Med Glas (Zenica) 2025;22(2)
https://doi.org/10.17392/1942-22-02

Med Glas (Zenica)

ORIGINAL ARTICLE

Clinicopathological features of young-onset breast cancer patients based on molecular subtypes at H. Adam Malik Hospital

Raka Dutra Pratama[1], Pimpin Utama Pohan[2], Dedy Hermansyah[2]

[1]Department of Surgery, [2]Division of Surgical Oncology, Department of Surgery; Faculty of Medicine, Universitas Sumatera Utara

ABSTRACT

Aim To examine and evaluate the clinicopathological characteristics of young-onset breast cancer across molecular subtypes in patients from Southeast Asia, with a specific focus on those treated at H. Adam Malik Hospital, Indonesia.

Methods A descriptive observational study with a cross-sectional design was conducted on medical records of breast cancer patients aged <40 years treated at H. Adam Malik Hospital from January 2017 to December 2022. Data included demographic, clinical, histopathological, and immunohistochemical findings.

Results Among the 104 patients, 71 (69.2%) had T4 tumours, and 49 (47.1%) had NST-type tumours. Most cases lacked Estrogen Receptor (ER), (72, 69.2%) and Progesterone Receptor (PR), 71 (68.3%), expression. A total of 41 patients had poorly differentiated tumours, with the majority at stage IV. The HER-2 positive subtype was most common, 39 (37.5%), followed by Luminal B, 31 (29.8%), and TNBC, 22 (21.2%).

Conclusion Young-onset breast cancer predominantly features advanced stages, aggressive histopathological grades, and a high prevalence of HER2-positive and Luminal B subtypes. These findings highlight the importance of early detection and personalized treatment approaches.

Keyword breast cancer, cross-sectional studies, medical records, molecular subtypes, young adult

INTRODUCTION

Breast cancer is a malignant tumour that develops in breast tissue, originating either from the ductal epithelium or the lobules (1). It is the second most common cancer globally and the leading type of cancer affecting women worldwide (2,3). Breast cancer incidence increases from year to year with estimated 2.1 million diagnosed in 2018 (24.2% of all cancer cases) (2). According to the International Agency for Research on Cancer (IARC), the prevalence of breast cancer in the young age group (20–39 years) in 2022 reached 247,196 cases globally, with 163,208 cases reported from the Asian continent (3). In the Southeast Asia region, there were 137,514 new breast cancer cases in 2022, representing 4.17% of the total cancer incidence, and Indonesia accounted for 9,609 cases (4). Additionally, in 2018, Indonesia recorded 58,256 new breast cancer cases, comprising 16.7% of the region's total number of cases (3,4).

Breast cancer ranks as the fifth leading cause of cancer-related deaths globally, accounting for 626,679 fatalities, and remains the primary cause of cancer deaths among women (3). In 2018, Indonesia ranked 8th in the world for the number of new breast cancer cases and 4th for breast cancer-related mortality (5,6). Breast cancer is more likely to occur in older women, with the incidence starting to increase when women are over 40 years of age, and the highest incidence when women are over 70 years old (5). However, Research from Washington University School of Medicine indicates that breast cancer diagnoses in women under 50 have been steadily increasing over the past two decades, with a more pronounced rise in recent years (7). Young breast cancer is often found to have higher tumour grade and poor differentiation compared to older women (8). Studies showed that young women are most often diagnosed at stage II-III with grade III on histopathology of invasive ductal carcinoma resulting in a worse prognosis (9).

Breast carcinoma has a heterogeneous histology and molecular profile (10). Based on the histological classification, there are approximately 20 types of histopathological features of breast tumours, while based on the molecular profile, breast cancer is divided into 4 molecular subtypes, luminal A, luminal B, HER2-overexpression and basal like or triple negative (11). Research in Argentina reported that young breast cancer tends to present with the HER2 overexpression molecular subtype (12). This contrasts with a retrospective study in China, which found that very young patients predominantly exhibited the Luminal B subtype (13). However, the results of these two studies have

***Corresponding author:** Dedy Hermansyah
Division of Surgical Oncology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara
Postal address of the institution:
Phone number un the institution:
Email: dedi.hermansyah@usu.ac.id
ORCID ID: https://orcid.org/0000-0002-5980-2556

| Submitted: 30. Jan. 2025. Revised: 06 Jun. 2025. Accepted: 08 Jun. 2025.

confirmed that young breast cancer is associated with more aggressive tumour types with lymphovascular invasion and high grading (12,13).

Despite the global recognition of breast cancer as a heterogeneous disease with distinct molecular subtypes, there remains a paucity of data concerning the clinicopathological features of young-onset breast cancer in Indonesia. Studies have primarily focused on general population, often overlooking age-specific nuances. For instance, research indicates that luminal subtypes are more prevalent in older Indonesian women, while Basal-like/TNBC and HER2-positive subtypes are more frequent in younger patients (14). At Haji Adam Malik General Hospital, while there have been studies on breast cancer subtypes, detailed investigations into the clinicopathological characteristics of young-onset patients remain scarce (15). This gap underscores the need for focused research to inform tailored diagnostic and therapeutic strategies for this demographic.

The aim of this study was to examine and evaluate the clinicopathological characteristics of young-onset breast cancer across molecular subtypes in patients from Southeast Asia, with a specific focus on those treated at H. Adam Malik Hospital, Indonesia.

MATERIALS AND METHODS

Materials and study design

The study used descriptive observational research design with a cross-sectional approach (single-point observation). All patients treated at Haji Adam Malik Medan from January 2017 to December 2022 were involved. Secondary data taken from medical records were used.

To determine clinicopathological features, measurement of variables was performed as follows: age, grading, tumour size, lymph node involvement, histology type and stage.

Medical records of breast cancer patients aged <40 years who were treated at Haji Adam Malik General Hospital, Medan were analysed. The sample in this study was taken using a total sampling technique, where the entire population met the inclusion and exclusion criteria.

The inclusion criteria were young female patients who were diagnosed with breast cancer at the age of <40 years treated at Haji Adam Malik General Hospital Medan in January 2017 – December 2022 and young female breast cancer patients who had undergone physical examination, histopathological examination and clinical examination.

Methods

Descriptive statistical analysis was conducted to summarize the demographic characteristics of young-onset breast cancer patients. Subsequently, clinical characteristics of the study population were also analysed according to the American Joint Committee on Cancer (AJCC) (16): Tumour size (T) - T1 indicates tumours ≤2 cm, T2 >2-≤5 cm, T3 >5 cm, and T4 includes tumours of any size with direct extension to the chest wall or skin; lymph node involvement (N) classified from N0 (no regional lymph node metastasis) to N3 (extensive regional lymph node involvement), based on the number and location of affected nodes; distant metastasis (M) categorized as M0 (no distant metastasis) or M1 (presence of distant metastasis), with further description of metastatic sites (e.g., bone, liver, lungs, brain).

Histopathological analysis was performed on biopsy specimens obtained from patients. This included evaluation of tumour type, grade, and other morphological features under haematoxylin and eosin (H&E) staining, classified according to the World Health Organization (WHO) breast tumour classification system (the number of the reference from the reference list).

Immunohistochemical (IHC) analysis was conducted to assess the expression of key biomarkers, including oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67. The molecular subtypes were determined based on these markers as follows: Luminal A - ER+ and/or PR+, HER2−, low Ki-67; Luminal B - ER+ and/or PR+, HER2− or HER2+, high Ki-67; HER2-enriched - ER−, PR−, HER2+; Triple-negative breast cancer (TNBC) - ER−, PR−, HER2−.

The results of the histopathological and immunohistochemical analyses were used to stratify patients into molecular subtypes for further clinicopathological correlation.

Statistical analysis

Data analysis was carried out descriptively. The data set was subjected to a data distribution normality test to determine the distribution of the data. The normality test used was the Kolmogorov Smirnov test and $p<0.05$ was considered as non-normally distributed data. In categorical variables, the data are displayed in the form of frequencies and percentages. In numerical variables with a normal distribution, the descriptive parameters used are mean and standard deviation, while numerical, non-parametric variables were presented by median and range (min-max).

RESULTS

The research was carried out using total sampling and data on all breast cancer patients as well those collected along the way. At the start of the data collection, there were 4,973 breast cancer patients who received treatment at H. Adam Malik General Hospital in Medan in the period between 2017 and 2022. Considering that the research was conducted on breast cancer patients aged <40 years, 4,076 patients were excluded, thus 897 patients were available for the research. When the initial analysis was carried out, 793 patients were excluded due to incomplete medical record data, leaving a total of 104 breast cancer patients aged < 40 years treated at the Haji Adam Malik Hospital in Medan who underwent descriptive data analysis.

In this study, descriptive data analysis was carried out in relation to the demographic characteristics of patients. Of the 104 patients analysed, it was found that the mean age of young breast cancer patients was 35.8 years with a standard deviation of 4.05 years. The median age of the research sample was 37 years with the youngest being 17 and the oldest being 40 years old. Then, descriptive data analysis was carried out on the clinical characteristics of the research sample. This includes tumour size (T), lymph node involvement (N), distant metastases (M), location of metastases, and breast cancer staging.

The majority of the patients, 71 (69.2%) were diagnosed with T4 stage tumour. Most patients also presented with N1 lymph node involvement, 58 (55.8%) of the total sample. The majority of patients came with distant metastases, 53 (51%). Therefore, from the TNM analysis according to the AJCC, it was found that the majority of patients presented with stage IV, 53 (51%). Most of the patients had IDC and NST types,

48 (46.2%) and 49 (47.1%) respectively. However, this study was able to identify 2 types of histopathological characteristics which were quite unique, namely mucinous carcinoma and sebaceous carcinoma with one (1%) patient each. Histopathological examination showed that 41 patients had a histopathological grading of poorly differentiated tumours (Table 1).

Table 1. Clinical characteristics of the study sample

Variable	
Age (years)	
Mean (±SD)	35.84 ± 4.05
Median (min-max)	37 (17-40)
	No (%) of patients
Tumour size	
T1	1 (1%)
T2	5 (4.8%)
T3	26 (25%)
T4	72 (69.2%)
KGB involvement	
N0	22 (21.2%)
N1	58 (55.8%)
N2	18 (17.3%)
N3	6 (5.7%)
Distant metastases	
M0	51 (49%)
M1	53 (51%)
Metastasis location	
Bone	19 (31.6%)
Pleura	14 (23.3%)
Brain	6 (10%)
Heart	10 (16.6%)
Lungs	11 (18.3%)
Organ involvement in metastasis	
One	47 (88.6%)
More than one	6 (11.3%)
Staging	
I	0
IIa	3 (2.9%)
IIb	8 (7.7%)
IIIa	9 (8.7%)
IIIb	28 (26.9%)
IIIc	3 (2.9%)
IV	53 (51%)
Histopathological characteristics	
IDC	48 (46.2%)
NST	49 (47.1%)
ILC	5 (4.8%)
Mucinous carcinoma	1 (1%)
Sebaceous carcinoma	1 (1%)
Histopathological grading	
I	32 (30.8%)
II	31 (29.8%)
III	41 (39.4%)
Total	104 (100%)

IDC, Invasive Ductal Carcinoma; NST, No Special Type; ILC, Invasive Lobular Carcinoma, MC, Mucinous Carcinoma; SC, Sebaceous Carcinoma

On immunohistochemical examination it was found that the majority of cases did not express ER and PR, which was seen in 72 (69.2%) and 71 (68.3%) patients, respectively. However, most of the patients showed positive HER-2 expression, 62 (59.6%). The same thing was also seen in Ki-67 expression, which was dominated by patients with positive Ki-67 immunohistochemical expression, 59 (56.7%) (Table 2).

Among immunohistochemical subtypes the HER-2 positive subtype dominated in 39 (37.5%), followed by Luminal B with 31 (39.8%) and TNBC with 22 (21.2%) patients (Table 2).

Table 2. Immunohistochemical characteristics of the study sample

Clinical variable	No (%) of patients	
	Negative	**Positive**
ER expression	72 (69.2)	32 (30.8)
PR Expression	71 (68.3)	33 (31.7)
HER2 expression	42 (40.4)	62 (59.6)
Ki-67 expression	45 (43.3)	59 (56.7)
Immunohistochemical subtypes (No; %)		
Luminal A	12 (11.5%)	
Luminal B	31 (29.8%)	
HER-2 (+)	39 (37.5%)	
TNBC	22 (21.2%)	

DISCUSSION

This study was conducted at Haji Adam Malik Central General Hospital in Medan. The hospital was selected as the research site due to its status as the primary general hospital and referral centre in North Sumatra Province.

The results of this study are in accordance with previous research on breast cancer incidence among young American woman. It is reported that breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women between the age of 20 to 49 years of age (7).

In the United States, approximately 1 in 196 women under the age of 40 is diagnosed with breast cancer (16). Adolescents and young adults aged 15–39 face unique challenges when dealing with the breast cancer diagnosis (17). Since 2004, the incidence of invasive breast cancer among young adult women in the United States has risen, primarily due to an increase in diagnoses among younger women (18). Breast cancer is the most prevalent malignancy in individuals aged 15–39, accounting for 30% of cancers in young women (16). According to SEER, 5.6% of all invasive breast cancers occur among young women (19).

Existing research indicates that the proportion of young breast cancer patients in China is significantly higher than in Western countries. For instance, a study published in Frontiers in Oncology in 2020 found that the median age of breast cancer patients in China was about 45–49 years, compared to 62–64 years in the United States (20). Additionally, a study published in Cancer Research UK in 2024 reported that breast cancer incidence rates in the UK had increased by 4% over the past decade, with rates in women aged 25–49 increasing by 17% (21). These findings suggest that different geographic regions and ethnicities have varying age predilections for breast cancer.

From TNM staging, women aged <40 years had a diagnosis of breast cancer at a more advanced stage and a significantly higher proportion of grade IV tumours compared with middle-aged

women. (22) Overall, younger women were more likely to have advanced stage tumours at the time of diagnosis. In Rosenberg's 2024 study, women under 40 years of age were more likely to present with larger tumour sizes and more advanced stages of breast cancer at the time of diagnosis, compared to those aged older (23). Meanwhile, research by Eiriz et al in 2021 found that the distribution of patients according to a stage at diagnosis was as follows: 82 (47.6%) patients had early stage breast cancer (stages I and II), 77 (44.7%) had breast cancer carry on (24). This can reinforce studies conducted by researchers, which indicate that breast cancer in younger individuals is often associated with a greater degree of invasiveness.

In this study, HER2-positive is the subtype that contributes to more metastases to the CNS, while luminal type tumours are the subtype that spread more frequently to the bone. Proportionally, the prevalence of immunohistochemical subtypes in metastases was higher in HER2-positive and TNBC (24).

The research conducted at H. Adam Malik Hospital in Medan, Indonesia, provides valuable insights into the clinicopathological characteristics of young-onset breast cancer patients, but it is not without limitations. Being a retrospective study, it relies heavily on secondary data extracted from medical records spanning from January 2017 to December 2022. This approach, while practical, is inherently constrained by the quality and completeness of the records. Notably, a significant number of patients—793 out of 897 initially considered—were excluded due to incomplete data, which raises concerns about potential selection bias and may limit the representativeness of the final sample of 104 patients. This small sample size, though sufficient for descriptive analysis, restricts the statistical power of the findings, particularly when examining rare histopathological types like mucinous or sebaceous carcinoma, each represented by only one case.

The study's focus on a single tertiary referral hospital further narrows its scope. H. Adam Malik Hospital, as a central referral facility in North Sumatra, is likely to attract patients with more advanced or complex cases, which could skew the results toward higher-stage and more aggressive tumours. This single-centre design limits the generalizability of the findings to other regions or populations, especially considering the geographic and ethnic variations in breast cancer incidence and characteristics highlighted in the manuscript. For instance, the study notes differences in age predilections between developed countries and regions like China, suggesting that the findings may not fully capture the diversity of young-onset breast cancer across Indonesia or globally.

Another constraint is the cross-sectional nature of the study, which captures a snapshot of clinicopathological features without tracking patient outcomes over time. This lack of longitudinal follow-up means the research cannot shed light on critical aspects such as survival rates, treatment responses, or disease recurrence, which are essential for understanding the long-term implications of young-onset breast cancer. Additionally, the study's exclusive focus on patients under 40 years of age, while deliberate, prevents direct comparisons with older breast cancer patients, who may exhibit distinct tumour characteristics and prognoses, as referenced in the introduction.

The analysis of molecular subtypes—Luminal A, Luminal B, HER2-positive, and triple-negative breast cancer (TNBC)—is a strength, but it is limited by the absence of deeper molecular or genetic profiling, such as BRCA1/2 mutations, which could further explain the aggressive nature of these tumours in young women. The study also employs a total sampling technique, including all eligible patients, but this approach does not account for potential biases in patient presentation, such as those with access to a referral hospital being more likely to have advanced disease. Moreover, the research does not delve into the treatments received by these patients, such as surgery, chemotherapy, or targeted therapies, which could influence the observed clinicopathological outcomes and their interpretation.

Finally, while the study used descriptive statistics and the Kolmogorov-Smirnov test to assess data normality, it lacks more advanced statistical analyses, such as multivariate models, to explore relationships between clinicopathological features and molecular subtypes. This limits the depth of the findings and the ability to draw robust conclusions about associations or predictive factors. These limitations collectively underscore the need for caution when interpreting the results and highlight opportunities for future research to adopt prospective designs, include larger and more diverse cohorts, incorporate treatment data, and explore additional molecular markers to better understand young-onset breast cancer.

In conclusion, this study highlights the aggressive nature of young-onset breast cancer among patients treated at H. Adam Malik Hospital. The predominance of high-grade tumours, advanced clinical stages, and aggressive molecular subtypes such as HER2-positive and triple-negative breast cancer underscores the urgent need for early detection and diagnosis in patients aged <40 years. The findings also suggest the importance of integrating molecular subtyping into routine clinical evaluation to enable more precise, personalized treatment strategies. Future efforts should prioritize public health initiatives that raise awareness among younger populations and improve access to diagnostic and genetic screening services. Additionally, prospective multicentre studies are warranted to validate these findings and better understand the prognostic impact of molecular subtypes in young Indonesian breast cancer patients.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

Author contributions statement

Conceptualization, supervision, and validation: PUP and DH; methodology, formal analysis, and data curation: RDP; writing original draft, analysis, and visualization: RDP; review draft and project administration: DH.

REFERENCES

1. Menon G, Alkabban FM, Ferguson T. Breast Cancer. 2024 Feb 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. PMID: 29493913.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. Cancer J Clin 2020; 70(1):7-30. DOI: 10.3322/caac.21590
3. Sung H, Ferlay J, Siegel RL (2021). Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71(3), 209-49. DOI: 10.3322/caac.21660
4. International Agency for Research on Cancer (IARC). Global Cancer Observatory: Cancer Today. Indonesia Fact Sheet. 2022. Accessed December 6, 2023. https://gco.iarc.who.int/media/globocan/factsheets/populations/360-indonesia-fact-sheet.pdf
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. DOI: 10.3322/caac.21492
6. World Cancer Research Fund. Breast Cancer Statistics. 2018. Accessed August 18, 2022. https://www.wcrf.org/preventing-cancer/cancer-statistics/breast-cancer-statistics
7. Xu S, Murtagh S, Han Y, Wan F, Toriola AT. Breast Cancer Incidence Among US Women Aged 20 to 49 Years by Race, Stage, and Hormone Receptor Status. JAMA Netw Open. 2024;7(1):e2353331. DOI: 10.1001/jamanetworkopen.2023.53331
8. Liu Y, Zheng L, Zhang X. Breast cancer in young women: A clinicopathological and molecular analysis of 315 cases. BMC Cancer. 2020;20(1):278. DOI: 10.1186/s12885-020-06839-w
9. Eugênio DSG, Souza JA, Chojniak R, Bitencourt AGV, Graziano L, et al. Breast cancer features in women under the age of 40 years. Rev Assoc Med Bras. 2016;62(8):755-761.
10. Ellis MJ, Perou CM. The implications of breast cancer subtypes. N Engl J Med. 2013;369(23):2334-2338. DOI: 10.1056/NEJMp1313707
11. Lakhani SR, Ellis IO. WHO Classification of Tumours of the Breast. 4th ed. Lyon: IARC; 2012. ISBN: 978-9283224358
12. Fabiano V, Mandó P, Rizzo M, Ponce C, Coló F, et al. Breast Cancer in Young Women Presents With More Aggressive Pathologic Characteristics: Retrospective Analysis From an Argentine National Database. JCO Glob Oncol. 2020;6:639–646. DOI: 10.1200/JGO.19.00228
13. Ye X, Zhou X, He Q, Wang Z, Wang J, Ji M. Clinicopathological features and prognoses of very young patients (≤35 years) with breast cancer: a retrospective population-based study in China. Chin Med J (Engl). 2023;136(12):1488–1490. DOI: 10.1097/CM9.0000000000002635
14. Widiana IK, Irawan H. Clinical and Subtypes of Breast Cancer in Indonesia. Asian Pac J Cancer Care. 2020;5(4):281-285. DOI: 10.31557/APJCC.2020.5.4.281
15. Natanael Y, Siregar DR, Siregar KB, Rohmawati L. Clinicopathological Profile Of Her2 Positive (Non-Luminal) Breast Cancer Subtype At Haji Adam Malik General Hospital From 2020-2021. Diponegoro Med J. 2024;13(1):1-7. DOI: 10.14710/dmj.v13i1.37533
16. Zhu H, Doğan BE. American Joint Committee on Cancer's Staging System for Breast Cancer, Eighth Edition: Summary for Clinicians. Eur J Breast Health. 2021;17(3):234–238. DOI: 10.4274/ejbh.galenos.2021.2021-4-3
17. Asare EA, et al. Addressing unique challenges in breast cancer care for adolescents and young adults. JCO Oncol Pract. 2021;17(10):525-533. DOI: 10.1200/OP.20.00793
18. Johnson RH, et al. Incidence of metastatic breast cancer in young women has increased since 2004. Cancer Epidemiol Biomarkers Prev. 2021;30(1):63-69. DOI: 10.1158/1055-9965.EPI-20-0905
19. Cathcart-Rake EJ, Ruddy KJ, Bleyer A, Johnson RH. Breast Cancer in Adolescent and Young Adult Women Under the Age of 40 Years. JCO Oncol Pract. 2021;17(6):305–313. DOI: 10.1200/OP.20.00793
20. Yuan Y, Wang Z, Li S. Trends in the epidemiology of breast cancer in China: A study of 41,104 cases. Front Oncol. 2020;10:957. DOI: 10.3389/fonc.2020.00957
21. Cancer Research UK. Breast Cancer Incidence Statistics. 2024. Accessed November 20, 2024. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive
22. Fredholm H, Magnusson K, Lindström LS, Tobin NP, Lindman H, Bergh J, et al. Breast cancer in young women and prognosis: How important are proliferation markers? Eur J Cancer. 2017;84:278–289. DOI: 10.1016/j.ejca.2017.07.044
23. Rosenberg SM, Zheng Y, Ruddy K, Poorvu PD, Snow C, et al. Helping ourselves, helping others: the Young Women's Breast Cancer Study (YWS) – a multisite prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 years and younger. BMJ Open. 2024;14(6):e081157. DOI: 10.1136/bmjopen-2023-081157
24. Eiriz IF, Vaz Batista M, Cruz Tomás T, Neves MT, Guerra-Pereira N, Braga S. Breast cancer in very young women—a multicenter 10-year experience. ESMO Open. 2021;6(1):100029. DOI: 10.1016/j.esmoop.2020.100029