Original articles

Clinicopathological and immunohistochemical profiles of early-onset breast cancer in women under 45 years old

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Abstract

Background: Early-onset breast cancer (EOBC), defined as breast cancer in women under 45 years, is often associated with more aggressive biological behavior and poorer prognosis compared to older patients.

Objectives: (1) To evaluate the clinicopathological, immunohistochemical characteristics, and molecular subtypes of EOBC; (2) To investigate the associations between selected clinicopathological features and immunohistochemical profiles.

Materials and methods: A retrospective cross-sectional study was conducted on 72 patients with invasive breast cancer aged under 45 years who underwent treatment at Hue University of Medicine and Pharmacy Hospital between January 2023 and December 2025. The study was carried out from November 2025 to May 2026.

Results: The majority of tumors were > 2 cm, with a high rate of lymph node metastasis (61.1%); most patients presented at stage II (54.2%). Invasive carcinoma of no special type (83.3%) and histological grade II (56.9%) predominated. Hormone receptor positivity was observed in 70.8% (ER) and 69.4% (PR) of cases, while a high Ki-67 index (≥ 20%) was present in 69.4%. Luminal B was the most common molecular subtype (38.0%). Significant associations were found between tumor size and clinical stage, as well as between histological grade and both hormone receptor status and molecular subtype ($p < 0.05$).

Conclusion: EOBC in this study demonstrates aggressive clinicopathological features and distinct molecular profiles, highlighting the critical role of tumor biology in disease behavior and its potential therapeutic implications.

Keywords: *early-onset breast cancer; immunohistochemistry; molecular subtype.*

1. INTRODUCTION

Breast cancer (BC) is the most common malignancy and the leading cause of cancer-associated death in women worldwide. In Vietnam, according to GLOBOCAN 2022, BC is also the most prevalent cancer, accounting for 28.9% of all cancers in women, with a mortality rate of 8.3% [1].

Although breast cancer has traditionally been more commonly diagnosed in women aged 50 years and older, its incidence among younger women is increasing, likely due to changes in lifestyle and exposure to risk factors. Early-onset breast cancer is defined as breast cancer occurring in women aged under 45 years [2, 4]. This group accounts for a substantial proportion of all breast cancer cases, ranging from 5% to 25%, depending on the study, country, and ethnicity [5]. Compared with older patients, younger women tend to present with more aggressive biological behavior, characterized by higher histological grade, lymph node metastasis, more advanced stages at diagnosis, and a higher risk of recurrence, consequently leading to poorer outcomes [5-8].

Currently, breast cancer is classified into molecular subtypes based on the expression of ER, PR, HER2, and Ki-67, including Luminal A (ER/PR positive, HER2 negative, and low Ki-67), Luminal B, HER2-enriched, and triple-negative subtypes [9]. Identification of these molecular subtypes plays a crucial role in guiding treatment strategies and predicting prognosis. EOBC is often associated with more aggressive tumor biology, frequently presenting as estrogen receptor–negative, triple-negative, or HER2-positive subtypes, with higher Ki-67 expression and an increased risk of recurrence and metastasis [5].

To date, in Vietnam, there remains a lack of studies focusing on the histopathological characteristics and immunohistochemical profiles of EOBC. Therefore, this study was conducted with the following objectives: (1) To evaluate the clinicopathological and immunohistochemical characteristics, as well

as molecular subtypes of EOBC (< 45 years); (2) To investigate the associations between selected clinicopathological features (tumor size, clinical stage, histological grade) and immunohistochemical profiles (hormone receptor status, Ki-67 index, and molecular subtypes)

2. MATERIALS AND METHODS

2.1. Subjects

2.1.1. Inclusion criteria

- Female patients diagnosed with invasive breast cancer confirmed by histopathological examination.
- Age under 45 years at the time of diagnosis.
- Patients who underwent surgical resection or biopsy with available tumor tissue for histopathological and immunohistochemical analysis.
- Availability of complete clinical and pathological data, including tumor size, lymph node status, stage, histological type, and grade, and immunohistochemical markers (ER, PR, HER2, Ki-67).

2.1.2. Exclusion Criteria

- Patients who received neoadjuvant therapy before tissue sampling.
- Cases with incomplete clinical or pathological data.
- Recurrent breast cancer, carcinoma in situ, or metastatic cancer to the breast from other primary sites.
- Presence of other synchronous malignancies.

2.2. Research methods

2.2.1. Study design

A descriptive cross-sectional study with retrospective data collection.

2.2.2. Place and time: At Hue University of Medicine and Pharmacy Hospital from November 2025 to May 2026.

2.2.3. Sample size

A total of 72 patients diagnosed with invasive breast cancer who presented for examination and treatment at Hue University of Medicine and Pharmacy Hospital between January 2023 and December 2025.

2.2.4. Analytical Techniques and Evaluation Criteria

Hematoxyline and Eosin (HE) staining was used to investigate histopathological features, including:

- Histological subtypes were assessed according to the 2019 World Health Organization (WHO) classification [10].
- Histological grade was evaluated using the modified Scarff–Bloom–Richardson grading system.

Immunohistochemical Technique and Interpretation Criterias [11].

- Disease stage was evaluated according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM classification system [12].
- IHC staining was performed to detect the expression of ER, PR, Her2, and Ki-67 using four monoclonal antibodies: ER, PR, Her2, and Ki-67.
- Slide staining: The IHC staining procedure was performed using the Ventana BenchMark GX automated system, with a total duration of approximately 6 hours.
- Evaluation of IHC staining results:

+ ER, PR: According to ASCO/CAP guidelines, ER and PR are considered positive when ≥ 1% of tumor cell nuclei show staining [13].

+ HER2: According to the ASCO/CAP 2018 guidelines[14]:

• 0 (Negative): No membrane staining observed, or incomplete and faint membrane staining in ≤ 10% of the tumor cells.

• 1+ (Negative): Incomplete and faint membrane staining in > 10% of tumor cells.

• 2+ (Equivocal): Complete membrane staining with weak to moderate intensity in > 10% of tumor cells.

• 3+ (Positive): Complete and strong membrane staining in > 10% of tumor cells.

+ Ki-67: The Ki-67 proliferation index was calculated as the percentage of positively stained tumor cells among all tumor cells in hotspot areas (regions with the highest Ki-67 labeling). According to the 2015 St. Gallen International Breast Cancer Conference, Ki-67 was categorized as low (< 20%) and high (≥ 20%).

+ Molecular subtypes: Based on the immunohistochemical expression of ER, PR, HER2, and Ki-67, BC was classified into the following subtypes:

• Luminal A: ER positive (+) and/ or PR positive (+), HER2 negative (-), Ki-67 < 20%.

• Luminal B/ HER2 +: ER (+) and/or PR (+), HER2 (+), Ki-67 ≥ 20%

• Luminall B/ HER2 -: ER (+) and/or PR (+), HER2 (-), Ki-67 any

• HER2-enriched: HER2 (+), ER (-), and PR (-).

• Basal-like (triple-negative): ER (-), PR (-), HER2 (-).

2.3. Data analysis

All collected data were analyzed using SPSS software (version 26.0). Qualitative variables were presented as frequencies and percentages, while quantitative variables were expressed as mean ± standard deviation. The Chi-square test or Fisher's exact test was applied to evaluate the associations between qualitative variables. A p-value < 0.05 was considered statistically significant.

2.4. Ethical considerations

This study was approved by the Institutional Review Board (IRB) of Hue University of Medicine and Pharmacy according to Decision No H2025/691.

3. RESULTS

3.1. Clinicopathological and immunohistochemical characteristics of early onset breast cancer

Table 1. Clinical, histopathological characteristics

Features		n	Percentage (%)
Age	< 30	2	2.8
	30 - < 35	5	6.9
	35 - < 40	25	34.7
	40 - < 45	40	55.6
	39.5 ± 3.7 years (29 - 44)		
Tumor size	≤ 2 cm	24	33.3
	> 2 - ≤ 5 cm	38	52.8
	> 5 cm	10	13.9
Lymph node status	Negative	28	38.9
	Positive	44	61.1
Tumor Stage	I	12	16.7
	II	39	54.2
	III	19	26.4
	IV	2	2.8
Histological types	No special type	60	83.3
	Lobular	2	2.8
	Mucinous	4	5.6
	Medullary	2	2.8
	Metaplastic	1	1.4
	Mixed	3	4.2
Histological grade	I	4	5.6
	II	41	56.9
	III	27	37.5

The mean age was 39.5 ± 3.7 years (ranging from 29 to 44 years), with the majority of patients in the 40 - < 45 age group (55.6%). Tumors were predominantly > 2 cm, with a high rate of lymph node metastasis (61.1%). Most patients presented with stage II (54.2%), followed by stage III (26.4%). Invasive carcinoma of no special type was the most common histological subtype (83.3%), and most tumors were of tumor differentiation grade II (56.9%), followed by grade III (37.5%).

Table 2. Expression patterns of Immunohistochemical markers

IHC features		n	Percentage (%)
ER expression	Positive	51	70.8
	Negative	21	29.2
PR expression	Positive	50	69.4
	Negative	22	30.6
ER (+), PR (+)		47	65.3

ER (+), PR (-)		4	5.6
ER (-), PR (+)		3	4.2
ER (-), PR (-)		18	25.0
HER2	Positive	14	19.7
	Negative	57	80.3
Ki-67	< 20 %	22	30.6
	≥ 20 %	50	69.4

Most tumors were ER-positive (70.8%) and PR-positive (69.4%). HER2 overexpression was observed in 19.7% of cases. A high Ki-67 index (≥ 20%) was noted in the majority of patients (69.4%), indicating a high proliferative activity. Most tumors showed concordant hormone receptor positivity (ER+/PR+, 65.3%).

Table 3. Molecular subtypes

Molecular subtypes	n	Percentage (%)
Luminal A/HER2 negative, Ki 67 < 20%	20	28.2
Luminal B/HER2 negative, Ki-67 ≥ 20%	27	38.0
Luminal B/HER2 positive	7	9.9
HER2 enriched	7	9.9
Triple negative	10	14.1

Luminal B (HER2-negative, Ki-67 ≥ 20%) was the most common molecular subtype (38.0%), followed by Luminal A (28.2%). Triple-negative breast cancer accounted for 14.1% of cases, while HER2-enriched and Luminal B/HER2-positive subtypes were less frequent (each 9.9%).

3.2. The association between selected clinicopathological and immunohistochemical profiles

Table 4. Association between tumor size and histopathological features

Features		Tumor size			P
		≤ 2 cm	>2 - ≤ 5 cm	> 5 cm	
Lymph node involvement	Negative	11 (39.3%)	14 (50%)	3 (10.7%)	0.642
	Positive	13 (29.5%)	24 (54.5%)	7 (15.9%)	
Disease stage	I	11 (91.7%)	1 (8.3%)	0 (0%)	**0.001**
	II	10 (25.6%)	23 (59%)	6 (15.4%)	
	III	3 (15.8%)	12 (63.2%)	4 (21.1%)	
	IV	0 (0%)	2 (100%)	0 (0%)	
Histological grade	I	1 (25%)	2 (50%)	1 (25%)	0.786
	II	16 (39%)	20 (48.8%)	5 (12.2%)	
	III	7 (25.9%)	16 (59.3%)	4 (14.8%)	

While no significant association was observed between tumor size and lymph node involvement or histological grade (p > 0.05), tumor size was significantly associated with disease stage (p = 0.001), with larger tumors more frequently presenting at advanced stages.

Table 5. Association between hormone expression status and histopathological features

ER/ PR expression		Histological grade			P
		I	II	III	
ER	Negative	0 (0%)	8 (38.1%)	13 (61.9%)	**0.017**
	Positive	4 (7.8%)	33 (64.7%)	14 (27.5%)	

PR	Negative	0 (0%)	8 (36.4%)	14 (63.6%)	**0.007**
	Positive	4 (8%)	33 (66%)	13 (26%)	
ER/ PR expression		**Lymph node involvement**			
		Negative	**Positive**		
ER	Negative	8 (38.1%)	13 (61.9%)		0.929
	Positive	20 (39.2%)	31 (60.8%)		
PR	Negative	8 (36.4%)	14 (63.6%)		0.771
	Positive	20 (40%)	30 (60%)		

A significant association was found between hormone receptor status and histological grade. ER-negative and PR-negative tumors were more frequently associated with higher histological grade (grade III) ($p<0.05$). By contrast, no significant association was observed between ER or PR expression and lymph node involvement ($p > 0.05$).

Table 6. Association between Molecular subtypes and histopathological features

		Molecular subtypes					P
		Luminal A (ER/PR+, HER2, Ki-67 < 20%)	**Luminal B (ER/PR+, HER2-, Ki-67 ≥ 20%)**	**Luminal B (ER/PR+, HER2+)**	**HER2 enriched (ER-, PR-, HER2+)**	**Triple negative (ER-, PR-, HER2-)**	
Histological grade	I	2 (50%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)	
	II	18 (43.9%)	13 (31.7%)	4 (9.8%)	3 (7.3%)	3 (7.3%)	**0.012**
	III	0 (0%)	12 (46.2%)	3 (11.5%)	4 (15.4%)	7 (26.9%)	
Lymph node involvement	Negative	12 (42.9%)	7 (25%)	2 (7.1%)	2 (7.1%)	5 (17.9%)	0.149
	Positive	8 (18.6%)	20 (46.5%)	5 (11.6%)	5 (11.6%)	5 (11.6%)	

A significant association was observed between molecular subtypes and histological grade ($p<0.05$). HER2-positive and triple-negative subtypes were more frequently associated with higher histological grade (grade III), whereas Luminal A tumors were more commonly observed in lower grades (grade I). No significant association was found between molecular subtypes and lymph node involvement ($p>0.05$).

4. DISCUSSION

4.1. Clinicopathological and immunohistochemical characteristics of early-onset breast cancer

Breast cancer occurring in women under 45 years of age accounts for approximately 5% to 25% of all cases, with variations depending on the study, country, and ethnicity [5]. The age of patients at the time of initial diagnosis is associated with both disease incidence and prognosis [15]. Young age has been identified as an independent prognostic factor associated with poorer survival [16]. Early-onset breast cancer refers to breast cancer diagnosed in women younger than 45 years, although the exact age threshold may vary across studies [2, 6, 8, 16, 17]. This study focused on young women (< 45 years) with histopathologically confirmed breast carcinoma. The mean age at initial diagnosis in our study was 39 ± 3.7 years (ranging from 29 to 44 years), consistent with the findings of M.A. Caparlar et al. (2023), in which the mean age was 38.8 ± 5.4 years (ranging from 24 to 45 years) [16].

In our study, early-onset breast cancer (< 45 years) demonstrated several aggressive clinicopathological features. Tumor size was predominantly > 2 cm, with the majority of tumors measuring > 2 to ≤ 5 cm (52.8%), accompanied by a high prevalence of nodal metastasis (61.1%). Most tumors were diagnosed at stage II, followed by stage III (54.2% and 26.4%, respectively). Regarding tumor size, our findings are consistent with those reported by Pavani et al. (2024) [6], Mai Chi Thanh et al. (2024) [15], and A. Pinto et al. (2022) [8], who reported that tumors measuring 2–5 cm accounted for 57.1%, 69.6%, and 57.6% of cases, respectively, supporting the observation that tumors in younger patients tent to be larger (> 2 cm). Axillary lymph node status is an important prognostic factor influencing recurrence and survival outcomes [15]. Our findings are consistent with those

reported by Iraj Feizi et al. (2023) [18] and A. Pinto et al. (2022) [8], who observed a high proportion of patients with lymph node metastasis (88.9% and 56%, respectively). In contrast, Mai Chi Thanh et al. (2024) [15] and Pavani et al. (2024) [6] reported lower rates of nodal involvement (35.3% and 35.7%, respectively). The observed differences may be explained by variations in population characteristics, healthcare accessibility, screening practices, and levels of community awareness. In breast cancer, disease stage plays a crucial role in treatment and prognosis [15]. In our study, stage II was the most common stage (54.2%), followed by stage III (26.4%) and stage I (16.7%). Similar findings have been reported by Mai Chi Thanh et al. (2024) [15] and A. Pinto et al. (2022) [8], suggesting that a considerable proportion of young patients are diagnosed at advanced stages. This may be explained by limited access to screening programs and the reduced sensitivity of mammography in younger women with dense breast tissue [5, 19]. Histologically, invasive carcinoma of no special type was the most common histological subtype (83.3%), consistent with previous reports [6, 8, 15, 20]. Regarding histological grade, most tumors in our study were grade II (56.9%), followed by grade III (37.5%), while grade I was the least common (5.6%). These findings are in line with those reported by Mai Chi Thanh et al. (2024), with corresponding proportions of 78.3%, 15%, and 6.7% for grades II, III, and I, respectively [15].

Regarding immunohistochemistry, the majority of patients exhibited positive hormone receptor expression, with ER and PR positivity rates of 70.8% and 69.4%, respectively, and 65.3% of cases demonstrating co-expression of both receptors. These findings are comparable to those reported by Mai Chi Thanh et al. (2024), who observed corresponding positivity rates of 73.4%, 64%, and 62.5% for ER, PR, and dual receptor expression, respectively, indicating that a substantial proportion of patients may benefit from endocrine therapy [15]. In addition, the proportion of HER2-positive patients in our study (19.7%) was lower than that reported in several other studies, including those by Mai Chi Thanh et al. (2024), Pavani et al. (2024), and M.A. Capalar et al. (2023), with corresponding rates of 62.9%, 26.1%, and 27.5%, respectively [6, 15, 16], which may be attributed to differences in patient characteristics, tumor biology, or study populations. A total of 69.4% of patients had a Ki-67 ≥ 20%, consistent with the findings of P. Akakpo et al. (2024), who reported 84.2%, reflecting high proliferative activity characteristic of more aggressive tumor behavior in young women.

In our study, the distribution of molecular subtypes showed that Luminal B/HER2-negative was the predominant subtype (38.0%), followed by Luminal A (28.2%), while the triple-negative subtype accounted for 14.1%. These findings differ to somewhat from those reported by Mai Chi Thanh et al. (2024), in which the proportions of Luminal B/HER2-negative, Luminal A, and triple-negative were 24.6%, 20.3%, and 10.1%, respectively [15]. Such differences may be attributed to variations in classification criteria, study population characteristics, sample size, and methods of immunohistochemical assessment.

Notably, the predominance of the Luminal B subtype, together with a considerable proportion of triple-negative cases and a high Ki-67 index, reflects the aggressive biological behavior of breast cancer in young women, characterized by high proliferative activity and a more aggressive phenotype compared with older patients. Previous studies have also demonstrated that early-onset breast cancer is associated with a higher prevalence of unfavorable molecular subtypes, such as Luminal B and triple-negative, which are linked to an increased risk of recurrence and poorer prognosis [5].

4.2. The association between selected clinicopathological and immunohistochemical factors

In our study, tumor size was not significantly associated with lymph node metastasis or histological grade ($p > 0.05$), suggesting that lymph node involvement is not only dependent on tumor size but may also be influenced by other biological characteristics of the tumor such as histological type, tumor grade, the presence of lymphovascular invasion, and molecular subtype [21]. Nonetheless, tumor size was significantly associated with disease stage ($p < 0.05$), with larger tumors tending to be diagnosed at more advanced stages, consistent with the natural progression of breast cancer.

When analyzing the association between hormone receptor expression and histological grade, both ER and PR showed statistically significant correlations with tumor grade ($p = 0.017$ and $p = 0.007$, respectively). Specifically, ER/PR-negative tumors tended to be associated with higher histological grades, particularly grade III, reflecting more aggressive biological behavior. In contrast, all grade I tumors in our study co-expressed ER and PR. These findings are consistent with those reported by A. Nonni et al. (2024), who found that all grade I tumors expressed ER and PR, whereas most grade III tumors were ER- and PR-negative [22]. This suggests that low-grade tumors are more likely to express

hormone receptors, respond better to endocrine therapy, and therefore have a more favorable prognosis.

We observed that HER2-enriched and triple-negative subtypes were more frequently associated with higher histological grades (grade III), whereas the Luminal A subtype was predominantly found in lower grades (grades I and II). A statistically significant association between tumor grade and molecular subtype was identified ($p < 0.05$). These findings are consistent with the established biological behavior of breast cancer subtypes, in which more aggressive subtypes tend to exhibit poorer differentiation and higher proliferative activity. However, our results differ from those reported by A. Nonni et al. (2024), who found that triple-negative tumors were less frequently associated with higher histological grades [22]. This discrepancy may be explained by differences in sample size, patient population, or study design between the two studies.

Compared to late-onset breast cancer (LOBC) which is characterized by lower histological grades and favorable Luminal A dominance, our EOBC cohort displayed a distinctly more aggressive phenotype [1, 18]. Clinically, the high proportions of tumors > 2 cm (66.7%), advanced stages II-III (80.6%), and lymph node metastasis (61.1%) in young patients contrast sharply with older cohorts, where tumors are often caught earlier (Stage I) due to active screening and lower breast density [1, 8, 18]. Furthermore, while Luminal A typically exceeds 50% in LOBC, Luminal B predominated in our study (38.0%), and high-risk subtypes (triple-negative and HER2-enriched) comprised 24.0% of cases [1, 5, 9]. The high proliferation status (Ki-67 ≥ 20% in 69.4%) also underscores the rapid growth inherent to EOBC compared to indolent postmenopausal tumors [1, 16, 23]. These disparities reinforce that breast cancer in the young is a distinct biological entity requiring intensified therapeutic strategies [1, 5, 9].

This study has several limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. In addition, survival outcomes and long-term follow-up data were not available, thereby precluding further evaluation of prognostic significance.

5. CONCLUSION

Based on the analysis of 72 breast cancer cases in patients under 45 years of age, and despite certain limitations, several conclusions can be drawn. Early-onset breast cancer is characterized by aggressive clinicopathological features, including high histological grade, a high frequency of lymph node metastasis, advanced stage at diagnosis, increased proliferative activity, and a predominance of the Luminal B subtype. Significant associations between hormone receptor status, molecular subtypes, and histological grade further highlight the critical role of tumor biology in determining disease behavior. These findings provide valuable insights for prognostic evaluation and therapeutic decision-making in young breast cancer patients.

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