



Impact of HER2 status on clinicopathological characteristics and pathological complete response to neoadjuvant chemotherapy in triple-negative breast cancer

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Abstract

Purpose HER2-low triple-negative breast cancer (TNBC) accounted for up to 34%–39% of primary TNBC and 22.2%–32% of metastatic TNBC. Our study aims to explore the relationship between HER2 expression and clinicopathological characteristics, analyze the impact of HER2 expression on the pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) in TNBC.

Methods This study involved 191 patients with TNBC who underwent operation after NAC from October 2021 to August 2022. Clinicopathological characteristics and the frequency of pCR were compared between HER2-low and HER2-0 TNBC.

Results 42.2% (81/191) patients in our cohort were HER2-low. They exhibited differences in menopausal status, body mass index (BMI), androgen receptor (AR) expression, and histological grade ($P < 0.05$). Particularly, in HER2-low TNBC, AR was associated with tumor size, lymph node metastase, histological grade, and the incidence of multifocal disease ($P < 0.05$). The total pCR rate of entire cohort was 39.8%. Tumor size ($P = 0.025$), AR status ($P = 0.033$) and histological grade ($P = 0.007$) were significantly associated with the pCR rate of them, while the HER2 status did not exert a similar association. The multivariate analysis revealed that BMI ($P = 0.004$) and histological grade ($P < 0.001$) were associated with pCR of HER2-low TNBC, while tumor size ($P = 0.034$) and AR ($P = 0.034$) were associated with pCR of HER2-0 TNBC, respectively.

Conclusions In our cohort, HER2-low TNBC patients exhibits specific clinical characteristics and response features to NAC.

Keywords Triple-negative breast cancer · HER2-low · Clinicopathological characteristics · Pathological complete response

Introduction

Triple-negative breast cancer (TNBC) is an intertwined disease exhibits highly heterogeneity, lacks effective therapeutic target, and resulting in poor prognosis [1]. Therefore, novel therapeutic options are urgently needed and extensive research have conducted on anti-HER2 agents [2]. Currently, HER2 status is determined based on combined interpretation of immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) routinely. In 2018, the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) proposed that tumors with IHC 0, 1 + or 2 + and FISH negative are HER2-negative; tumors

with IHC 3 + or 2 + and FISH positive are HER2-positive [3]. In TNBC, HER2 expression levels are ranging from IHC 0 to IHC 2 + and FISH negative. Recently, HER2-low breast cancer, which are defined as IHC 1 + or 2 + and FISH negative, have sparked intense interest. TNBC has been reclassification into HER2-low and HER2-0 subgroups [4]. Furthermore, HER2-low accounted for up to 34%–39% of primary TNBC and 22.2%–32% of metastatic TNBC [5, 6]. Historically, HER2-low patients cannot be benefited from conventional anti-HER2 therapies [7]. Nowadays, the novel antibody–drug conjugates (ADCs) have taken encouraging efficiency in HER2-low TNBC patients [8]. In addition, researches investigating the potential of HER2 vaccines and bispecific antibodies are under development [9].

About 10% to 50% of TNBC are androgen receptor (AR) positive and this subtype of TNBC characterized with distinct molecular features [10]. However, little is known about the molecular mechanism underlying HER2-low in AR-positive TNBC. The relationship between AR expression and

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clinicopathological characteristics of patients with different HER2 levels is still elusive. More data about HER2-low in AR-positive TNBC are urgently needed to explore effective therapeutic strategies for them.

The evaluation of neoadjuvant chemotherapy (NAC) efficacy can be conducted on the attainment of pathological complete response (pCR). In TNBC, pCR is highly correlated with favorable prognosis and has been regarded as a surrogate for forecasting prognosis such as event-free survival and overall survival (OS) [11]. However, the biology and pathology differences of HER2-0 and HER2-low TNBC and their response to standard NAC remains poorly investigated and controversial. Studies have shown that there was a similar pCR rate among these two groups, while HER2-low TNBC patients harbor aggressive clinicopathological features and worse prognosis [12]. In contrast, this population was found to have prolonged breast cancer-specific survival [13]. Therefore, further investigation which reclassify TNBC into HER2-0 and HER2-low is urgent needed, comprehensive understanding of their biological and responses to therapy may enable individualized treatment strategies.

We analyzed the correlation of HER2 levels with clinicopathological characteristics in TNBC patients, and further analyzed their correlation according to AR status. Then, we evaluated the predict value of HER2 expression on the frequency of attaining a pCR in the NAC setting.

Methods

Study design and participants

We included 191 patients diagnosed with TNBC who met the inclusion and exclusion criteria in the First Affiliated Hospital of Jinzhou Medical University from October 2021 to August 2022. The basic and clinicopathological information of their core needle biopsy in initial pre-treatment status were collected from medical records, including age, menopausal status, body mass index (BMI), tumor size, lymph node metastasis, AR, Ki-67 index, histological grade, HER2, and with or without multifocal disease. Inclusion criteria: ① unilateral TNBC without distant metastasis; ② received NAC followed national and international guidelines and underwent surgery after completing NAC; ③ clinicopathological information and follow-up data were obtainable. Exclusion criteria: ① male breast cancer patients; ② patients with history of other malignancies; ③ patients who received unsystematic NAC or had severe complication. Evaluation criteria for pCR was no invasive cancer in the breast and axillary lymph nodes (ypT0/is, ypN0). AR status was evaluated by professional pathologists and AR positivity (1:100, Tenda) was defined as $\geq 1\%$ percentage of nuclear staining cells in IHC.

HER2 evaluation

The HER2 status were evaluated by standard IHC (1:200, Roche) and FISH according to the ASCO/CAP guideline. Tumors with IHC 0 was defined as HER2-0, and tumors with IHC 1 + or IHC 2 + and FISH-negative was defined as HER2-low.

Statistical analysis

All analyses were performed using SPSS software (version 25). Chi-square analysis was used to test for the association of categorical variables. Univariate and multivariable logistic regression analysis were performed to assess the predictive factors for pCR. $P < 0.05$ was considered statistically significant.

Results

Relationship between HER2 expression and clinicopathological characteristics.

By HER2 expression level, 191 patients were enrolled into two groups: 81 (42.4%) patients were HER2-low TNBC and 110 (57.6%) patients were HER2-0 TNBC. Compared with HER2-low TNBC, HER2-0 TNBC exhibited more patients with premenopausal status ($P = 0.011$), BMI < 25 ($P < 0.001$), AR-negative ($P < 0.001$), and histological grade I/II ($P = 0.031$) (Table 1). There were no significant differences in other terms.

Relationship between AR expression and clinicopathological characteristics of patients with different HER2 levels.

According to different AR and HER2 levels, patients were enrolled into four groups. In HER2-low TNBC group, 35 (43.2%) patients were AR-negative and 46 (56.8%) patients were AR-positive; in HER2-0 TNBC group, 86 (78.2%) patients were AR-negative and 24 (21.8%) patients were AR-positive. Within the HER2-low TNBC group, AR-positive patients had smaller tumors ($P = 0.007$), fewer lymph node metastases ($P = 0.002$), lower histological grade ($P = 0.008$), and a lower incidence of multifocal disease ($P = 0.022$). The remaining clinicopathological characteristics were statistically insignificant ($P > 0.05$) (Table 2).

Univariate and multivariate analysis for pCR in TNBC.

We assessed the impact of each clinicopathological characteristic on pCR in TNBC. The total pCR rate of all enrolled patients was 39.8%. The univariate analysis showed that age

Table 1 Correlation of HER2 expression with different clinicopathological characteristics

Characteristics	Total	HER2-low TNBC (N=81) N (%)	HER2-0 TNBC (N=110) N (%)	χ^2	<i>P</i>
Age (year)					
<45	45	21 (25.9)	24 (21.8)	0.437	0.509
≥45	146	60 (74.1)	86 (78.2)		
Menopausal status					
Premenopausal	95	32 (39.5)	63 (57.3)	5.890	0.011*
Postmenopausal	96	49 (60.5)	47 (42.7)		
BMI					
<25	114	33 (40.7)	81 (73.6)	20.979	<0.001*
≥25	77	48 (59.3)	29 (26.4)		
Tumor size					
T1-T2	157	70 (86.4)	87 (79.1)	1.712	0.132
T3-T4	34	11 (13.6)	23 (20.9)		
Lymph node metastasis					
Negative	77	34 (47.9)	43 (39.1)	0.161	0.400
Positive	114	47 (52.1)	67 (60.9)		
AR					
AR-negative	121	35 (43.2)	86 (78.2)	24.574	<0.001*
AR-positive	70	46 (56.8)	24 (21.8)		
Ki67					
≤20%	26	7 (8.6)	19 (17.3)	2.955	0.064
>20%	165	74 (91.4)	91 (82.7)		
Histological grade					
I/II	108	39 (48.1)	69 (62.7)	4.035	0.031*
III	83	42 (51.9)	41 (37.3)		
Multifocal disease					
No	158	63 (77.8)	95 (86.4)	2.406	0.088
Yes	33	18 (22.2)	15 (13.6)		

**P* < 0.05 was considered statistically significant

(OR: 2.066; 95% CI 1.050–4.064; *P* = 0.036), tumor size (OR: 0.334; 95% CI 0.155–0.718; *P* = 0.005), AR status (OR: 2.154; 95% CI 1.147–4.043; *P* = 0.017) and histological grade (OR: 0.340; 95% CI 0.187–0.620; *P* < 0.001) were significant factors associated with pCR, respectively. Furthermore, multivariate analysis showed tumor size (OR: 0.393; 95% CI 0.173–0.892; *P* = 0.025), AR status (OR: 2.072; 95% CI 1.059–4.053; *P* = 0.033), and histological grade (OR: 0.414; 95% CI 0.219–0.783; *P* = 0.007) were independent factors for pCR. There was no statistical significance of pCR among patients with different menopausal status, BMI, lymph node metastasis status, Ki-67 expression levels, HER2 expression levels, and with and without multifocal disease (*P* > 0.05) (Table 3).

Univariate and multivariate analysis for pCR in HER2-low and HER2-0 TNBC

We further assessed the impact of clinicopathological characteristics on the frequency of pCR in TNBC with distinct

HER2 expression levels, as demonstrated in Tables 4 and 5. The pCR rate was 34.6% in HER2-low patients and 42.7% in HER2-0 patients, the difference was not statistically significant. In HER2-low TNBC patients, BMI (OR: 0.346; 95% CI 0.126–0.951; *P* = 0.040) and histological grade (OR: 0.121; 95% CI 0.040–0.372; *P* < 0.001) were significant factors associated with pCR, respectively. Furthermore, multivariate analysis showed BMI (OR: 0.165; 95% CI 0.048–0.567; *P* = 0.004) and histological grade (OR: 0.072; 95% CI 0.020–0.257; *P* < 0.001) were still the independent factors for pCR of HER2-low TNBC. While in HER2-0 TNBC patients, tumor size (OR: 0.326; 95% CI 0.125–0.852; *P* = 0.022), AR status (OR: 2.864; 95% CI 1.037–7.910; *P* = 0.042) and Ki-67 level (OR: 0.285; 95% CI 0.088–0.924; *P* = 0.037) were significant factors associated with pCR, respectively. Furthermore, multivariate analysis showed tumor size (OR: 0.337; 95% CI 0.123–0.923; *P* = 0.034) and AR status (OR: 2.973; 95%

Table 2 Correlation of AR expression with different clinicopathological characteristics of patients with different HER2 expression levels

Characteristics	Total	HER2-low TNBC (N=81)				Total	HER2-0 TNBC (N=110)			
		AR-negative (N=35) N (%)	AR-positive (N=46) N (%)	χ^2	P		AR-negative (N=86) N (%)	AR-positive (N=24) N (%)	χ^2	P
Age (year)										
<45	21	11 (31.4)	10 (21.7)	0.972	0.232	24	16 (18.6)	8 (33.3)	2.386	0.105
≥45	60	24 (68.6)	36 (78.3)			86	70 (81.4)	16 (66.7)		
Menopausal status										
Premenopausal	32	14 (40.0)	18 (39.1)	0.006	0.559	63	48 (55.8)	15 (62.5)	0.343	0.365
Postmenopausal	49	21 (60.0)	28 (60.9)			47	38 (44.2)	9 (37.5)		
BMI										
<25	33	17 (48.6)	16 (34.8)	1.565	0.153	81	65 (75.6)	16 (66.7)	0.768	0.265
≥25	48	18 (51.4)	30 (65.2)			29	21 (24.4)	8 (33.3)		
Tumor size										
T1-T2	70	26 (74.3)	44 (95.7)	7.732	0.007*	87	68 (79.1)	19 (79.2)	<0.001	0.619
T3-T4	11	9 (25.7)	2 (4.3)			23	18 (20.9)	5 (20.8)		
Lymph node metastasis										
Negative	34	8 (22.9)	26 (56.5)	9.249	0.002*	43	35 (40.7)	8 (33.3)	0.427	0.342
Positive	47	27 (77.1)	20 (43.5)			67	51 (59.3)	16 (66.7)		
Ki67										
≤20%	7	4 (11.4)	3 (6.5)	0.606	0.349	19	14 (16.3)	5 (20.8)	0.272	0.400
>20%	74	31 (88.6)	43 (93.5)			91	72 (83.7)	19 (79.2)		
Histological grade										
I/II	39	11 (31.4)	28 (60.9)	6.901	0.008*	69	56 (65.1)	13 (54.2)	0.962	0.228
III	42	24 (68.6)	18 (39.1)			41	30 (34.9)	11 (45.8)		
Multifocal disease										
No	63	23 (65.7)	40 (87.0)	5.189	0.022*	95	76 (88.4)	19 (79.2)	1.350	0.200
Yes	18	12 (34.3)	6 (13.0)			15	10 (11.6)	5 (20.8)		

* $P < 0.05$ was considered statistically significant

CI 1.031–8.577; $P = 0.044$) were independent factors for pCR of HER2-0 TNBC.

Discussion

Given the dearth of validated therapeutic targets of TNBC and its unfavorable prognosis, continuous endeavors are being made to meet the unmet need of efficacious treatment alternatives for them [14]. The antibody of ADCs specifically binds to cell-surface proteins and translocate into cell, then release high concentration cytotoxic payloads [15]. Fam-trastuzumab deruxtecan (T-DXd), a novel HER2-targeted ADC prolonged survival of HER2-low patients, was the first FDA-approved therapeutic approach for advanced HER2-low breast cancer [16, 17]. With the significant anti-tumor activity and substantial bystander effect of ADCs, the traditional binary classification pattern of HER2 has been broken, a lot of research have focused on HER2-low breast cancer for comprehensively characterize them [18]. We

characterized the clinicopathological features of HER2-low and HER2-0 TNBC and compared their response to NAC.

HER2-low TNBC occupied 42.4% of our entire cohort and they exhibited a higher proportion of postmenopausal status, BMI > 25, AR-positive, and high histological grade patients. Our result suggest HER2-low may take a propensity toward high-risk prognostic factors in TNBC. Within TNBC, a positive relation between HER2 and AR expression was recently reported. Concordance with our results, AR was an independent factor associated with HER2 status [13, 19]. In the molecular apocrine tumors, a specific subgroup of TNBC with AR expressing, the percentage of HER2-low was higher than that of HER2-0 [20]. Similarly, the higher prevalence of HER2-enriched subtype in the luminal androgen receptor subtype of TNBC supporting our results [21]. However, the clinicopathological characteristics of TNBC with different patterns of HER2 and AR expression remains poorly investigated. Particularly, we categorized patients into subgroups based on HER2 and AR expressions. In our cohort, AR-negative patients were inclined to have large tumor sizes, lymph node metastasis, high histological grade,

Table 3 Clinicopathological characteristics associated with pCR in the entire cohort

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Age (year)						
<45	Ref		0.036*	Ref		0.060
≥45	2.066	1.050–4.064		2.026	0.971–4.226	
Menopausal status						
Premenopausal	Ref		0.953			
Postmenopausal	1.018	0.570–1.816				
BMI						
<25	Ref		0.056			
≥25	0.562	0.311–1.015				
Tumor size						
T1-T2	Ref		0.005*	Ref		0.025*
T3-T4	0.334	0.155–0.718		0.393	0.173–0.892	
Lymph node metastasis						
Negative	Ref		0.913			
Positive	1.033	0.573–1.865				
AR						
AR-negative	Ref		0.017*	Ref		0.033*
AR-positive	2.154	1.147–4.043		2.072	1.059–4.053	
Ki67						
≤20%	Ref		0.155			
>20%	0.513	0.204–1.286				
Histological grade						
I/II	Ref		<0.001*	Ref		0.007*
III	0.340	0.187–0.620		0.414	0.219–0.783	
HER2						
HER2-low	Ref		0.207			
HER2-0	1.465	0.810–2.652				
Multifocal disease						
No	Ref		0.224			
Yes	1.650	0.736–3.698				

OR Odds ratio; Ref. reference

**P* < 0.05 was considered statistically significant

and multifocal disease in HER2-low TNBC patients. Owing to the highly clinical efficacy and well tolerated side effects, AR inhibitor have spurred a new era of treatment approach for AR-positive TNBC patients [22]. The combining use of enzalutamide and trastuzumab have taken durable disease control for HER2 and AR-positive patients, the analysis of the AR-positive HER2-low TNBC patients may provide a reference for further combined treatment scheme in this targetless subtype [23].

In the entire cohort of our study, tumor size, AR status, and histological grade were independent factors for the rate of pCR. Specially, we explored the significant factors associated with pCR in HER2-low and HER2-0 TNBC patients respectively. In HER2-low TNBC patients, BMI < 25 and histological grade I/II presented a higher probability to attain pCR. While in HER2-0 TNBC patients, smaller tumor size

and AR-positive were identified as independent positive factors for pCR. The effect of HER2-low in efficiency of NAC was unclear at present. In this study, HER2 expression level had no effect on the frequency of pCR. In a study of 2310 patients, the pCR rate of HER2-0 patients was higher than that of HER2-low patients in hormone receptor (HR) positive group, but no difference of pCR was seen in TNBC group [5]. Coherently, another study found that the pCR rate of HER2-0 group was a little lower than HER2-low group with no statistical difference [24]. Basing on existing results, HER2 expression may not associated with the efficacy of NAC in TNBC [25, 26].

We analyzed pCR as a surrogate for survival based on the FDA recommendation and pCR is an important evaluation index in NAC of TNBC. Patients who could not obtain pCR receive additional adjuvant capecitabine therapy have

Table 4 Univariate and multivariate analysis for pCR in HER2-low TNBC

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Age (year)						
<45	Ref		0.148			
≥45	2.121	0.766–5.876				
Menopausal status						
Premenopausal	Ref		0.056			
Postmenopausal	0.373	0.136–1.026				
BMI						
<25	Ref		0.040*	Ref		0.004*
≥25	0.346	0.126–0.951		0.165	0.048–0.567	
Tumor size						
T1-T2	Ref		0.144			
T3-T4	0.382	0.105–1.387				
Lymph node metastasis						
Negative	Ref		0.555			
Positive	1.321	0.542–3.329				
AR						
:AR-negative	Ref		0.371			
:AR-positive	1.524	0.606–3.835				
Ki67						
≤20%	Ref		0.631			
>20%	1.470	0.305–7.084				
Histological grade						
I/II	Ref		<0.001*	Ref		<0.001*
III	0.121	0.040–0.372		0.072	0.020–0.257	
Multifocal disease						
No	Ref		0.901			
Yes	1.073	0.354–3.251				

OR Odds ratio; Ref. reference

**P* < 0.05 was considered statistically significant

become the standard treatment in TNBC [27]. While the association between HER2 level and the survival of TNBC patients remains controversial. In early-stage TNBC, HER2-low group showed a shorter DFS and OS [28]. Some studies observed no significant survival value of HER2 expression in TNBC [25, 29, 30]. In contrast, it was found that HER2-low predicted a significant longer OS in early-stage TNBC [31]. Similarly, another analysis found that DFS and OS were significantly longer in the HER2-low group [26]. The lack of distinction between HER2 IHC 0 and 1+ by pathologists could be a crucial cause of the inconsistent results. Therefore, highly concordance in HER2 scoring is indispensable to further characterize HER2-low TNBC.

Our study presents some limitations. The sample size of is limited, and patients were selected from a single-center. A larger scale analysis is needed to further prove our conclusions rigorously. Moreover, due to the short follow-up duration, it was not feasible to assess the long-term prognosis of them. However, pCR served as an alternative

surrogate endpoint for prediction of prognostic in TNBC. Consequently, we will scientifically conduct long-term follow-up to draw more conclusive conclusions.

Conclusion

This study revealed the biological properties and clinical features of HER2-low and HER2-0 TNBC, provides a crucial foundation of the predictive value on pCR and prognostic significance for them from a clinical perspective. In particularly, this study shed new light on HER2-low TNBC with different AR status, our analysis can potentially guiding research direction and providing clinical implications on the possibility of combined AR inhibition and novel ADCs treatment.

Table 5 Univariate and multivariate analysis for pCR in HER2-0 TNBC

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Age (year)						
< 45	Ref		0.105			
≥ 45	2.141	0.854–5.370				
Menopausal status						
Premenopausal	Ref		0.174			
Postmenopausal	1.710	0.789–3.704				
BMI						
< 25	Ref		0.147			
≥ 25	0.531	0.225–1.250				
Tumor size						
T1-T2	Ref		0.022*	Ref		0.034*
T3-T4	0.326	0.125–0.852		0.337	0.123–0.923	
Lymph node metastasis						
Negative	Ref		0.764			
Positive	0.888	0.410–1.925				
AR						
AR-negative	Ref		0.042*	Ref		0.044*
AR-positive	2.864	1.037–7.910		2.973	1.031–8.577	
Ki67						
≤ 20%	Ref		0.037*	Ref		0.066
> 20%	0.285	0.088–0.924		0.323	0.097–1.080	
Histological grade						
I/II	Ref		0.104			
III	0.522	0.239–1.143				
Multifocal disease						
No	Ref		0.163			
Yes	2.373	0.705–7.983				

OR Odds ratio; Ref. reference

**P* < 0.05 was considered statistically significant

Author contributions Yue Shi contributed to conceptualization, data curation, investigation, project administration, validation, writing—original draft. Heng Lu contributed to formal analysis, investigation, methodology, resources, visualization. Yiqi Zhang contributed to conceptualization, resources, supervision, funding acquisition, writing – review & editing.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The authors declare no competing interests.

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