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Triple-negative breast cancer: from classical clinicopathological features to androgen receptor profile

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Abstract

Triple-negative breast cancer (BC) represents an extensively analyzed entity to establish the overall framework of clinicopathological characteristics, with an impact on defining prognostic and predictive factors. The relationship between triple-negative BC and androgen receptor (AR) is far from being clarified. We aimed to evaluate the classical clinicopathological spectrum that characterized a triple-negative BC, focusing on AR expression. The study group comprised 124 cases of triple-negative BC. The main clinicopathological parameters were extracted from medical records. The immunohistochemical (IHC) exam was run using the following antibodies: anti-estrogen receptor (ER), anti-progesterone receptor (PR), anti-human epidermal growth factor receptor (HER2/neu), anti-Ki67 and anti-AR. AR immunoexpression was assessed as absent (completely negative) or present (unrelated to percentages and intensity). Data were statistically analyzed. AR expression was positive in 78 (63%) cases and negative in 46 (37%) cases. Among the study group, 28 cases exhibited an AR percentage ranging from 1% to 10%, 15 cases showed a percentage between 11% and 50%, while 12 cases had AR values between 51% and 75% and 23 cases fell within the AR range of 76% to 100%. No significant differences between AR immunoexpression (negative *versus* positive), clinicopathological characteristics and survival parameters were found. Statistically significant differences were registered between histological type, tumor stage, distant metastasis, tumor-infiltrating lymphocytes (TILs), treatment and residual cancer burden (RCB), and survival parameters. Thus, our results sustain that AR does not affect the biological behavior of triple-negative BC.

Keywords: triple-negative breast cancer, androgen receptor, prognostic factor.

Introduction

Breast cancer (BC) is the dominant form of cancer among women globally, ranking second in incidence after lung cancer and fourth in mortality after colorectal, liver and lung cancer [1–3].

The concept of molecular classification in BC proposed in 2000 has as its scientific basis the identification of biological forms of cancer that share common characteristics both in terms of molecular profile and therapeutic approach [4]. Four defined molecular classes, known as luminal A, luminal B, human epidermal growth factor receptor (HER2/neu), and triple negative were confirmed in 2012 by the Cancer Genome Atlas program [5]. Currently, the BC molecular subtypes guide the therapeutic options.

The triple-negative BC represents about 10–15% of all BC cases, being defined by the lack of hormonal receptors – namely estrogen receptor (ER) and progesterone receptor (PR) – and HER2/neu, together with a high proliferation index, giving it an aggressive pattern. Patients have a 66% higher risk of presenting with high-grade tumors at diagnosis [6].

Subclassifications based on trait uniqueness analyzed by immunohistochemical (IHC) profiling and genomic ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) sequencing have been proposed for triple-negative BC [7–10]. The identified entities are defined as basal-like 1 (BL1) type, basal-like 2 (BL2) type, mesenchymal (M) type, mesenchymal stem-like (MSL) type, immunomodulatory (IM) type and luminal androgen receptor (LAR) type. It is worth mentioning the report of quadruple-negative BC in which, in addition to the absence of ER, PR and HER2/neu immunoexpression, androgen receptor (AR) expression is also lost. This variant is expressed in about 10–43% of triple-negative BC [11].

The new subclassification has not yet been introduced into clinical practice [12]. However, the literature confirms that neoadjuvant therapy, including pathological complete response (pCR), is dependent on these entities [13]. The BL1 variant had the highest rate of pathological response, whereas the BL2 and LAR variants have the lowest rate [13, 14].

The relationship between triple-negative BC and AR is important for therapeutic decisions [14]. AR is predominantly expressed in LAR subtype [14]. However, the reports on AR significance as a prognostic factor are contradictory.

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Aim

Within this context, our study aims to evaluate the classical clinicopathological spectrum that characterized a triple-negative BC group of patients; additionally, we focused on the AR expression along with the clinicopathological outlines, developing a correlational analysis to highlight its influence on tumor behavior.

Patients, Materials and Methods

Patients

The study group comprised 124 patients diagnosed with triple-negative BC between January 2018 and December 2022 at the Department of Pathology, Regional Institute of Oncology, Iaşi, Romania. The major selection criterion was the diagnostic classification in the triple-negative subtype based on the IHC profile: ER, PR, and HER2/neu. The main clinicopathological parameters were collected from medical records. These parameters were established in accordance with the classification of breast tumors afforded by *World Health Organization* (WHO) [15], and included age, histological type, histological characteristics, tumor grade, clinical and pathological tumor–node–metastasis (TNM) stage, tumor-infiltrating lymphocytes (TILs), first-line treatment, residual cancer burden (RCB), progression-free survival (PSF) and overall survival (OS). It is worth mentioning that out of a total of 124 patients, 99 (79.8%) patients underwent surgical treatment after neoadjuvant therapy. For the 25 (20.2%) cases unqualified for surgery, the microscopic exam of the surgical resection specimen could not be performed. Consequently, the assessment of the pathological characteristics, such as pTMN, lymphatic, vascular and perineural invasion, respectively, and RCB was exclusively conducted in the subgroup composed of 99 cases.

Ethical approval was granted from the Ethics Board responsible for research ethics at the Grigore T. Popa University of Medicine and Pharmacy, Iaşi, and the Regional Institute of Oncology, Iaşi, respectively.

Tissue samples and histopathological exam

Specimens were obtained through either needle core biopsy or radical mastectomy. Following collection, they underwent fixation in 10% neutral buffered formalin and were processed to obtain paraffin-embedded blocks for standard histopathological exam. Sections of 4–5 µm-thick were cut, placed on slides, deparaffinized using xylene and gradually rehydrated with ethanol in reducing concentrations, and stained with Hematoxylin–Eosin (HE).

Immunohistochemical exam

The initial IHC exam was run using the classical antibody panel for BC diagnosis, namely ER, PR, HER2/neu and Ki67. In the next stage, the IHC exam was complemented with AR expression analysis (Table 1).

The IHC protocol included the following steps: dewaxing in xylol, rehydration in ethanol baths with decreasing concentrations, heat-induced antigen retrieval using a target retrieval solution with pH 6 at 98°C for 20 minutes, inhibition of endogenous peroxidase activity in a solution of hydrogen peroxide, incubation with the primary antibody at room temperature for 60 minutes, and visualizations of the reaction with the appropriate detection system. The positive control consisted of positive BC tissue for ER, PR and HER2/neu, tonsil for Ki67 and prostate tissue for AR. Negative control was done by excluding the primary antibody.

Table 1 – ***Clones, dilutions and expression for antibodies***

Antibody	Clone, source	Dilution	Cellular localization
ER	Anti-ER (SP1) – rabbit monoclonal antibody (Roche, Basel, Switzerland)	RTU	Nuclear
PR	Anti-PR (1E2) – rabbit monoclonal antibody (Roche, Basel, Switzerland)	RTU	Nuclear
HER2/neu	Anti-HER2/neu (4B5) – rabbit monoclonal antibody (Roche, Basel, Switzerland)	RTU	Membrane
Ki67	Anti-Ki67 (30-9) – rabbit monoclonal antibody (Roche, Basel, Switzerland)	RTU	Nuclear
AR	Anti-AR (SP107) – rabbit monoclonal antibody (Thermo Fisher Scientific, Waltham, MA, USA)	1:500	Nuclear

AR: Androgen receptor; ER: Estrogen receptor; HER2/neu: Human epidermal growth factor receptor; PR: Progesterone receptor; RTU: Ready-to-use.

Immunoexpression assessment

The Allred scoring system was applied to evaluate nuclear positivity for ER and PR [16]. The scoring method involved the proportion score (PS), graded from 0 to 5 to represent the positive tumor cell's percentage, and intensity of staining (IS), graded from 0 to 3 to denote staining strength. PS values delineated specific ranges: 0 (0%), 1 (<1%), 2 (1–10%), 3 (11–33%), 4 (34–66%), and 5 (67–100%). IS was evaluated across a spectrum ranging from 0, indicating no detectable staining, to 3, representing the highest level of observed immunoreactivity. Total scores (TS) were calculated by summing PS and IS scores, where TS 0 and 2 were deemed negative, and TS from 3 to 8 were considered positive. Thus, TS of 0, 1 and 2 were considered as valuable for triple-negative BC diagnosis.

HER2/neu status assessment adhered to established criteria which categorized immunoreactivity into four distinct scores [17]. A score of 0 indicated either a complete absence of immunoreactivity or immunoreactivity present in less than 10% of tumor cells. Conversely, a score of 1+ signified faint weak immunoreactivity observed in more than 10% of cells, with only a portion of the membrane exhibiting positivity. For a score of 2+, either weak or moderate immunoreactivity, completely marking the membrane, was detected in over 10% of cells, or intense staining was visible in less than 30% of cells. Lastly, a score of 3+ was assigned when more than 30% of tumor cells displayed uniform membrane staining, suggestive of positivity, often characterized by a homogeneous chicken-wire pattern. Thus, score 0 and score 1+, regarded as negative immunoreaction, were considered for triple-negative BC diagnosis.

AR evaluation was assessed based on the nuclear staining on entire sections [18, 19]. The fractions of positively marked nuclei within malignant cells, varying between 1% and 100%, were evaluated, disregarding the immunostaining intensity. According to the percentage, we used four intervals, as follows: 1% to 10%, 11% to 50%, 51% to 75% and 76% to 100%. Finally, AR immunoexpression was categorized as absent (completely negative) or present (unrelated to percentages and intensity), resulting in two classes: AR absent and AR present.

Ki67 values were quantified as the percentage of nuclei exhibiting positive immunostaining throughout the tumor, with no regard to staining intensity [20]. A median score of 50% immunopositive cells served as the delineation point, distinguishing between lower expression (Ki67 score below 50%) and higher expression (Ki67 score above 50%) [20].

Statistical analysis

All obtained results were analyzed by using the facilities provided by Statistical Package for Social Sciences (SPSS) software ver. 19 (SPSS Inc., Chicago, IL, USA), running χ^2 (*chi*-squared) and Fisher's exact test, respectively, for nominal variable correlations, and Kaplan–Meier curves and *log*-rank test for survival data. The *p*-value less than 0.05 indicated statistical significance.

Results

Baseline clinicopathological parameters

Within the analyzed cohort, the mean age was 58.73 ±12.2 years; the youngest individual was 33 years old, while the oldest was 85.

For most patients, namely 109 (87.9%) cases, the established diagnosis was invasive ductal carcinoma – not otherwise specified (NOS), indicating a common form of BC. Ten (18.1%) cases presented metaplastic carcinoma, whereas the remaining five (4%) cases encompassed various other subtypes, representing less frequent histological variations within the study cohort. Figure 1 (A–D) illustrates different histological types of BC.

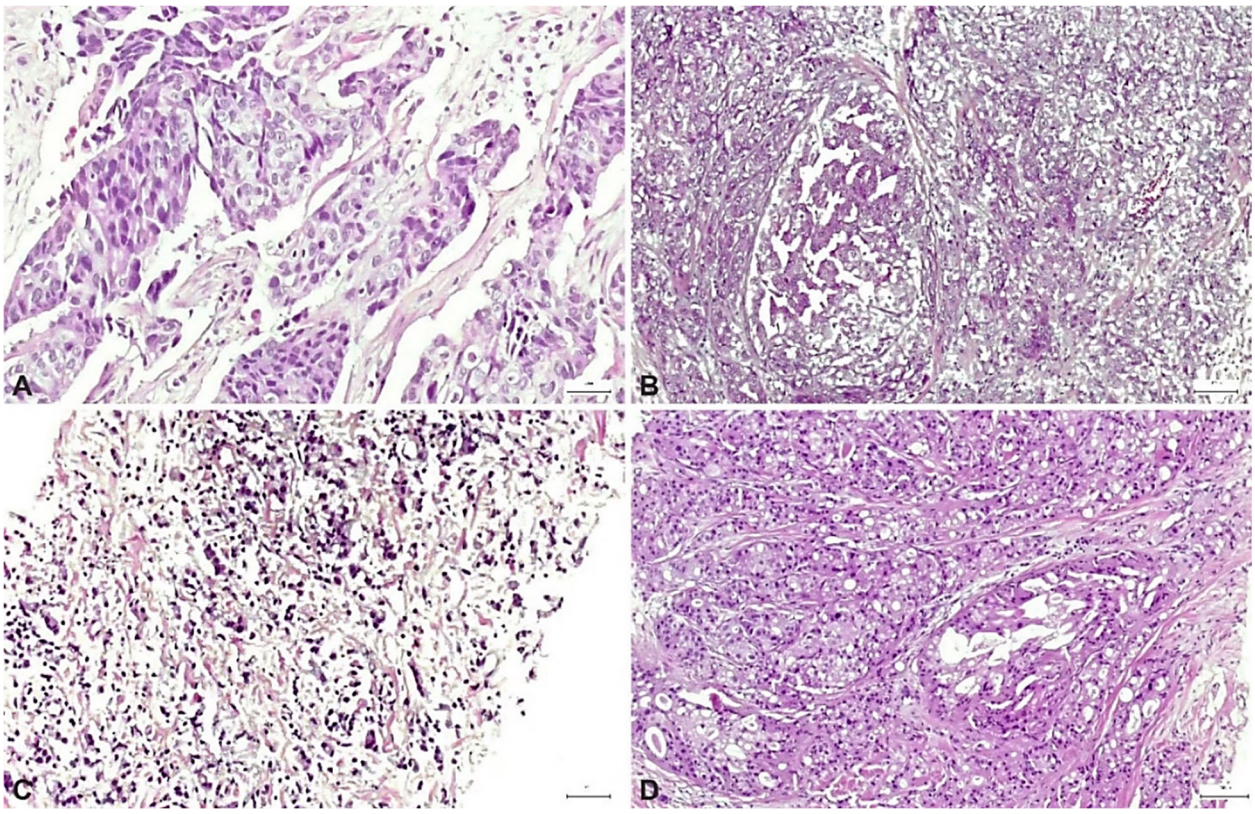

Figure 1 – ***Different histological subtypes of triple-negative breast carcinoma: (A) Invasive ductal carcinoma, NOS; (B) Invasive ductal carcinoma with medullary pattern; (C) Lobular carcinoma; (D) Apocrine carcinoma. HE staining: (A and C) ×200; (B and D) ×100. HE: Hematoxylin–Eosin; NOS: Not otherwise specified.***

Among the study group, three (2.4%) cases were categorized as G1, signifying well-differentiated tumors with a lower level of morphological abnormality, 18 (14.5%) cases were classified as G2 – moderately differentiated tumors, with a mild level of abnormality, and 103 (83.1%) cases were graded as G3, denoting poorly differentiated tumors with the highest level of abnormality and aggressiveness.

In the study group, the distribution of cases in relation to clinical tumor stage was as follows: 11 (8.9%) cases in T1 (small size tumor, with a maximum of 20 mm); 65 (52.4%) cases in T2 (tumor size more than 20 mm, with a maximum of 50 mm); 13 (10.5%) cases in T3 (tumor size more than 50 mm); 35 (28.2%) cases in T4 (any size, but extension to chest wall or skin). Additionally, the clinical node stage indicated: 32 (25.8%) cases in N0; 56 (45.2%) cases in N1; 22 (17.8%) cases in N2; 14 (11.2%) cases in N3. Based on imaging examination upon diagnosis, 99 (79.8%) cases had no clinical or imaging proof of distant metastases (M0), whereas the other 25 (20.2%) cases presented distant metastases (M1). Based on the clinical TMN, tumor staging indicated stage II as the most prevalent (48 cases – 38.7%), followed by stage III (44 cases – 35.5%) and stage IV (25 cases – 20.2%), while stage I (seven cases – 5.6%) comprises the smallest percentage within the cohort.

Histopathology established the following grouping of pathological tumor stage: 40 (32.3%) cases in pT1, 40 (32.3%) cases in pT2, seven (5.6%) cases in pT3, 12 (9.6%) cases in pT4, and no data available for 25 (20.2%) cases. In terms of pathological lymph node involvement, 52 (41.9%) cases presented N0 stage, 28 (22.6%) cases were categorized as N1, 12 (9.7%) cases were observed in N2, seven (5.6%) cases were classified as N3 category, and no data were accessible for 25 (20.2%) cases.

The evaluation of lymphatic invasion reveals 42 (33.8%) cases of cases exhibiting tumor emboli, while 57 (46%) cases showed no signs of invasion; 25 (20.2%) cases remained unspecified. Similarly, vascular invasion analysis yields further insights: positive results were obtained in 24 (19.4%) cases, contrasting with no tumor emboli in 75 (60.4%) cases, and 25 (20.2%) cases with no available data. Furthermore, perineural invasion assessment revealed nerve infiltration in 18 (14.5%) cases, 81 (65.3%) cases without nerve involvement, and 25 (20.2%) cases with unavailable information.

The diversity of TILs was evident: 72 (58%) cases exhibited low-grade TILs, reflecting a subdued immune response; in 31 (25%) cases, an intermediate-grade TILs suggested a moderate immune reaction; high-grade TILs, detected in 21 (17%) cases, signified an active immune response to the tumor.

Regarding the Ki67 expression, less than 50% of positive tumor cells was seen in 15 (12%) cases, whereas 109 (88%) cases exceeded 50%.

The RCB analysis within our study cohort showed that 12 (9.7%) cases achieved a complete response – RCB 0, 20 (16.1%) cases were classified as RCB I, 44 (35.5%) cases fell into the RCB II and 23 (18.5%) cases were categorized as RCB III; no data were accessible for 25 (20.2%) cases.

Androgen receptor assessment

The IHC analysis of AR expression indicated immunopositivity in 78 (63%) cases, while negative immunoexpression was observed in 46 (37%) cases. Among the study group, 28 cases (22.6% of total group, 35.9% of all positive cases) exhibited an AR percentage ranging from 1% to 10%, 15 cases (12.1% of total group, 19.2% of all positive cases) showed a percentage between 11% and 50%, while 12 cases (9.7% of total group, 15.4% of all positive cases) had AR values between 51% and 75% and 23 cases (18.6% of total group, 29.5% of all positive cases) fell within the AR range of 76% to 100%. Figure 2 (A–D) illustrates the wide range of AR positive immunoexpression.

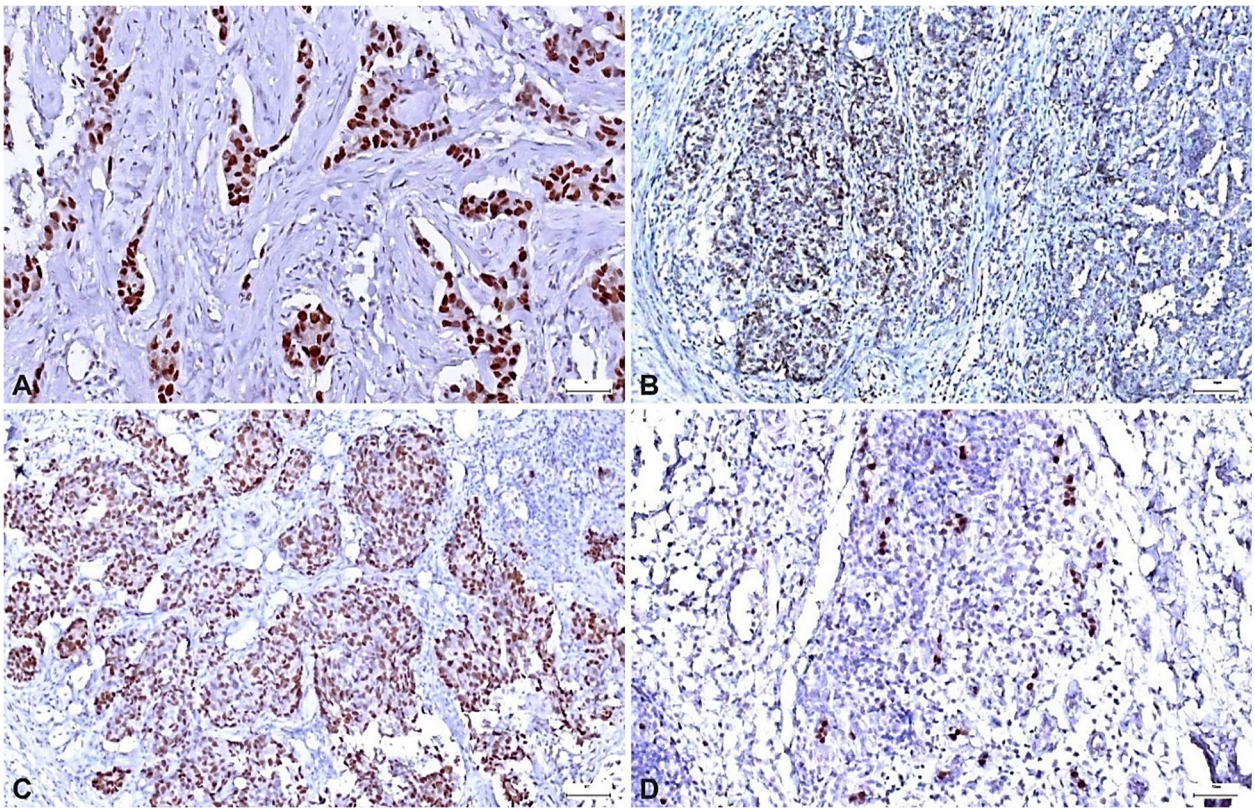

Figure 2 – ***Different AR immunoexpression: (A) Percentage of positive tumor cells over 76%; (B) Percentage of positive tumor cells between 11–50%; (C) Percentage of positive tumor cells between 51–75%; (D) Percentage of positive tumor cells less than 10%. Immunohistochemistry, anti-AR antibody: (A and D) ×200; (B and C) ×100. AR: Androgen receptor.***

Correlations between classical clinicopathological characteristics and androgen receptor

The statistical analysis showed no significant differences between AR immunoexpression (negative *versus* positive) and clinicopathological characteristics (Table 2).

Correlations between classical clinicopathological characteristics and androgen receptor, and survival parameters

Univariate analysis confirmed statistically significant differences for PFS, in relation to the histological type (p=0.011), tumor staging, distant metastasis and first-line treatment (p<0.000), intensity of TILs (p=0.004), and RCB (p=0.019), respectively.

Poor OS was statistically significant correlated with histological type (p=0.045), tumor staging, lymphatic, vascular and perineural invasion, metastatic lesions, first-line treatment (p<0.000), and RCB (p=0.015), respectively.

However, no significant differences in survival parameters in relation to AR status was found (PFS: p=0.637; OS: p=0.746), suggesting no association between AR immunoexpression and the biological course of disease.

Table 2 – ***Androgen receptor immunoexpression related to clinicopathological characteristics***

Clinicopathological parameters	AR immunohistochemical expression					p-value
	Negative (*n*=46)		*Positive* (*n*=78)		*NA*	
	n	%	*n*	%	*n (%)*	
Age (median)						
≤61 years old	27	41.54%	38	58.46%		0.283
>61 years old	19	32.20%	40	67.80%		
cT						
cT1	1	9.10%	10	90.90%		0.150
cT2	25	38.46%	40	61.54%		
cT3	7	53.84%	6	46.16%		
cT4	13	37.14%	22	62.86%		
cN						
cN0	10	31.25%	22	68.75%		0.240
cN1	24	42.86%	32	57.14%		
cN2	5	22.73%	17	77.27%		
cN3	7	50%	7	50%		
cM						
cM0	37	37.76%	61	62.24%		0.768
cM1	9	34.62%	17	65.38%		
pT					25 (20.2%)	
pT1	12	30%	28	70%		0.376
pT2	18	45%	22	55%		
pT3	4	57.14%	3	42.86%		
pT4	4	33.33%	8	66.67%		
pN					25 (20.2%)	
pN0	21	40.38%	31	59.62%		0.948
pN1	10	35.71%	18	64.29%		
pN2	4	33.33%	8	66.67%		
pN3	3	42.86%	4	57.14%		
Lymphatic invasion					25 (20.2%)	
L0	21	36.84%	36	63.16%		0.713
L1	17	40.48%	25	59.52%		
Vascular invasion					25 (20.2%)	
V0	28	37.33%	47	62.67%		0.704
V1	10	41.67%	14	58.33%		
Perineural invasion					25 (20.2%)	
Pn0	32	39.51%	49	60.49%		0.626
Pn1	6	33.33%	12	66.67%		
Histological grade						
G1	2	66.67%	1	33.33%		0.546
G2	7	38.89%	11	61.11%		
G3	37	35.92%	66	64.08%		
Histological type						
Invasive ductal carcinoma NOS	41	37.61%	68	62.39%		0.884
Metaplastic carcinoma	3	30%	7	70%		
Other types	2	40%	3	60%		
Stage at diagnosis						
I	1	14.29%	6	85.71%		0.510
II	20	41.67%	28	58.33%		
III	17	38.64%	27	61.36%		
IV	8	32%	17	68%		
RCB					25 (20.2%)	
0	3	25%	9	75%		0.323
I	6	30%	14	70%		
II	18	40.91%	26	59.09%		
III	11	47.83%	12	52.17%		
TILs						
Low grade, <10%	26	36.11%	46	63.89%		0.791
Intermediate grade, 10–50%	13	41.94%	18	58.06%		
High grade, >50%	7	33.33%	14	66.67%		
Ki67 index						
≤50%	5	33.33%	10	66.67%		0.748
>50%	41	37.61%	68	62.39%		

AR: Androgen receptor; *n*: No. of cases; NA: Not available; NOS: Not otherwise specified; RCB: Residual cancer burden; TILs: Tumor-infiltrating lymphocytes.

Discussions

Triple-negative BC represents an extensively analyzed entity to establish the overall framework of clinico-pathological characteristics, with an impact on defining prognostic and predictive factors. The constant concern to decipher the biological particularities of triple-negative BC has included, among the list of major topics of interest, the association of AR as a hormonal influence element in a non-hormonal carcinogenic profile. AR is a type I nuclear receptor, included in the sexual steroid receptor family, with a role in stimulating cell growth and proliferation through involvement in signaling pathways implicated in breast carcinogenesis [21, 22].

Several studies in the mainstream aimed at the investigation of AR involvement in triple-negative BC. Unlike the luminal subtype, where AR has an inhibitory effect on tumor growth, in the triple-negative subtype, it stimulates tumor development [23]. The obtained results present a wide degree of variability, so contradictory data have not made it possible to formulate a general conclusion that settles the value of AR in this diagnostic entity. Therefore, the relationship between triple-negative BC and AR is far from being clarified.

Within this context, our study focuses on the general profile of triple-negative BC, including the analysis of AR variability and its relationships with tumor traits, thus extending the knowledge on its involvement in breast carcinogenesis.

In our study group, 78% of cases presented AR positive status, a result that exceeds the upper limit documented in the literature. Variable percentages for AR positivity are reported in triple-negative BC cases, especially in the LAR subtype. Recent data indicate intervals between 18–41% [24–26], or 17.1–38% [27–32], and also a higher percentage of 50% [33] is stated. The variability of positivity critically depends on the threshold set to define a positive or negative AR profile. This threshold, differing according to the working group, has values either less than 1% or less than 10% [27–33].

The presence of AR expression is correlated with an average age ranging between 45.3–58.4 years old [24, 25, 27–29, 34]. Our study group had the mean age of 58.73±12.2 years (range 33–85 years) in alignment with literature, and no correlation was found with AR status (positive *versus* negative). Most studies do not confirm a relationship between AR and patients' age [26, 31, 35, 36]. Moreover, the age parameter in relation to AR urges multiple discussions because such an evaluation can be influenced by demographic factors, according to which normal AR status differs depending on geographic location [33, 37].

Despite the relatively large number of analyzed cases and the increased AR positivity rate, our study revealed no statistically significant differences between AR immuno-expression and all clinicopathological characteristics, and survival parameters. These results suggested no association between AR status and the biological course of triple-negative BC. The statistical analysis applied for the survival times confirmed only the prognostic role of histological type, tumor stage, distant metastases, TILs, first-line treatment and RCB for PFS, and the relationship between histological type, tumor stage, lymphovascular and perineural invasion, metastatic lesions, first-line treatment and RCB, as negative prognostic factors, and OS.

The literature review shows several studies confirming the association between positive AR and a less aggressive biological profile mirrored through low clinical stage, low histological grade, low mitotic rate, lymphovascular invasion [28], lymph node metastases [25–28, 34, 35, 38, 39], increased five-year disease-free survival (DFS) and OS [18, 24, 26, 29, 30, 34, 36, 40–44]. However, in a single study, positive AR is associated with increased Ki67 levels [45].

Conversely, negative AR is correlated with a more advanced nodal pathological stage and increased risk of recurrence [25, 30, 31, 34, 35, 38, 39, 46, 47].

Discordant results reveal the relationship between positive AR and increased mortality [42], unfavorable prognosis [41]. Thus, positive AR has been considered a predictor for short DFS and OS in the context of negative lymph node status [48], but without predictive value in the presence of metastatic lymph nodes [48].

Nonetheless, other studies indicate the absence of correlation between AR status, clinicopathological characteristics [33], DFS or OS [27, 35, 39, 44, 45] – these data being consistent with our results.

Several arguments can justify the discordant results in the literature, and also the discrepancy of our data with some of the already published studies. We underline the marked diversity in the design of the studies, starting from the number of patients analyzed, the applied therapy [33], the duration of follow-up, the chosen anti-AR antibody type, and the quantification method. Further discussions can be developed if we consider the relationship between survival times, different types of therapy (radiation therapy, chemotherapy, mastectomy, lumpectomy), and AR status, positive or negative [33].

Conclusions

The analysis of AR's value as a prognostic factor and/or therapeutic target is currently being investigated through multiple studies. Our study did not validate the correlation of AR status and classical clinicopathological characteristics, including survival parameters. Thus, our results sustain that AR does not affect the biological behavior of triple-negative BC. However, our data confirm the high proportion of invasive ductal carcinoma NOS within triple-negative BC cases, and the relationship between several clinicopathological parameters, PFS and OS, highlighting their prognostic significance.

Conflict of interests

Authors declare no conflict of interests.

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