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ORIGINAL ARTICLE

Androgen receptor expression in triple negative breast carcinoma and its association with the clinicopathological parameters

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Abstract

Introduction: Androgen receptor (AR) is the most frequently expressed biomarker in all subtypes of breast carcinoma. Triple negative breast carcinoma (TNBC) is breast carcinoma that lacks oestrogen and progesterone receptors immunoexpression as well as absence of *HER2/neu* gene amplification. This makes targeted therapy not feasible in this cancer and hence has poorer prognosis. Detecting AR expression could be another milestone in the management of TNBC, as AR is a prognostic, predictive marker and potential index for targeted treatment. This study aimed to assess expression of AR in TNBC by immunohistochemistry and its association with clinicopathological parameters. *Methods:* We analysed the expression of AR in 97 TNBC cases from Penang General Hospital for a period of 3 years (2014 to 2017). Androgen receptor immunoreactivity was considered positive if ≥ 1% of tumour cells nuclei were stained irrespective of staining intensity. *Results:* The prevalence of AR expression in TNBC was 31% (30/97), with the proportion of AR-positive tumour cells ranged from 1% to 90%. These include 23 invasive carcinomas, no special type (NST) and 7 other invasive carcinoma subtypes (papillary, lobular, clear cell and medullary carcinomas). Sixty-seven cases (69%) that showed AR immunonegativity were invasive carcinomas, NST (n=60), clear cell carcinoma (n=1) and metaplastic carcinoma (n=6). Androgen receptor immunoexpression was inversely correlated with tumour grade (p=0.016), but not the tumour stage, tumour size and nodal status. *Conclusion:* AR is expressed in about one-third of TNBC and loss of AR immunoexpression does not predict adverse clinical outcomes. Larger cohorts for better characterisation of the role of AR immunoexpression in TNBC are warranted.

Keywords: Androgen receptor; triple negative, invasive breast carcinoma, tumour grade, tumour stage

INTRODUCTION

Breast carcinoma is the most common malignancy in women. According to Malaysian Cancer Statistic 2007-2011, breast carcinoma was the most common cancer among female in Malaysia, accounted for 32.1% of all malignancy with the overall age-specific incidence rate (ASR) of 31.1 per 100,000 population.[1] Another epidemiological study in year 2012 by The International Agency for Research in Cancer (GLOBOCAN), the estimated ASR for breast carcinoma in Malaysia was 38.7 per 100,000 population.[2] This had shown that the incidence rate of breast carcinoma in Malaysian population was almost maintaining for the past 8 years.

Overall, the survival rate of breast carcinoma for Malaysian women is poor although it has improved for the past three decades. According to the largest Malaysian population-based study of 10,000 breast carcinoma patients diagnosed between January 2000 and December 2005 by Health Informatics Centre, Ministry of Health Malaysia, the National Cancer Registry and the National Mortality Registry, the five-year overall survival rate was 49%.[3] There has been a steady improvement in patient survival in recent decades as a result of a combination of early detection due to the advances in mammographic screening[4] and adjuvant systemic chemotherapy.[5]

Identification of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) as predictive

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and prognostic markers in breast carcinoma has been one of the major achievements of the past several decades. With the identification of these biological markers, targeted treatments (such as tamoxifen, aromatase inhibitors, and trastuzumab) can be used instead of systemic chemotherapy to reduce the undesirable systemic side effects of nonspecific chemotherapy.[6,7] The prognosis and outcome among patients with ER, PR and/or HER2 positive breast carcinoma has improved with the usage of targeted therapies. However, there are approximately 10% to 24% of breast carcinoma fall into the category of triple negative breast carcinoma (TNBC) which lack of ER, PR (by immunohistochemistry), and HER2 expression (by immunohistochemistry and/or gene amplification).[8] Thus, this group of patients is excluded from the benefits of targeted therapies.[9] Study has demonstrated that this group of patients is associated with poorer prognosis as evidenced by lowest five-year survival rate and worst overall survival compared with other breast cancer subtypes.[10] Triple negative breast carcinoma is also found to be associated with larger tumour size, higher histological grade and lymph node involvement at diagnosis, which displays a more aggressive and adverse clinical course.[11]

A large-scale local study on molecular subtyping of the breast carcinoma which involved 1034 cases in Malaysia has shown that there are 48% luminal A (ER and PR positive, HER2 negative), 12% luminal B (ER, PR, and HER2 positive), 29% TNBC and 11% HER2 overexpressing subtypes (ER and PR negative, HER2 positive). It is postulated that there may be ethnic differences in the risk of developing different subtypes of breast carcinoma as the prevalence of different subtypes are varied among different ethnics. The indigenous population of Sarawak had the highest incidence (37%) of TNBC compared to Chinese (23%) and Malays (33%), and this remain significant after adjusting for other variables including age. HER2 overexpression was more frequent among the Malays (29%) compared to Chinese (22%) and the indigenous population (21%).[12] This study had indicated a higher incidence of TNBC in Malaysian compared to western populations. Unfortunately, chemotherapy is the only standard treatment option available for TNBC. The search for more predictive biomarkers is the primary aim and goal of breast carcinoma research at present.

In an effort to identify additional predictive biomarkers, we studied androgen receptor (AR) expression in breast carcinoma. AR has emerged as a potential multifaceted biomarker. AR was found to be the most frequently expressed biomarker in all subtypes of breast carcinoma (70% to 80%)[13,14] as well as the frequency of 10% to 75% in TNBC tumours.[15,16] A study conducted in Singapore found that AR expression was observed in 38% of TNBC, with the proportion of stained tumour cells ranging from 1 to 95%.[17] AR was also found to be the commonly expressed biomarker even among the higher-grade breast cancer.[18]

Interestingly, recent molecular data suggested that TNBC is not a single entity per se, but a heterogeneous disease that can be further subcategorised into four molecular subtypes i.e. basal-like-1, basal-like2, mesenchymal and luminal AR (LAR). LAR is a distinct TNBC subgroup with high AR expression. Notwithstanding its aggressive clinical behaviour, TNBC is generally regarded more chemosensitive compared with others given the higher cellular proliferation in this tumour. However, LAR was found to be rather resistance to chemotherapy.[19] Ongoing clinical trials targeting AR-expressing TNBC with anti-androgen therapies such as bicalutamide, enzalutamide and abiraterone had shown promising results, and thus may shift the existing treatment strategies to improve clinical outcomes.[19]

Androgen plays a role in normal breast physiology and therefore AR signalling is becoming increasingly recognised as an important contributor toward breast carcinogenesis. Studies have proven the potential oncogenic effect with AR activation. According to the study by Zhu and colleagues,[20] they demonstrated that activated AR increased cell viability and reduced cell apoptosis in AR-positive mesenchymal stem-like TNBC cell lines. AR antagonist such as bicalutamide was found to inhibit cell proliferation in a dose-dependent manner as well as inducing early apoptosis *in vitro*. The mechanisms involved were by increasing the expression of p73 and p21, meanwhile negatively regulating p53 and cyclin D1.[20]

Thike and colleagues revealed that AR expression by immunohistochemistry was associated with good prognosis in ER- and PR-negative breast carcinoma; while the loss of AR expression was associated with early onset, high nuclear grade and negative ER, PR and HER2 expression status in breast carcinoma. The overall survival showed a trend of improvement

in AR expressing TNBC.[17] The aim of our study was to investigate the immunohistochemical detection of AR in TNBC in our local population and to correlate its expression with the clinicopathological parameters.

MATERIALS AND METHODS

Patients and Tissue Samples

This cross-sectional and descriptive study examined the histologic materials, reports and medical records of all patients with triple negative breast carcinoma diagnosed in Penang General Hospital from January 2014 to December 2017. Triple negative breast carcinoma was defined by negativity towards oestrogen receptor, progesterone receptor and HER2 according to the American Society of Clinical Oncology/ College of American Pathologists (ASCO/CAP) Guidelines.[21] Clinicopathological parameters including age, ethnicity, histologic grade and subtype, associated ductal carcinoma in situ (DCIS) and its extent, lymphovascular invasion, presence of axillary lymph node metastasis and distance metastatic status were reviewed.

Sampling Method

Histological slides were retrieved and reviewed. The desired formalin-fixed, paraffin-embedded tissue blocks with tumour were chosen for AR immunohistochemical staining. In order to avoid sampling bias in our study, the analysis was performed on whole tissue sections rather than using tumour tissue microarrays technique.

Immunohistochemistry (IHC)

Paraffin embedded tissue sections were cut at three micrometres thick, dried, deparaffinized and rehydrated using standard procedures. AR antibody was applied to the tissue section as per manufacturer's protocol with heat-induced epitope retrieval followed by endogenous peroxidase blocking and then incubation with primary antibody (Monoclonal Mouse anti-human Androgen Receptor, clone AR441, Dako, Denmark, 1:150 dilution). Secondary antibody with HRP Polymer Mouse DAKO REAL™ EnVision™, Code No. K5007) and DAB chromogen solution was used for visualisation. The slides were then counterstained with Mayer's Haematoxylin. Benign prostatic tissue which acted as positive control was added to each automated IHC run to confirm the validity of the antibody.

Staining Interpretation

The extents (% tumour cells) of staining by tumour cells were recorded. Tumour was considered as immunopositive for AR when there was brown nuclear staining in 1% or more of the tumour cell nuclei regardless of staining intensity, whereby those with nuclear staining less than 1% was regarded as negative.

Data Processing and Analysis

All data and results were processed and analysed statistically using Statistical Package for the Society Study (SPSS) version 22.0. The association between clinicopathological parameters and immunohistochemistry expression of AR in the tumour cells were tested using chi-square ($\chi 2$), student T and Mann-Whitney tests. A p-value of < 0.05 was considered as statistically significant.

RESULTS

A total of 97 TNBC patients, who fulfilled the inclusion and exclusion criteria were included in the study. The majority ethnic was Chinese (n = 69, 71.1%) followed by Malay (n = 18, 18.6%) and Indian (n = 10, 10.3%). The youngest age at diagnosis was 32 years (ranged from 32 – 83 years, mean = 58.4). Most of the cases were Modified Bloom and Richardson grade 3 tumour (n = 76, 78.4%), followed by 19 cases (19.6%) and 2 cases (2%) of grade 2 and 1 tumours respectively. Eighty-six percent of the cases were of invasive carcinoma, no special type (NST). The rest of the cases (n = 14, 14.4%) were pure metaplastic carcinoma or mixed invasive carcinoma, NST with metaplastic carcinoma (n = 6), invasive lobular carcinoma (n = 3), medullary carcinoma (n = 2), glycogen rich clear cell carcinoma (n = 2) and invasive papillary carcinoma (n = 1). The tumour size ranged from 10 mm to 240 mm with a mean size of 48.3 mm.

Of the total 97 TNBC cases, AR was expressed in 30 (31%) cases, with the proportion of AR-positive tumour cells ranged from 1% to 90% (mean 40%, median 25%). These included 23 invasive carcinomas, NST and seven other carcinoma subtypes (invasive papillary, invasive lobular, clear cell and medullary carcinomas) (Fig. 1). Sixty-seven (69%) cases that displayed AR immunonegativity were invasive carcinoma, NST (n = 60), clear cell carcinoma (n = 1) and metaplastic carcinoma (n = 6). Further subgroup analysis revealed that the mean age for AR-positive cases was 61.2 years (ranged 34 – 83,

median 60.5); whereby those with AR-negative cases were relatively younger with mean age of 57.2 years (ranged 32 – 79, median 58.0).

Fifty-seven (75%) out of 76 tumours with higher histological grade (grade 3) did not express AR. On the contrary, all (100%) grade 1 tumours exhibited AR immunoreactivity ($p < 0.05$). Noteworthy, we observed that more than half of the tumours with size larger than 20 mm (n = 59, 57.3%) and those with positive nodal status (n = 42, 75%) displayed AR immunonegativity, although were not proven statistically significant. In addition, AR immunoexpression were not significantly associated with other clinicopathological parameters such as tumour histological subtypes, the presence of DCIS components, lymphovascular invasion and distance metastasis, as illustrated in Table 1.

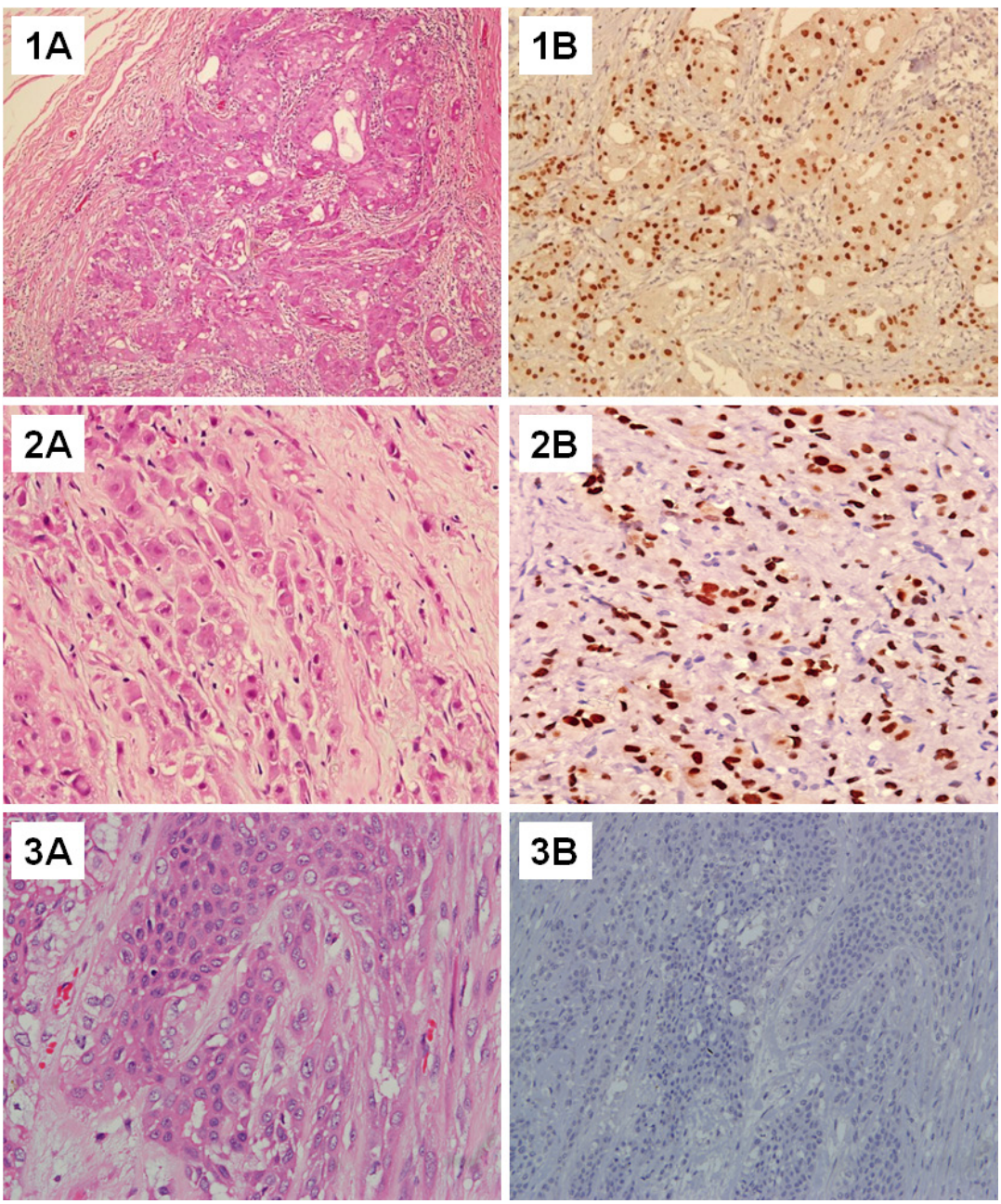

FIG. 1: (1A) Invasive carcinoma, no special type, displaying nuclear positivity (1B) for androgen receptor (400x). (2A) Invasive lobular carcinoma, with (2B) nuclear immunoreactivity for androgen receptor (400x). (3A) Metaplastic carcinoma, which shows (3B) immunonegativity for androgen receptor (400x).

TABLE 1: Correlation between androgen receptor expression and clinicopathological parameters

Clinicopathological parameters	Total	AR-positive	AR-negative	p-value
Age (years) (mean 58.4, median 59, range 32-83)				0.144[T]
< mean age	47	13 (27.7%)	34 (72.3%)	
≥ mean age	50	17 (34.0%)	33 (66.0%)	
Ethnicity				0.661[C]
Malay	18	5 (27.8%)	13 (72.2%)	
Chinese	69	23 (33.3%)	46 (66.7%)	
Indian	10	2 (20.0%)	8 (80.0%)	
Tumour size (mm) (mean 48.3, median 43.0, range 10-240)				0.331[M]
< 20	14	6 (42.9%)	8 (57.1%)	
≥ 20	83	24 (28.9%)	59 (57.3%)	
Histological grade				0.016[C]*
1	2	2 (100.0%)	0 (0.0%)	
2	19	9 (47.4%)	10 (52.6%)	
3	76	19 (25%)	57 (75%)	
Histological subtype				0.095[C]
IDC	83	23 (27.7%)	60 (72.3%)	
Non-IDC	14	7 (50.0%)	7 (50.0%)	
Associated DCIS				0.291[C]
Absent	53	14 (26.4%)	39 (73.6%)	
Present	44	16 (36.4%)	28 (63.6%)	
Associated extensive DCIS				0.631[C]
Absent	36	12 (33.3%)	24 (66.7%)	
Present	8	4 (50.0%)	4 (50.0%)	
Lymphovascular invasion				0.056[C]
Absent	38	16 (42.1%)	22 (57.9%)	
Present	59	14 (23.7%)	45 (40.8%)	
Axillary lymph node status				0.282[C]
pN0	41	16 (39.0%)	25 (61.0%)	
pN1	28	7 (25.0%)	21 (75.0%)	
pN2	18	3 (16,7%)	15 (833%)	
pN3	10	4 (40.0%)	6 (60.0%)	
Distance metastases				0.984[C]
Present	8	3 (37.5%)	5 (62.5%)	
Absent	89	27 (30.3%)	62 (69.7%)	
Stage group				0.132[C]
Stages 1 and 2	57	21 (36.8%)	36 (58.8%)	
Stages 3 and 4	40	9 (22.5%)	31 (77.5%)	

Notes: *statistically significant; [C] *P*-value derived from chi-square test; [T]*P*-value derived from student T test; [M]*P*-value derived from Mann-Whitney test

DISCUSSION

Triple negative breast carcinoma (TNBC) neither expresses hormone receptors nor HER2, making chemotherapy with or without radiotherapy remains the only therapeutic tool of management. This group of tumours is believed to be more aggressive with increased likelihood of distance recurrence and death. Studies conducted in western countries revealed that TNBC tends to be found in the younger age group.[22] However, this trend was not observed in our study population, in which the mean age of diagnosis of TNBC was 58.4 years. Similar finding was reported in a study conducted in Sarawak, Malaysia, in which the authors observed that younger Malay and native of Borneo do not account for higher rate of TNBC. In fact, an opposite trend was seen among the Chinese women, whereby TNBC tends to occur at older age group.[12]

Lin and colleagues revealed that among the 1028 breast carcinoma cases in Taiwan, women under 50 years of age had significantly more luminal A tumour and fewer TNBC than women over 50 years of age.[23] In agreement with these authors, cohort effect is our consideration: as reproductive patterns in Asia are changing rapidly, younger women are at greater risk for luminal A breast carcinoma subtype due to Westernisation (fewer pregnancies, late age at first birth and shorter duration of breastfeeding) compared with the older populations.

Demographically, TNBC was found to occur predominantly in Chinese ethnicity (71.1%) in our study. This observation was different from the previous study in Sarawak, in which TNBC was significantly more frequent among the natives of Borneo (37%) and Malays (33%) than Chinese (23%). Our postulation was that Chinese constitute the plurality of Penang Islands' population: the 2010 Malaysian Census indicated that about 53% of Penang inhabitants were of Chinese descent,[24] thus making the proportion of cases were predominantly of Chinese ethnicity. Larger scale study crosses all states in Malaysia may be required to minimise the selection bias.

The prevalence of AR expression in TNBC was highly variable according to many published data, ranging from 10%,[13] 20%,[25] 22%,[26] 25%,[27] 30%,[28] 38%[17] to 53%.[29] Amongst the factors that underlie the wide range of AR expression are: (1) variation in defining positivity of ER, PR, AR and HER2 amplification in the cancer cells, (2) variation in patient selection from archival specimen (primary versus metastases) and (3) the use of different assay for AR testing. In our study, we found that the prevalence of AR expression in TNBC was 30%, using the cut off of 1% immunoreactivity for AR staining. With the similar cut point of 1% nuclear immunoreactivity to define positive AR immunoexpression, the reported prevalence of AR expression were parallel across different studies: 32.5%,[15] 36%[8] and 38%.[17] Standardisation of the defining criteria to increase validity and reliability of the result interpretation is hence warranted.

Noteworthy, the cut off value for defining AR immunopositivity was varied widely from 1%,[8,17,30] 5%,[27] 10%[29,31] to 25%.[26] This becomes a major inherent problem when comparing results across different studies. This effect can be shown by different findings reported by He and colleagues.[27] In their study, they utilised a cut off levels of $\geq$ 5%, and they found that there was a higher frequency of nodal metastases in patients with AR-negative tumours compared to those with AR-positive tumours, as well as disease-free survival and overall survival were statistically shorter in those AR-negative tumours.[27] In contrast to the study conducted by Tang and colleagues, with the cut off level of $\geq$ 10%, they reported that AR expression was correlated with the histological grade of tumours, however was not correlated with nodal metastases in TNBC.[31] By utilising the same cut off of 10%, Park and colleagues found that there was no impact on survival on both AR positive and negative group in TNBC.[32] Luo and colleagues (utilised cut off value of 25%) reported that AR immunopositivity was correlated with lower tumour grade, less nodal metastases, better five years disease-free and overall survival.[26] Thus, variation in defining immunopositivity in carcinoma cells is a confounding factor in analysing and comparing these different reported data in literature. We strongly recommend that a standard cut off value should be employed to define AR immunopositivity across studies to ensure reliable and reproducible study outcomes.

Eighty-five percent of TNBC cases in our study were of invasive carcinoma, no special type. This was similarly observed with the previous studies. There were only three cases of invasive lobular carcinoma in our study which explained the rare occurrence of TNBC phenotype in invasive lobular carcinoma. All these three cases were positive for AR (with staining proportion of tumour cell staining of 25%, 80%, 90%). It has been shown that AR immunostaining is frequently positive in apocrine and lobular carcinoma, whereas less

common in mucinous, metaplastic and medullary carcinoma.[15] McNamara and colleagues also concluded the same rarity of triple negative phenotype invasive lobular carcinoma; however, it reported that triple negative phenotype invasive lobular carcinoma had relatively lower incidence of AR expression, which was discordant with our findings.[16] The inconsistency in the observation could be due to sample size limitation. Hence, further investigation is required to clarify this observation.

Our study revealed that the mean age for AR-negative cases were younger (mean age: 57.2 years) than those with AR-positive cases (mean age: 60.5 years) ($p > 0.05$). Similar observation was also reported by Kneubil and colleagues, in which they found that among the 34 TNBC cases, AR-positive patients were slightly older (mean age: 55.3 years) than AR-negative patients (mean age: 50.5 years) however was too not statistically significant.[33] Similarly, with larger number of patients (n = 135), Astvatsaturyan and colleagues gave the similar conclusion, in which the mean age of AR-positive patients was significantly older (mean age: 61.4 years) than that of AR-negative patients (mean age: 54.8 years).[34] The statistical insignificance in our study was possibly related to a smaller number of patients recruited.

The potential prognostic role of AR expression in TNBC is still largely debatable.[8,17,26,28,32] In our study, analysis of the relationship of AR expression and clinicopathological parameters revealed that positive immunostaining was inversely correlated with higher histological grade. These results were in concordance with previous studies.[15,17,19,35] However, the tumour stage (including tumour size, nodal status and distance metastasis) was not proved to be significantly different between the AR-positive and AR-negative groups. Our findings concurred with a large scale study carried out by Thike and colleagues in Singapore who recruited a total of 699 TNBC,[17] using similar cut off value of $\geq 1\%$ for defining AR immunoreactivity. They reported that disease-free survival was significantly better in AR-positive TNBC, with a trend for improved overall survival. Thus, the authors concluded that the loss of AR in TNBC carried worse prognosis. In agreement with them, our study indirectly signified that AR expression is associated with less aggressive tumour behaviour.

Intriguingly, variable immunoreactivity for basal markers such as epidermal growth factor receptor (EGFR) and CK5/6 in AR-expressing TNBC was reported, with the former being more frequently expressed (76% vs 20%).[34] Additional information on EGFR immunoexpression status allowed stratification of TNBC patients further into three prognostic risk categories: (1) low risk (AR+EGFR-) which represents the LAR molecular subtype with the best prognosis, (2) high risk (AR-EGFR+) and (3) intermediate risk (AR+EGFR+ and AR-EGFR-). The low risk (AR+EGFR-) TNBC category represents the LAR molecular subgroup with the best prognosis and could potentially benefit from anti-androgen targeted therapies, while high risk (AR-EGFR-) TNBC denotes the basal molecular phenotype with the worst clinical outcomes and chemotherapy being the only standard of care.[34]

In conclusion, AR immunoexpression is found significantly associated with lower histological grade tumour in agreement with others, although loss of AR immunoexpression does not predict adverse clinical outcomes. Larger cohorts for better characterisation of the role of AR immunoexpression in TNBC are warranted. Embarking future studies on analysing AR expression in different molecular subtypes of TNBC (such as basal-like or non-basal-like) as well as its long-term clinical outcome would provide new insight to our understanding of TNBC.

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REFERENCES

1. Azizah AM, Nor Saleha IT, Noor Hashimah A, Asmah ZA, Mastulu W. Malaysian National Cancer Registry Report 2007-2011, Malaysia Cancer Statistics, Data and Figure. *Natl Cancer Institue*. 2016; 16: 203.
2. Yip CH, Pathy NB, Teo SH. A review of breast cancer research in Malaysia. *Med J Malaysia*. 2014; 69: 8-22.
3. Abdullah NA, Wan Mahiyuddin WR, Muhammad NA, et al. Survival rate of breast cancer patients in Malaysia: a population-based study. *Asian Pac J Cancer Prev*. 2013; 14(8): 4591-4.
4. Kopans DB. Just the Facts: Mammography Saves Lives With Little If Any Radiation Risk To the

Mature Breast. *Health Phys*. 2011; 101(5): 578-82.
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. *Lancet*. 2008; 371(9606): 29-40.
6. Maximov PY, Lee TM, Jordan VC. The discovery and development of selective estrogen receptor modulators (SERMs) for clinical practice. *Curr Clin Pharmacol*. 2013; 8(2): 135-55.
7. Slamon D, Eiermann W, Robert N, *et al*. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011; 365(14): 1273-83.
8. Safarpour D, Pakneshan S, Tavassoli FA. Androgen receptor (AR) expression in 400 breast carcinomas: is routine AR assessment justified? *Am J Cancer Res*. 2014; 4(4): 353-68.
9. Carey LA. Directed therapy of subtypes of triple-negative breast cancer. *Oncologist*. 2010; 15(suppl 5): 49-56.
10. Dent R, Trudeau M, Pritchard KI, *et al*. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res*. 2007; 13(15 Pt 1): 4429-34.
11. Haffty BG, Yang Q, Reiss M, *et al*. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. *J Clin Oncol*. 2006; 24(36): 5652-7.
12. Devi CRB, Tang TS, Corbex M. Incidence and risk factors for breast cancer subtypes in three distinct South-East Asian ethnic groups: Chinese, Malay and natives of Sarawak, Malaysia. *Int J Cancer*. 2012; 131(12): 2869-77.
13. Niemeier LA, Dabbs DJ, Beriwal S, Striebel JM, Bhargava R. Androgen receptor in breast cancer : expression in estrogen receptor-positive tumors and in estrogen receptor-negative tumors with apocrine differentiation. *Mod Pathol*. 2009; 23(2): 205-12.
14. Chottanapund S, Van Duursen MBM, Navasumrit P, *et al*. Effect of androgens on different breast cancer cells co-cultured with or without breast adipose fibroblasts. *J Steroid Biochem Mol Biol*. 2013; 138: 54-62.
15. Mrklić I, Pogorelić Z, Ćapkun V, Tomić SŽ. Expression of androgen receptors in triple negative breast carcinomas. *Acta Histochem*. 2013; 115(4): 344-8.
16. McNamara KM, Yoda T, Takagi K, Miki Y, Suzuki T, Sasano H. Androgen receptor in triple negative breast cancer. *J Steroid Biochem Mol Biol*. 2013; 133(1): 66-76.
17. Thike AA, Yong-Zheng Chong L, Cheok PY, *et al*. Loss of androgen receptor expression predicts early recurrence in triple-negative and basal-like breast cancer. *Mod Pathol*. 2014; 27(3): 352-60.
18. Moinfar F, Okcu M, Tsybrovskyy O, *et al*. Androgen receptors frequently are expressed in breast carcinomas: Potential relevance to new therapeutic strategies. *Cancer*. 2003; 98(4): 703-11.
19. Gerratana L, Basile D, Buono G, *et al*. Androgen receptor in triple negative breast cancer: a potential target for the targetless subtype. *Cancer Treat Rev*. 2018; 68: 102-10.
20. Zhu A, Li Y, Song W, et al. Antiproliferative Effect of Androgen Receptor Inhibition in Mesenchymal Stem-Like Triple-Negative Breast Cancer. *Cell Physiol Biochem*. 2016; 38(3): 1003-14.
21. Fitzgibbons PL, Bose S, Chen YY, *et al*. Protocol for the Examination of Specimens From Patients With Invasive Carcinoma of the Breast. 2018;(January):1-32. Available from www.cap.org/cancerprotocols.
22. Dent R, Trudeau M, Pritchard KI, *et al*. Triple-negative breast cancer: Clinical features and patterns of recurrence. *Clin Cancer Res*. 2007; 13(15): 4429-34.
23. Lin CH, Liau JY, Lu YS, *et al*. Molecular subtypes of breast cancer emerging in young women in Taiwan: Evidence for more than just westernization as a reason for the disease in Asia. *Cancer Epidemiol Biomarkers Prev*. 2009; 18(6): 1807-14.
24. Department of Statistics M. Population Distribution by Local Authority Areas and Mukims. *Popul Hous Census Malaysia*. 2010.
25. Pristauz G, Petru E, Stacher E, *et al*. Androgen receptor expression in breast cancer patients tested for BRCA1 and BRCA2 mutations. *Histopathology*. 2010; 57(6): 877-84.
26. Luo X, Shi Y-X, Li Z-M, Jiang W-Q. Expression and clinical significance of androgen receptor in triple negative breast cancer. *Chin J Cancer*. 2010; 29(6): 585-90.
27. He J, Peng R, Yuan Z. Prognostic value of androgen receptor expression in operable triple-negative breast cancer : a retrospective analysis based on a tissue microarray. 2012: 406-10.
28. Micello D, Marando A, Sahnane N, Riva C, Capella C, Sessa F. Androgen receptor is frequently expressed in HER2-positive, ER/PR-negative breast cancers. *Virchows Arch*. 2010; 457(4): 467-76.
29. Qi JP, Yang YL, Zhu H, *et al*. Expression of the androgen receptor and its correlation with molecular subtypes in 980 Chinese breast cancer patients. *Breast Cancer Basic Clin Res*. 2011; 5(1): 1-8.
30. Tsutsumi Y. Apocrine carcinoma as triple-negative breast cancer: Novel definition of apocrine-type carcinoma as estrogen/progesterone receptor-negative and androgen receptor-positive invasive ductal carcinoma. *Jpn J Clin Oncol*. 2012; 42(5): 375-86.
31. Tang D, Xu S, Zhang Q. The expression and clinical significance of the androgen receptor and E-cadherin in triple-negative breast cancer. 2012: 526-33.
32. Park S, Koo JS, Kim MS, *et al*. Androgen receptor expression is significantly associated with better outcomes in estrogen receptor-positive breast cancers. *Ann Oncol*. 2011; 22(8): 1755-62.
33. Kneubil MC, Godoy AEG, Coelho GP, *et al*. Androgen receptor expression in triple negative breast cancer and its relationship to prognostic factors. *Rev Bras Mastol*. 2017; 27(3): 199-205.
34. Astvatsaturyan K, Yue Y, Walts AE, Bose S. Androgen receptor positive triple negative breast cancer: Clinicopathologic, prognostic, and predictive features. *PLoS ONE*. 2018; 13(6): 1-16.
35. Wang C, Pan B, Zhu H, Zhou Y, *et al*. Prognostic value of androgen receopro in triple negative breast cancer: a meta-analysis. *Oncotarget*. 2016; 7: 46482-91.