CORRELATION BETWEEN HER2-LOW EXPRESSION WITH CLINICOPATHOLOGIC CHARACTERISTICS AND ITS PROGNOSTIC VALUE IN EARLY-STAGE TRIPLE-NEGATIVE BREAST CANCER AT VIETNAM NATIONAL CANCER HOSPITAL

Phung Thi Huyen[1], Nguyen Thi Hoa[1], Hoang Thi Hoai[2], Nguyen Thanh Long[1*], Nguyen Dinh Thach[1]

ABSTRACT

Background: HER2-low expression impacts on clinical features and prognosis in early-stage triple-negative breast cancer (TNBC) remain unclear. Our aim was to evaluate its prognostic value and correlation with clinicopathological characteristics in this population.

Methods: A retrospective study of 126 patients with early-stage TNBC who did not undergo neoadjuvant systemic therapy in Vietnam National Cancer Hospital from January 2018 to December 2019, HER2 expression was evaluated using the 2018 ASCO/CAP guidelines, Tumor-infiltrating lymphocyte scores (TILs) assessment were assessed based on the guide of an international TILs research group in 2014, using 40% as the cut-off.

Results: Among the 126 patients, with a median age of 54.7±11.4 years, 74.6% were HER2-0 and 25.4% were HER2-low. Compared to HER2-0 tumors, HER2-low tumors were associated with higher age (p=0.02), lower Ki67 score (p=0.05), and lower tumor-infiltrating lymphocyte (p=0.005). During a median follow-up of 54 months, the univariate analysis revealed that patients with HER2-low tumors had a worse overall survival (OS) compared to those with HER2-0 tumors (83.3% vs. 69.6%, p=0.04). However, in the multivariate analysis, HER2 expression did not show a significant association with OS. Instead, independent predictors of OS were identified as tumor-infiltrating lymphocyte scores scores (TILs) (p=0.02; HR=0.17; 95%CI 0.04-0.77) and nodal status (p=0.002; HR=3.8; 95%CI 1.6-9.1).

Conclusions: This study suggests that HER2-low expression is associated with a lower immune response and worse survival outcome in early-stage TNBC patients compared to HER2-0 tumors. Further investigations is needed to explore the potential of more refined classification and novel strategies that may improve the prognosis for HER2-low TNBC patients.

Keywords: Breast cancer; triple negative; Her2-low; Her2-0; TILs.

[1]Vietnam National Cancer Hospital;
[2]Institut Gustave Roussy.

*Corresponding Author: longnguyen.hmu@gmail.com

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1. INTRODUCTION

Breast cancer is the most common cancer among women, with an increasing number of cases and being one of the leading causes of cancer-related mortality [1]the American Cancer Society estimates the numbers of new cancer cases and deaths that will occur in the United States in the current year and compiles the most recent data on cancer incidence, mortality, and survival. Incidence data were collected by the Surveillance, Epidemiology, and End Results Program; the National Program of Cancer Registries; and the North American Association of Central Cancer Registries. Mortality data were collected by the National Center for Health Statistics. In 2017, 1,688,780 new cancer cases and 600,920 cancer deaths are projected to occur in the United States. For all sites combined, the cancer incidence rate is 20% higher in men than in women, while the cancer death rate is 40% higher. However, sex disparities vary by cancer type. For example, thyroid cancer incidence rates are 3-fold higher in women than in men (21 vs 7 per 100,000 population. Triple-negative breast cancer (TNBC) is a subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), accounting for 15-20% of all breast cancer cases. TNBC is associated with rapid disease progression and a poorer prognosis compared to other subtypes [2]. Since TNBC is defined by the absence of hormone receptors and HER2 negativity, endocrine therapy and HER2-targeted therapy are not applicable. Chemotherapy remains the mainstay of treatment, with an emerging role for immunotherapy [3]. The HER2-negative group includes the HER2-0 subgroup (score 0 on immunohistochemistry (IHC)) and the HER2-low subgroup (HER2 1+ on IHC or HER2 2+ on IHC with a negative Dual-ISH or FISH result). Studies have suggested differences in prognosis between HER2-low and HER2-0 cases. The DESTINY-Breast04 clinical trial demonstrated that trastuzumab deruxtecan is highly effective in metastatic HER2-low breast cancer [4].

Thus, it has been hypothesized that the risk of recurrence and treatment efficacy may vary between HER2-low and HER2-0 cases in early-stage TNBC. These findings support the use of HER2 status as a prognostic factor and the development of new treatment strategies for TNBC in the future. Such insights may contribute to personalized treatment approaches for TNBC patients.

In Vietnam, the impact of low HER2 expression on tumor clinical characteristics and prognostic value in early-stage TNBC has not been extensively studied. Therefore, this study aims to evaluate the association between HER2 expression, clinical characteristics, and prognostic value in early-stage TNBC among Vietnamese patients.

2. METHODS

2.1. Study subjects

This retrospective study was conducted on 126 patients diagnosed with non-metastatic triple-negative breast cancer (TNBC) based on surgical specimens at Vietnam National Cancer Hospital from January 2018 to December 2019. HER2 expression was evaluated according to the 2018 ASCO/CAP guidelines and tumor-infiltrating lymphocytes (TILs) were assessed based on the 2014 guidelines of the International TILs Working Group, using a threshold of 40%.

2.2. Inclusion criteria

- Female patients who underwent surgery as the initial treatment (without prior neoadjuvant therapy) and were histopathologically confirmed to have primary breast carcinoma based on surgical specimens.

- No history of second primary cancer.

- Complete medical records with sufficient data for the study. Availability of histopathological slides and paraffin blocks meeting the requirements for hematoxylin and eosin (HE) staining and immunohistochemistry (IHC).

- Patients confirmed to have negative estrogen receptor (ER), progesterone receptor (PR), and HER2 status (IHC 0+, 1+ or 2+ with a negative FISH/Dual-ISH result) in surgical specimens.

2.2. Exclusion criteria

Incomplete medical records lacking necessary information for the study.

2.3. Research methods

A cross-sectional descriptive study was conducted to determine HER2 status, the proportion of tumor-infiltrating lymphocytes, and their association with histopathological characteristics and survival outcomes in TNBC.

2.4. Study procedure

- Identify patients diagnosed with TNBC from January 2018 to December 2019.

- Review medical records and collect relevant data for the study.

- Record histopathological findings based on HE and IHC staining for ER, PR, HER2, Ki67 and assess TILs.

- Evaluate HER2 expression according to the 2018 ASCO/CAP guidelines and assess TILs using the 2014 International TILs Working Group criteria, with a cutoff threshold of 40%.

3. RESULTS

3.1. Association between HER2 status and clinical, paraclinical characteristics and tumor-infiltrating lymphocytes (TILs)

Table 1. Association between HER2 status and clinical, paraclinical characteristics

Characteristics	HER2-0 (n=94)	HER2-low (n=32)	p-value
Age (years), Mean ± SD	53.3 ± 11.0	58.6 ± 10.8	0.02
Tumor Stage (T-stage)			0.30
- T1 (%)	48 (51.1)	13 (40.6)	
- T2-3 (%)	46 (48.9)	19 (59.4)	
Nodal Status			0.22
- Negative (%)	67 (71.3)	26 (81.3)	
- Positive (%)	27 (28.7)	6 (18.8)	
Histological Grade			0.19
- Grade 1-2 (%)	40 (42.6)	19 (58.4)	
- Grade 3 (%)	54 (57.4)	13 (40.6)	
Ki67 (%)			0.05
- ≤ 50% (%)	24 (25.5)	14 (43.8)	
- > 50% (%)	70 (74.5)	18 (56.3)	
Vascular Invasion			0.06
- No (%)	91 (96.8)	28 (87.5)	
- Yes (%)	3 (3.2)	4 (12.5)	
TILs, No. (%)			0.005
- Low (%)	46 (48.9)	26 (81.3)	
- High (%)	48 (51.1)	6 (18.8)	

Our study included 126 patients, with a mean age of 54.7 ± 11.4 years. The mean age was 53.3 ± 11.0 years in the HER2-0 group and 58.6 ± 10.8 years in the HER2-low group. Among the participants, 74.6% had HER2-0 expression, while 25.4% had HER2-low expression (HER2 1+ on IHC or HER2 2+ on IHC with a negative Dual-ISH or FISH result). A total of 51.1% of HER2-0 cases and 40.6% of HER2-low cases were diagnosed at T1 stage. Most patients in both groups were node-negative after surgery (71.3% in HER2-0 vs. 81.3% in HER2-low).

Compared to HER2-0 patients, HER2-low patients were significantly older (58.6 ± 10.8 years vs. 53.3 ± 11.0 years, p = 0.02) and had lower Ki67 expression (p = 0.05). Additionally, TIL levels were significantly lower in the HER2-low group compared to HER2-0 (p = 0.005). These differences were statistically significant (p < 0.05). Other factors, such as tumor stage, nodal status, histological grade, and vascular invasion, did not show statistically significant differences between HER2-0 and HER2-low groups (p > 0.05).

3.2. Association between HER2 status and overall survival (OS)

The median follow-up time in our study was 54 months. Univariate analysis showed that patients with HER2-low tumors had a lower 5-year overall survival (OS) rate compared to those with HER2-0 tumors (69.6% vs. 83.3%, p = 0.04). However, in multivariate analysis, HER2 expression was not a statistically significant independent predictor of OS. Instead, independent prognostic factors for OS included TILs (p = 0.02; HR = 0.17; 95% CI 0.04-0.77) and lymph node metastasis (p = 0.002; HR = 3.8; 95% CI 1.6-9.1).

Table 2. Multivariate analysis of factors associated with overall aurvival (OS)

Factor	p-value	HR	95% CI
Age (≤50 vs. >50 years)	0.17	1.88	0.77-4.61
Ki67 (≤20% vs. >20%)	0.84	0.89	0.30-2.70
Lymph Node Metastasis (Negative vs. Positive)	0.002	3.84	1.61-9.10
Tumor Stage (T1 vs. T2-3)	0.08	2.31	0.88-6.06
TILs (Low vs. High)	0.02	0.17	0.04-0.77
Vascular Invasion (No vs. Yes)	0.85	0.83	0.88-6.42
HER2 Status (0 vs. Low)	0.08	2.55	1.05-6.16

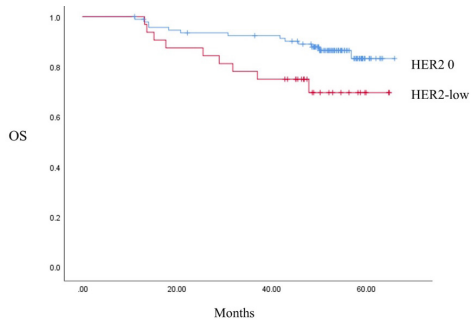

Figure 1. Kaplan-Meier survival curve based on HER2 Status

4. DISCUSSION

Triple-negative breast cancer (TNBC) is associated with rapid disease progression and a poorer prognosis compared to other subtypes [2]. Studies have shown differences in prognosis between HER2-low and HER2-0 groups [5]. Therefore, we focused on investigating the relationship between HER2 status and clinical, pathological characteristics, as well as survival outcomes in patients with early-stage TNBC. In our cohort, 25.4% of patients exhibited HER2-low

expression (HER2 1+ by IHC or HER2 2+ by IHC with a negative Dual-ISH or FISH result), a rate similar to the findings of Tomomi et al [6].

HER2-low was identified as a poor prognostic factor in both univariate and multivariate analyses for disease-free survival (DFS) in stage I TNBC in Tomomi's study. In our study, univariate analysis showed that patients with HER2-low tumors had a lower 5-year overall survival (OS) rate compared to those with HER2-0 tumors. Consistent with previous research, our study also demonstrated a better prognosis in patients with high tumor-infiltrating lymphocytes (TILs) [7].

We found a correlation between TILs and HER2 status. The TILs level was higher in the HER2-0 group compared to the HER2-low group ($p = 0.005$). According to Xi et al., TNBC with HER2-0 status exhibits a more active immune tumor microenvironment than the HER2-low group, as indicated by macrophage polarization and the accumulation of a large number of CD8+ T cells [8]. Additionally, in TNBC patients, HER2-low tumors have a lower pathological complete response rate than HER2-0 tumors and are associated with a weaker immune response [9]. This study suggests that HER2-low expression is associated with a lower intratumoral immune response and worse survival outcomes in patients with early-stage TNBC compared to the HER2-0 group.

5. CONCLUSION

This study suggests that HER2-low expression is associated with a lower intratumoral immune response and poorer survival outcomes in patients with early-stage TNBC compared to the HER2-0 group.

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