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# The Association between Age Groups with Clinicopathologic and Molecular Subtypes of Breast Cancer Patients

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**ABSTRACT**

**Introduction:** The increase in incidence proportion of breast cancer disease among young patients < 40 years old is exceeding that of older patients. The purpose of the research is to know the differences between clinicopathologic and molecular subtypes between patients < 40 years old and ≥ 40 years old.
**Methods:** The conducting research on Medical Records (MR) was an observational analytic method with a cross-sectional design. The independent variable was age. Dependent variables were histopathological type, stage of disease, grade of tumor, and molecular subtype of cancer. Univariate analyses to describe the samples. The differences between those variables according to age groups were analyzed by a bivariate statistic and the odds ratio with a confident interval (CI) of 95% of each variable would be displayed by binary logistic regression statistic.
**Results:** The most prevalent age of breast cancer patients was in the range of 50-59 years (47%), the mean age of 53.66 ± 0.977 years, in the range of 29 years old to 86 years old, and patients aged < 40 years was 12%. Ductal carcinoma type (89.7%), stage III tumor (40.2%), poor differentiation grade III (60.7%), and luminal A subtype (42.7%) were the most prevalent clinicopathologic and molecular subtypes. There weren't differences between histopathologic type, stage of disease, and molecular subtype with age. The histopathologic grade was different from the age variable (p=0.015). Old age had worse histopathologic differentiation than young age (OR 2.166; 95% CI 0.973-4.823).
**Conclusions:** There weren't significant differences between stage and molecular subtypes of breast cancer between age groups. There was poorer histopathologic differentiation in patients ≥ 40 years.

***Keywords: breast cancer; age; stage;histopathology grade; molecular subtype***

## INTRODUCTION

The incidence and mortality rates of breast cancer in the world are increasing annually. In 2012, estimated at 14.1 million new cases and 8.2 million deaths were associated with cancer. The Age-standardized Incidence Rate (ASIR) and mortality in breast cancer women were 43.3/100.000 and 12.9/100.000[1]. In 2018, estimated at 18.1 million new cases and 9.6 million were deaths related to cancer. The ASIR and mortality for women with breast cancer were 46.3/100.000 and 13/100.000[2]. In 2020, estimated at 19.3 million new cases and 10 million deaths are

associated with cancer. The ASIR and mortality of women with breast cancer are 47.8/100.000 and 13.6/100.000[3]. The ASIR in 2012 breast cancer in Indonesia was 40.3/100.000[4]. In 2020, there are 396.914 cancer diagnoses, 65.858 (16.6%) women breast cancer, 22.340 (9.6%) mortality, and 30.8% new cancer cases among women[5].

The prognostic factors of breast cancer are important for patient treatment. There are age, stage, histopathologic grade, disease stage, mitosis counts, Ki67 expression proliferation index, hormonal state, and HER-2/neu expression[6,7]. The medical therapy choices for breast cancer patients are adjusted according to those factors[8].

Relating to the age group, the clinicopathologic characteristics of patients <40 years old are different from those of older ages, but the differences are not consistent between one study and another[9–14]. Young breast cancer patients <40 years old must get attention with the recently high prevalence and incidence compared to the older patients[13,14,15]. The molecular subtypes of breast cancer, which can be divided into luminal A, luminal B, HER-2/neu enriched, and Triple Negative Breast Cancer (TNBC), could also be different[18,19].

The prognostic factors are not only important for the treatment choice, but also to predict the course of the disease[16]. This study is aimed to find the differences in histopathological types, stage of disease, histopathological grade, and molecular subtypes of breast cancer based on age group.

## METHODS

The conducting research, on Bethesda Hospital Yogyakarta Medical Records patients from 2013 to 2019, was an observational analytic method with a cross-sectional design. The selection of the sample was in the consecutive sample. The inclusion criteria are the complete MR. MR of male breast cancer and no record of histopathology and cytopathology will be excluded from the study. There are complete 117 Medical Records, the data are age, histopathology type, stage of disease, histopathological grade, and molecular subtype. The age of patients was divided into three set groups< 40 years, 40-49 years, 50-59 years, and ≥ 60 years. Type of histopathology, stage of disease, histopathology grade, and molecular subtype classified according to the records on MR.

The statistical analyses were undertaken multistep process. For step 1, descriptive statistics were used to describe the samples. In step 2, the samples were divided according to three sets of age groups (1st < 40 years, 40-49 years, 50-59 years, ≥ 60 years, 2nd < 40 years and ≥ 60 years and 40-59 years; 3th < 40 years and ≥ 40 years) that presenting the differences of clinicopathology between the age groups. The data was weighted by percentage and analyzed by chi-square test. The chi-square test from SPSS 21 for 2 x 2 tables, and from chi-square calculator, up to 5 x 5 (Chi-Square), for 2xk or 3xk tables. The variables that had significance at < 0.05 would be analyzed by multivariate, in step 3, binary logistic regression methods to assess the adjusted association between age and independent variables.

### Ethics approval and consent to participate

This study got ethical clearance from Bethesda Hospital Yogyakarta number 916/C.16/FK/2019 and 135/KEPK-RSB/XII/20.

## RESULTS

### Characteristics of breast cancer patients (descriptive statistic step 1)

The most prevalent age of breast cancer patients in the range of 50-59 years (47%), with the mean age being 53.66 ± 0.977 years, in the range of 29 years old to 86 years old, and the patients' age < 40 years is 12%.

The clinicopathologic characteristic of the breast cancer patients describes in table 1.

Ductal carcinoma type (89.7%), stage III tumor (40.2%), poor differentiation grade III (60.7%), luminal A subtype (42.7%) is the most prevalent clinicopathologic and molecular subtype profile of breast cancer.

Table 1. Characteristic and frequency of breast cancer according to age, histopathologic type, stage of disease, histopathologic grade and molecular subtype

| Characteristics | | Frequency (%) |
|---|---|---|
| Age | < 40 years | 14 (12%) |
| | 40 – 49 years | 21 (17.9%) |
| | 50 – 59 years | 55 (47%) |
| | ≥ 60 years | 27 (23.1%) |
| Histopathologic Type | Ductal carcinoma | 105 (89.7%) |
| | Others of ductal carcinoma | 12 (10.3%) |
| Stage | I | 8(6.8%) |
| | II | 44 (37.6%) |
| | III | 47 (40.2%) |
| | IV | 18 (15.4%) |
| Histopathologic grade | I | 10 (8.5%) |
| | II | 36 (30.8%) |
| | III | 71 (60.7%) |
| Molecular Subtype | Luminal A | 50 (42.7%) |
| | Luminal B | 18 (15.4%) |
| | HER-2 neu | 34 (29.1%) |
| | Triple Negative Breast Cancer | 15(12.8%) |

**Difference between clinicopathology and age (bivariate analyses step 2)**

**First bivariate analysis.** The patients' clinicopathology characteristics according to divided age are described in table 2. The ductal carcinoma types and non-ductal carcinoma types were the highest in the age group 50-59 years. Stage II of disease in age group < 40 years dan ≥ 60 years and stage III of disease in the age group 40-59 years are the most common stage proportions. **Second bivariate analysis.** According to this finding, age was divided into two groups, 1st young age (< 40 years) and postmenopausal age (≥ 60 years) and 2nd pre-menopause and menopause age ( 40-59 years), the clinicopathologic profiles didn't show a significant difference, between low stage ( I, II) and high stage (III,IV) (p = 0.062), positive and negative hormonal state (p=0.26), Estrogen Receptor (ER) positive and negative (P=0.34), Progesterone Receptor (PgR) positive and negative (p=0,455), HER-2/neu positive and negative (p=0.163), TNBC yes and no (p=0.466). **Third bivariate analysis.** Age was divided into two groups < 40 years and ≥ 40 years, low stage (I, II) and high stage (III, IV) did not show a significant difference (p=0.111). Histopathological grade showed a significant difference, more poorly differentiated in patients ≥ 40 years (p=0.015). The molecular subtype of breast cancer (p=0.289), ER positive and negative (p=0.706), PgR positive and negative (p=0.758), HER-2/neu positive and negative (p=0.167), and TNBC yes and no (p=0.498) did not show a significant difference.

Table 2. Clinicopathology characteristic of breast cancer according to age groups in frequency and percentage

| Characteristic | | Age (years) | | | |
|---|---|---|---|---|---|
| | | < 40 | | ≥ 40 | |
| | | < 40 | 40 - 49 | 50 - 59 | ≥ 60 |
| Age | Mean | 35.86±2.85 | | 56.08±8.75 | |
| Histopathology | Ductal | 13 (92.9%) | 19 (90.5%) | 49 (89.1%) | 24 (89.7%) |
| | Non-Ductal | 1 (7.1%) | 2 (9.5%) | 6 (10.9%) | 3 (11.1%) |
| Stage | I | 1 (7.1%) | 2 (9.5%) | 3 (5.5%) | 2 (7.4%) |
| | II | 8 (57.1%) | 7 (33.3%) | 17(30.9%) | 12 (44.4%) |
| | III | 5 (35.7%) | 8 (38.1%) | 24 (43.6%) | 10 (37%) |
| | IV | 0 (0%) | 4 (19%) | 11 (20%) | 3 (11.1%) |
| Histopathologic grade | I | 4 (28.6%) | 1 (4.8%) | 4 (7.3%) | 1 (3.7%) |
| | II | 4 (28.6%) | 7 (33.3%) | 15 (27.3%) | 10 (37%) |
| | III | 6 (42.9%) | 13 (61.9%) | 36 (65.5%) | 16(59.3%) |
| Molecular Subtype | Luminal A | 3 (6%) | 11 (22%) | 24 (48%) | 12 (24%) |
| | Luminal B | 4 (22.2%) | 3 (16.7%) | 9 (50%) | 2 (11.1%) |
| | HER-2/neu | 5 (14.7%) | 5 (14.7%) | 13 (38.2%) | 11 (32.4%) |
| | TNBC | 2 (13.3%) | 2 (13.3%) | 9 (60%) | 2 (13.3%) |

**Association between significant variable and age (multivariate analysis step 3)**

The histopathologic differentiation was the only independent variable significantly associated with dependent variable age groups (<40years and ≥ 40 years), entered into the binary logistic regression. The patients ≥ 40 years had worse histopathological differentiation compared with those < 40 years (OR 2.166; 95% CI 0.973-4.823).

## DISCUSSION

The mean age of breast cancer patients at Bethesda Hospital Yogyakarta was 53.66 ± 0.977 years, the median was 53 years, the age < 40 years was 12% and the youngest age was 29 years, the oldest age was 86 years. The same mean age in other studies was 53.15±10.89 years (range from 31-81 years).[17] In other studies, the median age was 49 years (range 22-92 years) in Singapore[18], the median age of female patients was 45 years and those aged <40 years were 33.2% in Saudi Arabia[19], the median age in Jordan is 51–52 years[9]. Breast cancer patients in Pakistan are expected to shift to a younger age from Women aged 60-64 years to 50-64 years from 2016 to 2025 and ages 30-34 years are expected to increase from 70.7 to 130.6% during 2020-2025 compared to 2015[17]. Patients aged < 40 years in Hungary were around 5% in 2004-2008 and increased by 13% in 2009[14], while in the United States per 100,000 young people, 16.3 diagnoses of breast cancer in 1935 increased to 38.5 breast cancer diagnosis in 2015[20]. The possible explanation of the increasing incidence in young age population are increasing environmental exposures, such as Endocrine-Disrupting Chemical (EDC), exogenous hormone, obesity, physical inactivity, dietary factors, industrial and agriculture chemicals, air pollutants and polycyclic aromatic hydrocarbons in as early as of life[21,22,23].

Aggressive characteristics of breast cancer aged < 40 years compared to age ≥ 40 years in this study did not show a significant difference in stage and molecular subtypes of breast cancer but show a significant difference in the degree of differentiation. A poorer degree of differentiation showed by age group ≥ 40 years. Age is an important prognostic factor because many studies have shown differences in tumor characteristics between

young breast cancer patients (< 40 years) and older breast cancer patients (≥40 years), that younger breast cancer patients have more aggressive clinicopathology characteristics and have a worse prognosis. The aggressive characteristics are positive axillary lymph node metastases, tumor size T-3/4, molecular subtype[18] positive HER-2/neu[8,11] and TNBC[9,11] histopathologic differentiation grade 3, lymphovascular invasion, higher stage[7,18], p53 positive, MIB-1 positive, high mitotic index[10]. The same study showed that the aggressive characteristics of breast cancer patients at a young age were not different from those in old age, there was no difference in the stage and grade of differentiationalie[8,11] but very young patients (< 35 years) showed differences in disease stage[11,12], tumor size[7], lymph node metastases, HER-2/neu status[18]. Other studies have shown that there are transitional genetic changes before the age of 40 years with low expression of the markers ER, PgR, luminal cytokeratosis, bcl2, and high expression of Ki67, HER2/neu and p53; as opposed to female patients over 70 years of age; while the age of 40-70 years is the transition of this genetic change[24].

The study limitation is the survival analysis with multivariate analysis was not carried out, because of the limitation of time and methods to follow up on patients' survival.

## CONCLUSIONS

This study did not show the difference between young age (<40 years) and older age (≥40 years) in histopathologic type, stage and molecular subtype, but the histopathologic grade was different between those age group. Those aged ≥ 40 years showed a higher degree of differentiation. Aggressive characteristics of young age breast cancer patients did not show in this study. Future studies need more big sample size to investigate breast cancer risk factors, clinicopathology, molecular characteristics, and the survival of breast cancer patients younger than 40 years to describe the differences with the older patients.

**Competing interest**

The author(s) declare no competing interest in this study.

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