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Research Article

CLINICOPATHOLOGICAL SIGNIFICANCE OF IMMUNOHISTOCHEMICAL PD-L1 AND ANDROGEN RECEPTOR EXPRESSIONS IN TRIPLE NEGATIVE BREAST CANCERS

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ABSTRACT

Objective: Triple negative breast cancers (TNBC), a subset of breast cancers are high-grade, and related to younger age, higher risk of recurrence, higher incidence of metastases and poorer prognosis. Currently, there is increasing evidence of a dynamic interaction between the breast cancer and immune system. Luminal Androgen Receptor (LAR) subtype is dependent on Androgen Receptor (AR) signaling and represents a novel subtype of TNBC with a distinct prognosis that offers an opportunity for the development of targeted therapeutics. In this study, we aimed to investigate the immunohistochemical expression of Programmed death ligand 1(PD-L1) and AR and their correlations with clinical parameters in TNBC.

Materials and Methods: Sixtyfour patients who received a primary diagnosis of TNBC from surgical material at Aydın Adnan Menderes University Faculty of Medicine Hospital Department of Pathology between 2013-2019 were available for this study. Demographic and histopathological characteristics were obtained from archival reports. PD-L1 and AR immunohistochemical stains were applied to sections prepared from the blocks.

Results: The mean age was 53,47±15,044(range 28-84 years). The percentage of PD-L1 positivity was %57,8 and AR positivity was %26,6. There was a significant correlation PD-L1 positivity with Ki67 proliferation index(p=0.009), and lymphovascular invasion(p=0.009) and no correlation between PD-L1 and other parameters. No significant correlation was found between AR and clinicopathologic parameters.

Conclusion: PD-L1 and AR are important prognostic markers for TNBC and identify important groups for targeted therapies. PD-L1 positive cases are associated with poor prognostic markers and further studies in larger groups are needed for both markers.

Keywords: Triple negative breast cancer, PD-L1, AR, Ki67, immunohistochemistry.

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INTRODUCTION

Triple negative breast cancer (TNBC) is a subset of breast cancers that lack expression of the progesterone receptor (PR), estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2). According to hormone receptor positive breast cancer TNBC is related to younger age, higher risk of recurrence, higher incidence of metastases and poorer prognosis (1). Despite the wide range of morphologies, the majority of TNBCs are high-grade, with tumor cells showing large nuclear size, solid growth pattern and geographic necrosis (2). This molecular heterogeneity has led to the lack of FDA-approved targeted therapies for TNBC (3).

Programmed death ligand 1 (PD-L1) is a transmembrane glycoprotein of haplotype 1 of the immunoglobulin superfamily, so named because of its association with the apoptotic program. PD-L1 is widely expressed on the surface of B lymphocytes, natural killer cells, monocytes, vascular endothelial cells and macrophages (4). It was also upregulated in tumor cell lines such as ovarian cancer, lymphoma and melanoma, suggesting a close relationship with tumor initiation and development (4). There is increasing evidence of a dynamic interaction between the immune system and breast cancer (5). PD-L1 immunohistochemical expression in breast cancer is about %10-30 and TNBC shows the highest percentage of PD-L1 positivity (6). Taken together, identifying the PD-1/PD-L1 pathway is of clinical importance.

Lehmann et all identified four subtypes of TNBC, each displaying unique ontologies. The TNBC subtypes include two basal-like (BL1 and BL2), mesenchymal (M) and luminal androgen receptor (LAR) (3). The LAR subtype is enriched for hormone-regulated pathways and is dependent on androgen receptor (AR) signaling, is distinct from unselected TNBC, is predominantly subclassified in the non-basal subset, and represents a novel subtype of TNBC with a distinct prognosis that offers an opportunity for the development of targeted therapeutics (7).

In this study, we aimed to investigate the immunohistochemical expression of PD-L1 and AR and their correlations with clinical parameters in TNBC and to determine the groups suitable for targeted therapy.

MATERIALS AND METHODS

Sixtyfour patients who received a primary diagnosis of TNBC from surgical material at Aydın Adnan Menderes University Faculty of Medicine Hospital Department of Pathology between 2013 and 2019 were available for this study. Demographic and histopathological characteristics were obtained from archival reports. Hematoxylin and eosin-stained sections of each patient were re-evaluated. Blocks with the most tumor cells and the least necrosis were selected (Figure 1).

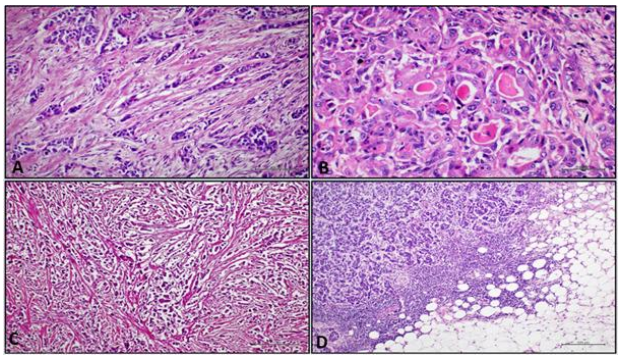

Figure 1. A. Invasive breast carcinoma, no special type x100 HPF, Hematoxylin&Eosin. **B.** Acinic cell carcinoma x200 HPF, Hematoxylin&Eosin. **C.** Invasive micropapillary carcinoma, x100 HPF, Hematoxylin&Eosin. **D.** Invasive breast carcinoma medullary pattern, x100 HPF, Hematoxylin&Eosin

In addition, ER, PR, HER2, Ki67 immunohistochemistry slides were reviewed according to the American Society of Clinical Oncology/American Society of Pathologists (ASCO/CAP) breast cancer guidelines.

PD-L1 and AR immunohistochemical staining

Three-micron sections of 64 formalin-fixed, paraffin-embedded tissue blocks were cut and mounted on positively charged poly-L-lysine (Micro Slides Snowcoat X-tra, Surgipath, Richmond, IL, USA) coated slides and stored overnight in an oven at 37 degrees Celsius. Immunohistochemistry was performed using the avidin-biotin complex system. PD-L1 (Anti-Programmed Death Ligand 1 [22C3] monoclonal mouse, code: 22C3, 1/20-1/50 dilution, Agilent Technologies, Santa Clara, CA) and AR (Anti-Androgen Receptor antibody [AR 441] monoclonal mouse, code: AR441, 1/25-1/50 dilution, ABCAM, Cambridge, UK) stainings were applied to selected sections. Finally, the slides were sealed with mounting solution. Positive control evaluation for PD-L1 and AR was performed using positively stained tissue. Tonsil tissue was used for PD-L1 and non-neoplastic breast tissue for AR. Immunohistochemical staining was evaluated by light microscopy (Olympus BX53, Tokyo, Japan) at x100, x200 and x400 magnifications. Photomicrographs were taken using a high-resolution video camera (Olympus DP 22, Japan) attached to an Olympus BX-53 model microscope (Olympus Co., Tokyo, Japan).
Immunohistochemical PD-L1 staining was evaluated on tumor tissue. The presence of complete membranous

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staining in at least %1 of tumor cells was classified as positive. Cytoplasmic or incomplete membranous staining was considered as negative (Figure 2).

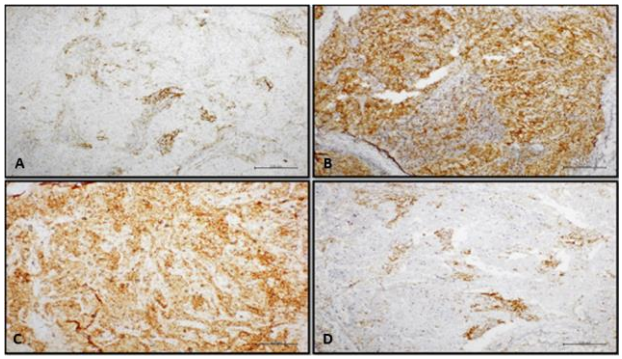

Figure 2. PD-L1 immunohistochemical complet membranous staining positive at different rates in different triple negative breast cancer sites, x100 HPF: **A** and **D**- Examples of focal staining, **B** and **C**- Examples of diffuse staining

Immunohistochemical AR staining was evaluated on tumor tissue. The percentage of stained cells was determined in 1000 tumor cells. The presence of %10 or more nuclear staining was classified as positive. Cytoplasmic or less than %10 nuclear staining was considered as negative (Figure 3).

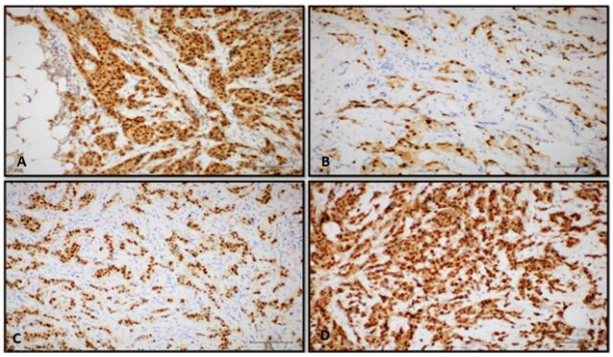

Figure 3. AR immunohistochemical nuclear staining positive at different rates in different triple negative breast cancer sites, x100 HPF: **A** and **D-** Examples of focal diffuse staining, **B** and **C-** Examples of diffuse staining.

Statistical analysis

Statistical analyses were performed using SPSS 22.0 Package Program. Descriptive statistics were performed for all parameters entered as a dataset. Descriptive statistics were expressed as number and percentage for categorical variables, minimum and maximum for numerical variables, mean and standard deviation. Due to insufficient sample size for some parameters, the Mann-Whitney U test was used for binary variables that did not show a normal distribution, and the one-way ANOVA test was used for multiple variables. Box-whisker plots were generated for the parameters that showed statistically significant differences as a result of the Mann-Whitney U and one-way ANOVA tests. The alpha level of statistical significance was accepted as $p \leqslant 0.05$.

RESULTS

Clinical and histopathological findings

64 patients included in this study. The clinicopathologic features of the cases are summarized in Table 1.

Table 1. Clinicopathologic features of triple negative breast cancer cases

		Mean±SD (Minimum-Maximum)	
Age		53.47±15.044 (28-84)	
Tumor Size		2.764±1.8635 (0,4-9)	
		n	**%**
Surgery Type	Lumpectomy	46	71.9
	Mastectomy	18	28.1
Laterality	Right	36	56.2
	Left	28	43.8
Localization	Retro areolar	3	4.7
	Lower outer quadrant	8	12.5
	Lower inner quadrant	5	7.8
	Upper outer quadrant	38	59.4
	Upper inner quadrant	10	15.6
Histologic Type	IBC, NST	49	76.5
	IMK	7	10.9
	IBC Medullary pattern	6	9.4
	ILK	1	1.6
	Asinic cell carcinoma	1	1.6
Histologic Grade	1	1	1.6
	2	21	32.8
	3	42	65.6
pT	1	35	54.7
	2	21	28.1
	3	7	10.9
	4	1	1.6
pN	0	36	56.3
	1	18	28.1
	2	7	10.9
	3	3	4.7

SD: Standard deviation, IBC: Invasive breast carcinoma, NST: No special type, IMK: Invasive micropapillary carcinoma, ILK: Invasive lobular carcinoma

At the time of diagnosis, 28 (43.8%) patients had lymph node metastasis. 40 (62.5%) patients had histopathologic lymphatic and vascular invasion. 23 (35.9%) patients had concomitant ductal carcinoma in situ (DCIS). 52 (81.3%) patients had a Ki67 index greater than 20%. 4 (6.3%) patients had tumors at surgical margins.

PD-L1 expression

Immunohistochemical PD-L1 staining was positive in 37 cases (57.8%) and negative in 27 cases (42.2%). The relationship of the cases with clinical parameters

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according to PD-L1 immunohistochemical staining is summarized in the Table 2. Distant metastasis was observed in 5 PD-L1 positive cases and DCIS in 11 cases. Lymphovascular invasion was observed in 26 of 37 PD-L1 positive cases (p=0.009).

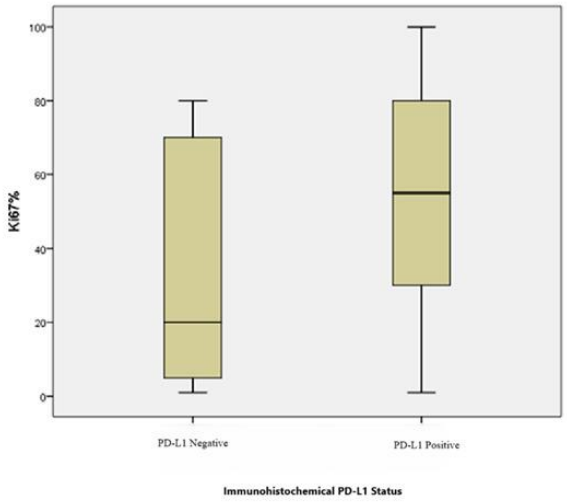

Figure 4. Association between immunohistochemical PD-L1 Status and Ki67 Proliferation index

In other words, there was a significant correlation between PD-L1 and lymphovascular invasion. In addition, the mean Ki67 of PD-L1 positive cases was 55.43, while the mean Ki67 of PD-L1 negative cases was 35.14 (p=0.009). A significant correlation between PD-L1 and Ki67 increase was also observed (Figure 4).

AR expression

Immunohistochemical AR staining was positive in 17 cases (%26.6) and negative in 47 cases (%73.4). The relationship of the cases with clinical parameters according to AR immunohistochemical staining is summarized in the Table 3. Lymphovascular invasion was detected in 10 (58.8%) AR positive cases (p=0.717), distant metastasis in 3 (17.6%) (p=0.623) and DCIS in 6 (35.3%) (p=0.949). The mean Ki67 of AR positive cases was 44.13±30.84, while that of negative cases was 42.85±31.39 (p=0.937). There was no significant relationship between AR and clinicopathological parameters.

DISCUSSION

Currently, breast cancer management and classification is based on histological grade, stage, metastasis status as well as molecular subtyping of the tumor. Molecular subtyping is performed by immunohistochemical Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor (HER2) and

Table 2. Association between PD-L1 positivity and clinicopathologic parameters

		Positive Mean±SD		Negative Mean±SD		p
Age		54.32±14.95		53.77±14.16		0.835
Tumor size		3.14±2.06		2.51±1.72		0.310
		n	**%**	**n**	**%**	
Surgery	Lumpectomy	24	64.8	22	81.5	0.7
	Mastectomy	13	35.2	5	18.5	
Localization	Retroareolar	1	2.7	2	7.4	0.947
	Lower quadrant	8	21.6	5	18.5	
	Upper quadrant	28	75.7	20	74.1	
Laterality	Right	20	54.1	16	59.2	0.526
	Left	17	45.9	11	40.8	
Histological type	IBC NST	29	78.4	20	74.1	0.727
	ILK	1	2.7	0	0	
	IMK	4	10.8	3	11.1	
	IBC medullary pattern	3	8.1	3	11.1	
	ACC	0	0	1	3.7	
Histologic Grade	1	1	2.7	0	0	0.589
	2	10	27	11	40.8	
	3	26	70.3	16	59.2	
pT	1	16	43.3	19	70.4	0.32
	2	15	40.5	6	22.2	
	3	5	13.5	2	7.4	
	4	1	2.7	0	0	
pN	0	20	54.1	16	59.2	0.64
	1	9	24.3	9	33.4	
	2	5	13.5	2	7.4	
	3	3	8.1	0	0	

SD: Standard deviation, IBC: Invasive breast carcinoma, NST: No special type, IMK: Invasive micropapillary carcinoma, ILK: Invasive lobular carcinoma, ACC: Acinic cell carcinoma

Ki67 proliferation index (8, 9). TNBC usually presents as of high-grade invasive carcinoma and has a higher rate of early recurrences, often with distant metastases and is associated with poorer prognosis. It is more common in younger premenopausal women (10). Menopause is an important risk factor for breast cancer and has different molecular characteristics. In one study, TNBCs accounted for the majority of cases under 30 years of age (9). Despite the progress about tumor biology, clinical outcomes for TBNC unfortunately remain unsatisfactory (10). In our study the youngest patient was 24 years old and the average age was about 53 years. The 6 molecular subtypes

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identified by Lehmann et al. according to gene expression profile show different clinical course and different responses to treatment (3). However, response to current target therapies is still poor and the systemic treatment option is cytotoxic drugs. It is necessary to find new markers to elucidate better treatment responses and drug resistance (11). Therefore, our study evaluates PD-L1 and AR immunohistochemical staining and provides new information for classification and targeted therapies in TNBCs, a heterogeneous group.

Evasion of antitumor immunity is a hallmark of cancer development and progression. Tumors use multiple mechanisms to evade recognition by the host immune system, including expression of the negative T-cell regulatory molecule PD-L1 (12). PD-L1 is a transmembrane protein expressed on both tumor-infiltrating lymphocytes and cancer cells. The binding of PD-L1 on tumor cells to PD-1 on T lymphocytes is one of the potential mechanisms for tumor escape from the immune system (13). Immune-checkpoint blockade therapies are being investigated and developed for a variety of tumor types, including breast cancer (2). PD-L1 positivity in breast cancer is mostly associated with triple negative subtype (14). Importantly increased PD-L1 expression on the surface of TNBC cells had functional consequences on T cells including decreasing their proliferation and increasing apoptosis (12).

Table 3. Association between AR positivity and clinicopathologic parameters

		Positive Mean±SD		Negative Mean±SD		p
Age		54.32±14.95		53.77±14.16		
Tumor size		3.14±2.06		2.51±1.72		
		n	**%**	**n**	**%**	
Surgery	Lumpectomy	11	64.8	35	74.5	0.447
	Mastectomy	6	35.2	12	25.5	
Localization	Retroareolar	1	5.9	2	4.3	0.126
	Lower quadrant	1	5.9	15	31.9	
	Upper quadrant	15	88.2	30	63.8	
Laterality	Right	13	76.5	23	48.9	0.072
	Left	4	23.5	24	51.1	
Histological type	IBC NST	15	88.2	34	72.3	0.202
	ILK	-		1	2.1	
	IMK	2	11.8	5	10.6	
	IBC medullary pattern	-		6	12.9	
	ACC	-		1	2.1	
Histologic Grade	1	1	5.9	-		0.413
	2	6	35.2	15	31.9	
	3	10	58.9	32	68.1	
pT	1	12	70.6	23	48.9	0.265
	2	3	17.6	18	38.2	
	3	1	5.9	6	12.9	
	4	1	5.9	-		
pN	0	11	64.8	25	53.2	0.723
	1	3	17.6	15	31.9	
	2	3	17.6	4	8.5	
	3	-		3	6.4	

SD: Standard deviation, IBC: Invasive breast carcinoma, NST: No special type, IMK: Invasive micropapillary carcinoma, ILK: Invasive lobular carcinoma, ACC: Acinic cell carcinoma

In a systematic analysis by Stovgaard et al. summarizing 37 studies with immunohistochemical PD-L1 application in breast cancers including different numbers of patients between 64-3916, positivity was found between 0-83%. (15). In our study PD-L1 expression was %57,8. This may be due to the size of the tumoral area evaluated in different studies, the lack of a standardized evaluation system and the use of different clones. Wimberly et al. showed that PD-L1 expression level can give 4-fold different results between different areas even in a breast cancer patient. Intratumoral heterogeneity has also been demonstrated in other organs. (14). Because of this clear heterogeneity, it is necessary to evaluate PD-L1 in resected material in blocks containing a large tumor area. In our study, the blocks with the most tumors among the resected specimens were used.

Immunohistochemical Ki67 is a proliferation marker and its application is essential especially in TNBCs as it provides information about prognosis and survival (11). In our study there was a significant correlation between PD-L1 positivity and Ki67 proliferation index (p=0.009). Many studies in the literature have found a positive correlation between PD-L1 immunohistochemical positivity and Ki67 proliferation index (6, 11, 16, 17). Lymphovascular invasion is the pathway of tumor spread, and it shows aggressive tumor behavior by causing tumors to differentiate between adjacent lymphatics and blood vessels (18). In our study there was also a significant association between PD-L1 expression and lymphovascular invasion (p=0.009). Various studies have investigated the relationship between PD-L1 and prognosis, but different results have been obtained. The prognostic value of PD-L1 is not clear (11, 15). In our study, as PD-L1 positivity increased, Ki67 proliferation index and lymphovascular invasion increased. This suggests that PD-L1 positivity has a poor prognostic value. Therefore, the targeted treatment regimen for this PD-L1-positive subset of TNBC is even more important.

Another promising and potential marker in TNBCs is the AR (11). AR is a type 1 nuclear receptor and acts as an intranuclear transcription factor responsible for gene expression. It is present in numerous tissues in both sexes,

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including bone, liver, brain, and breast (18). While other nuclear steroid hormone receptors, ER and PR, are widely used, the biological role of AR is still under investigation (19). The expression of the antigen AR has been documented in approximately 70–90% of breast cancers. Furthermore, the expression of this antigen varies between 10% and 50% in TNBC (20). AR is thought to have an inhibitory effect in luminal subtype breast cancer but stimulates tumor growth in TNBC. (21). Although there is evidence for AR in breast cancer pathogenesis, its role in TNBC is not clear (19). Although AR expression can be expressed in all molecular subtypes, it is mainly characteristic of the LAR subtype. It is expressed in 10-90% of TNBCs (11). In studies using a cutoff of 10% for AR positivity, this positivity was found between 17.1-38% (22-26). In this study we used a cutoff of 10% and found %26,6 of TNBCs expressed AR, which was in line with previous reports. The absence of a universally applicable principle is attributable to the considerable heterogeneity observed in the results of diverse studies, thereby giving rise to an ambiguous relationship between AR and TNBC (21).

AR is expressed in two types of mammary epithelial cells. One is luminal epithelial cells and the other is metaplastic apocrine cells. In the latter, the cells are mostly components of fibrocystic disease and most of them are ER and PR negative. In the former it commonly expressed with ER, PR. Although tumors arising from these different origins have common AR expression, their morphology and treatment response are likely to be different (19). According to the literature, AR positivity in several studies has been associated with less aggressive biological behavior, such as lower clinical stage, lower histologic grade, lower mitosis count and lymphovascular invasion (19, 25, 27, 28). Numerous other studies have found significant associations between AR expression and poor prognostic clinicopathological parameters such as large tumor diameter, high tumor grade, high clinical stage, high number of lymph node metastases (27, 29-32). However, the results from our study showed no statistical significance between clinical or pathological parameters and AR status. These include the histological subtype, laterality, tumor localization, tumor grade, tumor size, tumor stage, nodal status, Ki-67 score and lymphovascular invasion. The differences seen in the results are clearly related to the different methods used. These differences are likely due to the cutoff used, the number of patients, and the histopathologic scoring of AR. However, many studies in the literature have shown that there is no association between clinical and pathologic parameters and AR, which is consistent with our study (11, 18, 21, 33).

In a study of 125 patients, immunohistochemistry for AR and PD-L1 in TNBC was performed and a significant relationship was found between them. High tumor and nuclear grade was observed in cases where they were simultaneously expressed, while in cases where they were negative, an association with metastasis was observed (11). In another study of 197 patients, PD-L1 was found to be 3 times more positive in AR-positive patients (13). In our study, no significant correlation was found between AR and PD-L1. This may be related to the small number of patients compared to the above mentioned studies.

CONCLUSION

Response to current target therapies in TNBC is poor and the systemic treatment option is cytotoxic drugs. Molecular heterogeneity has led to the lack of FDA-approved targeted therapies for TNBC. It is necessary to find new markers to elucidate better treatment responses and drug resistance. Therefore, our study provides new information for targeted therapies by evaluating PD-L1 and AR immunohistochemical staining. Immune-checkpoint blockade therapies are being investigated and developed for a variety of tumor types, including breast cancer. PD-L1 positivity in breast cancer is mostly associated with triple negative subtype. Our study highlighted that due to intratumoral heterogeneity, PD-L1 should be evaluated from blocks containing large tumor areas. There was a significant correlation PD-L1 positivity with Ki67 proliferation index (p=0.009), and lymphovascular invasion (p=0.009). PD-L1 positive cases appear to be associated with a poor prognosis and thus associated with lower overall survival. However, this disadvantage can be overcome with monoclonal antibody therapies directed against PD-L1. AR is thought to have an inhibitory effect in luminal subtype breast cancer but stimulates tumor growth in TNBC. Many studies in the literature have shown that there is no association between clinical and pathologic parameters and AR, which is consistent with our study. However, there are conflicting studies and the relationship between AR and TNBC needs to be clarified. In TNBCs, PD-L1 and AR are two important markers that will determine the appropriate group for treatment and prognosis, and standardization in studies and evaluation in larger cohorts is essential.

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None

Authorship contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis

were performed by Büşra Ekinci. The first draft of the manuscript was written by Büşra Ekinci. Finding and designing the topic of the project, statistics and control was done by Nesibe Kahraman Çetin, İbrahim Halil Erdoğdu, İbrahim Meteoğlu. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availibity statement

The data that support the findings of this study are available on request from the corresponding author.

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

Ethics

This study was approved by the Ethics Committee for Noninvasive Clinical Trials of Aydın Adnan Menderes University. Approval number 2018/1343.

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