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A Study of Androgen Receptor Expression in Triple Negative Breast Cancer

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Abstract

Background: Breast cancer, the most common malignancy among women, is the second leading cause of death from cancer among women with deaths, accounting for 14% of all deaths from cancer among women. To study prevalence and prognostic importance of AR expression in TNBC. **Martial and Methods**: The study was performed at Nizam's Institute of Medical Sciences Hyderabad from January 2020 to July 2021. Retrospective and prospective observational study was performed on 56 patients with TNBC were included. All patients underwent immunohistochemistry study for expression of AR. Based on result, patients were divided into 2 groups, AR +ve TNBC and AR-ve TNBC. **Results**: Prevalence of AR +ve in TNBC patients was 41%. Mean age at the time of diagnosis for androgen receptor +ve TNBC is 53.1 yr. in our study, DCIS expression was noted only in AR +ve group. AR expression was not associated with stage (p= 0.09), grade (p= 0.07), size of tumor (p=0.27), nodal status (p= 0.08), age at diagnosis (p= 0.59) LVI and PNI (p> 0.05) and menopausal status (p=0.3). **Conclusion**: A substantial portion of TNBC is AR +ve (41%) AR expression was noted more commonly in postmenopausal women. AR expression was not associated with stage, age at diagnosis, histological grade, size of tumor, lymph node involvement, menopausal status, LVI and PNI.

Keywords: AR expression, breast cancer, immunohistochemistry, menopausal status, TNBC.

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Introduction

Breast cancer is the most common malignancy among women, estimated to develop in women in world. Furthermore, it is the second leading cause of death from cancer among women with deaths, accounting for 14% of all deaths from cancer among women in 2014.[1]
There is substantial interest in identification of novel markers that could be used as prognostic or predictive markers and therapeutic targets. Expression of estrogen receptor (ER), progesterone receptor (PR) and Human Epithelial Growth Factor Receptor 2 (Her2) as

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predictive and/or prognostic markers has been well established in multiple studies and has led to a major shift in treatment approach from nonspecific chemotherapy to more targeted treatments reducing the undesirable systemic side effects of chemotherapy.[2-3]

These targeted approaches have improved prognosis and outcome among patients with ER, PR and/or HER2 positive breast carcinomas. Patients with triple negative breast cancer (TNBC) accounting for approximately 10% to 24% of all breast cancers,[4,5] are excluded from the benefits of such targeted therapies.[6] Recently, there has been substantial interest in identifying novel therapeutic options for TNBC, the role of androgens and androgen receptor (AR) as a potential multifaceted biomarker. Available studies have provided divergent opinions on the role of androgens in TNBC and correlation of AR expression with prognosis, clinical outcome and chemosensitivity in various settings.[6,7] Frequently co-expressed with ER, PR and/or Her2, AR is the most commonly expressed receptor among all types of breast cancer with a frequency of 6.6-75% among TNBC cases.[7]

Material and Methods

A retrospective and prospective observational study at Nizam's Institute of Medical Sciences from January 2020 to July 2021 in patient with triple negative breast cancer study group.

Inclusion Criterion

1. Patient with invasive ductal breast cancer with ER, PR and HER-2 neu receptor negativity on tissue diagnosis.

Exclusion criterion

1. Patients with pure intraepithelial neoplasias (in situ carcinomas).
2. Patient who received chemotherapy and or radiotherapy before the tissue dignosis of ER, PR and Her-2 neu.

Sample Size

Calculating the sample size of prevalence study: AR is the most commonly expressed receptor among all types of breast cancers, with a frequency of 6.6 to 75% in TNBC cases.[7] So we will consider mean frequency of 40% therefore p value in our study is 0.4 The following formula is used:

$$n = \frac{Z^2 \ \ p(1-p)}{d^2}$$

Where n = sample size

Z = statistic for a level of confidence is 95%

P = expected prevalence in our study

d = margin of error

Based on our institute previous data keeping confidence level of 95 % and margin of error 7.5 % the sample size is calculated as 163. Informed written consent of all patients will be taken before being made part of the study. A clearance from the Institute's ethical committee will be sought. The patient presenting with triple negative breast cancer (TNBC) as well as tissue blocks of previously operated TNBC patients will be retrieved to undergo IHC for AR receptor expression. Pure intraepithelial neoplasias (in situ carcinomas) will be excluded. For immunohistochemical and FISH analysis, 4-micron thick serial tissue sections prepared from formalin-fixed, paraffin embedded blocks will be used. In addition to immunohistochemical assessment of HER2, FISH will be performed on selected cases. The thresholds suggested by the 2011 ASCO/CAP guidelines for ER/PR and the 2007 ASCO/CAP guidelines for HER2 interpretation. ER (estrogen receptor) and PR (progesterone receptor) assays were considered positive if at least 1% of tumor cells' nuclei show positivity regardless of intensity (1+ to 3+). We will apply the same approach for androgen receptor (AR) and considered at least one percent nuclear staining of any intensity (1+ to 3+) as a positive AR assay. For immunohistochemical (IHC) assessment of HER2, the results were semi-quantitatively

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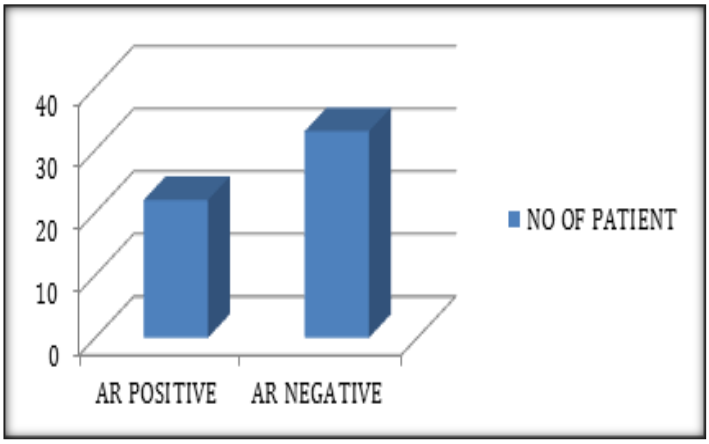
scored on a scale of 0 (no staining or faint/weak membrane staining in ≤10% of tumor cells), 1+ (faint partial membrane staining detected in >10% of invasive tumor cells), 2+ (weak to moderate complete membrane staining in >10% of invasive tumor cells) and 3+ (uniform, intense membrane staining in >30% of invasive tumor cells). Scores of 0 and 1+ are considered negative, 2+ is indeterminate, and 3+ is positive. A fluorescent in situ hybridization (FISH) ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2 was considered positive; a ratio of 1.8 to 2.2 was considered indeterminate and <1.8 was considered negative.

Results

This study included 56 female patients having invasive ductal carcinoma with are negative for ER, PR and Her 2 neu receptor expression.

Table 1: Androgen receptor status in triple negative breast cancer (TNBC)

AR status	No of patients	Percentage
AR positive	23	41%
AR negative	33	59%



In our study we found out that AR positivity is seen in 23/56 (41%) of patients and AR negativity is seen in 33/56(59%).

Table 2: Age distribution

Age in years	No of AR positive patients	No of AR negative patients
< 45	8 (35%)	14(42%)
> 45	15(65%)	19(58%)

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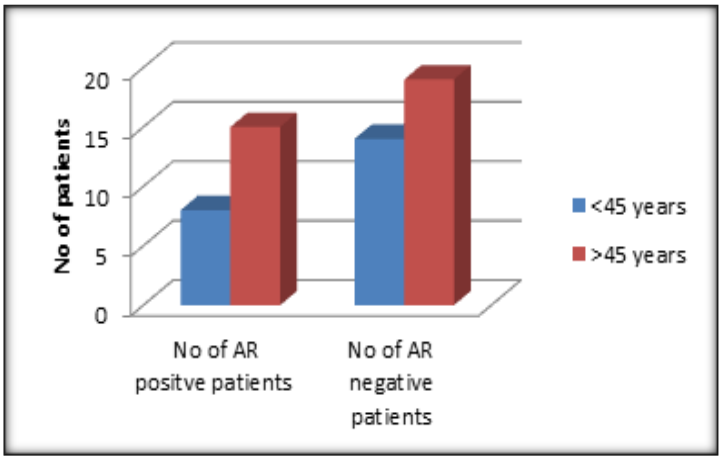
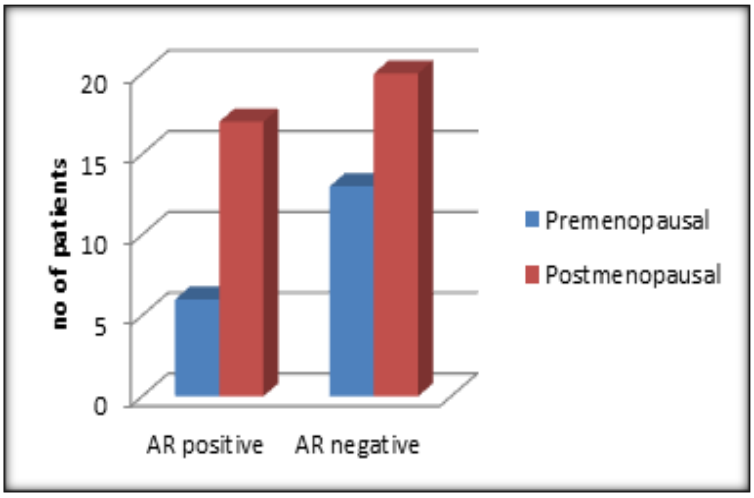


Both the groups compared using Fisher's exact test, p = 0.5919 (not significant, NS).

Table 3: Menopausal status

Menopausal status	No of AR positive patients	No of AR negative patients
Pre-menopausal	6(26%)	13(39%)
Post-menopausal	17(74%)	20(61%)



In our study, we found out 22% of females was premenopausal & 78% were postmenopausal in AR positive group (p < 0.006, which is significant). In AR negative group, 39% were premenopausal and 61% were postmenopausal. (p <0.2228, NS).
Menopausal status is compared between AR positive and AR negative group which is found to be non-significant (z =0.3007).

Table 4: Tumour 'T' stage distribution in AR positive and negative TNBC

T stage	No of AR positive patients	No of AR negative patients
T 1	1(4%)	7(21%)
T 2	12(53%)	17(52%)
T 3	7(30%)	7(21%)
T 4	3(13%)	2(6%)

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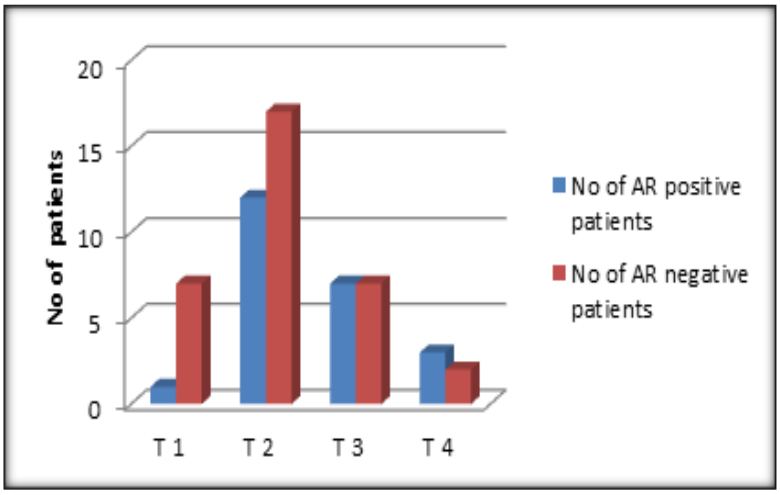
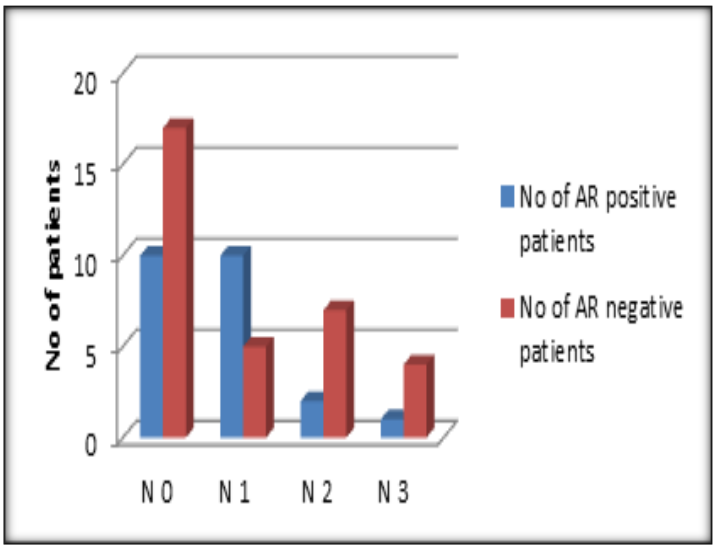


T stage is compared between AR positive and AR negatine and we found that there is no statistical significance between these two groups (p=0.27238).

Table 5: Lymph Nodal 'N' stage in AR positive and AR negative patients

N stage	No of AR positive patients	No of AR negative patients
N 0	10(44%)	17(52%)
N 1	10(44%)	5(15%)
N 2	2(8%)	7(21%)
N 3	1(4%)	4(12%)



N stage is compared between AR positive and AR negative and we found that there is no statistical significance between these two groups (p=0.09045).

Table 6: Histological grade

Histological grade	No of AR positive patients	No of AR negative patients
Grade I	1(4%)	8(24%)
Grade II	14(61%)	12(36%)
Grade III	8(35%)	13(40%)

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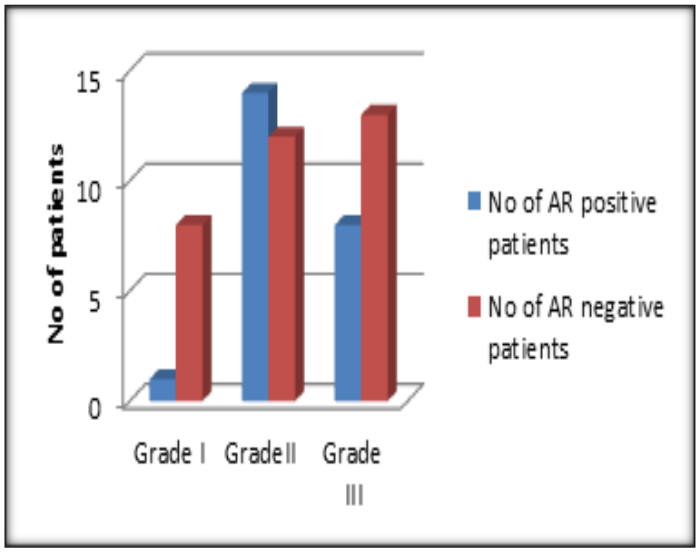
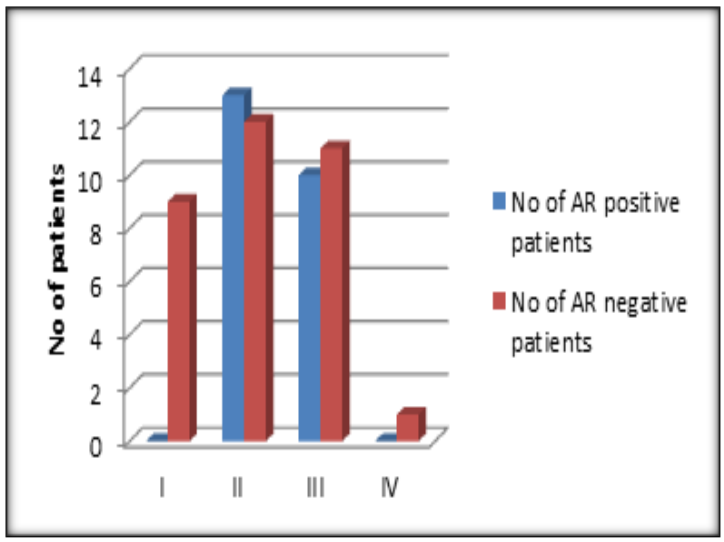


Histological grade is compared between AR positive and AR negatine and we found that there is no statistical significance between these two groups (p=0.07548).

Table 7: pTNM stage

TNM stage	No of AR positive patients	No of AR negative patients
Stage I	0(0%)	8(24%)
Stage II	13(56%)	12(36%)
Stage III	10(44%)	12(36%)
Stage IV	0(0%)	1(4%)



In our study most of the AR positive cases belongs to stage II and III (90%), whereas AR negative cases to stage I and II (60%). We have reported only one stage IV case (T2N2aM1) in AR negative group with solitary bone metastasis in L -1 vertebra.

Table 8: Duct cell carcinoma in situ (DCIS) component in AR positive and AR negative TNBC

	No of AR positive patients	No of AR negative patients
DCIS positive	7(30%)	0(0%)
DCIS negative	16(70%)	33(100%)

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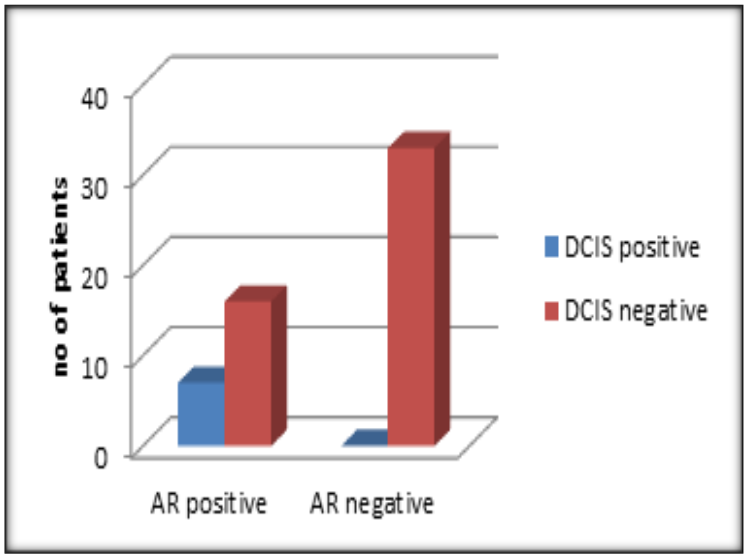
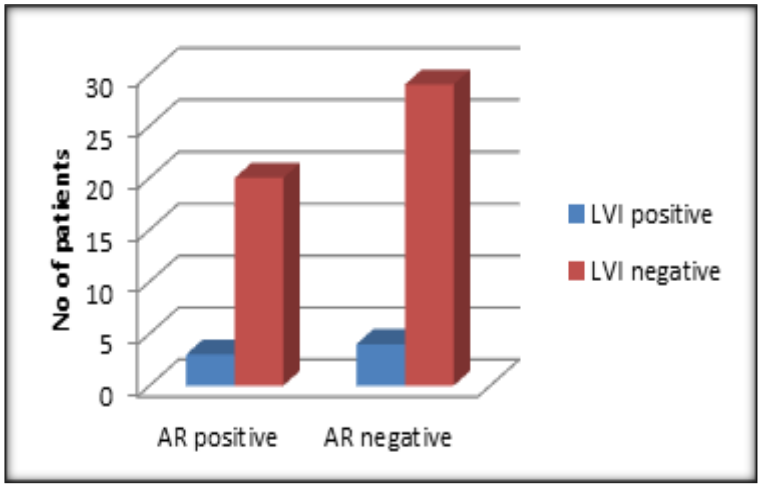


In our study we noted that DCIS positivity was seen only in AR positive triple negative breast cancer patients but p =0.0246.

Table 9: Lymphovascular invasion (LVI) status

LVI status	No of AR positive patients	No AR negative patients
Positive	3(13%)	4(12%)
Negative	20(87%)	29 (88%)



In this study there is no statistically significant difference between LVI status in AR positive and AR negative group (p>0.05).

Table 10: Perineural invasion (PNI) status

PNI status	No of AR positive patients	No of AR negative patients
Positive	3(13%)	1(3%)
Negative	20(87%)	32(97%)

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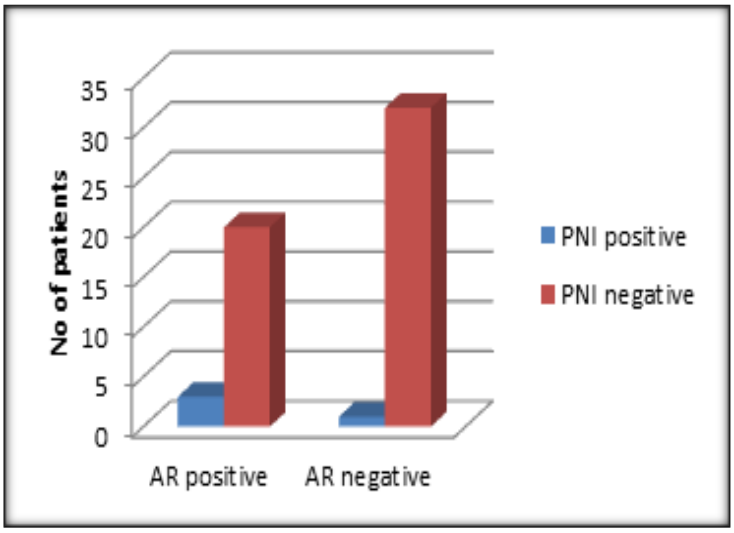

As only one PNI positive patient is seen in AR negative group, so PNI expression amongst AR positive and AR negative group cannot be statistically compared as cell size is < 5.

Table 11: Summary of observation and results

Categorical variables	**No of AR positive TNBC patients N = 23/56**	**No of AR negative TNBC patients N = 33/56**	**P value**
1.Age in years			
a) below 45	8(35%)	14(42%)	p-0.5919
b)above 45	15(65%)	19(58%)	
2.Menopausal status			
a)Premenopausal	6(26%)	13(39%)	p-0.3007
b)Postmenopausal	17(74%)	20(61%)	
3.Histological grade			
a) Grade I	1(4%)	8(24%)	p-0.0754
b) Grade II	14(61%)	12(36%)	
c) Grade III	8(35%)	13(40%)	
4.T stage			
a) T 1	1(4%)	7(21%)	p-0.272
b) T 2	12(53%)	17(52%)	
c) T 3	7(30%)	7(21%)	
d) T 4	3(13%)	2(6%)	
5.N stage			
a) N 0	10(44%)	17(52%)	p-0.0854
b) N 1	10(44%)	5(15%)	
c) N 2	2(8%)	7(21%)	
d) N 3	1(4%)	4(12%)	
6.TNM stage			
a) I	0(0%)	8(24%)	p-0.0945
b) II	13(56%)	12(36%)	
c) III	10(44%)	12(36%)	
d) IV	0(0%)	1(4%)	
7.DCIS (+)	7(30%)	0(0%)	NS
8.LVI (+)	3(13%)	4(12%)	NS
9.PNI (+)	3(13%)	1(3%)	NS

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Descriptive statistics of the study sample are presented in [Table 11], by AR expression status. AR expression was not associated with stage (P=0.0945), grade (P=0.0754), size of tumor (P=0.272), nodal status (P=0.0854), age at diagnosis (P=0.5919), LVI and PNI (P>0.05) and menopausal status (p=0.3007). In our study DCIS expression was noted only in AR positive group with a p value of 0.0246.

Discussion

TNBC represents a group of breast cancer with poor prognosis, owing to aggressive tumor biology and lack of targeted therapy-like HER2 blocking agents or hormonal therapy. However, several reports suggested that TNBC could represent a heterogeneous group comprising different subtypes with different clinical outcomes. Many published studies have attempted to identify new biomarkers to combine with those available in clinical practice to sub-classify TNBC into different prognostic groups and to select patients who are candidates for more aggressive therapy regimens.

The main findings of this study pertain to the lack of a significant prognostic effect mediated by AR immunohistochemical expression. AR positivity was not associated either with the compendium of clinicopathological findings (grade, stage, tumour size, nodal status, menopausal status, LVI and PNI)

In our study AR positivity was noted in 41% (23/56) of TNBC patients, which is compatible with the literature [Table 12]; Giuseppina Rosaria Rita Ricciardi,[8] et al reported AR positivity in 26.6%. In another study conducted by Damoun Safarpour et al,[9] reported that 18 (36%) of the triple negative tumours were AR positive. Nevertheless, occasionally lower frequencies of AR expression among TNBC have been reported, with Rakha et al,[10] presenting 13% AR immunopositivity rate in their series and Gonzalez-Angulo et al,[11] reporting 16.5% high AR levels via reverse-phase protein arrays.

Table 12: Various studies on the frequency of AR positivity among triple negative breast carcinomas (TNBC),[9]

Study	Total no of patients	No of TNBC patients	No of AR + in TNBC	AR positivity definition
Sutton et al, 2012	Not available	121	38(31.4%)	≥ 1%
Mrklic, et al, 2013	1849	124(6.7%)	27(32.4%)	≥ 1%
Tang e al, 2012	980	158(16%)	84(53.1%)	≥ 10%
Tsutsumi, 2012	325	51(15.6%)	21(41.1%)	≥ 1%
In this study		56	23(41%)	≥ 1%

He et al,[12] have retrospectively analyzed the prognostic value of AR in 287 patients TNBC treated at Sun Yat-sen University Cancer Center between January 1995 and December 2008. The AR expression was found in 74 patients (25.8%). This study demonstrated that the expression of AR is a favorable prognostic factor in terms of both OS (HR 0:34, p = 0.011) and DFS (HR 0:40, p = 0.008). In fact, both the DFS and the OS in patients were better in AR-positive patients compared to those negative (87.0% vs. 74.2% and 94.2% vs 82.3%, respectively).

Yu et al,[13] identified a 7-gene signature, including AR that may predict outcome among TNBC with known resistance to neoadjuvant chemotherapy. They confirmed the significantly positive correlation between AR expression and favourable survival in TNBC patients; indeed higher AR expression predicted a better relapse-free survival in patients with chemo resistant TNBC patients.[14]

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In Indian population, menopause normally occurs between the age of 45-50 yrs.[15,16] Therefore In present study we have divided patients into two groups i.e. age < 45 years and > 45 years. We found that in AR+ve group, 8/23(35%) of patient were < 45 yrs of age and 15/23(65%) were > 45 yrs of age. In AR-ve group, 14/33(42%) were < 45 yrs of age and 19/33(58%) were > 45 yrs of age (p=0.5919).

A study conducted by Mirco Pistelli et al,[17] showed that patients were divided into two groups < 50 years and >50 years. In AR positive group 34.6% were less than 50 and 46.6 were more than 50 years (0.9). Hence they concluded that AR expression is not associated with age at the time of diagnosis. Another study conducted by Aris Giannos et al,[14] also showed the similar results (p= 0.105).

Table 13: study performed by different scientist

Author name	No of patients	Average age in years (range)
Agoff,[18]	78	54.9(26-91)
Luo,[19]	269	49(25-80)
Micelle,[20]	226	58.7(24-92)
Yu,[13]	327	52.5
		Average –(53.7)

In above studies the average age of presentation for AR positive TNBC patient is 53.7 years. Our study showed an average age of presentation for AR positive TNBC is 49.9 years.

Our study showed 17/23 (74%) AR positive patients were postmenopausal women compared to 20/33 (61%) in AR negative group (p=0.3). Mirco Pistelli et al,[17] reported that AR expression is not associated with menopausal status (p=0.8). Tang et al,[21] found that 75% (12/16) of AR+ patients are postmenopausal women compared to 43% (48/111) of patients in the AR- group. (P = 0.017).

In our study most of the AR positive patient had grade II i.e. 14/23 (61%) and AR negative patient had grade III disease. Incidence of grade I disease was more in AR negative group i.e.8/33 (24%). Aris Giannos et al,[14] mentioned that AR expression in TNBC is not associated with histological grade (p=0.999). Mrklic et al,[22] supported that AR expression was not associated with disease free survival or overall survival; nevertheless, their study pointed to an indirect prognostic role, as AR expression correlated inversely with higher mitotic score, clinical stage, histological grade, and Ki-67 proliferation index. A similar pattern was noted in the study by Rakha et al,[10] where the multivariate analysis did not point to any independent prognostic effect mediated by AR expression in TNBC, despite its associations with grade, development of recurrences, and distant metastases. Moinfar et al,[23] found AR expression in 88% of grade 1 invasive breast cancers compared to 47% of grade 3 tumors and concluded that AR is the most frequently expressed marker even among high grade breast carcinomas. Our study showed no association between AR expression and histogical grade (p=0.0754). We found no association between AR expression and the size of tumour (p=0.272).

Aris Giannos et al [14], He et al,[12] and Mirco Pistelli et al,[17] also reported the same findings. On the other hand, McNamara KM, et al,[24] and Witzel I et al,[25] found AR positive expression in combination with other markers has been linked to smaller tumor size.

In our study AR positive expression was related to lower nodal stage (N0, N1) which was about 88%. While in AR negative status high nodal stage was found (N2, N3), which was about 32%.McGhun et al reported that, AR-positive TNBC was more common in older patients and had a higher propensity for LN metastases (p=0.033).[26] Mirco Pistelli et al and Aris Giannos et al, have reported that in their study there is no association between AR expression and lymph nodal stage.

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McGhun et al in his study showed that 73% AR positive patients had peritumoural DCIS component. In our study only 7/23(30.4%) AR positive patients had peritumour DCIS component.Due to small size of our study, association of LVI and PNI with AR expression could not be ruled out.

This study, some limitations should be discussed and addressed. The quantification of AR expression was based on immunohistochemistry; more elaborate techniques, such as Western blot, would seem necessary for further validation of the present findings. At any case, the results of the alternative analysis treating AR expression as a continuous variable (Allred score) replicated the findings of the main analysis. Moreover, disease free survival was not available in our setting; therefore, the reproducibility of the overall survival-related findings upon disease free survival could not be examined. Furthermore, information regarding additional molecular indices associated with AR expression, such as PIK3CA mutations, was not available in our study. Finally, our results should be further validated in larger studies, as our small sample size may have limited the statistical power in our analysis.

Conclusion

Our study examined the prevalence, relationship between AR expression and clinical and prognostic outcomes in a cohort of 56 patients with TNBC. A substantial proportion of triple negative breast carcinomas are AR positive (41%), so it is important to include assessment of AR as part of routine evaluations for TNBC. AR expression was noted more commonly in postmenopausal women as compared to premenopausal women. DCIS component was present only in AR positive patients but as sample size is small, study with large sample size is required for validation of relationship between the two. In our study, we found that AR expression was not associated with stage, age at diagnosis, histological grade, size of tumour, lymph node involvement, menopausal status, LVI and PNI.

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