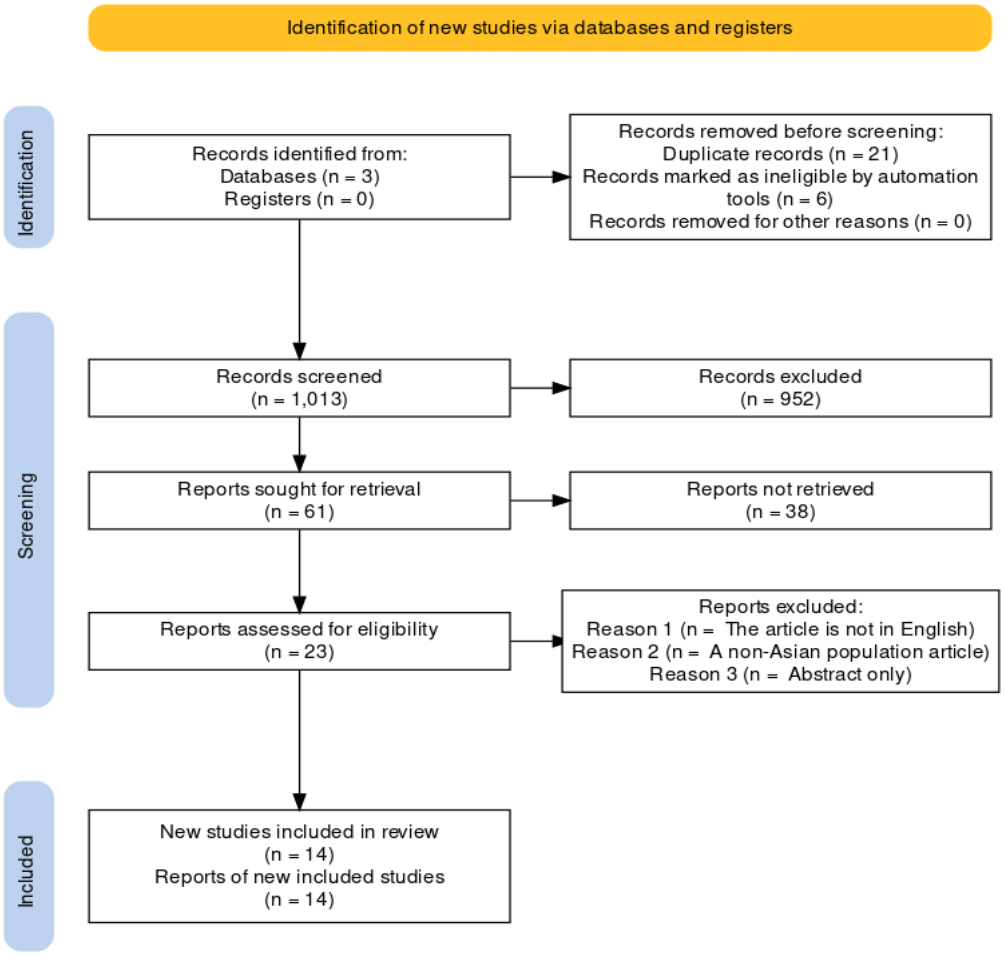

Figure 1. A PRISMA Flowchart for Selected Articles

evaluated *PD-L1* expression using IHC. According to the NOS quality evaluation, the investigations were of moderate to high quality.

Analysis of OS, DFS, and PD-L1 expression

We studied the link between OS, DFS, and PDL1 expression in BCs. All eight trials for OS and six for DFS were considered, with 4.111 and 3.071 participants, respectively. *PD-L1* overexpression was linked with the poorer OS than the absence of *PD-L1* in individuals diagnosed with BCs (HR = 1.58, 95% CI 1.04–2.40; P=0.03) (Figure 2). Overexpression of *PD-L1* was not linked with DFS (HR = 1.35, 95% CI 0.92–1.98; P =0.13) (Figure 3). There was found to be a significant amount of heterogeneity in OS (I^2=65%, P<0.01) and DFS (I^2=79%, P<0.01). Therefore, a model with random effects was utilized for the investigation.

Analysis of clinico and pathological characteristics

In this work, we analyzed clinicopathological features and *PD-L1* expression. *PD-L1* was elevated in histological grade III (OR =2.39, 95% CI 1.26 - 4.54; P =0.008), and positive node (OR =0.68, 95% CI 0.48-0.97; P<0.05). *PD-L1* overexpression was not linked with age (OR=1.06, 95% CI 0.62-1.82, P=0.83), size of tumor (OR=0.97, 95% CI 0.55-4.07, P=1.70), ER (OR =0.70,

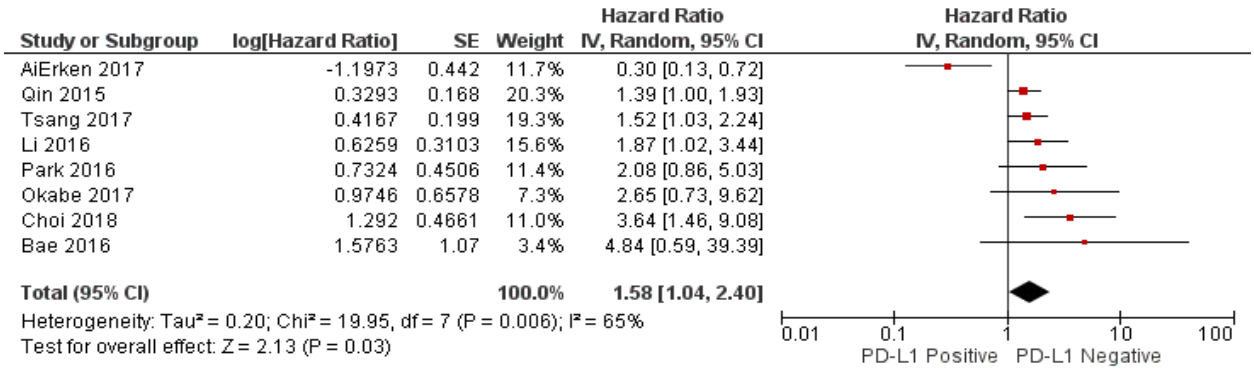

Figure 2. A Forest Plot Shows BCs Patients' Overall Survival (OS) Rate and PD-L1 Expression.

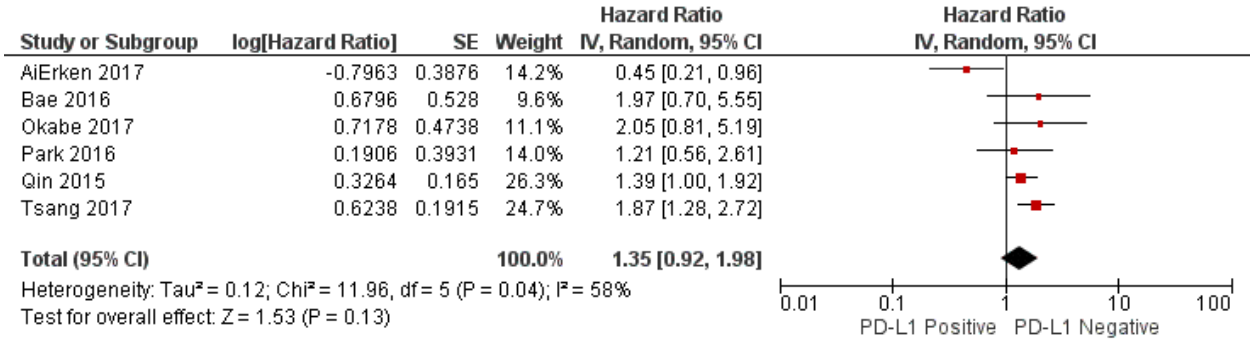

Figure 3. Disease Free Survival (DFS) Rate and PD-L1 Expression in BCs Patients are Shown in a Forest Plot

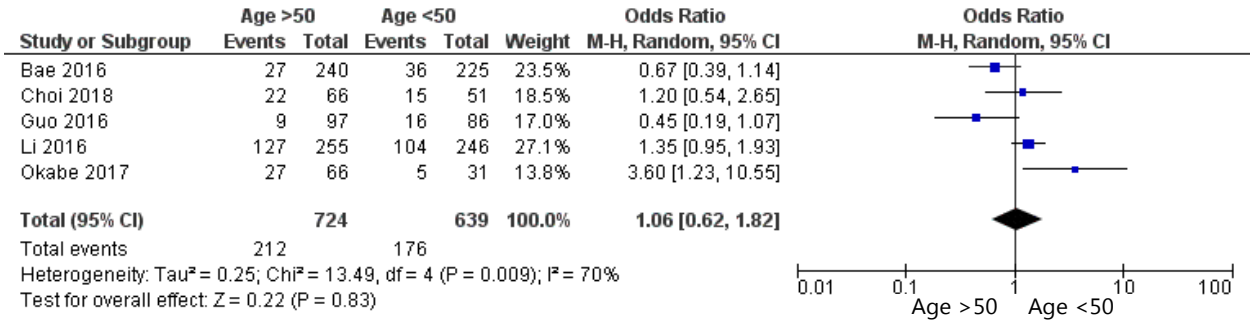

Figure 4A. Age Forest Plot

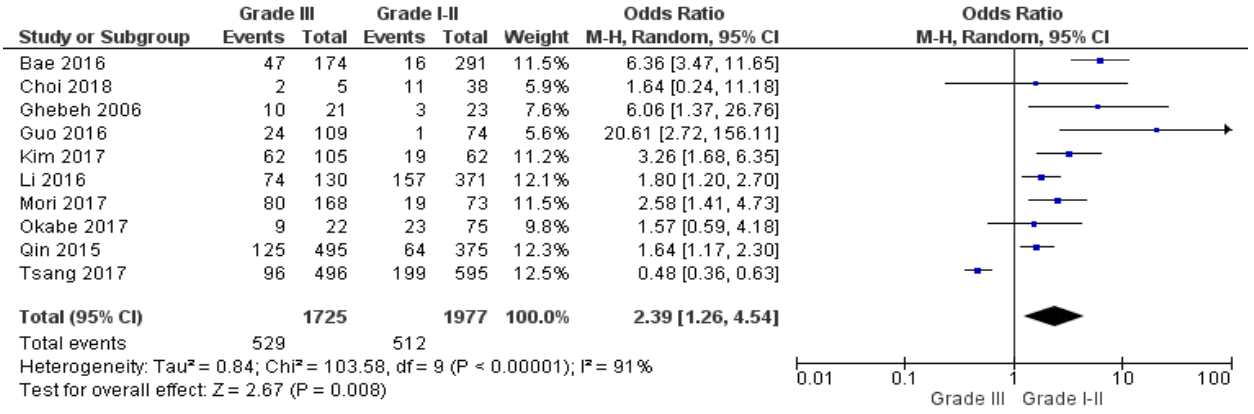

Figure 4B. Grade Forest Plot

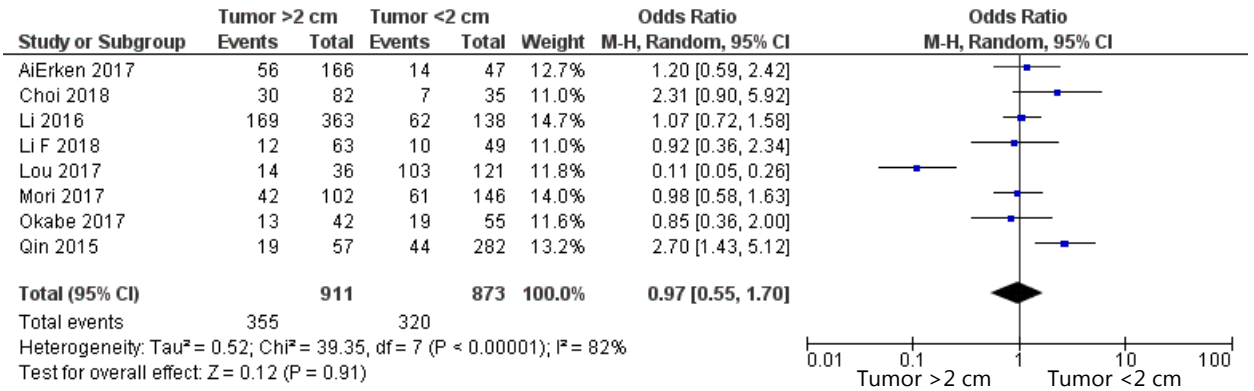

Figure 4C. Tumor Forest Plot

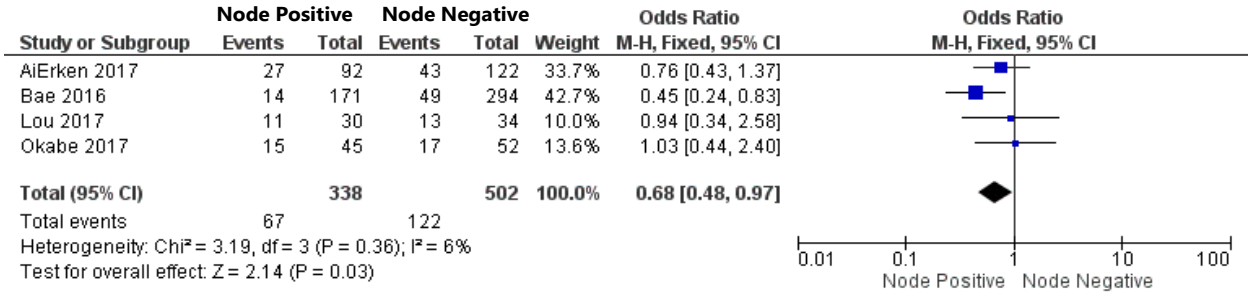

Figure 4D. Node Forest Plot

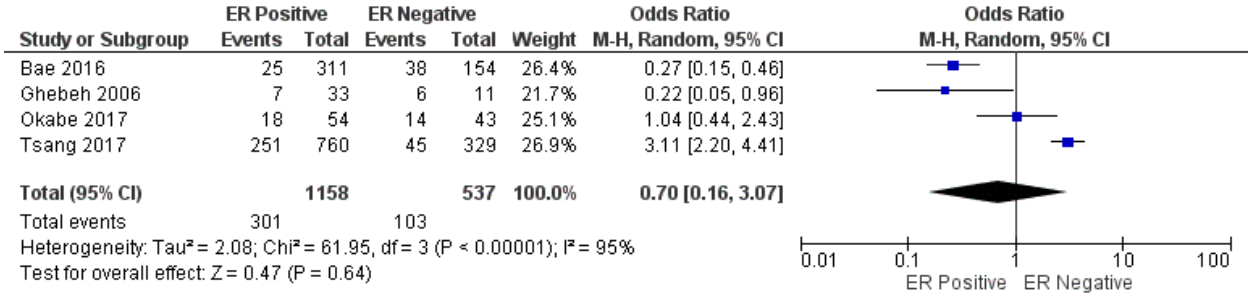

Figure 4E. ER Forest Plot

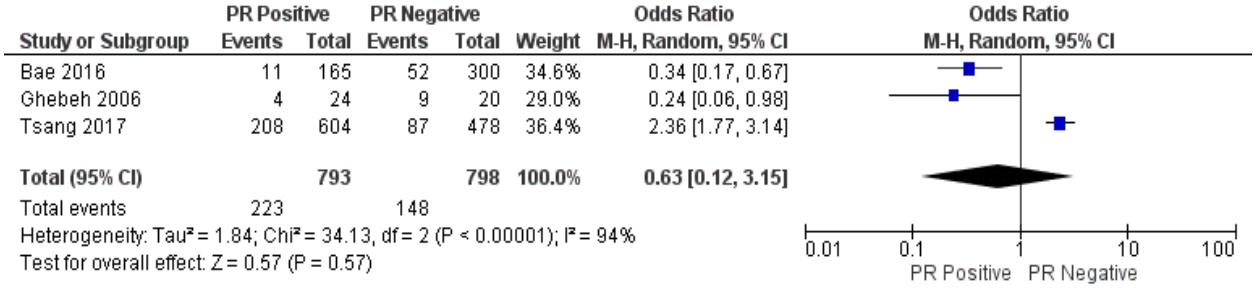

Figure 4F. PR Forest Plot

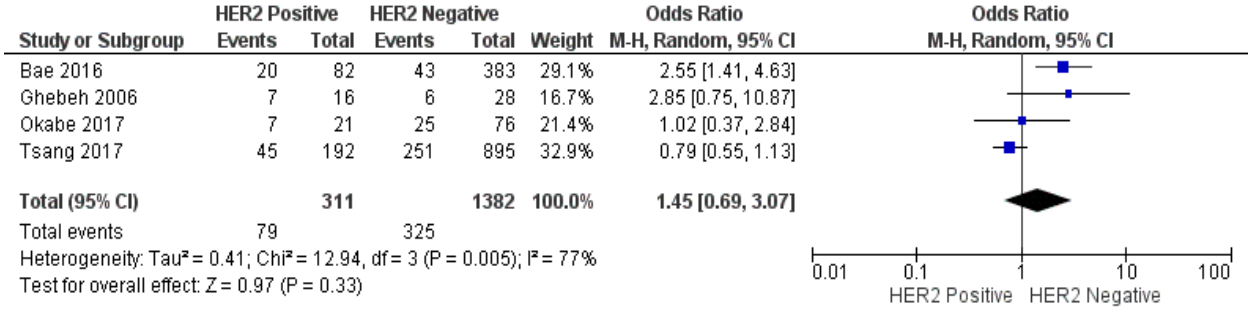

Figure 4G. HER2 Forest Plot

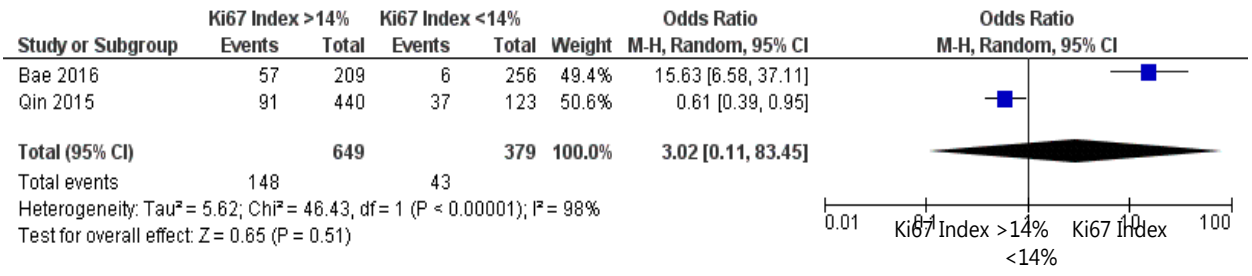

Figure 4H. Ki67 Forest Plot

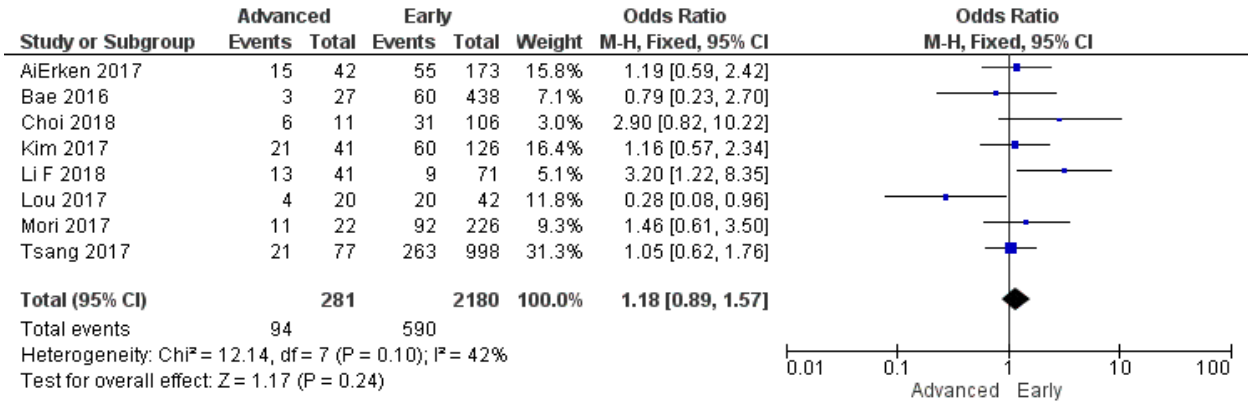

Figure 4I. Stadium Forest Plot

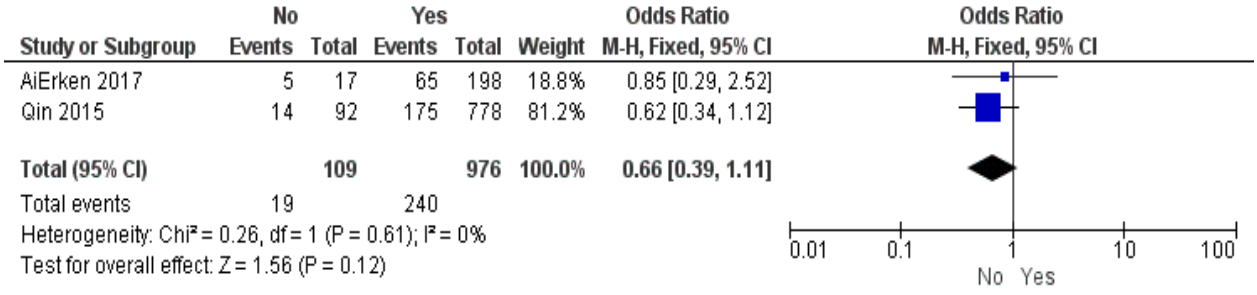

Figure 4J. Chemotherapy Forest Plot

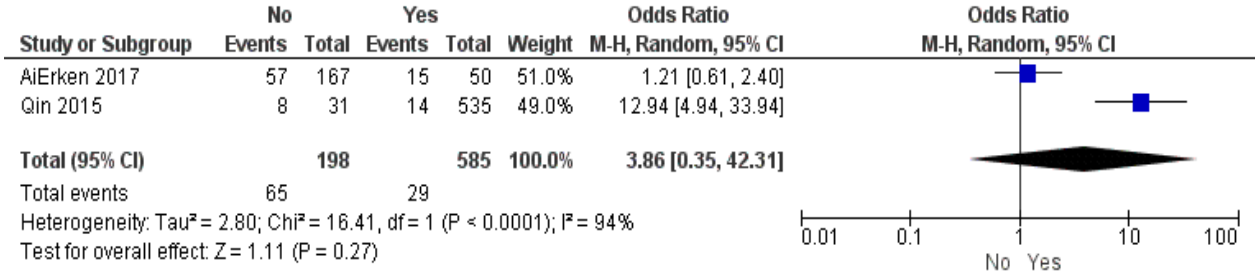

Figure 4K. Radiotherapy Forest Plot

95% CI 0.16-3.07; P=0.64), PR (OR=0.63, 95% CI 0.12-3.15; P=0.57), *HER2* (OR=1.45, 95% CI 0.69-3.07; P = 0.33), *Ki67* index (OR=3.02, 95% CI 0.11-83.45; P=0.51), staging tumor (OR=1.18, 95% CI 0.89-1.57; P = 0.24), chemotherapy status (OR=0.66, 95% CI 0.39-1.11; P = 0.12), and radiotherapy status (OR =3.86, 95% CI 0.35-42.31; P = 0.27) (Figure 4). During the course of the investigation of the node variable (P = 0.36; I^2=6%), staging (P=0.10, I^2 =42%), and chemotherapy (P = 0.61; I^2= 0 %), heterogeneity was not identified. Thus, a model with a fixed effect was adopted. The remainder of the analyses were carried out using the random effects model.

Heterogeneity and bias potential across studied

Data evaluating OS, DFS, *PD-L1*, and selected clinicopathological parameters revealed heterogeneity. This study adopted the random effect model, whereas the fixed effect model was applied to investigate the *PD-L1* and positive node status, staging, also treatment status. According to Egger's tests, publication bias did not impact the HR for OS and DFS in the included studies. These studies yielded respective P values of 0.74 and 0.39.

Discussion

There is evidence that both PD-1 and both of its ligands, *PD-L1* and PD-L2, are present in the tumor microenvironment, maintaining a balance between activation, immunopathology, and T-cell tolerance in prolonged periods of antigen exposure. Under certain conditions, cancer cells can avoid monitoring the immune system mediated by increased *PD-L1* expression. On tumor cells, *PD-L1* reaches out and attaches to its receptor tumor-specific T lymphocytes, which results in PD-1/*PD-L1* interactions. Due of this interaction, the proliferation and migration of T cells are slowed down, and cytotoxic mediators release. Additionally, this interaction stimulates the death of tumor-specific T cells and the development

of CD4+ T cells into FOXP3+ CD4+ regulatory T cells. This cascade of events disrupts the function of T cells, as a direct consequence, a decreased anti-tumor immune response (Wang et al., 2017; Carlsson et al., 2020).

It is assumed that increased *PD-L1* expression in BCs results either from the dynamic production of IFN during the anti-tumor immune response or from the activation of *PD-L1* gene expression of many related oncogenes, but the precise mechanism for this is not yet known. In the solid tumor, *PD-L1* overexpression has been related to multiple genetic changes, including the amplification of 9p24.1, the site of *PD-L1*. Due to the rarity of *PD-L1* copy number alterations, this does not appear to be the reason for elevated *PD-L1* expression in BCs. In addition, it is known that disturbances in signaling systems, such as hyperactivation of the PI3K pathway, can also increase *PD-L1* expression. According to an earlier study, AKT phosphorylation and PI3K pathway activation have been linked with high *PD-L1* due to PTEN loss. High *PD-L1* is particularly found in the luminal subtype, which can also be connected to PIK3CA mutations (Tsang et al., 2017).

Numerous studies have been conducted to establish if high *PD-L1* is linked with the worst prognosis or histological characteristics. However, there has been a lack of consistency in the outcomes. A comprehensive study of BCs patients was performed for the meta-analysis. High *PD-L1* was linked with lowering OS. Nonetheless, this *PD-L1* overexpression did not affect the DFS value of BCs patients. It is correlated with reduced TIL activity in patients with BCs overexpress *PD-L1*. *PD-L1* promotes tumor development by decreasing the amount of PD-1 TIL by aggressively blocking the immune system's response to tumor antigens (Tsang et al., 2017). Similar patterns are observed in ovarian, lung, stomach, and kidney (renal cell carcinoma) cancers (Bae et al., 2016).

PD-L1 expression was elevated in individuals with high histological grades, according to the findings of this investigation, as well as positive lymph node status. There was no connection between *PD-L1* overexpression and age, tumor size, estrogen receptors, progesterone receptors, *HER2* expression, *Ki67* index, tumor stage, chemotherapy, or radiation in this investigation (Rizka et al., 2021; Wihandani et al., 2021). A substantial correlation between high *PD-L1*, high histological grade and the presence of lymph node metastases was consistent with decreased patient survival. It is because high-grade BCs patients typically exhibit rapid proliferation and poor differentiation (Ghebeh et al., 2006; Kartini et al., 2023)

This research has many drawbacks. It will alter the variety of research subjects represented by the data comprised in the meta-analysis. Second, this meta-analysis did not assess the expression depending on BCs subtypes, so the influence remains unclear. In conclusion, overexpression of *PD-L1* was associated with a lowered OS in BCs patients. PDL1 expression was higher in persons with nodal positivity and histological grade III. However, additional it is necessary to conduct prospective research to provide further evidence and corroborate the findings of the current study conclusions.

Table 1. Characteristics of the Articles Considered in Our Baseline Research

Author	Year	Country	Number of Patients	Age, median (range)	IHC method	Antibody				PD-L1 positive	Follow-up Median (range)	Quality Assessment (score)
						Company	Source	Type	Clone	Cut-off		
Li (Li et al., 2016)	2016	China	501	53 (29-83)	H-score	Abcam, UK	Rabbit	PAB	ab58810	>100	231/501 (46.1)	64 (1-80)	7
Park (Park et al., 2016)	2016	South Korea	333	47 (28-78)	H-score	Abcam, UK	Rabbit	PAB	NA	>3	163/316 (51.6)	118 (5-154)	6
Qin (Qin et al., 2015)	2015	China	870	47 (21-84)	Percentage	Beverly, USA	Rabbit	MAB	NA	>5%	189/870 (21.7)	98 (17-265)	6
AiErken (AiErken et al., 2017)	2017	China	215	49 (27-78)	Percentage	Beverly, USA	Rabbit	PAB	NA	>50%	70/215 (32.6)	68 (7-159)	8
Bae (Bae et al., 2016)	2016	South Korea	465	mean. 52.3 (24-81)	H-score	Beverly, USA	Rabbit	MAB	E1L3N	>100	63/465 (13.5)	41 (1-158)	7
Choi (Choi et al., 2018)	2018	South Korea	539	50 (24-79)	Percentage	Abcam, UK	Rabbit	PAB	NA	>5%	117/539 (21.7)	53 (4-135)	6
Ghebeh (Ghebeh et al., 2006)	2006	Saudi Arabia	44	45	Percentage	Dako Corp.,	Rabbit	PAB	MIH1	>5%	13/44 (29.5)	NA	6
Guo (Guo et al., 2016)	2016	China	183	50	Percentage	Tucson, AZ	Rabbit	MAB	SP142	>10%	25/183 (13.7)	76.4	7
Kim (Kim et al., 2017)	2017	South Korea	167	(23-85)	Allred score	Canvers, USA	Rabbit	MAB	E1L3N	the sum of the 2 scores	81/167 (48.5)	1157 (43-1748)	8
Li F (Li, Ren and Wang, 2018)	2018	China	112	60	Percentage	Abcam, UK	Rabbit	PAB	NA	>50%	22/112 (19.6)	NA	8
Lou (Lou et al., 2017)	2017	China	64	55	Percentage	NA	NA	NA	NA	>50%	24/64 (37.5)	NA	7
Mori (Mori et al., 2017)	2017	Japan	248	mean. 57.4 (32-84)	Percentage	Beverly, USA	Rabbit	MAB	E1L3N	>50%	103/248 (41.5)	68 (2-150)	7
Okabe (Okabe et al., 2017)	2017	Japan	97	58 (27-84)	H-score	Abcam, USA	Rabbit	MAB	EPR1161(2)	>100	32/97 (57)	88.9	6
Tsang (Tsang et al., 2017)	2017	Hongkong	1091	mean. 54.5 (22-94)	Percentage	NA	NA	NA	NA	>5%	295/1091 (27)	63 (1-120)	7

Note: IHC, immunohistochemistry; PD-L1, programmed death ligand 1; UK, United Kingdom; USA, United States of America; AZ, Arizona; NA, not available; PAB, polyclonal antibody; MAB, monoclonal antibody

Table 2. Summary of Breast Cancer Patient Characteristics

Characteristic	Variable	Number of Studies	Model	Breast Cancer Total Sample	Value (%)	OR	95% CI	p
Age		5				1.06	0.62 - 1.82	0.83
	>50		Random	724	212 (29.2%)			
	<=50		Random	639	176 (27.5%)			
Grade		10				2.39	1.26 - 4.54	0.008
	III		Random	1725	529 (30.6%)			
	I-II		Random	1977	512 (25.8%)			
Tumor Size		8				0.97	0.55 - 1.70	0.91
	>2 cm		Random	911	355 (38.9%)			
	<= 2 cm		Random	873	320 (36.6%)			
Nodal Status		4				0.68	0.48 - 0.97	0.03
	Node Positive		Fixed	338	67 (19.8%)			
	Node Negative		Fixed	502	122 (24.3%)			
ER Status		4				0.70	0.16 - 3.07	0.64
	ER Positive		Random	1158	301 (25.9%)			
	ER Negative		Random	537	103 (19.1%)			
PR Status		3				0.63	0.12 - 3.15	0.57
	PR Positive		Random	793	223 (28.1%)			
	PR Negative		Random	798	148 (18.5%)			
HER-2 Status		4				1.45	0.69 - 3.07	0.33
	HER-2 Positive		Random	311	79 (25.4%)			
	HER-2 Negative		Random	1382	325 (23.5%)			
Ki67 Index		2				3.02	0.11 - 83.45	0.51
	>14%		Random	649	148 (22.8%)			
	<=14%		Random	379	43 (11.3%)			
Stage		8				1.18	0.89 - 1.57	0.24
	Advanced		Fixed	281	94 (33.4%)			
	Early		Fixed	2180	590 (27.0%)			
Chemotherapy		2				0.66	0.39 - 1.11	0.12
	No		Fixed	109	19 (17.4)			
	Yes		Fixed	976	240 (24.5%)			
Radiotherapy		2				3.86	0.35 - 42.31	0.27
	No		Random	198	85 (32.8%)			
	Yes		Random	585	29 (4.9%)			

OR, Odd ratio; CI, Confidence interval; ER, Estrogen receptor; PR, Progesteron receptor; HER-2, Human epidermal growth factor-2

Author Contribution Statement

Conceptual: PATA, IWS, DMW. Design: SW. Control/supervision: PATA, IGPS. Data collection/processing: SW, IPGSS. Extraction/analysis/interpretation: SW, PATA, IGPS. Literature review: IWS, DMW, IGPS. Writing the article: SW, IPGSS. Critical review: PATA, IWS, DMW, SW, IPGSS, IGPS. Everyone who contributed to the project has reviewed the final manuscript.

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General

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Ethical Declaration

This research does not require ethical approval as a meta-analysis.

Data Availability

This work incorporates data previously published by other authors, with all data included in the findings section.

Study Registration

This review's protocol was filed with the International Prospective Register of Systematic Reviews (PROSPERO), with the registration number CRD42023391913, and

the paper was produced in accordance with PRISMA principles.

Conflict of Interest

There was no disclosure of any potential conflicts of interest that existed.

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