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Young-Onset Breast Carcinoma Tends to Show a Higher Proportion of Triple-Negative Subtype: A Comparative Molecular and Pathological Analysis

Citra Dewi[1*], Novasari[2], Sandria[3]

[1,2,3]Mohammad Hoesin General Hospital/Department of Anatomical Pathology, Sriwijaya University, Palembang, Indonesia

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Corresponding author:
Citra Dewi
E-mail address:
citrafarahkayla@gmail.com

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ABSTRACT

Introduction. Breast carcinoma in young women is often associated with more aggressive molecular profiles and suboptimal therapeutic responses. This study was designed to compare the molecular and histopathological characteristics of patients younger than 40 years with those aged 40 years and above. **Methods.** This study employed a retrospective descriptive-analytic design using clinical and pathological data from 36 patients diagnosed with invasive breast carcinoma. All cases were collected from the Department of Anatomical Pathology at Mohammad Hoesin General Hospital in Palembang, Indonesia, in 2023. **Results.** The molecular subtype profile was similarly distributed across the two age categories, with no statistically significant difference by age ($p = 0.789$). However, the younger cohort showed a relatively higher proportion of triple-negative cases. Luminal B remained the most prevalent molecular subtype in both groups. Likewise, ER, PR, and HER2 expression showed no significant differences according to age ($p > 0.05$). All patients exhibited high Ki-67 expression, and grade III was the predominant histological grade in both groups. Dominant TILs were observed in only a small fraction of cases, with no statistically significant age-related difference. **Conclusion.** Although younger patients showed a relative proportion of triple-negative cases and all tumors demonstrated high proliferative activity, no statistically significant differences in molecular subtype distribution or other clinicopathological parameters were identified between the two age groups. Luminal B remained the predominant molecular subtype in both groups. These findings suggest that age-related biological differences may exist, but larger studies are needed to clarify this association.

1. Introduction

Based on GLOBOCAN estimates, breast cancer contributes 11.6% of all cancer diagnoses worldwide, with around 2.3 million newly reported cases and nearly 670,000 related deaths. These findings reinforce its position as the most frequently diagnosed cancer in women globally. In recent decades, a noticeable rise in incidence has also been reported among younger age groups. An estimated 66,000 new breast cancer cases and over 22,000 related deaths were reported in Indonesia in 2022, underscoring its major public health burden and confirming it as the leading cause of cancer incidence and mortality among women. Although most cases are diagnosed in women aged ≥40 years, breast cancer occurring at a younger age (<40 years) demonstrates distinct clinical and biological features. Compared with older patients, younger women are more frequently associated with aggressive tumor behavior, higher proliferative activity, and poorer prognosis.[1] Earlier studies have reported that breast cancer in younger women is more commonly linked to unfavorable molecular subtypes, including triple-negative and HER2-enriched, along with higher histopathological grades (Grade III). Furthermore, breast cancer in young women presents unique clinical challenges, including limited treatment options, higher recurrence risk, and greater psychosocial impact.[2,3]

The incorporation of molecular subtypes and biomarkers, including ER, PR, HER2, Ki-67, TILs, and LVI, has enabled a more individualized approach to breast cancer management. Several studies have demonstrated that breast cancer occurring in younger women tends to exhibit more aggressive biological features, including higher tumor grade, higher proliferation rates, and a greater prevalence of unfavorable molecular subtypes. However, most of these findings originate from Western or large multicenter cohorts, and data comparing molecular and pathological characteristics between younger and older breast cancer patients remain limited in many developing countries, including Indonesia. Differences in genetic background, lifestyle factors,

healthcare access, and screening practices may influence the clinicopathological profile of breast cancer across populations. Understanding these differences is important because molecular subtype distribution and tumor biology can directly influence therapeutic decisions, prognosis, and treatment response. Therefore, comparative analysis between age groups is needed to understand the differences in characteristics and their potential implications for therapy.[4,5] This study was conducted to evaluate differences in the molecular and pathological characteristics of breast cancer in patients aged <40 years and ≥40 years, with particular emphasis on molecular subtype distribution, hormone receptor expression, proliferative activity, and immunological as well as vascular features. The findings are expected to offer further insight into the biological behavior of breast cancer in younger patients and support the development of more targeted therapeutic strategies.

2. Methods

This study adopted a retrospective comparative cross-sectional approach utilizing clinical and pathological records of patients diagnosed with invasive breast carcinoma. It was performed at the Department of Anatomical Pathology, Mohammad Hoesin Hospital, Palembang, Indonesia, a tertiary referral institution that manages patients from South Sumatra and adjacent areas. All eligible cases identified between January and December 2023 were collected from the departmental pathology archive. A consecutive sampling technique was implemented, whereby all cases fulfilling the study requirements during the defined period were enrolled. The final dataset included 36 patients, encompassing all available cases that satisfied the inclusion criteria within that timeframe. The tumor specimen from each patient served as the unit of analysis. Eligible subjects were those with histopathologically verified invasive breast carcinoma, accessible formalin-fixed paraffin-embedded (FFPE) tissue blocks, and complete immunohistochemical (IHC) results. Cases were excluded if they involved recurrent tumors, metastases originating from other primary sites, inadequate tissue material, or incomplete clinicopathological and immunohistochemical records. Collected variables comprised age at diagnosis, histological subtype, histological grade, and immunohistochemical parameters, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki-67 proliferative index, tumor-infiltrating lymphocytes (TILs), and lymphovascular invasion (LVI). Molecular subtype classification followed the St. Gallen Consensus, consisting of luminal A, luminal B, HER2-enriched, and triple-negative categories.

Standard diagnostic immunohistochemical procedures were applied throughout the study. Positivity for ER and PR was assigned when nuclear staining involved more than 1% of tumor cells, following ASCO/CAP recommendations. HER2 was interpreted using a 0 to 3+ scoring scale, with 0–1+ regarded as negative, 3+ as positive, and 2+ as equivocal according to institutional practice. The Ki-67 index represented the proportion of stained tumor nuclei and was grouped into low (<20%) and high (≥20%) categories based on St. Gallen criteria. TIL assessment was performed on hematoxylin–eosin slides in accordance with the International TILs Working Group recommendations, whereas LVI was recorded when tumor emboli were identified within endothelial-lined vascular or lymphatic spaces.

Cases were subsequently stratified into patients aged <40 years and those ≥40 years. Distribution of clinicopathological parameters across both cohorts was then compared. Frequency and percentage were used to summarize categorical data. Fisher's exact test was selected for variables arranged in 2×2 tables, while molecular subtype distribution in the 2×4 table was analyzed using the Fisher–Freeman–Halton exact test. Because all tumors showed uniformly high Ki-67 expression, this variable was excluded from intergroup comparison. A p-value <0.05 was considered statistically significant. Data processing was completed using IBM SPSS Statistics version 26. Histopathological and IHC interpretation were performed by a certified pathologist as part of routine diagnostics. Archived data were anonymized after ethical clearance had been obtained. Ethical exemption was granted by the Health Research Ethics Committee of Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia (No. DP.04.03/D.XVII.06.08/ETIK/248/2025; September 16, 2025).

3. Results

This study analyzed 36 patients with histopathologically confirmed invasive breast carcinoma, including 5 patients aged <40 years and 31 patients aged ≥40 years. The clinicopathological features of the study population are presented in Table 1. As presented in Table 1, evaluation of molecular subtype patterns showed that the younger age group was predominantly composed of luminal B and triple-negative subtypes, whereas the older group was mainly characterized by luminal B (64.5%) with a smaller proportion of triple-negative cases. Statistical testing using the Fisher–Freeman–Halton exact test demonstrated no significant difference between the age groups (p = 0.789), suggesting that molecular subtype distribution was not significantly related to age category in this study.

Hormone receptor expression showed that most patients in both groups expressed ER and PR, although without statistically significant differences (ER p = 0.603; PR p = 0.637). Similarly, HER2 overexpression (3+) was not significantly different according to age category (p = 0.646), although the HER2-enriched subtype was only found in patients aged ≥40 years. These findings indicate that although

hormonal expression was relatively evenly distributed, no statistically significant difference in molecular profiles was observed across the two age groups.

All patients in this study showed positive Ki-67 expression, reflecting the high rate of cell proliferation in both groups. Histological grade III was found in most patients in both age groups, with no significant difference (p = 0.466), although all patients in the younger age group showed grade III tumors. This finding suggests that high-grade tumors were common in this cohort, particularly among younger patients.

Evaluation of Tumor-Infiltrating Lymphocytes (TILs) showed that the dominant pattern was found in only a small percentage of patients (1 case at a young age and 5cases at age ≥40 years), with a statistically insignificant distribution (p = 1.00). Similarly, Lymphovascular Invasion (LVI) was found in 40% of young patients and 64.5% of elderly patients, but without significant differences (p = 0.357).

4. Discussion

This study evaluated the molecular and pathological characteristics of breast cancer according to age group. The findings demonstrated that patients aged <40 years showed a greater frequency of luminal B and triple-negative subtypes**,** whereas patients aged ≥40 years were also predominantly classified as luminal subtype B. This pattern suggests that younger patients may tend to exhibit a biologically more aggressive tumor profile.[9] However, no significant variation in molecular subtype distribution was noted across the two age groups. Other variables, including ER, PR, HER2 expression, histological grade, TILs, and LVI, also did not show statistically significant differences.

In the present study, the younger age group showed a higher proportion of luminal B and triple-negative tumors, both of which are generally linked to increased proliferative potential and poorer clinical prognosis than luminal A tumors. Molecular classification of breast cancer has demonstrated that luminal B tumors commonly display elevated proliferation rates and more aggressive biological features compared with luminal A tumors.[10,11] In addition, triple-negative breast cancer (TNBC) is a distinct subtype defined by the lack of ER, PR, and HER2 expression and is frequently related to aggressive tumor behavior with limited options for targeted therapy.[12] However, from a clinical perspective, Triple Negative Breast Carcinoma remains challenging because it does not respond to conventional targeted therapies and is associated with a high recurrence risk.[12]

The biological differences between younger and older breast cancer patients may be related to variations in breast tissue physiology and tumor development pathways. Breast tissue in younger women is in a proliferatively active phase, rich in luminal and basal progenitor cells that have not yet fully differentiated. When malignant transformation occurs, these cells tend to develop into subtypes with characteristics of high proliferation and hormonal resistance. These cellular characteristics may contribute to the development of tumors with higher proliferative potential. Previous studies have also suggested that changes in genes related to cell cycle control and DNA repair may contribute to more aggressive tumor behavior in younger patients, although such mechanisms were not directly evaluated in the present study.[10,11]

Table 1. Distribution and Statistical Analysis between Age Groups

Variabel	Category	<40 Years	≥40 Years	Total	*p-value*
Molecular Subtype	Luminal A	0	3	3	0.789
	Luminal B	3	20	23	
	Triple Negative	2	7	9	
	HER2 Enriched	0	1	1	
ER	Positive	3	23	26	0.603
	Negative	2	8	10	
PR	Positive	2	18	20	0.637
	Negative	3	13	16	
HER2	Positive	1	11	12	0.646
	Negative	4	20	24	
Ki-67	High	5	31	36	–
	Low	0	0	0	
Histological Grade	II	1	3	4	0.466
	III	4	28	32	
TILS	Dominant	1	5	6	1.00
	Non-dominant	4	26	30	
LVI	Positive	2	20	22	0.357
	Negative	3	11	14	

Fisher exact test for 2x2 tables, and Fisher Freeman Halton exact test for 2x4 table, (-) no analysis

In the current study, hormone receptor expression (ER and PR) and HER2 overexpression did not significantly differ between age groups. These findings suggest that hormone receptor signaling remains a key biological pathway in breast cancer development and treatment response, but individual biomarker expression alone may not fully explain age-related differences in tumor behavior.[3] Although young women have high systemic estrogen levels, their tumors often show low or non-functional expression of ER and PR, indicating the presence of intrinsic hormonal resistance.[13] This may partly explain the occurrence of subtypes that are less dependent on hormonal signaling, such as TNBC and luminal B, although such a pattern was not statistically significant in the present study.

All tumors demonstrated a Ki-67 proliferation index ≥20%, indicating generally high proliferative activity in this cohort. High Ki-67 expression has been reported to be more frequently associated with aggressive tumor subtypes and poorer clinical outcomes.[13,14] The predominance of histological grade III tumors, particularly among younger patients, further supports the presence of high-grade tumor characteristics in this population. In addition, TP53 mutations that are common in luminal B and TNBC cause cell cycle dysregulation and resistance to apoptosis, reinforcing the aggressive nature of tumors.[15]

Tumor-infiltrating lymphocytes (TILs) represent an important component of the immune response within the tumor microenvironment and have been linked to therapeutic response in specific breast cancer subtypes.[12] In this study, TIL distribution was not significantly different between age groups. Similarly, the presence of lymphovascular invasion (LVI) showed no statistically significant difference between groups. Previous studies have suggested that stromal and microenvironmental factors may influence tumor progression and metastasis through interactions between tumor cells and surrounding stromal components.[16] Although TILs and LVI have been recognized as important prognostic and predictive biomarkers in selected breast cancer subtypes, especially triple-negative breast cancer, the limited sample size may have reduced the ability to identify significant differences.

This study has several limitations. First, the sample size was fairly small, particularly in the younger age group, which may limit statistical power to detect significant differences between groups. Second, the study was conducted in one tertiary referral center, which may introduce selection bias and reduce the generalizability to larger populations. Third, the study relied on retrospective archival data, and additional molecular alterations that may influence tumor biology were not assessed.

Notwithstanding these limitations, this study offers preliminary insight into the clinicopathologic features of breast carcinoma in younger women in a tertiary referral center in Indonesia. Future studies with larger multicenter cohorts and integrated molecular analyses are required to further elucidate the biological differences of breast cancer across age groups and to support more personalized therapeutic strategies.

5. Conclusion

This study showed that the molecular subtype profile was not significantly different across breast cancer patients aged <40 years and those aged ≥40 years, although a relative proportion of luminal B and triple-negative subtypes was observed in the younger group. These findings suggest potential differences in tumor biological characteristics may exist between age groups, but such differences were not statistically demonstrated in the present study. Other clinicopathological variables, such as hormone receptor expression, HER2 status, histological grade, TILs, and lymphovascular invasion, also did not show statistically significant differences. The predominance of high proliferative activity and high-grade tumors in this cohort highlights the heterogeneity of breast cancer across age groups.

These findings underscore the importance of comprehensive pathological and molecular evaluation in breast cancer patients to support appropriate risk stratification and treatment planning. Additional studies with larger sample sizes and multicenter cohorts are required to better clarify age-related differences in breast cancer biology.

6. Author Contribution

C.D conceived the original idea, designed the study, performed the data analysis, and wrote the manuscript. S. and N. contributed to data collection, sample preparation, and manuscript editing.

7. Acknowledgements

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