Original Article

The expression of programmed death-ligand 1 in patients with invasive breast cancer

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Background: The purpose of this study is to investigate the association between protein expression of programmed death-ligand 1 (PD-L1) and the clinicopathological features of patients with invasive breast cancer.

Methods: Clinicopathological data of 651 patients with invasive breast carcinoma were collected over a 1-year period. Patients whose breast tissue samples did not express genes for the estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor-2 (HER2) were classified as triple-negative breast cancer (TNBC). The correlations of PD-L1 expression with clinicopathological features and overall survival were determined using Pearson's correlation coefficient and logistic binary regression analysis, respectively.

Results: Positive expression of PD-L1 was detected in 47% of patients with invasive breast carcinoma, compared with 69.3% of TNBC patients (P<0.05). Furthermore, expression of PD-L1 in patients with invasive breast carcinoma was significantly correlated with WHO grade, tumor size, vascular invasion, pathological stage, and the expression of ER, PR, nuclear associated antigen Ki67 (Ki67), *p53* gene, cytokeratin 5/6 (CK5/6), and epidermal growth factor receptor (EGFR) (P<0.05). Logistic binary regression analysis showed that WHO grade, Ki67, p53, and EGFR were independent risk factors for the expression of PD-L1 in patients with invasive breast cancer. Moreover, PD-L1 expression in TNBC patients was significantly correlated with WHO grade, neuro-invasion, Ki67, CK5/6, and EGFR (P<0.05), but it was not correlated with age, tumor size, vascular invasion, number of lymph nodes, pathological stage, or the expression of ER, PR, p53, androgen receptor (AR), or vascular endothelial growth factor receptor (VEGFR) (P>0.05).

Conclusions: The high expression rate of PD-L1 in invasive breast cancer is closely related to some clinicopathological features. Thus, immunotherapy with PD-L1 inhibitors could be a potential treatment strategy for patients with invasive breast cancer.

Keywords: Breast cancer; clinicopathological characteristics; programmed death-ligand 1 (PD-L1); prognosis; protein expression

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Introduction

Breast cancer is the most common type of cancer in women and it is the second leading cause of cancer death among women (1). While the incidence of breast cancer is higher in developed countries, less developed countries have higher relative mortality. Approximately 1.2 million women are diagnosed with breast cancer annually, and the incidence continues to rise at a rate of 5% to 20% a year (1). The pathogenesis of breast cancer is complex and involves alterations in signaling pathways and other changes at a molecular level. Risk factors for the disease include obesity (particularly after menopause), high-dose irradiation to the chest at a young age, dense breast tissue (or increased glandular tissue), the use of hormone replacement therapy, and family history (2). Symptoms of breast cancer include the presence of a painless firm mass, persistent changes in the breast (thickening, swelling, dimpling, distortion, tenderness, skin irritation, redness, scaling, and prominent superficial veins), and changes in the nipple such as ulceration, retraction or inversion, and spontaneous discharge (2).

The clinical treatment for breast cancer is largely dependent on the histological and molecular characteristics of the tumor. Depending on the stage of the cancer, treatment may include surgery, radiotherapy, chemotherapy, targeted therapy, or hormone therapy (3). In advanced breast cancer, the goal of treatment is to prolong life and control the symptoms by using treatments that have low toxicity, thereby improving quality-adjusted life expectancy. However, the clinical effectiveness of treatment is reduced by the high rates of recurrence, and metastasis associated with the disease. Moreover, there is currently a dearth of sensitive biomarkers for the early diagnosis of breast cancer (3).

Programmed death-ligand 1(PD-L1), also known as cluster of differentiation 274 or B7 homolog 1, is a 40 kDa type1transmembrane protein that has been speculated to play a key role in the suppression of adaptive immunity during pregnancy, tissue allografts, autoimmune diseases, and hepatitis (4). PD-L1 expression in tumors can serve as a criterion for selecting patients who will benefit from immunotherapy (4). Programmed death 1 (PD-1) receptor is found on the surface of activated T cells, and forms part of the immune checkpoint that prevents the destruction of healthy host cells. Tumor cells can express surface PD-L1 or PD-L2. Binding of PD-L1 or PD-L2 to the PD-1 receptor inhibits T-cell activation (TCR) and leads to T cell apoptosis and the inhibition of cytokine production (5,6). Hence, PD-1 and its ligand, PD-L1, are key physiological suppressors of the cytotoxic immune reaction. Therefore, tumors with increased expression levels of PD-1 will likely result in poor prognosis. In fact, studies have reported levels of PD-L1 expression to be negatively correlated with the prognosis of patients and the degree of tumor malignancy (7). The activity of specific antitumor T cells was restored via checkpoint blockade using anti-PD-1 and anti-PD-L1 antibodies (7). Furthermore, the expression of PD-L1 has been shown to be altered in many solid tumors, such as lung, gastric, and colorectal cancers (6,8). However, little is known about the role of PD-L1 expression in the pathogenesis of breast cancer. This study aimed to investigate the associations between PD-L1 protein expression and the clinicopathological features of patients with invasive breast cancer.

We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/gs-20-824).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Affiliated Taikang Xianlin Drum Tower Hospital (NO. 2018-02) and informed consent was taken from all individual participants.

Patients and general information

A total of 651 female patients with invasive breast carcinoma were recruited over a from June 2019 to June 2020. The clinicopathological data of the patients are shown in *Table 1*.

Assay of hormone receptor status and classification of patients

Breast biopsies were taken from each patient and the expression of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) protein was assessed. Patients whose tissue samples did not express genes for these receptors were classified as

Triple Negative Breast Cancer (TNBC). Preoperative puncture biopsy was performed in this group of patients: (I) the clinician used an adjustable automatic biopsy gun to perform 4 rounds of biopsy on different areas of the patient's breast mass. (II) The specimens were immobilized

Table 1 Clinicopathological data of breast cancer patients

General information	n
Age (years)	
≤50	416
>50	235
Smoking	
Yes	60
No	591
Pathological type	
Alveolar	365
Adherent	143
Nipple	42
Mucus	14
Physical	32
Other types	55
Degree of differentiation	
Well differentiated	102
Moderately differentiated	429
Poorly differentiated	120
Clinical stage	
I	457
II	78
III	116
Lymph node metastasis	
Yes	111
No	540
Vessel invasion	
Yes	110
No	541
Nerve invasion	
Yes	27
No	624

with 10% neutral formalin solution and embedded with paraffin. (III) Paraffin sections with a thickness of 5 μm were prepared, stained with HE, and observed under an optical microscope.

Immunohistochemical staining

To measure the levels of PD-L1 expression, biopsies were taken from the patients, and the samples were processed for immunohistochemical staining. Tissue sections (3 μm thick) were deparaffinized, rehydrated, and incubated in 3% H_2O_2 for 10 minutes to reduce non-specific background staining. The tissue sections were then incubated in 10 mM citrate buffer (pH 6.0) for 15 minutes in a microwave oven, with agitation. This was followed by incubation with an Ultra V Block solution (Sigma, Shanghai, China) for 10 minutes at room temperature. A rabbit anti-PD-L1 monoclonal antibody (1:250) (Abcon Trading Co., LTD., Shanghai, China) was added, and the tissue sections were incubated for 2 hours at room temperature. Antibody binding was determined using the Ultra-vision LP System according to the manufacturer's instructions (Thermo Fisher Scientific, Waltham, MA, USA). The sections were developed using 3,3' Diaminobenzidine tetrahydrochloride (DAB), and counterstained with hematoxylin. The levels of PD-L1 expression were assessed using to the Allred scoring system. A score of 0 was considered to represent negative PD-L1 expression, while scores of 1+ to 4+ were interpreted as over-expression of PD-L1.

Correlation analysis

The relationships between the levels of PD-L1 expression and the clinicopathological characteristics of patients were determined using Pearson's correlation coefficient.

Univariate and multivariate analyses

Logistic binary regression analyses were used to predict the risk factors affecting PD-L1 expression in breast cancer patients.

Statistical analyses

Statistical analyses were performed using the SPSS software (Version 20.0). Groups were compared using Chi-square tests. Results were considered statistically significant when $P<0.05$.

Results

Expression levels of PD-L1 expression in breast cancer tissues

PD-L1 expression was observed in tumor-infiltrating lymphocytes in the breast cancer tissue samples, and

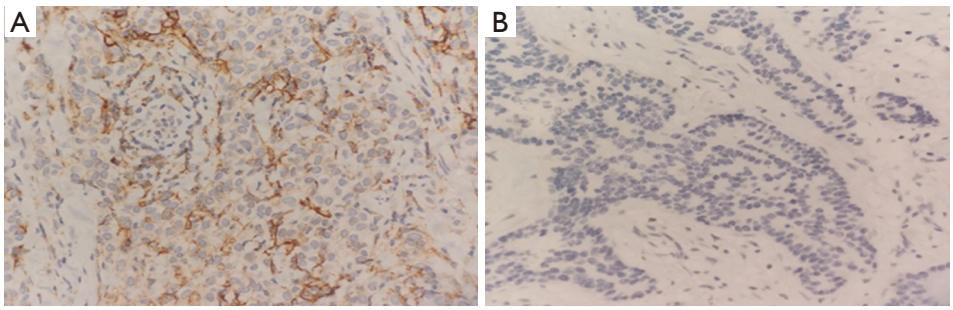

Figure 1 Immunohistological staining of breast tissue with anti-PD-L1 antibody. PD-L1 expression in breast cancer tissue punches. (A) Tissue punch showing strong PD-L1 expression (magnification ×200). (B) Tissue punch with no PD-L1 expression (magnification ×200). PD-L1, programmed death-ligand 1.

its expression was localized in the cytoplasm and cell membrane, presenting as diffuse brownish yellow granules (*Figure 1A*). It was not expressed in healthy human lymphocytes (*Figure 1B*). Positive expression of PD-L1 was detected in 47% of patients with invasive breast carcinoma, compared to 69.3 % of TNBC patients (P<0.05; *Tables 2*,*3*).

Correlations between PD-L1 expression and different clinicopathological characteristics of patients with invasive breast cancer

The expression of PD-L1 in patients with invasive breast cancer was significantly correlated with WHO grade, tumor size, vascular invasion, pathological stage, and positive expression of ER, PR, Ki67, p53, cytokeratin 5/6 (CK5/6), and epidermal growth factor receptor (EGFR) (P<0.05; *Table 2*).

Correlation of PD-L1 expression with different clinicopathological characteristics in patients with TNBC

In TNBC patients, the expression of PD-L1 was significantly correlated with WHO grade, neuro-invasion, and expression of Ki67, CK5/6, and EGFR (P<0.05, *Table 3*). However, it was not correlated with age, tumor size, vascular invasion, number of lymph nodes, pathological stage, or expression of ER, PR, p53, androgen receptor (AR), or VEGFR (P>0.05, *Table 3*).

Results of univariate analysis and multivariate analysis

Logistic binary regression single-factor and multivariate analysis revealed WHO grade, and Ki67, p53, and EGFR expression to be risk factors for PD-L1-expressing breast carcinoma (*Tables 4*,*5*).

Discussion

Breast cancer is a malignant tumor that originates from the epithelial cells of the terminal unit of the breast. Accounting for 10.4% of all cancers among women worldwide, it is the second most common non-skin cancer after lung cancer. Breast cancer ranks second as a cause of female tumor-related mortality (9). Although breast cancer is treatable if diagnosed early, the efficacy of current treatment strategies is generally unsatisfactory due to widespread chemo-resistance and the absence of any effective indicators that can predict and monitor disease progression. The high rate of metastasis associated with breast cancer contributes to poor prognosis and reduces the overall survival of patients (10). Metastatic or stage IV breast cancer is the most advanced type of breast cancer. In most stage IV cases, breast cancer spreads to nearby lymph nodes and further through the body to areas such as the bones, lungs, liver, and the brain (10). Annually, an estimated 1 million cases of breast cancer are diagnosed globally, with more than 170,000 cases classified as triple-negative breast cancer (TNBC) (11). TNBC is characterized by the negative expression of the ER and the PR, and an absence of HER2 protein overexpression. It is a subtype of breast cancer that overlaps with "basal-like" breast cancer (11). As there is currently no effective targeted therapy for TNBC, patients with this subtype tend to have a poor prognosis. At present, TNBC has been proved to be an immunogenic tumor, and the use of systemic immunotherapy enables the autoimmune system to directly destroy targeted tumor cells, which has been used as an effective treatment for TNBC (12).

Programmed death 1 (PD-1) is a receptor expressed on

Table 2 Correlations of PD-L1 expression with different clinicopathological characteristics of patients with invasive breast cancer

Clinical feature	n	PD-L1– (%)	PD-L1+ (%)	χ^2	P
Age (years)				0.004	0.951
≤50	280	148 (52.9)	132 (47.1)		
>50	371	197 (53.1)	174 (46.9)		
WHO grade				62.557	<0.001
I	97	65 (67.0)	32 (33.0)		
II	279	184 (65.9)	95 (34.1)		
III	275	96 (34.9)	179 (65.1)		
Tumor size (cm)				9.308	0.010
≤2	268	160 (59.7)	108 (40.3)		
2–5	357	175 (49.0)	182 (51.0)		
>5	26	10 (38.5)	16 (61.5)		
Vessel				6.910	0.009
Uninvaded	402	229 (57.0)	172 (43.0)		
Violated	248	115 (46.4)	133 (53.6)		
Nerve				0.171	0.679
Uninvaded	521	274 (52.6)	247 (47.4)		
Violated	130	71 (54.6)	59 (45.4)		
Lymph nodes				0.895	0.827
0	365	199 (54.5)	166 (45.5)		
1–3	172	89 (51.7)	83 (48.3)		
4–9	59	29 (49.2)	30 (50.8)		
≥10	55	28 (50.9)	27 (49.1)		
TNM staging				10.226	0.006
I	179	113 (63.1)	66 (36.9)		
II	346	169 (48.8)	177 (51.2)		
III	126	63 (50.0)	63 (50.0)		
HER2				3.889	0.143
Negative	309	165 (53.4)	144 (46.6)		
Unknown	152	89 (58.6)	63 (41.4)		
Positive	190	91 (47.9)	99 (52.1)		
ER				27.738	<0.001
Negative	204	77 (37.7)	127 (62.3)		
Positive	447	268 (60.0)	179 (40.0)		
PR				23.480	<0.001
Negative	253	104 (41.1)	149 (58.9)		
Positive	398	241 (60.6)	157 (39.4)		

Table 2 (*continued*)

Table 2 (*continued*)

Clinical feature	n	PD-L1– (%)	PD-L1+ (%)	χ^2	P
Ki67 (%)				45.106	<0.001
≤30	310	207 (66.8)	103 (33.2)		
>30	341	138 (40.5)	203 (59.5)		
AR				0.519	0.471
Negative	210	107 (51.0)	103 (49)		
Positive	441	238 (54.0)	203 (46.0)		
VEGFR				0.234	0.629
Negative	133	68 (51.1)	65 (48.9)		
Positive	518	277 (53.5)	241 (46.5)		
P53				30.359	0.000
Negative	315	202 (64.1)	113 (35.9)		
Positive	336	143 (42.6)	193 (57.4)		
CK5/6				16.786	0.000
Negative	547	309 (56.5)	238 (43.5)		
Positive	104	36 (34.6)	68 (65.4)		
EGFR				43.803	<0.001
Negative	560	326 (58.2)	234 (41.8)		
Positive	91	19 (20.9)	72 (79.1)		

PD-L1, programmed death-ligand 1; TNM: T, tumor, N, lymph node, M, metastasis; HER2, human epidermal growth factor receptor-2; ER, estrogen receptor; PR, progesterone receptor; AR, androgen receptor; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor.

the surface of T cells, B cells, and natural killer (NK) cells, where it regulates their activation and apoptosis. Its ligand, PD-L1, is expressed in some tumor cells, activated B and T cells, dendritic cells, macrophages, and fibroblasts (13). PD-L1, as a transmembrane protein immunosuppressive molecule of PD-1 ligand, can inhibit the activation process of T lymphocytes when combined with PD-1. Blockade of the PD-1/PD-L1 pathway with monoclonal antibodies (against PD-1 or PD-L1) is a promising therapeutic approach that is currently being trialed in various types of human cancers (14,15). The expression of PD-L1 has been shown to be altered in numerous solid tumors, such as breast cancer, lung cancer, gastric cancer, colorectal cancer, hepatocellular carcinoma, renal cell carcinoma, testicular cancer, and papillary thyroid cancer. Moreover, several meta-analyses have demonstrated that its overexpression signifies poor prognosis in many cancers (16). However, little is known about the expression of PD-L1 in breast cancer, and its prognostic significance remains unclear. A study by Costa *et al*. reported that 45 % of TNBC patients showed positive PD-L1 expression (17). The expression was positively correlated with tumor size, degree of differentiation, Ki-67 proliferation, negative ER and PR expression, and positive HER2 protein expression. However, PD-L1 was found to be negatively correlated with survival (18). In other studies, 20–25% of TNBC patients showed positive PD-L1expression (19,20). It has been reported that the levels of PD-L1 expression may be an important risk factor for breast cancer (21).

The results of this study showed that the positive expression rate of PD-L1 in invasive breast cancer was 47.0%, and the positive expression rate of TNBC, the special subtype, could also reach 69.3%, which was close to the above results. PD-L1 expression in patients with invasive breast cancer was significantly different in different WTO grades, tumor size, vascular invasion,

Table 3 Correlation of PD-L1 expression with different clinicopathological characteristics of patients with TNBC

Clinical feature	n	PD-L1– (%)	PD-L1+ (%)	χ^2	P
Age (years)				2.209	0.137
≤50	47	11 (23.4)	36 (76.6)		
>50	51	19 (37.3)	32 (62.7)		
WHO grade				14.984	0.001
I	9	3 (33.3)	6 (66.7)		
II	17	12 (70.6)	5 (29.4)		
III	72	15 (20.8)	57 (79.2)		
Tumor size (cm)				0.344	0.917
≤2	31	10 (32.3)	21 (67.7)		
2–5	64	19 (29.7)	45 (70.3)		
>5	3	1 (33.3)	2 (66.7)		
Vessel				0.581	0.446
Uninvaded	70	23 (32.9)	47 (67.1)		
Violated	28	7 (25.0)	21 (75.0)		
Nerve				4.731	0.030
Uninvaded	87	23 (26.4)	64 (73.6)		
Violated	11	7 (63.6)	4 (36.4)		
Lymph nodes				1.845	0.685
0	61	21 (34.4)	40 (65.6)		
1≤, ≤3	27	6 (22.2)	21 (77.8)		
4≤, ≤9	5	1 (20.0)	4 (80.0)		
≥10	5	2 (40.0)	3 (60.0)		
TNM staging				1.153	0.590
I	18	6 (33.3)	12 (66.7)		
II	68	19 (27.9)	49 (72.1)		
III	12	5 (41.7)	7 (58.3)		
Ki67 (%)				3.902	0.048
≤30	18	9 (50.0)	9 (50.0)		
>30	80	21 (26.3)	59 (73.8)		
AR				1.424	0.233
Negative	64	17 (26.6)	47 (73.4)		
Positive	34	13 (38.2)	21 (61.8)		
VEGFR				0.830	0.439
Negative	22	5 (22.7)	17 (77.3)		
Positive	76	25 (32.9)	51 (67.1)		

Table 3 (*continued*)

Table 3 (*continued*)

Clinical feature	n	PD-L1– (%)	PD-L1+ (%)	χ^2	P
P53				1.461	0.227
Negative	37	14 (37.8)	23 (62.2)		
Positive	61	16 (26.2)	45 (73.8)		
CK5/6				9.416	0.002
Negative	49	22 (44.9)	8 (16.3)		
Positive	49	27 (55.1)	441 (83.7)		
EGFR				7.338	0.007
Negative	66	26 (39.4)	4 (12.5)		
Positive	32	40 (60.6)	28 (87.5)		

PD-L1, programmed death-ligand 1; TNBC, triple-negative breast cancer; AR, androgen receptor; VEGFR, vascular endothelial growth factor receptor; CK5/6, cytokeratin 5/6; EGFR, epidermal growth factor receptor.

Table 4 Results of single-factor analysis

Clinical feature	B	S.E.	Wald	df	P	95 % CI for EXP (B)	
						Lower	Upper
WHO grade	0.298	0.151	3.874	1	0.049	1.347	1.001
Tumor size	0.237	0.194	1.485	1	0.223	1.267	0.866
Vascular invasion	0.279	0.198	1.988	1	0.159	1.322	0.897
Staging	–0.033	0.170	0.038	1	0.845	0.967	0.693
ER	–0.501	0.345	2.114	1	0.146	0.606	0.308
PR	0.106	0.328	0.104	1	0.747	1.112	0.584
ki67	0.552	0.199	7.689	1	0.006	1.737	1.176
P53	0.700	0.174	16.232	1	0	2.014	1.433
CK56	0.066	0.277	0.057	1	0.811	1.068	0.621
EGFR	1.188	0.297	16.000	1	0	3.281	1.833

ER, estrogen receptor; PR, progesterone receptor; EGFR, epidermal growth factor receptor. B mean regression coefficient; S.E. mean standard error; Wald mean chi-square value; df mean degree of freedom; CI mean confidence interval.

Table 5 Results of multivariate analysis

Clinical feature	B	S.E.	Wald	df	P	95 % CI for EXP (B)	
						Lower	Upper
WHO grade	0.413	0.144	8.208	1	0.004	1.139	2.003
Ki67	0.613	0.196	9.842	1	0.002	1.259	2.709
P53	0.734	0.172	18.226	1	<0.001	1.487	2.916
EGFR	0.251	0.284	19.412	1	<0.001	2.002	6.086

EGFR, epidermal growth factor receptor.

pathological stage, ER, PR, Ki67, P53, CK5/6 and EGFR (P<0.05); In TNBC patients, the expression of PD-L1 was significantly correlated with WHO grade, nerve invasion, Ki67, CK5/6 and EGFR (P<0.05). These results suggest that the expression of PD-L1 is closely related to most pathological features of patients with invasive breast cancer, which may reflect tumor burden. Further univariate and multivariate analysis showed that the expression of PD-L1 was significantly correlated with WHO staging, Ki67, P53 and EGFR. WHO staging, Ki67, P53 and EGFR were independent risk factors affecting the expression of PD-L1, and the expression level of PD-L1 might be related to these factors.

Conclusions

More and more evidence shows that the activation of PD-1/PD-L1 signaling pathway can restore T lymphocytes' control over tumor cells, making tumor cells unable to escape immune, thus killing tumor cells. This study confirmed that the PD-L1 in breast ductal carcinoma especially in the patients with TNBC high expression, and PD-L1 and some clinical pathological features between the complex and the close relation. This means that immunotherapy with PD-L1 inhibitors can be used as a potential treatment strategy for patients with invasive breast cancer with high expression of PD-L1, and providing theoretical basis for further research and clinical promotion.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Affiliated Taikang Xianlin Drum Tower Hospital (NO.2018-02) and informed consent was taken from all individual participants.

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