Clinical Significance of Androgen Receptor (Histo-score) in Non-metastatic, Hormonal Positive Her2-neu Negative Breast Cancer

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Abstract

Background & Objectives:

Androgen receptor (AR) is recently one of the most studied biomarkers in breast cancer, having a role in the genesis and development of breast cancer**.** The current study aims to detect the expression of AR in one hundred females, stage IIB and stage III, hormonal positive Her-2neu negative breast cancer patients and to relate its expression with overall survival (OS) and disease free survival (DFS) using histoscore (median H score).

Methods:

Histological tissue from breast tumors was examined by immunohistochemistry for AR expression and median H score was calculated.

Results:

Of 100 female with hormonal positive, Her2neu negative breast cancer cases identified, 19 cases (19%) were AR negative and 81 cases (81%) were positive AR. Using median H score, it was found that patients with earlier stage, lower histological grade and negativity for lymphovascular invasion had higher median H score (>120) reaching statistical significance.

Conclusion:

Our study revealed no statistical significant association between AR higher expression(H score>120) and OS or DFS compared to AR lower expression (median H score≤120). However, work on this special group (stage IIB and stage III, hormonal positive Her-2neu negative) using larger number of patient is recommended.

Keywords: androgen receptor, breast cancer, median histoscore & prognosis and outcome.

Introduction:

Androgen receptor (AR) is a steroid hormone nuclear receptor frequently expressed in breast cancer. The contribution of AR signaling in breast cancer carcinogenesis and progression and its clinical relevance as a prognostic factor and therapeutic target still unknown. [1]

Androgen Receptor (AR) is rising as an important marker in the pathogenesis of breast carcinoma. Studies have associated AR with better outcome in ER positive tumors, but this effect is not seen in ER negative tumors [2]. In the presence of estrogen receptor α (ER- alpha), AR has antagonizing effect with the ERα- induced effects, but in the absence of estrogens, AR may act as an ERα mimic, stimulating tumor formation. [3]

Studies indicated that AR has both inhibitory and stimulatory effects on different breast cancer cell lines' growth, which is considered to be modulated by the presence or absence of estrogen receptor (ER) expression.[4] Many studies also demonstrated conflicting results, reporting an association between androgen serum level and risk for development of breast cancer or no association at all. [5] Androgen could act as anti-estrogen in premenopausal women, whereas it acts as an estrogen agonist in postmenopausal women. [6]

The current study was therefore designed to evaluate AR expression by means of immunohistochemistry in non- metastatic hormonal positive and Her-2neu negative breast cancer cases.

Methods:

Study design:

This prospective study included 100 female patients; stage IIB and III, hormonal positive Her-2/neu negative cases recorded at south Egypt cancer institute from January 2017 to December 2019 and relate AR expression to clinical and pathological reports, overall survival (OS) and disease free survival (DFS).

Preparation of slides and staining:

Immunohistochemical staining was performed on 3-

µm tissue sections from the original paraffin blocks which were first deparaffinized and subsequently immersed in xylene and then rehydrated in solutions of decreasing grades of alcohol. Then sections were washed with phosphate-buffered saline (PBS) and heated in an 830W microwave oven for at least 15 minutes in 10mmol/L sodium citrate buffer (PH 6.0) for antigen retrieval. Then slides were submerged in peroxidase blocking solution (ready to use) for 10minutes aiming to inhibit activation of endogenous peroxidases. Then slides were washed with washing buffer in order to remove excess peroxidase blocking solutions. After that, slides were incubated with primary antibodies (mouse monoclonal, androgen receptor (YPA1811 1:300 dilution). In the negative control, the primary antibody was substituted by phosphate buffered saline. Rabbit anti-mouse horseradish peroxidase-conjugated secondary antibody was added and followed by incubation for about 20 minutes at room temperature. The color was developed by using diaminobenzidine (DAB). Then slides were heavily washed with PBS after each step. Finally, they were counter stained using Mayer's hematoxylin.

The immune staining was scored by a pathologist. AR positivity is defined as nuclear expression. We use 2 scoring system for androgen receptors. First, we chose cut off values >10% to assess AR positivity.[7] Second is median histoscore (H-Score), the score was given as the percentage of the immunopositive nuclei (0–100%) multiplied by a value corresponding to level of intensity (0 none, 1 weak, 2 moderate, and 3 strong). The score result ranged between 0 (no staining in the tumor) and 300. [8]

Statistics:

The collected data were tabulated, and statistically analyzed using Statistical Package for the Social Sciences (SPSS) program, software version 21. Descriptive statistics were done for analysis of quantitative data; as minimum and maximum of the range as well as mean±SD (standard deviation) for evaluating quantitative parametric data. The analyses were done for quantitative variables by using independent t-test. In qualitative data, analyses for independent variables were done by using Chi-square test for differences between proportions and Fisher's exact test for variables with small expected numbers. The level of significance was considered significant at $p \leq 0.05$, otherwise is non-significant.

Results:

Patients' and Tumor Characteristics

In the 100 studied cases, the age ranged between 22-75 years with a mean age of 50.09±11.21 years. The studied cases consisted of seventy-six patients premenopausal while twenty-four patients were postmenopausal. Forty patients were left sided breast cancer while sixty patients were right sided. Seventeen cases underwent breast conservative surgery and eighty-three cases underwent modified radical mastectomy (MRM). The mean follow-up duration for overall survival and disease-free survival was 33.69 ± 10.62 months (median, 33 months; range, 9-59 months), (Table 1). In the studied cases, the size of tumor was more than 2 cm in 90% of patients and the predominant pathologic type of tumor was invasive ductal carcinoma (86%). Most patients had lymph node positive (80%). Majority of patients were negative for lymph vascular invasion (55%). For perineural invasion, 13% was positive while 87% was negative.

Biomarker status

Eighty-three patients (83%) were estrogen receptors (ER) positive while seventeen patients (17%) were negative. Seventy-nine patients (79%) were progesterone receptors (PR) positive and twenty-one (21%) patients were negative.

AR expression was identified as number of nuclear staining and according to cut off point choosen, cases with >10% immunoreactivity were positive for AR while cases with ≤10% were negative , AR positivity was detected in 81 cases (81%) but 19 cases (19%) were AR negative Table (2). Regarding histoscore of androgen receptor, we choose median H score 120 with a median H score >120 for high AR immunoreativity while median H score ≤120 for low AR immunoreactivity. Table (3)

Association between AR expression with clinic-pathological data

Using chi-square test, it was found that (46 cases, 56.8%) with early stage (stage IIB) breast cancer have higher AR expression than patients with advanced stage (stage III) (35 cases, 43.2%) (p value<0.005). Also, high AR expression showed statistically significant association with cases that did not have lymphovascular invasion (p value <0.005). No statistical significant association was found between AR and other clinicopathological features (Table 4).

Considering correlation between H score of AR and demographic, clinical and pathological characteristics, it was found that patients with early stage, negativity for lymphovascular invasion and lower grade had strong immunoreactivity for AR by using median H score and they were statistically significant. (Table 5)

Outcome according to AR status

Our study demonstrates that 29 out of 100 developed metastases to different sites. Twenty-seven out of 29 metastatic cases were AR positive. Nine out of 27 of AR positive cases developed visceral metastasis while 18/27 developed non visceral metastasis. There is significant correlation between development of metastasis and AR status (p value 0.049). Table 4

Survival Analysis According to AR Status

This study showed that the high AR expression (median H score >120) had no significant association with overall survival or disease-free survival when compared with the low AR expression group (median H score ≤120). (Tables 6,7) (Figures 1,2)

Table (1): Clinicopathological characteristics of the studied 100 patients with breast cancer

Variable name		N = 100 N	(%)
Age (years), mean ± SD		50.09±11.21	
Median (range)		49.5 (22-75)	
Menopausal status	**Premenpausal**	76	(76.0)
	Postmenpausal	24	(24.0)
Surgery	**MRM***	83	(83.0)
	BCS**	17	(17.0)
Stage	**IIB**	49	(49.0)
	IIIA	23	(23.0)
	IIIB	12	(12.0)
	IIIC	16	(16.0)
Pathology	**IDC*****	86	(86.0)
	ILC****	12	(12.0)
	Medullary carcinoma	1	(1.0)
	Mucoid carcinoma	1	(1.0)
Tumor size	**T1**	7	(7.0)
	T2	55	(55.0)
	T3	20	(20.0)
	T4	15	(15.0)
	Tx	3	(3.0)
Lymph node Metastasis	**N0**	14	(14.0)
	N1	36	(36.0)
	N2	27	(27.0)
	N3	17	(17.0)
	Nx	6	(6.0)
LVI***	**Negative**	55	(55.0)
	Positive	45	(45.0)
Margin	**Negative**	94	(94.0)
	Positive	6	(6.0)
Grade	**Grade II**	87	(87.0)
	Grade III	13	(13.0)
Perineural invasion	**No**	87	(87.0)
	Yes	13	(13.0)

MRM=modified radical mastectomy, BCS= breast conserving surgery, IDC=invasive ductal carcinoma, ILC=invasive lobular carcinoma, LVI=lymphovascular invasion, SD = standard deviation

Table (2): Hormonal characteristics of the studied 100 patients with breast cancer

Variable name		N = 100 N	(%)
AR	**Negative**	19	(19.0)
	Positive	81	(81.0)
ER	**Negative**	6	(6.0)
	Positive	94	(94.0)
PR	**Negative**	18	(18.0)
	Positive	82	(82.0)

AR, Androgen receptor; ER, Estrogen receptor and PR, Progesterone receptor.

Table (3): Correlations of expression of AR (H score) and hormonal status of the studied participants

Variable name		AR-positive cases H-score ≤120 (n=48) N	(%)	H-score >120 (n=33) N	(%)	p-value
ER	Negative	3	(6.3)	2	(6.1)	1
	Positive	45	(93.8)	31	(93.9)	
PR	Negative	11	(22.9)	6	(18.2)	0.607
	Positive	37	(77.1)	27	(81.8)	

Data are presented in the form of number (percentage), * Significance defined by $p < 0.05$.

Table (4): Clinico-pathological details according to tumor AR expression in 100 patientswith breast cancer

Variable name		Androgen receptor Negative (n=19) N	(%)	Positive (n=81) N	(%)	p-value
Age (years), Mean ± SD		49.26 ± 11.89		50.28 ± 11.11		0.723
Median (range)		48 (30 – 66)		50 (22 – 75)		
Menopausal Status	**Pre-menopausal**	15	(78.9)	61	(75.3)	1
	Post-menopausal	4	(21.1)	20	(24.7)	
Surgery	**BCS**	4	(21.1)	13	(16.0)	0.734
	MRM	15	(78.9)	68	(84.0)	
Stage	**Early**	3	(15.8)	46	(56.8)	**0.001***
	Advanced	16	(84.2)	35	(43.2)	
Tumor size	**Tx**	1	(5.3)	2	(2.5)	
	≤ 2 cm	0	(0.0)	7	(8.6)	0.292
	> 2 cm	18	(94.7)	72	(88.9)	
Lymph	**No node**	1	(5.3)	13	(16.0)	0.296
	Node positive	18	(94.7)	68	(84.0)	
LVI	**Negative**	5	(26.3)	50	(61.7)	**0.005***
	Positive	14	(73.7)	31	(38.3)	
Margin	**Negative**	19	(100.0)	75	(92.6)	0.592
	Positive	0	(0.0)	6	(7.4)	
Grade	**Grade II**	16	(84.2)	71	(87.7)	0.708
	Grade III	3	(15.8)	10	(12.3)	
Peri-neural invasion	**No**	14	(73.7)	73	(90.1)	0.068
	Yes	5	(26.3)	8	(9.9)	
ER	**Negative**	1	(5.3)	5	(6.2)	1
	Positive	18	(94.7)	76	(93.8)	
PR	**Negative**	1	(5.3)	17	(21.0)	0.183
	Positive	18	(94.7)	64	(79.0)	
Outcome	**No metastasis**	17	(23.9)	54	(76.1)	**0.049***
	Metastatic	2	(6.9)	27	(93.1)	
Type of metastasis	**Visceral**	0	(0.0)	9	(33.3)	1
	Non viscera	2	(100.0)	18	(66.7)	

MRM=modified radical mastectomy, BCS= breast conserving surgery, IDC=invasive ductal carcinoma, ILC=invasive lobular carcinoma, LVI=lymphovascular invasion, Tx =tumor size unknown, ER, Estrogen receptor and PR, Progesterone receptor, SD= standard deviation

Table (5): Correlations of expression of AR (H score) and clinic-pathological details of the studied participants

Variable name		AR-positive cases				p value
		H-score ≤120 (n=48)		H-score >120 (n=33)		
		N	(%)	N	(%)	
Age groups	**< 50**	25	(52.1)	15	(45.5)	
	≥ 50	23	(47.9)	18	(54.5)	0.558
Menopausal status	**Premenopausal**	35	(72.9)	26	(78.8)	
	Postmenopausal	13	(27.1)	7	(21.2)	0.547
Surgery	**BCS**	8	(16.7)	5	(15.2)	
	MRM	40	(83.3)	28	(84.8)	0.855
Stage	**Early**	22	(45.8)	24	(72.7)	
	Advanced	26	(54.2)	9	(27.3)	0.016*
Tumor size	**Tx**	2	(4.2)	0	(0.0)	
	<=2 cm	3	(6.3)	4	(12.1)	0.430
	> 2 cm	43	(89.6)	29	(87.9)	
Lymph	**No node**	10	(20.8)	3	(9.1)	
	Node positive	38	(79.2)	30	(90.9)	0.157
LVI	**Negative**	25	(52.1)	25	(75.8)	
	Positive	23	(47.9)	8	(24.2)	0.031*
Margin	**Negative**	45	(93.8)	30	(90.9)	
	Positive	3	(6.3)	3	(9.1)	0.683
Grade	**Grade II**	39	(81.3)	32	(97.0)	
	Grade III	9	(18.8)	1	(3.0)	0.042*
Perineural invasion	**No**	42	(87.5)	31	(93.9)	
	Yes	6	(12.5)	2	(6.1)	0.462

Data are presented in the form of number (percentage), * Significance defined by $p < 0.05$. MRM=modified radical mastectomy, BCS= breast conserving surgery, IDC=invasive ductal carcinoma, ILC=invasive lobular carcinoma, LVI=lymphovascular invasion, Tx =tumor size unknown, ER, Estrogen receptor and PR, Progesterone receptor.

Table (6): Disease free survival according to AR (H score) result

DFS	Estimate ± SE		P-value
	≤ 120	> 120	
At 1 year	83.3±5.4%	90.9±5.0%	
At 2 year	68.8±6.7%	78.2±7.3%	0.213
At 3 year	60.2±8.2%	70.7±8.3%	

SE =standard Error

Table (7): Overall survival according to AR (H score) result

OS	Estimate ± SE		P-value
	≤ 120	> 120	
At 1 year	100.0±2.1%	100.0±0.0%	
At 2 year	95.5±3.1%	No cases	
At 3 year	91.7±4.8%	No cases	0.136
At 4 year	91.7±4.8%	No cases	

SE =standard Error

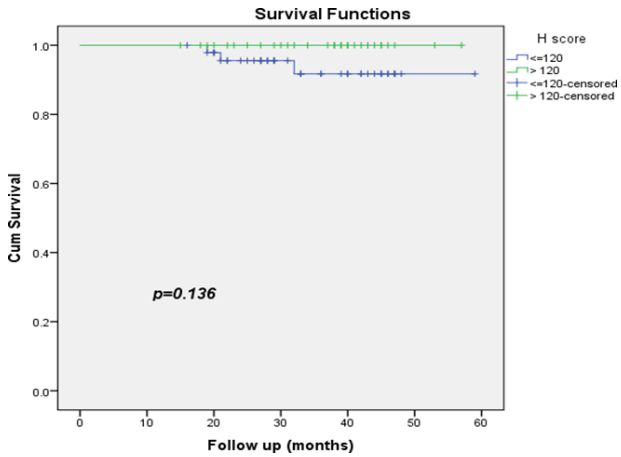

Figure (1): Overall survival according to AR (H score) result

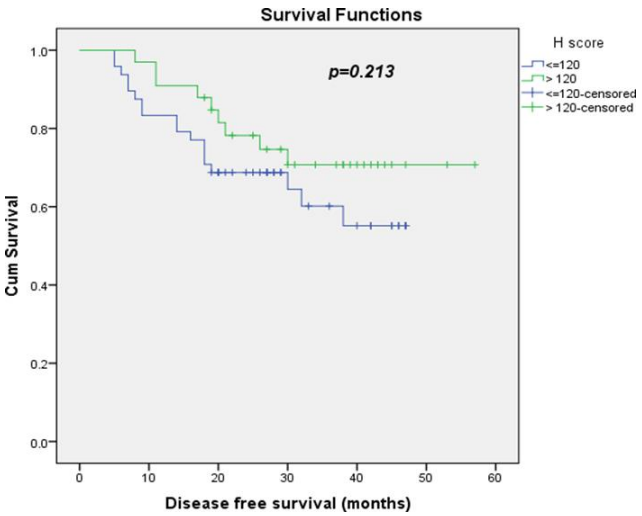

Figure (2): Disease free survival according to AR (H score) result

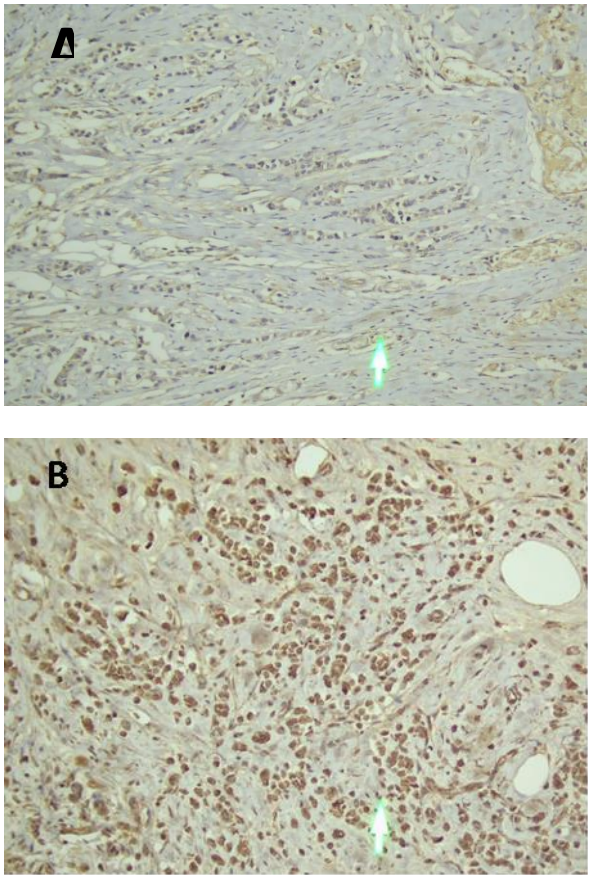

Figure (3): Immunohistochemical staining of androgen receptor: A) Negative staining, B) Positive nuclear staining

Discussion:

In the current study, AR nuclear immunostaining was detected in 81 cases (81%) out of the one hundred studied cases using >10% as a cut off value for androgen receptor positivity. Nineteen cases (19%) were AR negative. The definition of AR status particularly has been highly inconsistent. The ASCO mentioned the cutoff value for positivity for hormone receptor to be 1% of stained cells instead of 10%. [9] Many studies defined AR positivity according to the proportion score with a cut-off value of 10% using immunohistochemistry. [10,11]. Accordingly, cut off value of 10% was chosen in our study to be consistent with previous reports .

For scoring of AR positive cases, we used histoscore (H-score) with a median =120. Niemeier et al., (2010) [12] also used H-score for scoring of AR immunohistochemical expression, having a median score =150. Cohen et al., (2012) [13] mentioned that the H-score details the percentage of cells showing none, weak, moderate, or strong staining; thus giving a wide dynamic range (0–300). Hence, H-score can provide clinicians with more informative details regarding prognosis. That is why some institutes prefer to use H Score. On other side, Brouckaert et al., (2013) [14] mentioned that Allred score is the most established one and that a good cutoff to predict benefit from treatment targeting hormones is an Allred score of ≥3. In Allred score, intensity and proportion score were used consisting of six subgroups (0, no staining; 1, <1%; 2, between 1% -10%; 3, between 11% - 33%; 4, between 34% -66%; and 5, between 67%-100% of the cells staining). A total score was obtained by adding the proportion score and intensity score. The total score was calculated and given score from 0 to 8. [14]

In the current study, the median age of our studied sample was 49.5 ± 11.2 years with an age ranges from 22–75 years. The mean duration for follow-up for overall survival and disease free survival was 33.9± 11.2 months. Patients had relatively large tumor size at presentation (more than 2 cm in 90% of patients), predominant pathological subtype was invasive ductal carcinoma (86%), histological grade II (87%). More than half of patients (51%) were presented with stage III. Most of the studied sample had positive axillary lymph nodes.

In agreement to our study, Hwang et al., (2020) [7] postulated that the mean age was 53.3±12.3 years (median, 51.0 years; range, 25–87 years), more than half of patients had tumor size >2cm, 24% was stage II while 24.1 % for stage III and 25.1% for stage I. On contrary to our study, Gonzalez et al., (2008) [15] demonstrated that half of patients had an age ≤58years and 56/111 had an age above 58years. Most of patients (82/111) were postmenopausal, nearly half of patients had tumor size ≤2cm and more than half of patients (59%) were node negative. This difference may be explained by specific staging group we used and smaller size of the study sample.

The positive cases were scored by H-score with a median=120, and a range of (10-300). AR expression was higher in cases with earlier stage, lower histological grade and negativity for lymphovascular invasion and they were statistically significant (p value 0.016, 0.031, 0.042, respectively). Abdelaal et al., (2020) [16] showed that there was no significant difference between AR positive and AR negative cases regarding tumor size, tumor grade, HER-2 status, and lymph node status. Also, Yu et al., (2011) [17] showed that AR immunohistochemical expression had no relation to the parameters, such as tumor size, lymph node status, histological grade, and HER-2 status. On the contrary, Park et al. (2010) [3] mentioned that, AR showed significant immunohistochemical expression in patients with smaller tumor size ($p = 0.035$) and lower histologic grade ($p < 0.001$); the difference may be attributed to the different number of cases and different scoring system (Allred score) used by them.

Considering association between AR expression detected by median H score and hormonal status, we concluded that there is no significant association between high AR immunoreactivity (median H score >120) with the ER & PR status. On other side, Yu et al., (2011) [17] concluded that the AR expression was closely associated with the ER ($p < 0.001$) and the PR ($p = 0.035$) .AR-positive cases were found in 83.8%, 75.6%. 55.8%, and 39.0% for luminal A, luminal B, HER2 overexpressing, and basal breast cancer subtypes,

respectively. Vera-Badillo et al., (2014) [18] illustrated that AR-positive tumors were 74.8% and 31.8% in ER-positive and ER-negative tumors, respectively. This could be explained by competition between AR and ER for attaching to estrogen response elements (EREs) on specific genes. So the binding of AR to EREs reduces the estrogen proliferative action, thus responsible for anti-proliferative effects. On other side, ER can bind to androgen response elements (AREs), inducing the opposite effect. [6]

As regard survival, our study showed that the high AR expression group had insignificant association with overall survival or disease free survival when compared with the low AR expression group. Previous studies have reported consistent and inconsistent results. Agrawal et al., (2016) [19] reported that AR expression was not an independent prognostic factor for 10-year overall survival. Elebro et al., (2015) [20] showed that positive AR status was a favorable prognostic marker for disease free survival ($p = 0.025$). These differences could be explained by larger tumor size and different scoring system used by other studies.

On other side, Zhang et al., (2016) [21] revealed that a high expression of AR in breast cancer patients was associated with shorter overall survival.

Conclusion:

Our study revealed no statistical significant association between AR expression detected by median H score and OS or DFS. We recommend further research work on AR in this special histological type of hormonal positive Her2neu negative breast carcinoma; using larger sample size with accurate definition of AR immunoreactivity. This may give more chance to delineate whether those tumors can be amenable to future AR target therapy.

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