REVIEW

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Effect of Androgen receptors in Triple-Negative Breast Cancer Given Neoadjuvant Therapy: A Systematic Review and Meta-Analysis

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Abstract

Objective: Triple-negative breast cancer (TNBC) is a type of breast cancer that does not express the estrogen receptor (ER), the progesterone receptor (PR), or the human epidermal growth factor receptor 2 (*HER2*). TNBC has limited treatment targets, including the androgen receptor (*AR*). However, the therapeutic strategies-based *AR* expression in TNBC remains uncertain. The aim of this study is to compare the effect of neoadjuvant treatment on TNBC androgen receptor-positive versus receptor-negative patients. **Methods:** A systematic search was performed through databases to search for cohort studies that compared the effect of neoadjuvant treatment on TNBC androgen receptor-positive versus TNBC receptor-negative patients. The Mantel-Haenzel and Inverse Variance methods obtained a fixed-effects model of pooled odds or hazard ratios for the primary outcomes. **Results:** Fifteen cohort studies, including 2,713 patients with TNBC, were assessed. The effect of neoadjuvant chemotherapy is less superior on AR+ patients than AR- (OR = 0.60, p = 0.02). For survival outcomes, the AR+ subtype is associated with better 3-year DFS (HR = 0.93, p = 0.69) and 3-year OS (HR = 0.71, p = 0.20) compared with AR-. The statistical value is insignificant. **Conclusion:** The prognostic value of *AR* expression in TNBC is not fully understood, which is an inconclusive result.

Keywords: Androgen receptors- TNBC- Neoadjuvant therapy

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Introduction

Triple-negative breast cancer (TNBC), a subtype of malignant breast cancer first introduced in 2005, is defined as negative clinical testing for estrogen receptor (ERα), progesterone receptor (PR), and human epidermal growth factor receptor 2 (*HER2*) expression [1]. It represents around 20% of all malignant breast cancers and has the lowest 5-year survival rate compared to other breast cancer (BC) subtypes. Only one-fourth of TNBC patients show androgen receptor (*AR*) expression, further divided into triple-negative breast cancer AR-positive subtype (TNBC AR+). All the remaining TNBCs which do not express the *AR* are defined as quadruple-negative breast cancer (QNBC) or triple-negative breast Cancer AR-negative (TNBC AR-) [2-4].

The role of androgen hormone physiology in normal breast tissue is well established. Emerging data suggest that *AR* significantly influences breast cancer gene profiles and affects the tumorigenic properties of TNBC. Neoadjuvant chemotherapy (NAC) has become the standard treatment for BC patients with locally advanced or early stages [5]. Previous studies about *AR* expression indicated that AR-negative TNBC showed significantly poorer outcomes in disease-free survival (DFS) and overall survival (OS) than AR-positive TNBC, which suggested that *AR* expression could be a valuable prognostic marker in TNBC [6, 7]. A pathological complete response (pCR) means there is no invasive residual in the breast or nodes. Mohammed et al. [8] showed that TNBC AR+ had a lower rate of pCR compared with QNBC, suggesting that the AR+ subtype may have a partial chemoresistance. It is established that the higher response rate for chemotherapy in TNBC did not translate into improved survival outcomes. Nevertheless, many studies have suggested that achieving pCR is an effective surrogate marker for predicting long-term survival outcomes [9].

Previous meta-analysis study by Wang, showed AR positivity was associated with a lower risk of disease recurrence in TNBC (Wang et al., 2020). In contrast, Xu's metanalysis study showed a different result, *AR* expression in TNBC was not associated with disease-free survival

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(HR, 0.923; 95% CI, 0.671-1.271; P= 0.634), overall survival (HR, 0.910; 95% CI, 0.678-1.222; P= 0.531), distant disease-free survival (HR, 1.02; 95% CI, 0.96-1.08; P= 0.489), or recurrence-free survival (HR, 0.957; 95% CI, 0.462-1.982; P= 0.906) in TNBC [10]. The role of AR, which is still being debated, triggered the author to create this meta-analysis. The aim of this study is to compare the effect of neoadjuvant treatment on TNBC with androgen receptor-positive (AR+) versus TNBC receptor-negative (AR-) patients.

Materials and Methods

Search Strategy

To provide an evidence base for assessing neoadjuvant treatment outcomes in TNBC AR-positive versus TNBC AR-negative, we systematically reviewed the literature using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11].

A systematic search was performed through Pubmed, Science Direct, Scopus, Sage, Proquest, and the Cochrane Library from 2011 to July 2022. Cohort studies that compared the effect of neoadjuvant treatment on TNBC AR+ versus TNBC AR- patients were eligible for the study. The selection of included studies and data extraction were made following PRISMA guidelines.

For MeSH and free-text searches, the index terms "triple-negative breast cancer," "androgen receptor," "neoadjuvant," and "pathologic complete response" were used. The "related articles" feature in PubMed was used to extend each search and manual search using the original study's reference list. Two independent authors reviewed all studies identified by the search strategy, and a mutual agreement was obtained. If an article was not searchable, we searched for the article manually and contacted the author. There was no need for local ethical approval for this type of research. This research had a registration in PROSPERO with ID number CRD42022373168.

Eligibility criteria

All studies were included based on the following criteria: (1) the study was published in a peer-reviewed journal as a full-length article, including a randomized controlled trial, prospective, or retrospective comparison study; (2) patients who received neoadjuvant chemoradiotherapy; and (3) comparative studies should include all three of the following outcomes: pCR, disease-free survival (DFS), and overall survival (OS) between TNBC with AR+ versus TNBC AR-. Studies were excluded if (1) they do not clearly state clinical outcomes; (2) narrative review studies, duplicate publications, and editorials are also excluded; and (3) they are published in non-English languages.

Risk of bias

The Newcastle-Ottawa Scale (NOS) instrument was used to evaluate the risk of bias (RoB) in non-randomized research [12]. The NOS instrument's three domains are selection, comparability, and outcome. Studies with 7–9 points had a low risk of bias, those with 4–6 points had a moderate risk, and those with 0–3 points had a high risk of bias. We assessed potential bias in the published literature using a funnel plot.

Data Extraction and Management

Between TNBC with AR+ and TNBC AR-, the clinical outcomes were pCR, DFS, and OS. The data were extracted and entered into an Excel spreadsheet for further analysis. The discussion was used to settle any differences of opinion. The following data were extracted from each study: first author, year of publication, study design, sample size, pCR, DFS, OS, and hazard ratio for DFS and OS in both groups. This kind of paper does not need clearance from an institutional review board.

Statistical Analysis

Data eligible for meta-analysis were entered and analyzed using Review Manager, Version 5.4 (Cochrane Collaboration, Oxford, United Kingdom). Meta-analyses were performed according to PRISMA guidelines [13]. The Mantel–Haenzel method [14] obtained a fixed-effects model of pooled ORs. The Inverse Variance method obtained a fixed-effects model of pooled hazard ratios. The hazard ratios (HRs) for survival outcomes (DFS and OS) and the odds ratio (OR) for a binary outcome (pCR), as well as their 95% confidence intervals (CIs), were used to measure the efficacy and safety of the treatment strategies. For specific comparisons, an agent with HR for DFS and OS <1 or OR for pCR >1 was deemed preferable due to its contrast in efficacy. The studies' statistical significance was evaluated by the Z test, with significance set at $p < 0.05$. Heterogeneity among the studies was quantified using Cochran's Q-statistic and I^2 statistic. Substantial heterogeneity was considered to exist with a $p < 0.05$ or $I^2 > 50\%$, and the random-effects method was used after exploring the causes of heterogeneity. Otherwise, the fixed-effects method was used [15].

Results

There were 1,201 articles identified. A total of 889 articles were included after removing the duplicates. About 69 articles remained after eliminating 820 irrelevant articles. Subsequently, 51 articles were eliminated after being thoroughly examined. Therefore, 15 cohort studies met the criteria and were included in this study. This study flowchart is presented in Figure 1.

All fifteen studies (n = 2,713 patients) were included in this final analysis (n = 832 patients with TNBC AR-positive and n = 1.881 patients with TNBC AR-negative treated with neoadjuvant treatment). Our analysis included cohort studies consisting of 13 retrospective studies and 2 prospective studies (Table 1).

Risk of Bias

The risk of bias varied between studies. Nine studies were classified as high-quality studies (NOS 7-9). Six other studies were classified as having a high risk of bias. There are no studies with a very high risk of bias. The risk of bias scoring is projected in Table 2. Egger's test of asymmetry in funnel plot revealed no publication bias among studies (Figure 2).

Table 1. Main Characteristics of the Included Studies

First Author, Year	Study Design	N	N		pCR/pCR(%)		DFS		OS		Follow up	NOS
			AR+	AR-	AR+	AR-	HR	95% CI	HR	95% CI		
Di Leone, [28]	RS	145	20	125	5 (25)	47 (37.6)	NR	NR	NR	NR	30	6
Amrallah, [29]	RS	89	29	60	7 (24.1)	36 (60)	NR	NR	NR	NR	NR	6
Sunar, [30]	RS	84	25	59	NR	NR	1.39	0.21-9.21	1.47	0.54-3.99	NR	8
Hu, [31]	RS	360	118	242	NR	NR	0.467	0.27-0.80	0.488	0.27-0.89	64	8
Adamo, [32]	RS	99	17	82	NR	NR	0.34	0.07-1.65	0.67	0.32-1.402	62	8
Zhu , [33]	RS	165	59	106	12 (20.3)	23 (21.7)	1.001	0.498-2.013	NR	NR	41	7
Constantinous, [34]	PS	83	14	69	NR	NR	1.71	0.461-6.348	1.579	0.363-6.862	NR	6
Sang, [35]	RS	94	41	53	NR	NR	1.98	1.24-3.16	NR	NR	NR	6
Jiang, [36]	RS	434	248	186	NR	NR	2.26	1.16-4.41	NR	NR	91	8
Choi, [37]	RS	492	87	405	NR	NR	1.484	0.851-2.589	2.159	1.224-3.808	72	9
Pistelli, [38]	RS	81	15	66	12 (80)	54 (81.8)	1.24	0.36-4.24	0.93	0.19-4.56	52.4	7
Zaborwski, [39]	RS	137	40	97	NR	NR	0.87	0.54-1.41	0.56	0.19-1.67	41.8	6
Doberstein, [40]	RS	52	21	31	NR	NR	0.32	0.08-1.29	0.3	0.07-1.25	132	6
He, [41]	RS	287	74	213	NR	NR	0.47	0.23-0.95	0.34	0.14-0.83	72	9
Loibi, [42]	PS	111	24	87	7 (29.2)	29 (33.3)	0.38	0.12-1.21	0.14	0.02-0.98	60.5	7

RS, Retrospective Studies; PS, Prospective Studies; AR, Androgen Receptor; pCR, Pathologic Complete Response; DFS, Disease-Free Survival; OS, Overall Survival; HR, Hazard Ratio; CI, Confidence Interval; NR, Not Reported

Meta-Analysis of pCR Rates

Pathologic complete response (pCR) has predicted long-term outcome in several neoadjuvant studies and is therefore a potential surrogate marker for survival. Pathological complete response (pCR) is defined as disappearance of all invasive cancer in the breast after completion of neoadjuvant chemotherapy. For the primary endpoint pCR percentage, five trials were analyzed with 591 patients. The forest plot showed that the effect of neoadjuvant chemotherapy was less superior on AR+ patients compared to AR- (OR = 0.60, 95% CI 0.39–0.93; p = 0.02; Figure 3). A fixed-effect model was selected due to the insignificant heterogeneity among the studies (P = 0.19, I^2 = 34%). Suggesting that neoadjuvant therapy is more resistant in this AR+ subtype.

Meta-Analysis of Survival Outcomes

In this metaanalysis, the discussion regarding survival outcomes is divided into 2, namely Disease-free survival (DFS) and Overall survival (OS). Disease-free survival (DFS) refers to the time from random assignment to cancer recurrence from any cause. Overall survival (OS) was defined as the duration from the date of diagnosis to death or last follow-up, with no restriction on the cause of death. For survival outcomes, the AR+ subtype is associated with better 3-year DFS (HR = 0.93, 95% CI 0.63–1.36; p = 0.69) and 3-year overall survival (OS) (HR = 0.71, 95% CI 0.42–1.20; p = 0.20) compared with AR- subtype. The statistical value, however, is insignificant. Heterogeneity was significant on both DFS and OS (P < 0.05).

Discussion

Thirteen retrospective studies and two prospective studies, including 2,713 patients with TNBC, were assessed. Pathologic complete response (pCR) is defined as no invasive residual in the breast or node following neoadjuvant chemotherapy [8]. The forest plot in Figure 3 showed that the effect of neoadjuvant chemotherapy was less superior on AR+ patients than AR- (OR = 0.60, 95% CI 0.39–0.93; p = 0.02). A fixed-effect model was selected due to the insignificant heterogeneity among the studies (P = 0.19, I^2 = 34%). Our results are similar to a prior study by Loibl et al. [16] reported that despite a better prognosis, patients with AR+ tumors are less sensitive to chemotherapy.

Several retrospective studies have reported that patients with AR+ subtype tumors are less responsive to standard chemotherapy than other TNBC patients; and patients with AR+ TNBCs have a lower chance of achieving a pCR following neoadjuvant chemotherapy

Table 2. Neoadjuvant Therapy of the Included Studies

First Author, Year	Neoadjuvant therapy
Di Leone, [28]	Anthracyclines (epirubicin, 100 mg/m^2) and cyclophosphamide (500 mg/m2; triweekly for 4 cycles) and taxanes (docetaxel 70 mg/m^2; triweekly for 4 cycles); or carboplatin (100 mg/m2; weekly for 12 cycles).
Zhu, [38]	Not mentioned
Pistelli, [28]	Anthracycline containing, CMF
Loibl, [42]	TAC regimen (doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2, and docetaxel 75 mg/m^2).

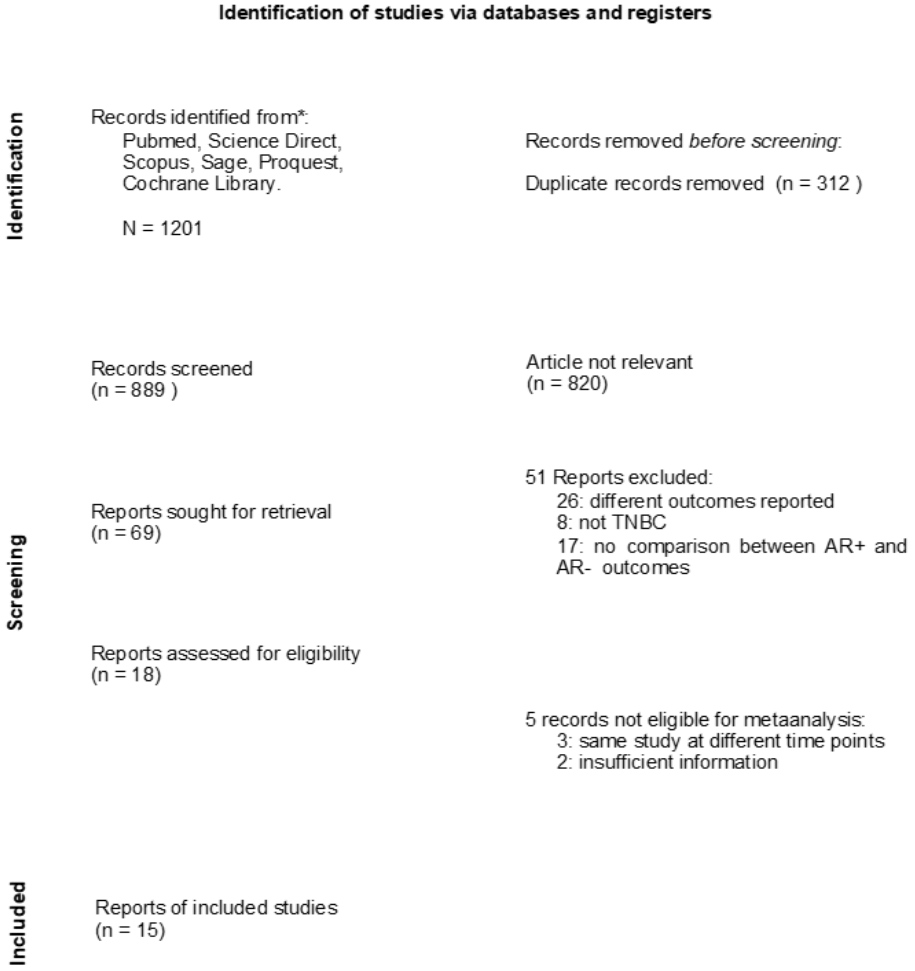

Figure 1. PRISMA Flow Diagram

[17]. These results highlight the need for additional non-chemotherapy-based therapeutic strategies in TNBC [18, 17]. This response is possibly due to the absence of additional therapies such as anti-androgens (bicalutamide and enzalutamide).

For survival outcomes, as shown on forest plots in Figures 4 and 5, the AR+ subtype is associated with better 3-year disease-free survival (DFS) (HR = 0.93, 95%CI 0.63–1.36; p = 0.69) and 3-year overall survival (OS) (HR = 0.71, 95% CI 0.42–1.20; p = 0.20) compared with AR- subtype. However, the statistical value is insignificant. Our results are similar to a prior meta-analysis by Xu et al. [10] which reported that *AR* expression did not have prognostic significance in treating TNBC. While

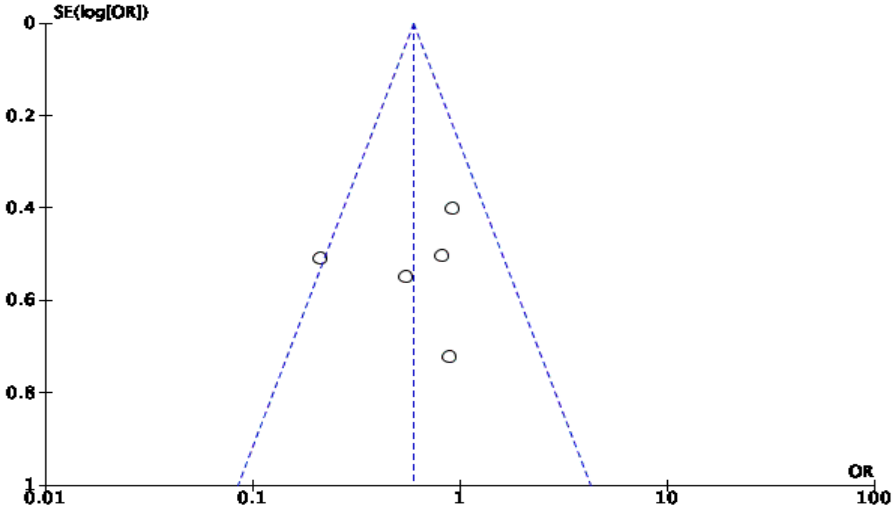

Figure 2. Funnel Plot

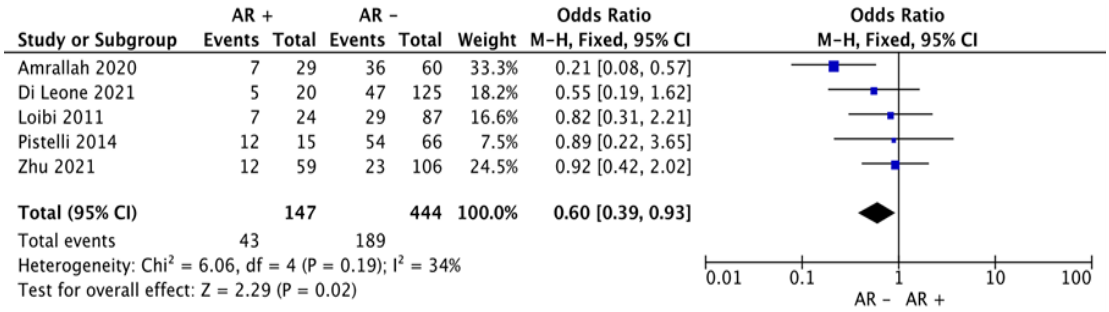

Figure 3. Forest Plot for Pathologic Complete Response (pCR) of Androgen Receptor-Positive Compared with Androgen Receptor-Negative

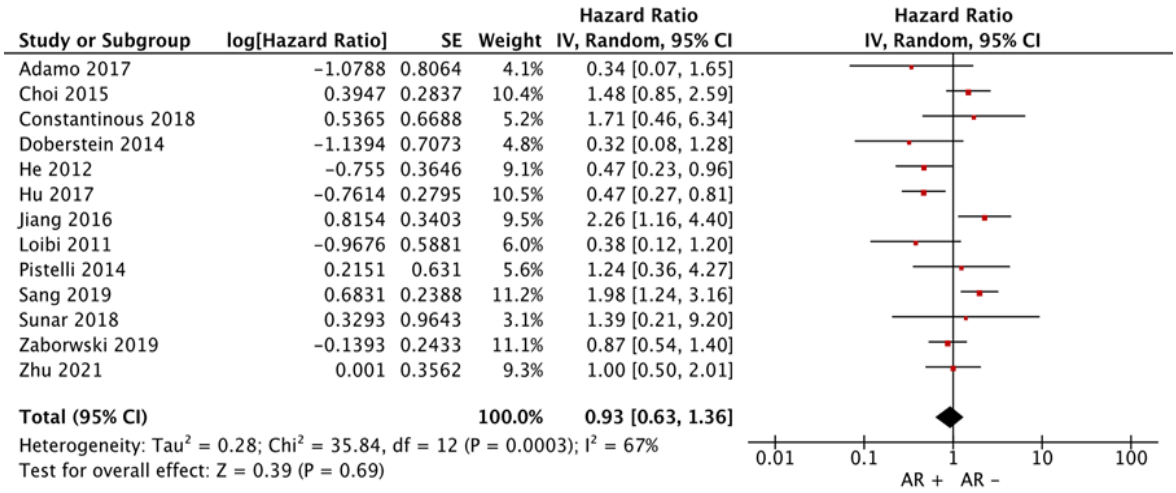

Figure 4. Forest Plot for Disease-Free Survival (DFS) of Androgen Receptor-Positive Compared with Androgen Receptor-Negative

a meta-analysis by Kim et al. showed that expressing *AR* was linked to better DFS (OR = 0.44, p = 0.002) and OS (OR = 0.26, p = 0.001) [19]. However, a meta-analysis by Wang et al. [20] comprising 2,826 TNBC patients with a 24.4% AR positivity, reported slight differences. Patients with *AR* expression tended to have a lower tumor grade ($p < 0.001$) but more lymph node involvement ($p < 0.01$). Although AR positivity was associated with improved DFS (HR = 0.809, $p < 0.05$), no benefit in OS was seen (HR = 1.27, p = 0.168) [20]. Qu et al. [21] also reported a meta-analysis of 5270 patients, which showed a 65.2% AR positivity with a benefit in DFS in the TNBC subgroup (HR = 0.4) but not in OS (HR = 1.17).

Thus, some meta-analyses supported an AR-positive correlation with better DFS, and only one meta-analysis supported an OS benefit. Our study, however, supported

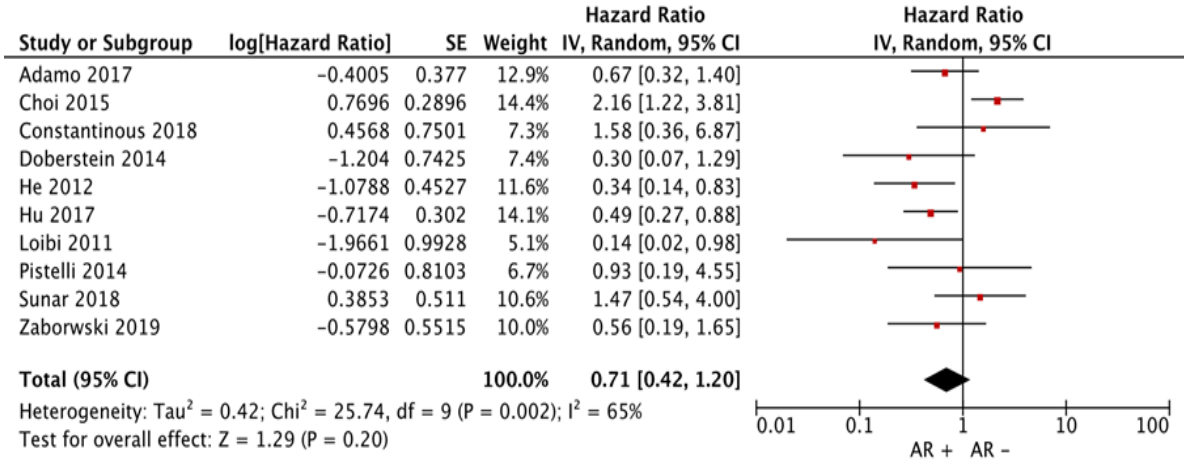

Figure 5. Forest Plot for Overall Survival (OS) of Androgen Receptor-Positive Compared with Androgen Receptor-Negative

the same conclusion for DFS and OS with a meta-analysis from Xu et al. [10] that reported that both are insignificant. The literature about the AR receptor's biological function is still limited. Thus, the prognostic value of *AR* expression in TNBC is not fully understood. *AR* is thought to act as a tumor suppressor in the case of ER-positive breast cancer cells, preventing the growth of tumors by competing with ER signaling for estrogen receptor binding [22]. This finding was also validated by a meta-analysis conducted by Vera-Badillo [23]. The androgen receptor mediates the activation of the MAPK signaling pathway, reducing proliferation. Continuous activation of the MAPK pathway by both AR+ and EGFR signaling results in cell death [24]. However, several studies have demonstrated that AR controls the growth, invasion, migration, and proliferation of Estrogen receptor-negative breast cancer cells in vivo [25]. Moreover, immunostaining of positive androgen receptors is associated with a lower clinical stage, mitotic score, and histological grade [26]. More studies are required to investigate this issue further.

Limitations

Limitations of our study include the retrospective nature and the low number of AR + events (832 patients) compared to AR - events (1.881 patients) analysis, which impose caution in results interpretation and further validation in additional studies.

In conclusion, our study is comparable to some prior studies that showed the effect of neoadjuvant chemotherapy was less superior on AR+ patients than AR-. While for survival outcomes, the AR+ subtype is associated with better 3-year DFS and 3-year OS compared with AR- subtype, with an insignificant statistical value. However, prior studies showed inconclusive results. Therefore, the prognostic value of *AR* expression in TNBC is not fully understood. More studies are required to investigate this issue further.

Author Contribution Statement

Ottofianus A.H Kalangi: Conception and design, Analysis and interpretation of the data, Statistical expertise. Tioky Sutjonong: Analysis and interpretation of the data, Drafting of the article. Erica A. Indrawan: Critical revision of the article for important intellectual content, Collection and assembly of data. Hayyan A. Pratama: Drafting of the article, Administrative, technical, or logistic support. Yohana Azhar: Statistical expertise, Final approval of the article. Asdi Wihandono: Conception and design, Drafting of the article, Critical revision of the article for important intellectual content

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Abbreviation

AR : Androgen receptor
DFS : Disease-free survival
ER : Estrogen receptor
HER2 : Human epidermal growth factor receptor 2
NAC : Neoadjuvant chemotherapy
OS : Overall survival
pCR : Complete pathological response
PR : Progesterone receptor
QNBC : Quadruple negative breast cancer
TNBC : Triple-negative breast cancer

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Brenton JD, Carey LA, Ahmed AA, Caldas C. Molecular Classification and Molecular Forecasting of Breast Cancer: Ready for Clinical Application? Journal of Clinical Oncology. 2005;23(29):7350-7360. doi:10.1200/JCO.2005.03.3845.
2. 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- 110. doi:10.1016/j.ctrv.2018.06.005.
3. Jiang HS, Kuang XY, Sun WL, et al. Androgen receptor expression predicts different clinical outcomes for breast cancer patients stratified by hormone receptor status. Oncotarget. 2106;7(27):41285-41293. doi:10.18632/oncotarget.9778.
4. Safarpour D, Pakneshan S, Tavassoli FA. Androgen receptor (AR) expression in 400 breast carcinomas: is routine AR assessment justified? Am J Cancer Res. 2014;16(4):353-368. doi:http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4106653.
5. Mougalian SS, Soulos PR, Killelea BK, et al. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. Cancer. 2015;121(15):2544-2552. doi:10.1002/cncr.29348.
6. Rakha EA, El-Sayed ME, Green AR, Lee AHS, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. Cancer. 2007;109(1):25-32. doi:10.1002/cncr.22381.
7. Tang D, Xu S, Zhang Q, Zhao W. The expression and clinical significance of the androgen receptor and E-cadherin in triple-negative breast cancer. Medical Oncology. 2012;29(2):526-533. doi:10.1007/s12032-011-9948-2.
8. Mohammed AA, Elsayed FM, Algazar M, Rashed HE, Anter AH. Neoadjuvant Chemotherapy in Triple Negative Breast Cancer: Correlation between Androgen Receptor Expression and Pathological Response. Asian Pacific Journal of Cancer Prevention. 2020;21(2):563-568. doi:10.31557/APJCP.2020.21.2.563.
9. Telli ML, Timms KM, Reid J, et al. Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer. Clinical Cancer Research. 2016;22(15):3764-3773. doi:10.1158/1078-0432.CCR-15-2477.
10. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349(jan02 1):g7647-g7647. doi:10.1136/bmj.g7647.
11. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603- 605. doi:10.1007/s10654-010-9491-z.
12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-e34.

doi:10.1016/j.jclinepi.2009.06.006.
13. Mantel N, Haenszel W. Statistical Aspects of the Analysis of Data From Retrospective Studies of Disease. JNCI: Journal of the National Cancer Institute. Published online April 1959. doi:10.1093/jnci/22.4.719.
14. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006;11(2):193-206. doi:10.1037/1082-989X.11.2.193.
15. Loibl S, Muller BM, von Minckwitz G, et al. Androgen receptor expression in primary breast cancer and its predictive and prognostic value in patients treated with neoadjuvant chemotherapy. Breast Cancer Res Treat. 2011;130(2):477-487. doi:10.1007/s10549-011-1715-8.
16. Santonja A, Sanchez-Munoz A, Lluch A, et al. Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy. Oncotarget. 2018;9(41):26406-26416. doi:10.18632/oncotarget.25413.
17. Echavarria I, Lopez-Tarruella S, Picornell A, et al. Pathological Response in a Triple- Negative Breast Cancer Cohort Treated with Neoadjuvant Carboplatin and Docetaxel According to Lehmann's Refined Classification. Clin Cancer Res. 2018;24(8):1845- 1852. doi:10.1158/1078-0432.CCR-17-1912.
18. Santonja A, Sanchez-Munoz A, Lluch A, et al. Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy. Oncotarget. 2018;9(41):26406-26416. doi:10.18632/oncotarget.25413.
19. Xu M, Yuan Y, Yan P, et al. Prognostic Significance of Androgen Receptor Expression in Triple Negative Breast Cancer: A Systematic Review and Meta- Analysis. Clin Breast Cancer. 2020;20(4):e385-e396. doi:10.1016/j.clbc.2020.01.002.
20. Kim Y, Jae E, Yoon M. Influence of Androgen Receptor Expression on the Survival Outcomes in Breast Cancer: A Meta-Analysis. J Breast Cancer. 2015;18(2):134-142. doi:10.4048/jbc.2015.18.2.134.
21. Wang C, Pan B, Zhu H, et al. Prognostic value of androgen receptor in triple negative breast cancer: A meta-analysis. Oncotarget. 2016;7(29):46482-46491. doi:10.18632/oncotarget.10208.
22. Qu Q, Mao Y, Fei X chun, Shen K wei. The impact of androgen receptor expression on breast cancer survival: a retrospective study and meta-analysis. PLoS One. 2013;8(12):e82650. doi:10.1371/journal.pone.0082650.
23. Peters AA, Ingman W V, Tilley WD, Butler LM. Differential effects of exogenous androgen and an androgen receptor antagonist in the peri- and postpubertal murine mammary gland. Endocrinology. 2011;152(10):3728-3737. doi:10.1210/en.2011-1133.
24. Vera-Badillo FE, Templeton AJ, de Gouveia P, et al. Androgen receptor expression and outcomes in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(1):djt319. doi:10.1093/jnci/djt319.
25. Garay JP, Karakas B, Abukhdeir AM, et al. The growth response to androgen receptor signaling in ERα-negative human breast cells is dependent on p21 and mediated by MAPK activation. Breast Cancer Res. 2012;14(1):R27. doi:10.1186/bcr3112.
26. Hickey TE, Robinson JLL, Carroll JS, Tilley WD. Minireview: The androgen receptor in breast tissues: growth inhibitor, tumor suppressor, oncogene? Mol Endocrinol. 2012;26(8):1252-1267. doi:10.1210/me.2012-1107.
27. Zhang L, Fang C, Xu X, Li A, Cai Q, Long X. Androgen receptor, EGFR, and BRCA1 as biomarkers in triple-negative breast cancer: a meta-analysis. Biomed Res Int. 2015;2015:357485. doi:10.1155/2015/357485.
28. Di Leone A, Fragomeni SM, Scardina L. Androgen receptor expression and outcome of neoadjuvant chemotherapy in triple-negative breast cancer. Eur Rev Med Pharmacol Sci. 2021;25:1910-1915.
29. Mohammed AA, Elsayed FM, Algazar M, Rashed HE, Anter AH. Neoadjuvant Chemotherapy in Triple Negative Breast Cancer: Correlation between Androgen Receptor Expression and Pathological Response. Asian Pacific Journal of Cancer Prevention. 2020;21(2):563-568. doi:10.31557/APJCP.2020.21.2.563.
30. Sunar V, T Dogan H, Sarici F, et al. Association between androgen receptor status and prognosis in triple negative breast cancer. J BUON. 2018;23(5):1325-1330.
31. Hu XQ, Chen WL, Ma HG, Jiang K. Androgen receptor expression identifies patient with favorable outcome in operable triple negative breast cancer. Oncotarget. 2017;8(34):56364-56374. doi:10.18632/oncotarget.16913.
32. Adamo B, Ricciardi GRR, Ieni A, et al. The prognostic significance of combined androgen receptor, E-Cadherin, Ki67 and CK5/6 expression in patients with triple negative breast cancer. Oncotarget. 2017;8(44):76974-76986. doi:10.18632/oncotarget.20293.
33. Zhu M, Liang C, Zhang F, Zhu L, Chen D. A Nomogram to Predict Disease-Free Survival Following Neoadjuvant Chemotherapy for Triple Negative Breast Cancer. Front Oncol. 2021;11. doi:10.3389/fonc.2021.690336.
34. Constantinous C, Papadopoulos S, Karyda E. Expression and Clinical Significance of Claudin-7, PDL-1, PTEN, c-Kit, c-Met, c-Myc, ALK, CK5/6, CK17, p53, EGFR, Ki67, p63 in Triple-negative Breast Cancer– A Single Centre Prospective Observational Study. In Vivo (Brooklyn). 2018;32(2). doi:10.21873/invivo.11238.
35. Sang M, Meng L, Ma C, et al. Effect of AR antagonist combined with PARP1 inhibitor on sporadic triple-negative breast cancer bearing AR expression and methylation mediated BRCA1 dysfunction. Biomedicine & Pharmacotherapy. 2019;111:169-177. doi:10.1016/j.biopha.2018.11.136.
36. Jiang HS, Kuang XY, Sun WL, et al. Androgen receptor expression predicts different clinical outcomes for breast cancer patients stratified by hormone receptor status. Oncotarget. 2106;7(27):41285-41293. doi:10.18632/oncotarget.9778.
37. Choi JE, Kang SH, Lee SJ, Bae YK. Androgen Receptor Expression Predicts Decreased Survival in Early Stage Triple-Negative Breast Cancer. Ann Surg Oncol. 2015;22(1):82-89. doi:10.1245/s10434-014-3984-z.
38. Pistelli M, Caramanti M, Biscotti T, et al. Androgen receptor expression in early triple negative breast cancer: Clinical significance and prognostic associations. Cancers (Basel). 2014;6(3):1351-1362. doi:10.3390/cancers6031351.
39. Zaborowski M, Pearson A, Sioson L, Gill AJ, Ahadi MS. Androgen receptor immunoexpression in triple-negative breast cancers: is it a prognostic factor? Pathology. 2019;51(3):327-329. doi:10.1016/j.pathol.2018.09.063.
40. Doberstein K, Milde-Langosch K, Bretz NP, et al. L1CAM is expressed in triple negative breast cancers and is inversely correlated with Androgen receptor. BMC Cancer. 2014;14(1):958. doi:10.1186/1471-2407-14-958.
41. He J, Peng R, Yuan Z, et al. Prognostic value of androgen receptor expression in operable triple-negative breast cancer: A retrospective analysis based on a tissue microarray. Medical Oncology. 2012;29(2):406-410. doi:10.1007/s12032-011-9832-0.
42. Loibl S, Muller BM, von Minckwitz G, et al. Androgen receptor expression in primary breast cancer and its predictive and prognostic value in patients treated with

neoadjuvant chemotherapy. Breast Cancer Res Treat. 2011;130(2):477-487. 410 doi:10.1007/s10549-011-1715-8.