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ORIGINAL ARTICLE

Impact of Androgen Receptor on Response to Adjuvant Hormonal Therapy in Luminal Breast Cancer

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ABSTRACT

Background: Contradictory reports regarding the role of the androgen receptor (AR) in breast cancer (BC). The current study aimed to evaluate the prognostic and predictive value of AR expression in postmenopausal luminal BC and response to tamoxifen (TAM) versus aromatase inhibitors (AIs).

Methods: A retrospective study included postmenopausal female patients with luminal BC treated with TAM or AI from February 2015 to December 2020.

Results:

Eighty percent of the patients had AR expression. Low grade, small tumor size, less involvement of lymph nodes, hormone receptor positive, low ki67, and her-2-ve were associated with AR +ve (p 0.001). Compared to 21.4% and 23.2% of AR-ve patients, only 16.2% of AR+ve patients experienced relapses and 10.5% died. The OS improvement for AR+ve patients was statistically significant (79.3 vs. 82.0 p 0.014), but the difference in DFS between AR-ve and AR+ve patients was not significant (74.5 vs. 75.6 p 0.11). In AR-ve patients, there was no significant difference between the TAM and AI groups in terms of DFS or OS (73.4 vs. 74.2, p 0.9; 78.2 vs. 78.9, p 0.84, respectively), but AR+ve patients, there was a statistically significant difference in DFS and a trend toward improved OS (71.2 vs. 77.7, p 0.04; 78.7 vs. 83.7, p 0.06, respectively)

Conclusions:

AR expression is associated with favorable pathological characteristics and a better survival outcome. Although our results showed improvement in DFS in patients who received AI in adjuvant settings, we still need more data to consider AR as a routine predictive marker in this scenario.

Keywords

Breast cancer, Aromatase Inhibitors, Tamoxifen, Survival, Adjuvant therapy

INTRODUCTION

Breast cancer (BC) is a hormone-dependent disease. The significance of steroid sex hormones in BC initiation and progression was confirmed more than 40 years ago. Antiestrogen medications are the backbone of care in the management of BC [1].

Patients with ER+ve BC experienced a reduction in both disease-related death and risk of contralateral BC after adjuvant hormonal therapy [2].

The androgen receptor (AR) is being identified as a new biomarker and a possible novel therapeutic target in the management of BC [3, 4].Many studies have reported a correlation between AR expression and ER expression. Up to 90% of ER+ve BCs express AR, and only 20% of ER+ve are AR+ ve [5-9].

Preliminary studies haveshown that the dual effect of AR on tumor progression can beoncogenic or suppressive [10].

However, there are controversial data regarding the prognostic value of the AR.Castellano I et al. reported that the coexpression of AR and ER was associated with improved survival outcome; this association was lost in other studies [11].

The effect of AR on BC relies on ER expression. Theoretically, in ER-ve BC, AR may stimulate tumor growth; however, there are data that contradict its value in this subtype [12-16].

In contrast, in ER+ve BC, AR may antagonize cellular proliferation. This phenomenon could be explained by the competitive inhibition of AR with ER or coregulators [17].The predictive value of the AR for theresponse to TAM and to AI is conflicting and limited.

The present study aimed to address our local experience by assessing AR expression as a prognostic biomarker in patients with ER+ve BC and as a predictive biomarker of AI and TAM in an adjuvant setting in luminal BC patients.

METHODS

Study design

A retrospective study included early BC patients who were diagnosed, treated, and followed up in the Surgical, Medical Oncology, and Clinical Oncology Departments, Faculty of Medicine, Zagazig University, Egypt, between February 2015 and December 2020. The inclusion criteria were early-stage ER+ve BC aged ≥18 years. ER and/or AR ≥ 1% was considered positive according to the College of American Pathologists and the American Society of Clinical Oncology [18].

Data collection and ethical statement

The demographic and pathological data of the patients were reviewedthrough medical files. The institutional review board (IRB##11216)) approved the study. Informed written consent was not obtained, as the study was retrospective.

Treatment protocols

We divided our patients into two cohorts: the first, treated with adjuvant TAM (20 mg/d); and the second, treated with AIs (letrozole 2.5 mg/d, anastrazole 1 mg/d,or exemestane 25 mg/d).

Follow up and end points

The endpoint was DFS in both cohorts, and the correlation with AR expression was assessed. DFS was defined as the time interval from the start of adjuvant treatment to disease recurrence, distant metastasis, new

contralateral BC, or death. The follow-up continued until December 2022.

STATISTICAL ANALYSIS

Continuous variables are expressed as the mean ± SD and median (range), and categorical variables are expressed as a number (percentage). Continuous variables were checked for normality by using the Shapiro–Wilk test. The Mann–Whitney U test was used to compare two groups of non-normally distributed variables. The percentages of categorical variables were compared using Pearson's chi-square test or Fisher's exact test where appropriate. Disease-free survival (DFS) was calculated as the time from the date of surgery to the date of relapse or the most recent follow-up in which no relapse was detected. Overall survival (OS) was calculated as the time from diagnosis to death or the most recent follow-up contact (censored). DFS and OS were stratified according to treatment intention and the results of the androgen receptor (AR) IHC. These time-to-event distributions were estimated using the Kaplan–Meier method and compared using the two-sided exact log-rank test. Cox regression analysis was used to construct univariate and multivariate models to identify independent predictors ofdisease-free survival and overall survival. All tests were two-sided. All the statistical analyses were performed using SPSS 22.0 for Windows (IBM, Inc., Chicago, IL, USA) and MedCalc Windows (MedCalc Software bvba 13, Ostend, Belgium).

RESULTS

Adjuvant hormonal therapy was administered to 570 BC patients, half of whom received TAM and the other half of whom received AI. The mean age ± standard deviation was 59.4 ±3.83 years in the TAM arm and 60.03± 4.31 years in the AI arm. AR expression was detected in 80% of patients in both the TAM arm and the AI arm. Except for grade (p=0.04), tumor size (p=0.01), and age (p=0.02), there were no significant differences in the clinicopathological features between the two arms. Table 1 illustrates the distribution of clinical and pathological characteristics across all patients.

A comparison between the AR+ve and AR-ve patients is shown in Table 2. A high grade (GIII), large tumor size (T4), more lymph node involvement (N2 and N3), hormone receptor negativity (ER or PR), high ki-67, and her-2 positivity were associated with AR-ve patients (p 0.001).

There were no significant differences in age (p 0.2), pathological subtype (p 0.43), grade (p 0.05), type of surgery (p 0.801), tumor size (p 0.293), lymph node (p 0.12), ER expression (p 0.085), PR expression (p 1.000), Ki67 expression (p 1.000), relapse (p 1.000), relapse (p value 1.000), or mortality (p 1.000).

In the AI arm, only the her2 + ve and luminal-like types were significantly different (p values of 0.001 and 0.046, respectively).

The outcomes differ to some extent in AR+ve patients. There were statistically significant differences in age (p=0.045), tumor size (p=0.001), and relapse (p=0.042). However, there were no significant differences in pathology subtype (p 0.77), grade (p 0.20), type of surgery (p 0.63), lymph node involvement (p 0.22), ER expression (p 0.55), PR expression (p value 0.60), Her2+ve (p 0.89), Ki-67 (p 0.62), molecular subtypes (p 0.63), or mortality (p 0.06).

A statistically significant difference was detected in patients who received TAM with AR-ve or AR+ve according to tumor grade (p 0.001), tumor size (p 0.001), lymph node involvement (p 0.001), ER expression (p 0.001), PR expression (p 0.005), Ki-67 expression(p 0.01), and molecular subtype (p 0.04). Moreover, the same association was observed in the patients who received AI (table 3).

The hormonal expression (ER, PR, AR) was significantly associated with OS in theunivariate modelaccording to binary logistic regression for predictors of OS among 570 BC patients, with p values of 0.03, 0.004, and 0.001, respectively. The unadjusted multivariate model, on the other hand, revealed a significant association with only PR expression (p=0.009) (Table 4).

Table 1: The clinical-pathological features of patients distributed across TAM and AI

Clinical-pathological features		TAM N=285 (%)	AI N=285 (%)	P value
Age Mean Std. Deviation Median (minimum-maximum)		59.4070± 3.83956 59.00 (50.00-71.00)	60.0386± 4.31039 60.00 (33.00-71.00)	0.02
Pathology	IDC	277 (97.2)	273 (95.8)	
Non-IDC		8 (2.8)	12 (4.2)	0.36
Grade	I	46 (16.1)	31 (10.9)	
II		188 (66.0)	215(75.4)	
III		51 (17.9)	39 (13.7)	0.04
Surgery	MRM	235 (82.5)	230 (80.7)	
BCS		50 (17.5)	55 (19.3)	0.58
Tumor Size	T1	40 (14.0)	37 (13.0)	
T2		153 (53.7)	177 (62.1)	
T3		55 (19.3)	56 (19.6)	
T4		37 (13.0)	15 (5.3)	0.01
lymph node (N)	0	59 (20.7)	70 (24.6)	
1		66 (23.2)	61 (21.4)	
2		115 (40.4)	109 (38.2)	
3		45 (15.8)	45 (15.8)	0.73
ER	Negative	215 (75.4)	201 (70.5)	
	Positive	70 (24.6)	84 (29.5)	0.18
PR	Negative	58 (20.4)	59 (20.7)	
Positive		227 (79.6)	226 (79.3)	0.91
AR	Negative	56 (19.6)	56 (19.6)	
Positive		229 (80.4)	229 (80.4)	1.00
Her-2	Negative	242 (84.9)	224 (78.6)	
		43 (15.1)	61 (21.4)	0.05
Ki-67	Low	108 (37.9)	104 (36.5)	
High		177 (61.2)	181 (63.5)	0.72
Molecular	luminal A like	90 (31.6)	78 (27.4)	
Subtype	luminal B like	195 (68.4)	207 (72.6)	0.27
Relapse	Absent	227 (79.6)	243 (85.3)	

Clinical-pathological features		TAM N=285 (%)	AI N=285 (%)	P value
present		58 (20.4)	48 (14.7)	0.07
Mortality	Alive	243 (85.3)	255 (89.5)	
	Died	42 (14.7)	30 (10.5)	0.13

TAM, tamoxifen; AI, Aromatase inhibitors; IDC, invasive duct carcinoma; MRM, modified radical mastectomy; BCS, breast conserving surgery; ER, Estrogen receptor; PR, progesterone receptor; AR, androgen receptor her-2, human epidermal growth factor receptor 2. Continuous variables were expressed as the mean ± SD & median (range); Categorical variables were expressed as a number (percentage), P-value<0.05 is significant.

Table 2: Clinical pathological features distributed through AR negative and AR positive patients

Clinical-pathological features		AR –ve N=112 (%)	AR +ve N=458 (%)	P value
Age Mean Std. Deviation		59.8929± 4.02326	59.6812± 4.10994	
Median (minimum-maximum)		61.00 (33.00-66.00)	59.00 (38.00-71.00)	0.14
Pathology	IDC	105 (93.8)	445 (97.2)	
Non-IDC		7 (6.2)	13 (2.8)	0.08
Grade	I	2 (1.8)	75 (16.4)	
II		65 (58.0)	338(73.8)	<0.001
III		45 (40.2)	45 (9.8%)	
Surgery	MRM	93 (83.0)	372 (81.2)	
BCS		19 (17.0)	86 (18.8)	0.65
Tumor Size	T1	14 (12.5)	63 (13.8)	
T2		27 (24.1)	303 (66.2)	
T3		49 (43.8)	62 (13.5)	<0.001
T4		22 (19.6)	30 (6.6)	
Lymph node (N)	0	1 (0.90)	128 (27.9)	
1		8 (7.1)	119 (26.0)	
2		59 (52.7)	165 (36.0)	<0.001
3		44 (39.3)	46 (10.)	
ER	Negative	47 (40.0)	369 (80.6)	
Positive		65 (58.0)	89 (19.4)	<0.001
PR	Negative	37 (33.0)	80 (17.5)	
Positive		75 (67.0)	378 (82.5)	<0.001
Her-2	Negative	69 (61.6)	397 (86.7)	
		43 (38.4)	61 (13.3)	<0.001
Ki67	Low	53 (47.3)	153 (33.4)	<0.001
	High	59 (52.7)	305 (66.6)	
Molecular	luminal A like	38 (33.9)	130 (28.4)	
Subtype	luminal B like	74 (66.1)	328 (71.6)	0.24
Relapse	Absent	86 (76.8)	384 (83.8)	
Present		26 (23.2)	74 (16.2)	0.07
Mortality	Alive	88 (78.6)	410 (89.5)	
	Died	24 (21.4)	48 (10.5)	0.002

IDC, invasive duct carcinoma; MRM, modified radical mastectomy; BCS, breast conserving surgery; ER, Estrogen receptor; PR, progesterone receptor; AR, androgen receptor her-2, human epidermal growth factor receptor 2. Continuous variables were expressed as the mean ± SD & median (range); Categorical variables were expressed as a number (percentage), P-value<0.05 is significant.

Table 3: Subgroup Analysis of hormonal therapy based on AR expression

Clinical-pathological features	TAM AR-ve N 56 (%)	TAM AR +ve N 229(%)	P value	AI AR-ve N 56 (%)	AI AR +ve N 229(%)	P value
Age: Mean ±Std. Deviation Median (minimum-maximum)	59.7±3.81 60(53-66)	59.3±3.98 59(50-71)	0.2	60.05±4.74 61(33-66)	60.03±4.20 60(38-71)	0.31
IDC Non-IDC (Pathology)	54(96.4) 2(3.6)	223(97.4) 6(2.6)	0.65	51(91.1) 5(8.9)	222(96.9) 7(3.1)	0.06
I II (Grade) III	2(2.6) 27(48.2) 2748.2)	44(19.2) 161(70.3) 24(10.5)	<0.001	0(0) 38(67.9) 18(32.1)	31(13.5) 177(77.3) 21(9.2)	<0.001
MRM BCS (Surgery)	47(83.9) 9(16.1)	188(82.1) 41(17.9)	0.74	46(82.1) 10(17.9)	184(80.3) 45(19.7)	0.76
T1 (tumor size) T2 T3 T4	9(16.1) 16(28.6) 20(35.7) 11(19.6)	31(13.5) 137(59.8) 35(15.3) 26(11.4)	<0.001	5(8.9%) 11(19.6) 29(51.8) 11(19.6)	32(14.0) 166(72.5) 27(11.8%) 4(1.7)	<0.001
N 0 (lymph node) N1 N2 N3	0(0) 2(3.6) 27(48.2) 27(48.2)	59(25.8) 64(27.9) 88(38.4) 18(7.9)	<0.001	1(1.8%) 6(10.7) 32(57.1) 17(30.4)	69(30.1) 55(24.0) 77(33.6) 28(12.2)	<0.001
ER Negative Positive	28(50.0) 28(50.0)	187(81.7) 42(18.3)	<0.001	19(33.9) 37(66.1)	182(79.5) 47(20.5)	<0.001
PR Negative Positive	19(33.9) 37(66.1)	39(17.0) 190(83.0)	0.005	18(32.1) 38(67.9)	41(17.9) 188(82.1)	0.01
Her-2 Negative Positive	44(78.6) 12(21.4)	198(86.5) 31(13.5)	0.13	25(44.6) 31(55.4)	199(86.9) 30(13.1)	<0.001
Ki67 Low High	29(51.8) 27(48.2)	79(34.5) 150(65.5)	0.01	30(53.6) 26(46.4)	74(32.3) 155(67.7)	0.003
Molecular luminal A like Subtype luminal B like	24(42.9) 32(57.1)	66(28.8) 163(71.2)	0.043	14(25.0) 42(75.0)	64(27.9) 165(72.1)	0.65
Relapse Absent Present	43(76.8) 13(23.2)	184(80.3) 45(19.7)	0.55	43(76.8) 13(23.2)	200(87.3) 29(12.7)	0.04
Mortality Alive Died	44(78.6) 12(21.4)	199(86.9) 30(13.3)	0.11	44(78.6) 12(21.4)	211(92.1) 18(7.9)	0.003

TAM, tamoxifen; AI, Aromatase inhibitors; IDC, invasive duct carcinoma; MRM, modified radical mastectomy; BCS, breast conserving surgery; ER, Estrogen receptor; PR, progesterone receptor; AR, androgen receptor her-2, human epidermal growth factor receptor 2. Continuous variables were expressed as the mean ± SD & median (range); Categorical variables were expressed as a number (percentage), P-value<0.05 is significant.

Table 4: Binary logistic regression for predictors of Overall Survival among 570 breast cancer patients

Predictors	B	Univariate model OR (95%CI)	P value	B	Unadjusted multivariate model OR (95%CI)	P value
Age (years)	- 0.050	0.952(.905-1.000)	0.05			
Pathology	-0.279	0.757(0.186-3.086)	0.69			
Grade I Grade II	0.282 -0.273	1.326(0.632-2.782) 0 .761(0.285-2.031)	0.29			
Surgery	-0.523	0.593(0.295-1.192)	0.14			
T1 T2 T3	0.736 0.778 1.071	2.088(0.826-5.279) 2.177(0.797-5.942) 2.918(0.978-8.708)	0.290			

Predictors	B	Univariate model OR (95%CI)	P value	B	Unadjusted multivariate model OR (95%CI)	P value
N1 N2 N3	0.530 0.018 0.571	1.699(0.836-3.454) 1.018(0.507-2.047) 1.770(0.837-3.743)	0.159			
ER	0.510	1.665(1.036-2.675)	0.035	0.383	1.466(0.879-2.446)	0.14
PR	-0.708	0.493(0.303-0.800)	0.004	0-.655	0.520(0.318-.850)	0.009
Her-2	-0.333	0.717(0.377-1.363)	0.310			
Ki-67	0-.432	0.649(0.409-1.031)	0.067			
AR	0-.602	0.548(0.335-0.895	0.016	0-.369	0.691(0.404-1.182)	0.177
Molecular subtype	0-.465	0.628(0.392-1.006	0.053			
Hormonal treatment	0-.346	0.708(0.443-1.130)	0.148			
Relapse	13.297	595377(0.0-844203)	0.533			

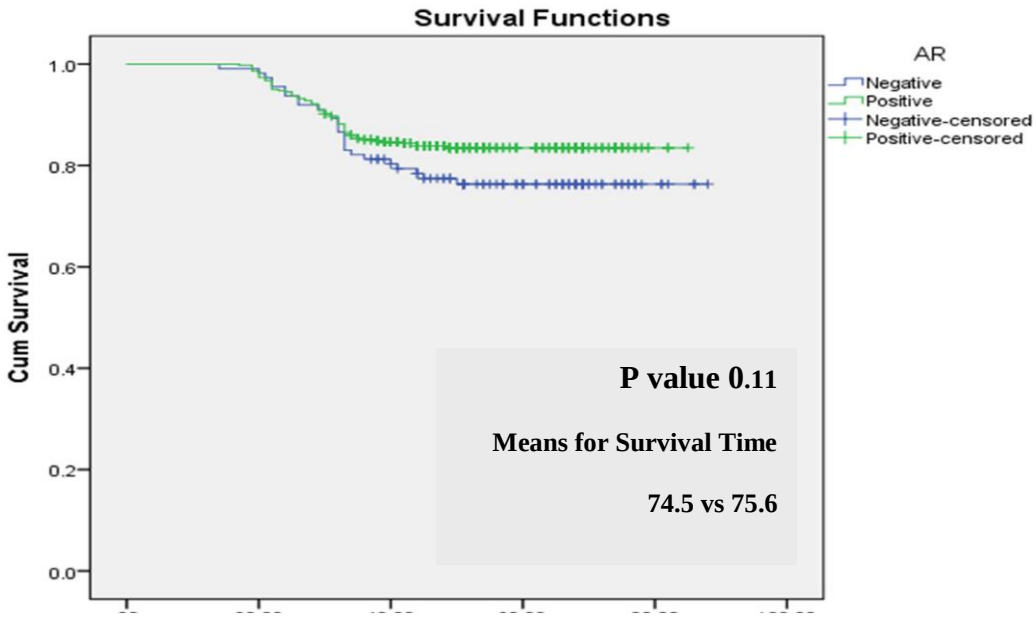
TAM, tamoxifen; AI, Aromatase inhibitors; IDC, invasive duct carcinoma; MRM, modified radical mastectomy; BCS, breast conserving surgery; ER, Estrogen receptor; PR, progesterone receptor; AR, androgen receptor her-2, human epidermal growth factor receptor 2.

Survival analysis

There was a trend toward better DFS with AI use than with TAM use (79.1 vs. 74.1, p 0.08), but there was no statistically significant difference in mOS (84.1 vs. 79.7, p 0.14).While there was no statistically significant difference in DFS between the AR-ve and AR+ve groups (74.5 vs. 75.6 p 0.11), the AR+ve patients had a statistically significant improvement in OS (79.3 vs. 82.0 p 0.014) (Fig 1a&b).

Among the AR-ve patients, there was no statistically significant difference in DFS or OS between the TAM and AI arms (73.4 vs. 74.2, p 0.9; 78.2 vs. 78.9, p 0.84; Fig. 2a and b). However, there was a statistically significant difference in DFS and a trend toward improved OS in the AR+ve patients (71.2 vs. 77.7, p 0.04; 78.7 vs. 83.7, p 0.06; Fig. 3a and
b).

Figure 1a



Disease Free Survival (months)

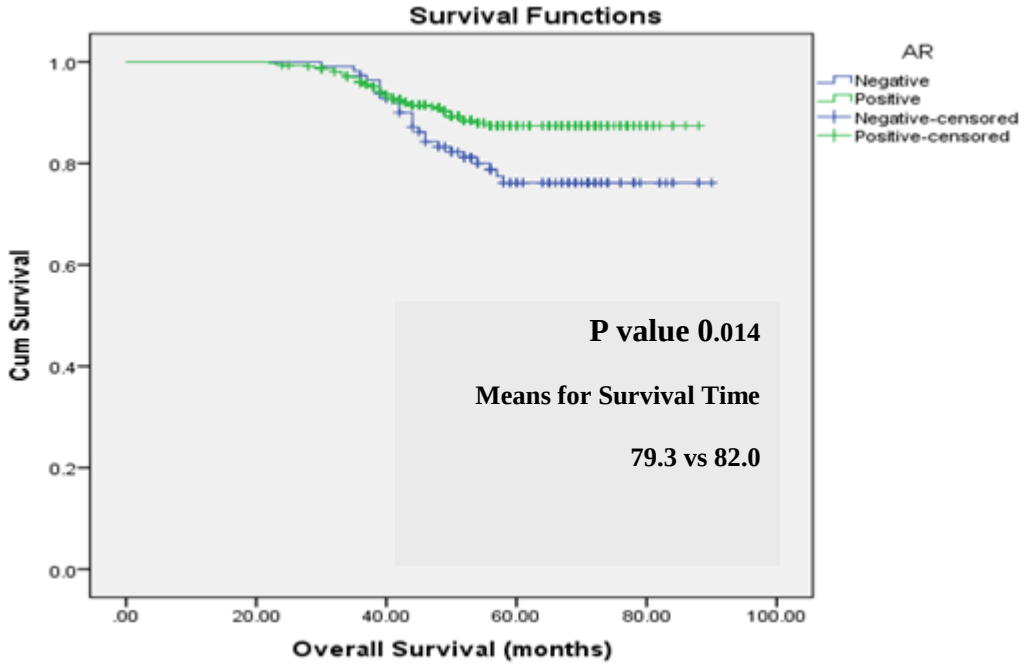


Figure 1b

Figure 1: Kaplan-Meier curve of survival analysis based on androgen receptor expression; negative vs positive (fig.1a, disease free survival and fig. b, overall survival)

Figure 2 a

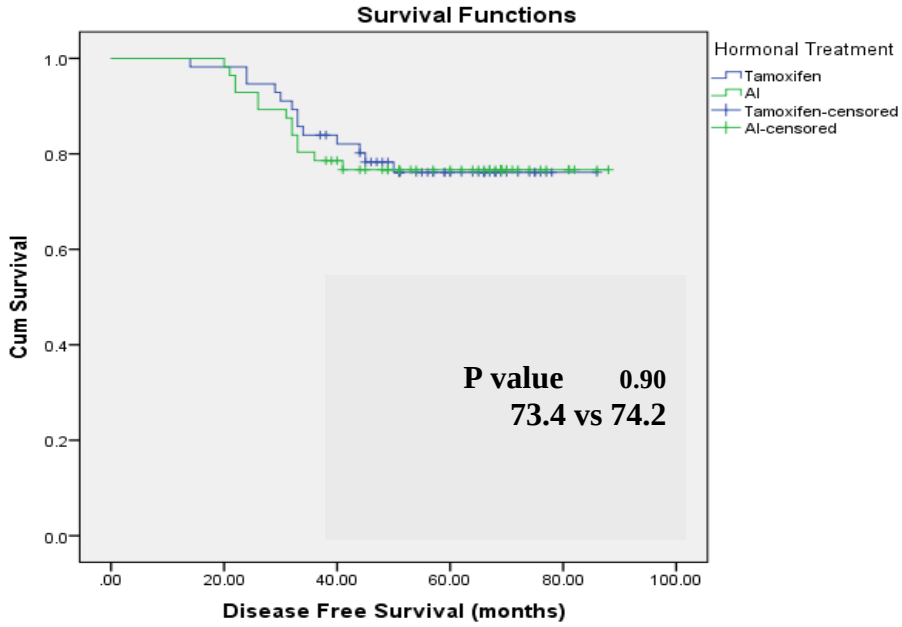


Figure 2a

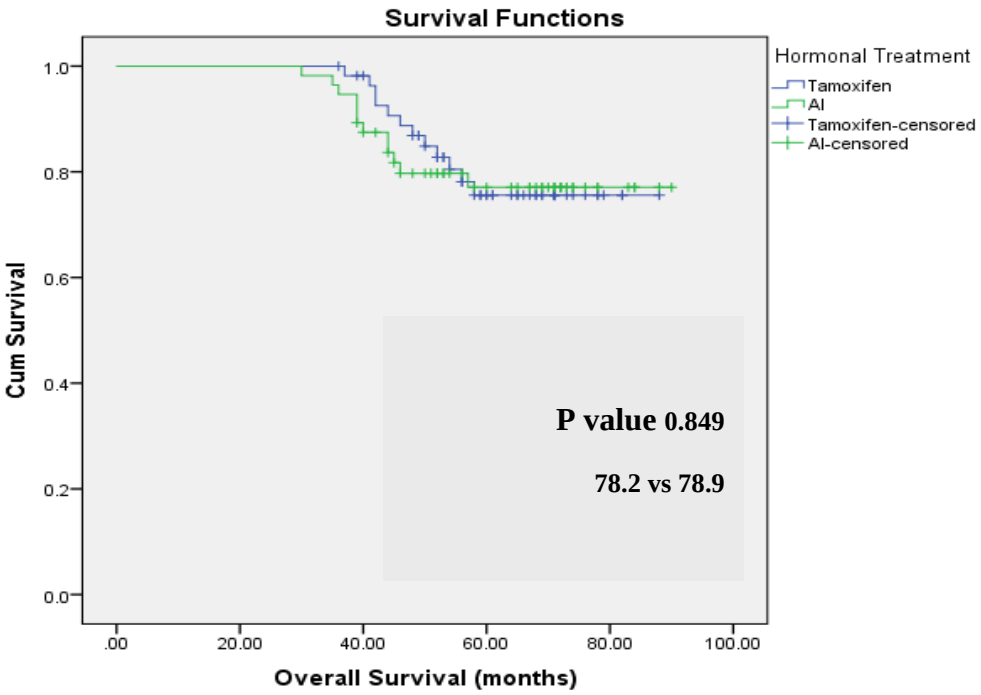


Figure 2b

Figure 2: Kaplan-Meier curve of survival analysis Androgen receptor negative (fig.2a, disease free survival and fig.2b, overall survival)

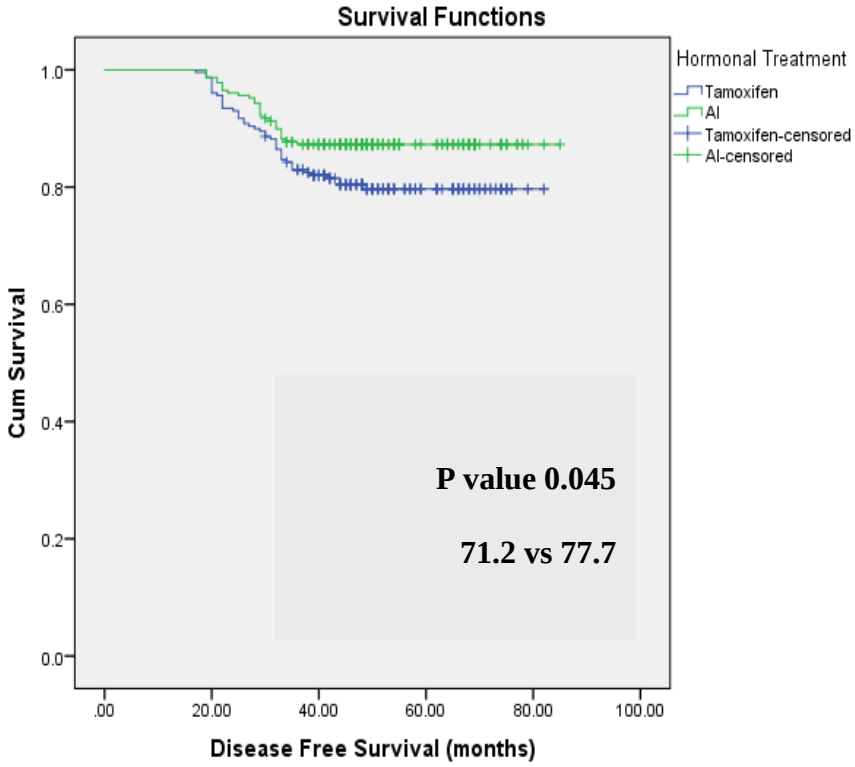


figure 3a

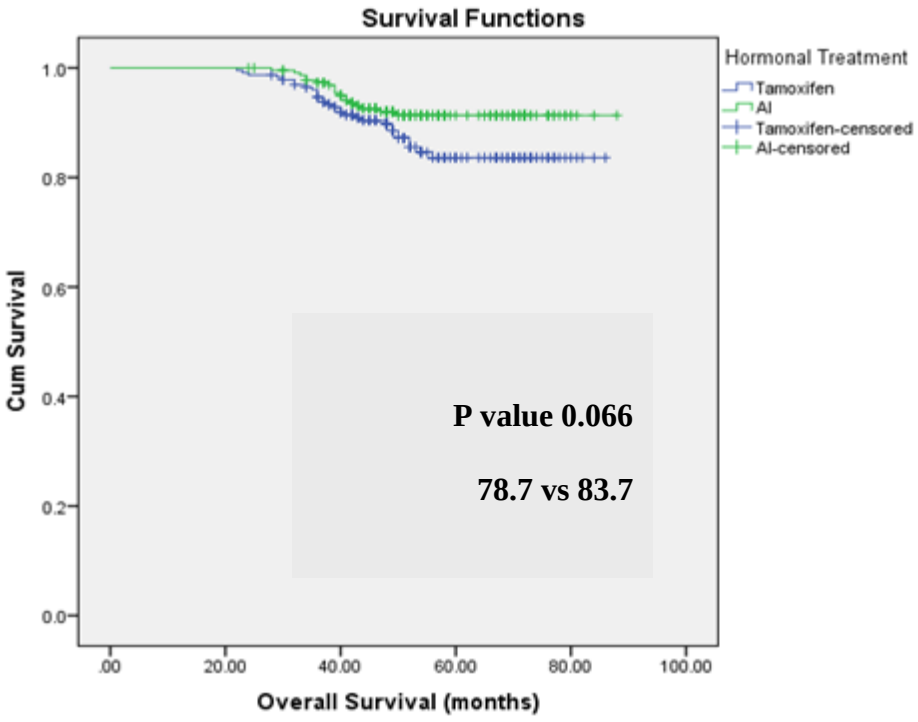


figure 3b

Figure 3: Kaplan-Meier curve of survival analysis Androgen receptor positive (fig.3a, disease free survival and fig.3b, overall survival)

DISCUSSION

The present study evaluated AR expression in luminal BC patients and its predictive role in adjuvant settings, whether for TAM or AI. AR expression was found in 80.4% of our patients who received either TAM or AI. Furthermore, AR+ve patients had favorable clinicopathological features, such as low tumor grade, small tumor size, and lymph node metastasis (p=0.001). Additionally, patients who were AR+ve experienced a better survival outcome; 16.2% of the patients relapsed, and 10.5% died, while 23.2% and 21.4% of the patients who were AR-ve; the p values were 0.07 and 0.002, respectively. Although there was no statistically significant difference in DFS between AR-ve and AR+ve patients in our study (74.5 vs. 75.6, p=0.11), OS improved in AR+ patients (79.3 vs. 82.0, p=0.014). The lack of statistical significance in terms of DFS in our study could be attributed to the relatively small sample size and the fact that most of our included patients had luminal B-like disease (approximately 70%). Many studies have reported similar findings [19-22].

The AR is a coming-out marker for BC. A retrospective study included 912 BC patients who had completed their therapy, which included surgery, radiotherapy, and systemic chemotherapy. The patients were divided into two groups: those who received no endocrine therapy and those who received 40 mg TAM daily. The investigators realized that AR+ve in the presence of ER-ve predicted a lower rate of recurrence (p 0.015), whereas AR-ve predicted the opposite (p 0.02) [23].

Many previous studies have shown that DFS and OS improve in AR+ve BC patients. In a retrospective and propensity score-matched study, 5765 BC patients were included to assess the prognostic value of AR in BC patients. The findings showed that AR had an independent role in both DFS and OS; the 5-

year DFS rates were 95.73% and 92.21%, while the OS rates were 98.84% and 95.94% for AR +ve and AR -ve patients, respectively [24].

Kraby et al. conducted another retrospective study in 1297 BC patients to assess AR in various molecular subtypes. Researchers have concluded that AR is more frequently linked to luminal A or grade III disease and is an independent predictor of better survival outcomes [25].

An association between improved DFS and AR+ve was found in a meta-analysis of thirteen studies involving 5648 patients (HR = 0.46, 95% CI 0.37–0.58) [16]. The inverse relationship between mortality in patients with ER+ve BC and AR expression has been supported by multiple epidemiological studies [16, 21, 26].

According to Cochrane and colleagues, a high AR/PR ratio may be beneficial for predicting TAM treatment failure [27]. Rangel et al., [28] and Bronte G et al., [29] verified the same findings.

Numerous studies have documented the conflicting effects of AR signalling in patients with ER+ve/-ve BC [30]. Epidemiological data indicate adverse effects [31, 32], beneficial effects, [33, 34] and no association [31, 35]. AR was evaluated for predictive value in advanced BC through a retrospective study involving 102 patients. The outcomes demonstrated that the AR was unable to predict the response to endocrine therapy [29].

Compared to those in the AR-ve and ER +ve patients, the concomitant positivity of AR and ER-ve BC was associated with a better prognosis. This could be explained by competition at the receptor level and consequent disruption of the ER-dependent transcription pathway [16]. Similarly, in the case of ER/PR-ve, AR increases the protumorigenic effect by enhancing the transcription of the ER [36].

There was no statistically significant difference in mOS (84.1 vs. 79.7, p 0.14), consistent with previous data regarding the response to TAM vs. AI in adjuvant settings [37, 38]. However, there was a trend toward better DFS with AI use than with TAM use (79.1 vs. 74.1, p=0.08).

Among the AR+ve patients in our study, there was a statistically significant difference in DFS and a trend toward improved OS (71.2 vs. 77.7, p 0.04; 78.7 vs. 83.7, p 0.06; however, these significant differences were lost in the case of AR+ve for TAM vs. AI (73.4 vs. 74.2, p =0.9; 78.2 vs. 78.9, p = 0.84, respectively). These outcomes matched those of numerous earlier studies.

In a study containing 938 BCs, improved DFS was observed with adjuvant chemotherapy and hormonal therapy in the case of AR+ve, while in another study; the improvement was observed in the case of hormonal therapy alone [39].

A ratio of AR/ER >= 2 was linked to a poor response to TAM in a study of 192 BC patients who were ER+ve; this could be because of how AR affects EGFR pathways. Given that AR is thought to have an antagonistic effect on ER+ve BC, we anticipate that these patients will benefit from AI. Inhibition of estradiol production by testosterone may lead to an increase in AR and, thereafter, tumor growth inhibition. The use of AR antagonists is desirable because these observations and reports show that AR may counteract the harmful effects of ER [27].

CONCLUSIONS

AR expression is associated with favorable

clinical and pathological characteristics and a better survival outcome. The TAM and AI groups did not significantly differ in terms of DFS or OS among AR-ve patients. Nonetheless, in AR+ve patients, there was a statistically significant difference in DFS and a trend toward improved OS. Owing to contradictory previous data and the lack of statistical significance in the present study, the use of AR expression as a guide for selecting adjuvant endocrine therapy is still immature.

Limitations

Given that all retrospective studies are prone to data bias, a small sample size and lack of adjustment represent the main limitations of these studies, and the need for prospective studies with larger sample sizes is mandated to obtain more accurate results.

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