



Histological and Clinical Stage Profiles of Young-aged Breast Carcinoma



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Alda Vania Sugiarto Hadiyanto^{1*}, Ika Pawitra Miranti², Yan Wisnu Prajoko³, Hermawan Istiadi²¹Faculty of Medicine, Diponegoro University, Indonesia²Department of Pathology Anatomy, Faculty of Medicine, Diponegoro University, Indonesia³Department of Surgery Science, Faculty of Medicine, Diponegoro University, Indonesia**Keywords:***Breast carcinoma
clinical stage
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Background: Breast cancer is the most common type of malignancy in women. Many studies report that the characteristics and prognosis of young-aged breast carcinoma are worse than in old age. Data on young-aged breast carcinoma in Indonesia is relatively lacking and always needs updates.

Objective: To determine the incidence and distribution based on histological profiles and clinical stage, as well as the association between molecular subtype with grade and clinical stage of young-aged breast carcinoma (<40 years old) at Dr. Kariadi General Hospital Center in 2018-2020

Methods: This research was an observational descriptive study using medical records of young-aged breast carcinoma patients which were recorded at Dr. Kariadi General Hospital Center from 1st January 2018 until 31st December 2020. The data were processed with Microsoft Excel and Statistical Package for the Social Sciences (SPSS).

Results: The results showed that there were 110 patients consisting of 25 people in 2018, 37 people in 2019, and 48 people in 2020. The most common histological and clinical stage was Invasive Breast Carcinoma of No Special Type (IBC-NST) with 75 people (68,18%), Luminal B with 53 people (48,18%), grade II with 71 people (64,65%), and stage IV with 45 people (40,09%). There is a significant association between molecular subtype and grade ($p=0.003$). There is no significant association between molecular subtype and clinical stage ($p=0.704$)

Conclusion: The incidence of young-aged breast carcinoma at Dr. Kariadi General Hospital Center in 2018-2020 was increasing every year. The most common histological profiles and clinical stage during that period were IBC-NST, Luminal B, grade II, and stage IV. There is a significant association between molecular subtype and grade

*) Correspondence to:
aldavania1210@gmail.com

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1. Introduction

Based on the Global Burden of Cancer (GLOBOCAN) 2020, breast cancer was the majority of malignancy case. Incidence of breast cancer in 2020 was in the first place, while the number of deaths due to the disease was fifth. The number of Asia's new cases in 2020 reached 45.4% of all new malignancy cases. New patients with this disease in Indonesia were the highest from other malignancies, reaching 65,858 cases.¹ Riset Kesehatan Dasar (Riskesdas) 2013 reported that breast was the second to servix cancer in Central Java.² One of the demographic factors of breast cancer is age.³ The percentage of breast cancer in 0-39 years old women was 10.96% of all new cases in the world.¹ There were 14% of 514 breast cancer patients at Sanglah Hospital Denpasar in 2014 -2016 who were <40 years old.⁴ Several studies

have reported that young-aged breast carcinoma has characteristics such as negative hormone receptor status and lower expression of HER2 which associates with severe clinical symptoms, lower survival rates, and poorer prognosis.^{5,6}

The prognostic factors of breast carcinoma are determined from several profiles which include histological type, estrogen and progesterone receptor status, HER2 expression, tumor grading, tumor size, presence or absence of axillary lymph node involvement, and distant metastases.⁵ World Health Organization (WHO) 2019 divides breast tumours into 5 major groups, one of them is epithelial tumour, consisting of carcinoma in situ and invasive carcinoma originating from the ducts or lobules of the breast.^{7,8} Ductal carcinoma is the most common in young people.^{4,9} The molecular subtypes of breast carcinoma are classified into Luminal A, Luminal B, HER2 over-expressive, and Triple Negative Breast

Cancer (TNBC) subtypes based on hormonal receptor status, HER2 expression, and Ki-67.¹⁰ A study reported that Luminal B is the most commonly found at ≤ 40 years old.¹¹ The grading of breast carcinoma is divided using the Nottingham system into grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated).¹² Young patients at Sanglah Hospital Denpasar in 2002-2012 mostly had grade II breast carcinoma.¹³ The Tumor, Nodes, and Metastasis (TNM) system is used to evaluate the clinical stage of breast carcinoma into stage 0-IV.¹⁴ A research at Sanglah Hospital Denpasar in 2014-2016 found that the most of young patients had stage III and IV.⁴

Descriptive study always needs to be updated. Despite the fact that the incidence of breast carcinoma was considered high, the data on this disease was relatively small. Young-aged breast carcinoma was rare, but various studies have addressed the poor prognosis of young-aged breast carcinoma. The association between some of the prognostic factors such as molecular subtype, tumor grade, and clinical stage can provide a prognostic picture of the patients. There has not been found any similar research at Dr. Kariadi General Hospital Center. This study aims to know the frequency of occurrence, distribution of histological profiles and clinical stage, as well as the association of molecular subtypes with the tumor grade and clinical stage of young-aged breast carcinoma in Dr. Kariadi General Hospital Center Semarang in 2018-2020.

2. Methods

descriptive-analytic study which was conducted from July to September 2021 at Medical Record Installation and Pathology Anatomy Laboratory of Dr. Kariadi General Hospital Center. The ethics number of this study was 209/EC/KEPK/FK-UNDIP/VI/2021, received from the Ethical Committee of Faculty of Medicine Diponegoro University. The data were collected from the medical records by using total sampling. The subjects were 110 young-aged breast carcinoma patients (<40 years old). The inclusion criteria were the subjects registered at Dr. Kariadi General Hospital Center from 1st January 2018 until 31st December 2020 and they were women. Damaged medical records or incomplete data including age, histological type, molecular subtype, tumor grade, and clinical stage of breast carcinoma were excluded from this study. According to the hormonal receptor status, HER2 expression, and Ki-67 level, the molecular subtypes of breast carcinoma were grouped into: Luminal A (ER+ and/or PR+ and HER-2/neu-, Low Ki-67), Luminal B (ER+ and/or PR+ and HER-2+, high Ki-67), HER2+ (ER-, PR- and HER2+), and TNBC (ER-, PR- and HER2-). The data were processed with Microsoft Excel and described in graphic or tabular form. The data of molecular subtypes, tumor grade, and clinical stage were analyzed statistically with the SPSS program using Chi-square test with categories merging since the expected count <5 of the

two tables were more than 20%. There is significant association between two variables if $p < 0.005$.

3. Results

The number of young-aged breast carcinoma was increasing every year. The mean age of the subjects was 33.84 years old. The median age of the subjects was 35 years old. The maximum age was 39 years old, while the minimum age was 23 years old. The graphic of incidence of young-aged breast carcinoma is presented in Figure 1

Table 1. Histological and Clinical Profiles of Young Aged Breast Carcinoma

Variable	N	%
Histological type		
IBC-NST	75	68,18
<i>Special Type</i>	12	10,91
<i>Mixed</i>	23	20,91
Total	110	100
Molecular subtype		
Luminal A	15	13,64
Luminal B	53	48,18
HER2+	20	18,18
TNBC	22	20
Total	110	100
Grade		
I	10	9,09
II	71	64,55
III	29	26,36
Total	110	100
Clinical stage		
I	4	3,64
II	26	23,64
III	35	31,82
IV	45	40,91
Total	110	100

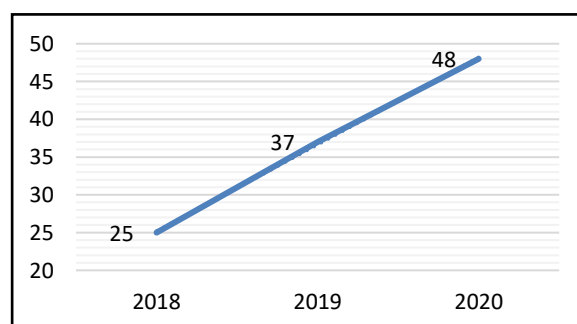


Figure 1. Incidence of Young-Aged Breast Carcinoma in 2018-2020

From a total of 110 patients, more than a half of the patients (68.18%) had Invasive Breast Carcinoma of No Special Type (IBC-NST). Luminal B could be found in 53

patients (48.18%), followed by TNBC with 22 patients (20.00%). There are 64.55% of the patients who had grade II breast carcinoma, while 26.36% of the patients had grade III breast carcinoma. The most common clinical stage was stage IV with 45 patients (40.92%), then followed by stage III with 35 patients (31.82%). The histological and clinical stage profiles of young-aged breast carcinoma are shown in Table 1.

All of the subtypes except TNBC had higher percentage of grade I and II tumor. TNBC had the highest percentage of grade III tumor (54,55%), followed by

Luminal B (24,35%) among other subtypes. There was a significant association between molecular subtype and tumor grade ($p=0.003$). All of the subtypes had higher percentage of stage III and IV ($>60.00\%$) than stage I and II. HER2+ had the highest percentage with 80,00%, then Luminal A, Luminal B, and TNBC. Molecular subtype had no significant association with clinical stage ($p=0.704$). The distribution and association between molecular subtypes with tumor grade and clinical stage is presented in Table 2.

Table 2. Association of Molecular Subtype with Tumour Grade and Clinical Stage

Table 2: Association of Molecular Subtype with Tumour Grade and Clinical Stage									
	Molecular Subtype								<i>P value</i>
	Luminal A		Luminal B		HER2+		TNBC		
	n	%	n	%	n	%	n	%	
Tumour grade									
I and II	12	80	40	75,47	19	95	10	45,55	0.003*
III	3	20	13	24,53	1	5	12	54,55	
Total	15	100	53	100	20	100	22	100	
Clinical stage									
I and II	4	26,67	15	28,3	4	20	8	36,36	0,704
III and IV	11	73,33	38	71,7	16	80	14	63,64	
Total	15	100	53	100	20	100	22	100	

Information: n number, % percentage, * significant

4. Discussions

The result of this study indicated that the trend of young-aged breast cancer was increasing during 2018-2020. The results of this study are supported by research conducted by Partini et al.⁴ at Sanglah Hospital Denpasar in 2014-2016 Houssein et al.¹⁵ presented a graph of the incidence of breast carcinoma aged <40 years in Asia during 1980-2000 having a steady increase. This increasing trend is considered to be the result of social and economic developments in Asian countries as the influence of the West arrived to the Asian population, such as increased obesity prevalence, earlier age of menarche, later age of menopause, increased screening and public awareness of breast cancer.^{16,17}

The most common histological type of breast carcinoma found in this study was IBC-NST (68.18%). This result was in line with previous studies conducted in Indonesia by Partini et al.⁴ and Rahmatya et al. [18], as well as a research in Croatia by Erić et al.[19]. All the results above were in accordance with various literatures and studies which stated that IBC-NST was the most common histological type of breast carcinoma among all types (70-96%).^{8,18,20}

Luminal A has a low Ki-67 level, while Luminal B has a high Ki-67 level.²¹ Cut-off for Ki-67 at RSUP Dr. Kariadi is 20%. This was supported by the previous study which stated the reliability of Ki-67 as a prognostic factor

using a cut-off of 20%.²² The most common molecular subtypes found in this study were Luminal B (48.18%) and TNBC (20.00%). Lee et al.²³ and Fredholm et al.²⁴ found Luminal B the most. Previous studies conducted by Kolečková et al.²⁵ and Ayuza et al.²⁶ found TNBC the most. These studies showed Luminal B and TNBC as the majority of molecular subtypes found in young women. This result was aligned with the hypothesis that the prognosis for young-aged breast carcinoma is worse than old age. Luminal B and TNBC are often associated with a worse prognosis than other subtypes.^{19,20}

In this study, the most common tumor grade was grade II (64.55%). This result was supported by previous studies conducted by Hartaningsih & Sudarsa¹³ and Firasi et al.²⁷. A study found the proportion of grade II and III at a young age was higher. Meanwhile, grade I often appeared in old age.²³

In this study, the most common clinical stage was stage IV (40.91%). The results of this study was similar to the previous study conducted by Tjokrowidjaja et al.²⁸ that stated that young people had a higher risk of distant metastases within 5 years. Besides being associated with its aggressiveness and poor survival rates, breast carcinoma was also associated with late diagnosis.²⁹ Research by Lee et al.³⁰ wrote that the causes of the delay include: lack of awareness about breast cancer at a young age, low suspicion of health workers regarding the occurrence of this disease at a young age,

recommendations for mammograms for women >40 or >50 years old, and varying physiological changes in young women during their pregnancy and lactation period. Based on the research by Djatmiko et al.³¹ delays in the management of breast carcinoma patients were caused by delays in patient arrival, late referrals, and delays in receiving therapeutic advice. The most common cause of delay in patient arrival was feeling that the tumor of the breast is not dangerous and the patient's fear toward the diagnosis and the medication.

The results of this study indicated that the presence of molecular subtypes was significantly related to the tumor grade. This result was in line with the research by Setyawati et al.³² which stated that Luminal A appeared mostly in grade I and the prognosis was good. Luminal A expressed the Fork head box A1 (FOX A1), GATA-3 and B-cell lymphoma 2 (Bcl-2) genes, which were correlated with grade I tumors. Other subtypes have been reported to be more aggressive. Luminal B had increased levels of proliferative genes and HER2. HER2+ was associated with high c-Met expression, survivin, EGFR, and oncogene level. HER2 and TNBC also had a significant association with p53 gene mutations. In this study, it was also found that Luminal B had a higher percentage of grade III (24.53%) than grade III in Luminal A (20.00%). The American Cancer Society stated that Luminal B tended to present with a higher grade than Luminal A.²⁰ TNBC and that Luminal B had a higher percentage of grade III than the other subtypes. The study of Ovcarićek et al.³³ found that the majority of TNBC had grade III tumors. Treatment development in TNBC was relatively lacking compared to other subtypes. Endocrine therapy and targeted anti-HER2 therapy had no effect on TNBC, thus treatment for TNBC patients was the same as the other subtypes.^{21,34}

This study found no significant association between molecular subtypes and clinical stage. However, based on the results of this study, the percentage of stage III and IV in Luminal B and TNBC subtypes was higher than stage I and II. This result was supported by the study of Inwald et al.³⁵ that stated that higher Ki-67 levels were associated with higher tumor stage and lymph node status. The study of Vuger et al.³⁴ also found that TNBC had a larger tumor size and lymph node metastasis.

The limitation of this study was some patient data were not available so it was excluded from this study.

5. Conclusion

Based on this study, the incidence of young-aged breast carcinoma (<40 years) at Dr. Kariadi General Hospital Center in 2018-2020 was 110 patients. The number of cases of breast carcinoma at young age in Dr. Kariadi in 2018-2020 was increasing every year. The majority of samples were found with the histological type of IBC-NST in 75 cases (68.18%), Luminal B molecular subtype in 53 cases (48.18%), grade II in 71 cases (64.55%), and stage IV in 45 patients (40.91%). There is a

significant association between molecular subtype and tumour grade ($p=0.003$).

Further researchers can examine the prevention of young-aged breast carcinoma and the relationship between the variables in this study. Further researchers can take more samples through data collection for more than 3 years.

Ethical Approval

All procedures have been approved by the issuance of ethical clearance No. 209/EC/KEPK/FK-UNDIP/VI/2021 from the Health Research Ethics Commission of The Faculty of Medicine, Diponegoro University, Semarang.

Conflicts of Interest

The authors declare that there was no conflict of interest.

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Author Contributions

Conceptualization, AVSH, IPM, and YWP; methodology, AVSH; software, AVSH; validation, IPM and YWP; formal analysis, AVSH; investigation, AVSH; resources, AVSH; data curation, AVSH; writing—original draft preparation, AVSH; writing—review and editing, AVSH, IPM, YWP, and HI; visualization, AVSH; supervision, IPM, YWP, and HI; project administration, AVSH

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