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ORIGINAL RESEARCH

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Serum NSE is an independent risk factor for positive PD-L1 in breast cancer patients

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Abstract

To investigate the relationship between the level of serum tumor markers and the expression of programmed cell death-ligand-1 (PD-L1) in breast cancer patients, and to explore the diagnostic value of serum tumor markers for the positive expression of PD-L1. The basic information, preoperative serum tumor markers and postoperative pathological results of 139 patients with breast cancer who received treatment for the first time in People's Liberation Army (PLA) General Hospital between 2019 and 2020 were collected. The relationship between preoperative tumor markers and postoperative pathological PD-L1 positive expression in breast cancer patients was analyzed, and binary and multivariate Logistic regression model was established to explore the predictive ability of various tumor markers for the positive expression of PD-L1. The serum level of neuron-specific enolase (NSE) was positively correlated with the expression of PD-L1. The level of NSE was statistically different between the two groups of PD-L1 (PD-L1 (0%) and PD-L1 ($\geq$1%)) ($p < 0.05$). Serum NSE level was better than carbohydrate antigen15-3 (CA15-3) in predicting the positive expression of PD-L1. The sensitivity and specificity were 0.786 and 0.545 when the cutoff value is 11.28, respectively. The area under receiver operating characteristic (ROC) curve (AUC) = 0.711. Serum NSE is an independent risk factor for positive expression of PD-L1.

Keywords

PD-L1; NSE; Breast cancer

1. Introduction

Breast cancer has overtaken lung cancer as the world's most common cancer [1]. In recent years, despite people's increased health awareness, the morbidity and mortality of breast cancer are still increasing year by year. It is calculable that by 2040, the number of newly diagnosed breast cancer will increase by about 40% and the number of deaths will increase by more than 50% [2]. PD-L1 is expressed in B cells, T cells, tumor cells, macrophages and dendritic cells, and is one of the important ligands of programmed death protein-1 (PD-1). PD-L1 is the focus of research in immunotherapy, and some studies have found that PD-L1 is expressed in breast cancer. The expression level of PD-L1 is related to the inhibition of T cell function. In tumor cells, PD-L1 binds to PD-1 receptors expressed on activated T cells and B cells to destroy the immune effect, and this immunosuppressant effect enables tumor cells to escape immune destruction [3]. The PD-1 receptor on T cells binds to its ligands PD-L1 and PD-L2 expressed by immune and tumor cells within the tumor microenvironment (TME), thereby shutting intratumoral T cells down [4, 5]. Accumulating studies have demonstrated that PD-L1 is closely related to lymph node metastasis, clinic pathological grade and molecular typing of breast cancer, and high PD-L1 expression was associated with poor prognosis in breast cancer [6, 7]. Disrupting PD-1 signaling pathways can unleash antitumor immune activity and generate meaningful clinical responses [5]. Therefore, detecting the expression of PD-L1 plays an important role in predicting the response to breast cancer treatment [8, 9]. Clinical detection of PD-L1 is typically conducted by immunohistochemistry of postoperative pathological tissues. Therefore, predicting the expression of PD-L1 is of great significance for prognosis. Serum tumor markers are commonly used clinical detection items, which have vital value in the diagnosis and prognosis of tumors. This paper retrospectively analyzed the relationship between the expression of PD-L1 in surgical pathological tissues and preoperative serum tumor markers, in order to find tumor markers that can predict the expression of PD-L1, and provide reference for the clinical diagnosis and treatment of breast cancer patients.

2. Materials and methods

2.1 Patients and controls

Inclusion criteria: (1) 139 patients (from 222 patients) with breast cancer, all of whom were hospitalized for the first time in PLA General Hospital from April 2019 to April 2020,

were pathologically diagnosed as breast cancer according to the 2022 National Comprehensive Cancer Network (NCCN) guidelines for Breast cancer, and their clinical stages were stage I–III; (2) No radiotherapy or chemotherapy before surgery. Exclusion criteria: Patients with other tumors.

2.2 Information collection

The experimental data and clinical stages of patients were obtained from the hospital case system. The patient's blood was collected on an empty stomach on the test day, and the blood was placed at room temperature and completely agglutinated before centrifugation (3500 r/min, 7 minutes). After centrifugation, the blood was tested on the machine in time. Tumor markers including Carcinoembryonic Antigen (CEA), Alpha Fetoprotein (AFP), carbohydrate antigen125 (CA125), carbohydrate antigen199 (CA19-9), carbohydrate antigen153 (CA15-3), carbohydrate antigen724 (CA72-4), cytokeratin fragment antigen (CYFRA211), NSE, Squamous Cell Carcinoma Antigen (SCC), Human Chorionic Gonadotropin (HCG), Ferritin (FERR), pepsinogen I (PGI), pepsinogen II (PGII) were tested before surgery. All tumor markers were measured by Roche COBAS-701 instrument (Basel, Switzerland) and its original reagents. PD-L1 test reagent comes from Roche. After testing, specimens are stored in a 2–8 °C refrigerator. Quality control was carried out on the test day to ensure accurate and reliable results. PD-L1 was detected by immunohistochemistry of pathological tissue, and the test results were evaluated by two independent pathologists respectively, and the three-level review system was strictly implemented.

2.3 Research methods

According to the results of PD-L1, all patients were divided into two groups: PD-L1 (0%) and PD-L1 (≥1%), and the differences in age, estradiol, body mass index (BMI), pregnancy history, age of menarche, age of menopause, ABO blood type, tumor location, tumor size, tumor staging, Tumor Node Metastasis (TNM) staging, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) were compared between the two groups, respectively. Tumor markers were compared among three groups. A binary Logistic regression model was established based on tumor markers to explore the predictive ability of each tumor marker to the positive expression of PD-L1.

2.4 Statistical analysis

SPSS 22.0 software (International Business Machines Corporation, Armonk, NY, USA) was used to analyze the data of each group. Quantitative data were uniformly expressed by median (50% (25%–75%)), and the comparison between the two groups of samples was conducted by independent sample t test. Wilcoxon rank sum test was used to compare the two samples. Binary Logistic regression analysis was used to predict risk factors, and receiver operating characteristic (ROC) curve was drawn to evaluate the positive differential prediction ability of each factor for PD-L1. $p < 0.05$ was considered statistically significant.

3. Result

3.1 Baseline characteristics

The basic information of 139 breast cancer patients is shown in Table 1. According to the PD-L1 grouping, 69 PD-L1 0% cases and 70 PD-L1 ≥1% cases were reported. Statistical analysis of age, BMI, gestational history, age of menarche and age of menopausal showed no difference between PD-L1 positive and negative groups ($p > 0.05$). The ABO blood type, tumor location, tumor staging, tumor size, TNM staging and the expression of ER, PR and HER-2 also showed no statistically significant between the two groups, as shown in Table 1.

3.2 Serum tumor markers in two PD-L1 groups

According to the expression of PD-L1, all patients were divided in two groups, PD-L1 (0%) and PD-L1 (≥1%) group. Serum tumor markers were compared between the two groups. NSE level showed statistically significant, NSE showed an increasing trend with the increase of PD-L1 positive ($p < 0.05$), as shown in Table 2.

3.3 Correlation analysis

The results of correlation analysis showed that PD-L1 expression was positively correlated with NSE, and the R-value was 0.400 ($p = 0.010$). As shown in Table 3.

3.4 Univariate and multivariate regression analysis of PD-L1 positive risk factors

By univariate and multivariate regression analysis of tumor markers, it was found that NSE was an independent risk factor for positive PD-L1 ($p < 0.05$), see in Table 4. The odds ratio (OR) value was 1.433. Therefore, NSE predicted that the risk of PD-L1 positive was 1.433 times higher than negative. In the multiple variables analysis, NSE was the influence factor of PD-L1 positive ($p < 0.05$).

3.5 Comparison of the efficacy of tumor marker in predicting PD-L1 positive in breast cancer patients

Based on the result of regression analysis, ROC curve was established. NSE and CA15-3 were included into the curve. NSE has higher sensitivity and specificity in predicting the positive PD-L1, and the area under ROC curve was 0.711 (AUC = 0.711), compared with CA15-3 (AUC = 0.505), showing better predictive efficacy. When NSE = 11.28, the sensitivity and specificity of prediction are at their maximum, was statistically significant ($p < 0.01$). See in Table 5 and Fig. 1. With the increase of NSE value, the positive rate of PD-L1 increased, indicating that NSE could positively predict the positive rate of PD-L1. As shown in Fig. 2.

4. Discussion

In recent years, increasingly attention has been paid to tumor immunotherapy, which might prevent tumor growth by inhibiting immune escape and restoring lymphocyte function.

TABLE 1. Baseline characteristics of patients with PD-L1 positive and negative breast cancer in this study.

Variable	Classification	PD-L1		*p*-value
		PD-L1 0% (n = 69)	PD-L1 ≥1% (n = 70)	
Age (yr, M (Q25∼Q75))		49 (43∼58)	48 (42∼55)	0.378
BMI (kg/m^2, M (Q25∼Q75))		23.9 (22.3∼26.5)	23.2 (21.9∼26.2)	0.396
Estradiol (pmol/L, M (Q25∼Q75))		296.12 (109.55∼493.37)	264.41 (132.89∼533.25)	0.554
Pregnancy history (times, M (Q25∼Q75))		1 (1∼2)	1 (1∼2)	0.881
Age of menarche (yr, M (Q25∼Q75))		14 (13∼15)	14 (13∼15)	0.723
Age of menopause (yr, M (Q25∼Q75))		51 (50∼54)	51 (48∼53)	0.593
Menopause or not (% (n/n))				
	Yes	31.9% (22/69)	29.5% (18/61)	0.850
	No	68.1% (47/69)	70.5% (43/61)	
ABO blood type (% (n/n))				
	A	17.4% (12/69)	31.1% (19/61)	0.098
	B	39.1% (27/69)	37.7% (23/61)	1.000
	AB	7.3% (5/69)	6.6% (4/61)	1.000
	O	36.2% (25/69)	24.6% (15/61)	0.184
Tumor location (% (n/n))				
	Left	52.2% (36/69)	49.2% (30/61)	0.861
	Right	47.8% (33/69)	50.8% (31/61)	
Tumor size (% (n/n))				
	<3.0 cm	79.7% (55/69)	72.1% (44/61)	0.410
	≥3.0 cm	20.3% (14/69)	27.9% (17/61)	
Tumor staging (% (n/n))				
	Stage I	36.2% (25/69)	31.1% (19/61)	0.581
	Stage II	44.9% (31/69)	45.9% (28/61)	1.000
	Stage III	18.9% (13/69)	23.0% (14/61)	0.666
TNM staging (% (n/n))				
Tumor size and extent (T)				
	T1	62.3% (43/69)	55.7% (34/61)	0.478
	T2	31.9% (22/69)	37.7% (23/61)	0.580
	T3	5.8% (4/69)	4.9% (3/61)	1.000
	T4	0.0% (0/69)	1.7% (1/61)	0.469
Lymph node metastasis (N)				
	N0	53.6% (37/69)	57.4% (35/61)	0.725
	N1	27.5% (19/69)	23.0% (14/61)	0.687
	N2	10.2% (7/69)	9.8% (6/61)	1.000
	N3	8.7% (6/69)	9.8% (6/61)	1.000
Distant metastasis (M)				
	M0	100% (69/69)	98.3% (60/61)	0.469
	M1	0.0% (0/69)	1.7% (1/61)	

TABLE 1. Continued.

Variable	Classification	PD-L1		*p*-value
		PD-L1 0% (n = 69)	PD-L1 ≥1% (n = 70)	
ER (% (n/n))				
	Negative	14.5% (10/69)	24.6% (15/61)	0.182
	Positive	85.5% (59/69)	75.4% (46/61)	
PR (% (n/n))				
	Negative	17.4% (12/69)	21.3% (13/61)	0.658
	Positive	82.6% (57/69)	78.7% (48/61)	
HER-2 (% (n/n))				
	0	17.4% (12/69)	11.5% (7/61)	0.457
	1+	24.6% (17/69)	11.5% (7/61)	0.070
	2+	37.7% (26/69)	42.6% (26/61)	0.594
	3+	20.3% (14/69)	34.4% (21/61)	0.078
TNBC (% (n/n))				
	Yes	0.0% (0/69)	1.7% (1/61)	0.469
	No	100% (69/69)	98.3% (60/61)	

TNBC: Triple negative breast cancer.

TABLE 2. Difference in expression of tumor markers between two PD-L1 groups.

Variable	PD-L1 (0%)	PD-L1 (≥1%)	*p*-value
CEA (μg/L, M)	1.65 (1.10∼2.08)	1.09 (0.80∼1.84)	0.057
AFP (μg/L, M)	2.90 (1.92∼3.57)	2.68 (1.99∼4.06)	0.715
CA125 (U/mL, M)	12.34 (8.95∼17.72)	14.25 (9.68∼21.70)	0.180
CA19-9 (U/mL, M)	9.47 (6.10∼18.11)	8.87 (6.29∼15.69)	0.761
CA15-3 (U/mL, M)	9.19 (6.60∼14.89)	10.11 (7.10∼14.41)	0.937
CA72-4 (U/mL, M)	2.15 (1.01∼5.07)	1.43 (0.99∼2.42)	0.106
CYFRA211 (ng/mL, M)	2.37 (1.95∼3.21)	2.53 (2.22∼2.96)	0.654
NSE (ng/mL, M)	11.22 (9.78∼12.33)	12.20 (11.35∼13.34)	0.011
SCC (ng/mL, M)	0.70 (0.50∼0.85)	0.60 (0.53∼0.90)	0.872
HCG (U/L, M)	0.10 (0.10∼1.97)	0.10 (0.10∼0.10)	0.051
FERR (ng/mL, M)	63.29 (18.89∼102.23)	50.45 (28.06∼99.79)	0.965
PGI (ng/mL, M)	49.80 (41.55∼64.65)	43.60 (36.29∼61.05)	0.165
PGII (ng/mL, M)	6.70 (5.55∼10.35)	6.20 (4.23∼12.65)	0.478

PD-L1: programmed cell death-ligand-1; CEA: Carcinoembryonic Antigen; AFP: Alpha Fetoprotein; CA: carbohydrate antigen; CYFRA: cytokeratin fragment antigen; NSE: neuron-specific enolase; SCC: Squamous Cell Carcinoma Antigen; HCG: Human Chorionic Gonadotropin; FERR: Ferritin; PGI: pepsinogen I; PGII: pepsinogen II.

TABLE 3. Correlation analysis between PD-L1 expression and tumor markers.

Variable	Correlation coefficient	*p*-value
CEA (μg/L)	−0.218	0.057
AFP (μg/L)	0.036	0.717
CA125 (U/mL)	0.133	0.181
CA19-9 (U/mL)	−0.030	0.763
CA15-3 (U/mL)	0.008	0.937
CA72-4 (U/mL)	−0.160	0.106
CYFRA211 (ng/mL)	0.058	0.657
NSE (ng/mL)	0.400	0.010
SCC (ng/mL)	0.021	0.874
HCG (U/L)	−0.279	0.060
FERR (ng/mL)	−0.006	0.966
PGI (ng/mL)	−0.179	0.167
PGII (ng/mL)	−0.092	0.483

CEA: Carcinoembryonic Antigen; AFP: Alpha Fetoprotein; CA: carbohydrate antigen; CYFRA: cytokeratin fragment antigen; NSE: neuron-specific enolase; SCC: Squamous Cell Carcinoma Antigen; HCG: Human Chorionic Gonadotropin; FERR: Ferritin; PGI: pepsinogen I; PGII: pepsinogen II.

TABLE 4. Logistic regression analysis of PD-L1 positive risk factors.

Variable	One variable			Multiple variables		
	OR	OR 95% confidence interval	*p*-value	OR	OR 95% confidence interval	*p*-value
CEA (μg/L)	0.701	0.549–1.070	0.099			
AFP (μg/L)	1.071	0.837–1.370	0.584			
CA125 (U/mL)	1.018	0.990–1.047	0.203			
CA19-9 (U/mL)	0.979	0.933–1.028	0.395			
CA15-3 (U/mL)	1.005	0.972–1.039	0.766			
CA72-4 (U/mL)	0.863	0.731–1.020	0.084			
CYFRA211 (ng/mL)	1.123	0.774–1.627	0.542			
NSE (ng/mL)	1.433	1.019–1.825	0.025	1.579	1.059–2.121	0.011
SCC (ng/mL)	0.908	0.157–5.233	0.914			
HCG (U/L)	0.501	0.252–0.996	0.060			
FERR (ng/mL)	0.996	0.989–1.003	0.278			
PGI (ng/mL)	0.989	0.964–1.015	0.423			
PGII (ng/mL)	1.008	0.911–1.116	0.877			

CEA: Carcinoembryonic Antigen; AFP: Alpha Fetoprotein; CA: carbohydrate antigen; CYFRA: cytokeratin fragment antigen; NSE: neuron-specific enolase; SCC: Squamous Cell Carcinoma Antigen; HCG: Human Chorionic Gonadotropin; FERR: Ferritin; PGI: pepsinogen I; PGII: pepsinogen II; OR: odds ratio.

TABLE 5. Efficacy of serum CA15-3 and NSE in predicting PD-L1 positive breast cancer patients.

Variable	AUC	CUTOFF	Sensitivity	Specificity	Accuracy	*p*-value
NSE (ng/mL)	0.711	11.280	0.786	0.545	0.656	0.010
CA15-3 (U/mL)	0.505	8.670	0.607	0.515	0.553	0.937

NSE: neuron-specific enolase; CA: carbohydrate antigen; AUC: area under curve.

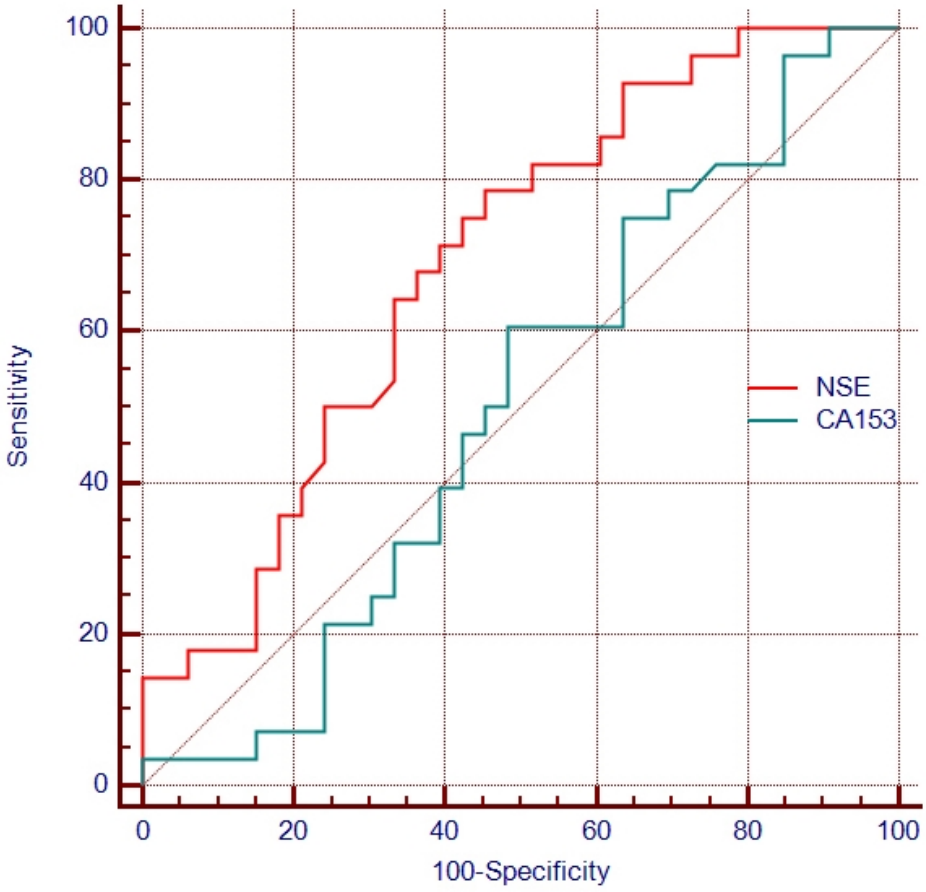

FIGURE 1. ROC curve of CA15-3 and NSE predicting PD-L1 positive breast cancer patients. NSE was better than CA15-3 in the positive diagnosis of PD-L1, and the area under ROC curve was the largest, the difference was statistically significant. NSE: neuron-specific enolase; CA: carbohydrate antigen.

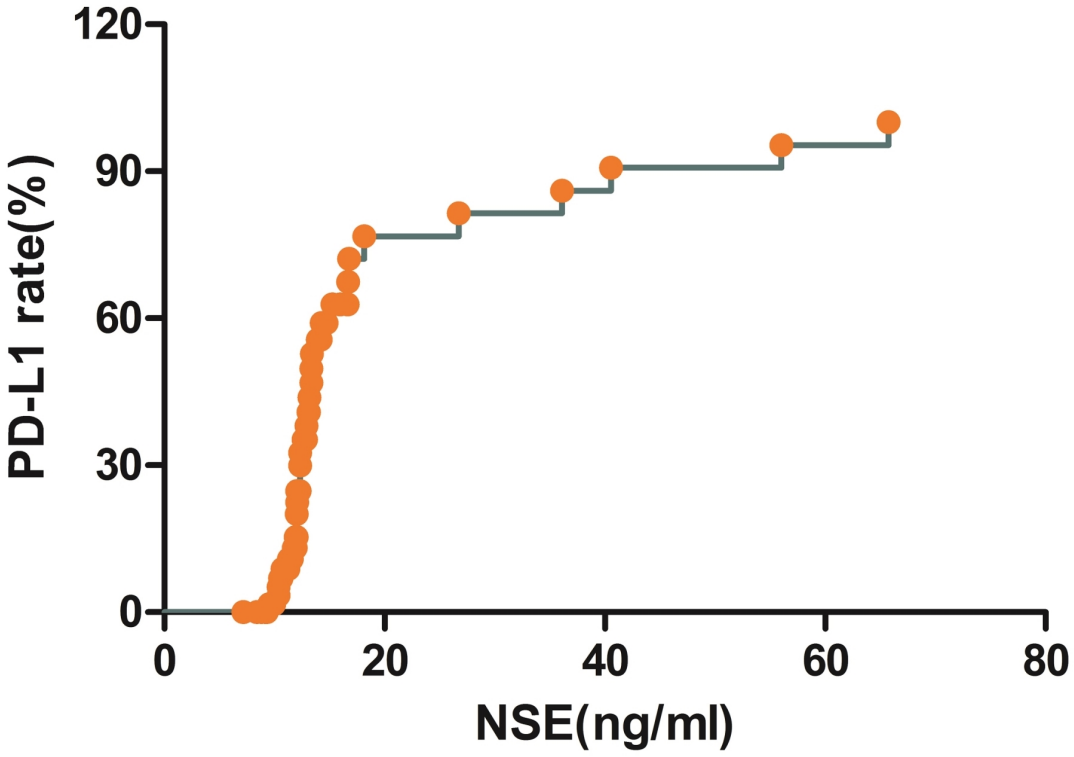

FIGURE 2. NSE level and PD-L1 positive risk function. With the increase of NSE level, the positive probability of PD-L1 increased. PD-L1: programmed cell death-ligand-1; NSE: neuron-specific enolase.

Breast cancer, a cancer originating from epithelial cells, was initially considered to be non-immunogenic, but a growing number of studies have confirmed that breast cancers can be immunogenic [10], showing resistance to chemotherapy and poor prognosis, and the molecules expressed by these cancer cells can be used as targets for immunotherapy [11]. Therefore, it is very important to understand the immune evasion mechanism of breast cancer cells and prevent it ahead within the treatment of breast cancer. In this study, we found that serum NSE is an independent risk factor for positive expression of PD-L1.

Previous studies have shown that the positive expression rate of PD-L1 in triple-negative breast cancer is higher than that in non-triple-negative breast cancer, which has been proven to be more sensitive to immunotherapy, such as PD-1/PD-L1 inhibitors [12]. However, studies have also demonstrated that HER-2+ breast cancers are also more likely to express the programmed death ligand-1 (PD-L1) in the TME than luminal breast cancers (expressing the estrogen receptor (ER) and/or progesterone receptor (PR)) [13, 14]. Accumulating data suggest that antagonists of PD-1/PD-L1 signaling can induce durable clinical responses not only in some patients with metastatic TNBC, but also have meaningful clinical activity in rare patients with ER+ HER-2− breast cancer as well [15]. Some solid tumors that express PD-L1 are more likely to respond to PD-1/PD-L1 blockade [16, 17], suggesting this may also be the case for breast cancers. In a study about humanized monoclonal antibodies that target PD-L1 (avelumab), 168 patients with breast cancer were enrolled regardless of either disease subtype, the result showed a 28% disease control rate. Though it appeared to be higher in TNBC, responses were observed in all breast cancer subtypes [18, 19]. Thus, although PD-L1 inhibitors are more prevalent in studies of triple-negative breast cancer, PD-L1 inhibitors may have a blocking effect on other breast cancers expressing PD-L1.

According to the 2022 NCCN Breast Cancer Guidelines [20], age, BMI, gestational history, age of menarche and age of menopause are all important factors affecting the prognosis of breast cancer. In our study, through the analysis of the basic information of patients, we found that there was no difference in these factors between patients with positive and negative PD-L1 expression. The reason may be that our study objects were patients with clinical stage I–III, so it was believed that age, BMI, gestational history, age of menarche and age of menopause were not correlated with the expression of PD-L1 in the early and middle stages of breast cancer.

NSE exists in nervous tissues and neuroendocrine tissues, and has been found to be associated with tumors originating from neuroendocrine tissues, such as neuroblastoma. In addition, NSE is often used in the auxiliary diagnosis, prognostic judgment, and recurrence monitoring of small cell lung cancer [21]. Previous studies on NSE mainly focus on lung cancer and neurogenic tumors. The value of NSE in the diagnosis and prognosis of breast cancer is rarely reported. In a study on non-small cell lung cancer, NSE level predicted the prognosis of patients treated with PD-1/PD-L1 inhibitors, among which, increased NSE level was associated with poor prognosis, indicating the correlation between increased NSE level and positive PD-L1 in lung cancer [22]. A recent study reported that NSE levels were negatively correlated with the survival rate of breast cancer patients, and could be used to reflect the angiogenesis rate of tumor tissues [23].

The detection of serum tumor markers has been routinely applied in clinical practice. Compared with the detection of PD-L1 expression, the detection of tumor markers is more convenient and fewer pricey, which is more conducive to monitoring at any time. The relationship between PD-L1 and serum tumor markers is rarely reported. Thus, the differences of common clinical tumor markers in different PD-L1 expression cases were retrospectively analyzed in this study. In this study, by exploring the relationship between preoperative tumor marker level and postoperative pathological PD-L1 expression, it was found that PD-L1 expression in breast cancer patients was weak-moderate correlated with NSE, and the level of NSE showed an increasing trend with the increase of PD-L1 positive, with statistical significance ($p < 0.05$). Based on these results, univariate and multivariate logistic regression was established, and it was found that NSE was an independent risk factor for positive PD-L1 ($p < 0.05$), and NSE predicted that the risk of PD-L1 positive was 1.433 times higher than negative. CA15-3 is the most important specific marker for breast cancer. Increased CA15-3 levels are often associated with breast cancer patients, which is of certain value for the diagnosis and postoperative follow-up of breast cancer, and is often used for the efficacy observation and prognosis estimation of breast cancer [24]. In this study, the predictive ability of NSE and CA15-3 for PD-L1 were compared. Through the establishment of ROC curve, it was found that NSE was better than CA15-3 in predicting the positive of PD-L1 in breast cancer, which may be related to the low sensitivity of CA15-3 in the early stage of breast cancer and the high positive rate of metastatic breast cancer detection [23].

This study has some limitations. The number of triple-negative breast cancers collected in this study was small, and most of them were non-triple-negative breast cancers or HER-2+ breast cancers. However, the relationship between NSE and PD-L1 found in this paper may also exist in triple-negative breast cancers. Our next research will increase the number of triple-negative breast cancers to further prove the conclusion of this study.

5. Conclusions

In conclusion, NSE is an independent risk factor for positive PD-L1, and NSE is correlated with positive PD-L1, and its predictive efficacy is better than that of traditional breast cancer tumor marker CA15-3 and HCG. Therefore, NSE is expected to be a tumor marker to predict the expression of PD-L1 in breast cancer patients.

ABBREVIATIONS

PD-L1, programmed cell death-ligand-1; NSE, neuron-specific enolase; PD-1, programmed death protein-1; CEA, carcinoembryonic antigen; AFP, alpha fetal protein; CA125, carbohydrate antigen125; CA19-9, carbohydrate antigen199; CA15-3, carbohydrate antigen153; CA72-4, carbohydrate

antigen724; CYFRA211, cytokeratin fragment antigen; SCC, squamous cell carcinoma antigen; HCG, human chorionic gonadotropin; FEER, Ferritin; PGI, pepsinogen I; PGII, pepsinogen II; BMI, Body mass index.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

XMW and LZ—designed the research study. XMW—Patient information and experimental results collected. XZ and JZN—analyzed the data. XMW and JZN—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was a retrospective analysis of clinical data, and exemption from informed consent was approved by the ethics committee of Chinese PLA General Hospital. All experimental protocols were approved by the ethics committee of Chinese PLA General Hospital (no. S2018-025-01), and all methods were carried out in accordance with relevant guidelines and regulations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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