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 12.9/100,0001. 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 13/100,0002. 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 13.6/100,0001. The ASIR in 2012 breast cancer in Indonesia was 40.3/100,0002. 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 women2.

The selection of the sample was in the consecutive sample. 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; 3rd < 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.

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

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%) | 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 - 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 (<40 years 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). In other studies, the median age was 49 years (range 22-92 years) in Singapore, the median age of female patients was 45 years and those aged <40 years were 33.2% in Saudi Arabia, the median age in Jordan is 51–52 years. 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. Patients aged < 40 years in Hungary were around 5% in 2004-2008 and increased by 13% in 2009, 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. 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.

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 prog nostic 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\(^1\)\(^8\),\(^1\)\(^1\) positive HER-2/neu\(^1\)\(^8\),\(^1\)\(^1\) and TNBC\(^9\),\(^1\)\(^1\) histopathologic differentiation grade 3, lymphovascular invasion, higher stage\(^7\),\(^1\)\(^8\), p53 positive, MIB-1 positive, high mitotic index\(^1\)\(^0\). 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 differentiation\(^8\),\(^1\)\(^1\) but very young patients (< 35 years) showed differences in disease stage\(^8\),\(^1\)\(^1\), tumor size\(^7\), lymph node metastases, HER-2/neu status\(^8\). 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\(^2\)\(^4\).

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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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar;136(5):E359–86.
2. 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 Nov;68(6):394–424.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209–49.
4. Sinaga ES, Ahmad RA, Shivalli S, Hutajulu SH. Age at diagnosis predicted survival outcome of female patients with breast cancer at a tertiary hospital in Yogyakarta, Indonesia. Pan Afr Med J. 2018 Nov;31:163–163.
5. Organization IA for R on CWHO. Indonesia. World Health Organization. 2022. p. 2.
6. Warjianto W, Soewoto W, Alifianto U, Wujoso H. Hubungan Reseptor Estrogen, Reseptor Progesteron dan Ekspresi Her-2/Neu Dengan Grading Histopatologi pada Pasien Kanker Payudara di RSUD dr. Moewardi Surakarta. Smart Med J. 2020;3(2):96.
7. Fitzgibbons PL, Page DL, Weaver D, Thor AD, Allred DC, Clark GM, et al. Prognostic factors in breast cancer.
8. Nguyen D, Yu J, Reinhold WC, Yang SX. Association of Independent Prognostic Factors and Treatment Modality with Survival and Recurrence Outcomes in Breast Cancer. JAMA Netw Open. 2020;3(7):1–11.

9. Kheirelseid EAH, Boggs JME, Curran C, Glynn RW, Dooley C, Sweeney KJ, et al. Younger age as a prognostic indicator in breast cancer: A cohort study. BMC Cancer. 2011 Aug;11(1):1–7.

10. Alieldin NH, Abo-Elazm OM, Bilal D, Salem SE, Gouda E, Elmongy M, et al. Age at diagnosis in women with non-metastatic breast cancer: Is it related to prognosis? J Egypt Natl Canc Inst. 2014 Mar;26(1):23–30.

11. Abdel-Razeq H, Iweir S, Abdel-Razeq R, Rahman FA, Almasri H, Bater R, et al. Differences in clinicopathological characteristics, treatment, and survival outcomes between older and younger breast cancer patients. Sci Rep. 2021 Dec;11(1):14340.

12. Aryandono T, Harjadi S. Breast cancer in young women: prognostic factors and clinicopathological features - PubMed. Asian Pacif J Cancer Prev. 2006. p. 6.

13. Fabiano V, Mandó P, Rizzo M, Ponce C, Colé F, Loza M, et al. Breast Cancer in Young Women Presents With More Aggressive Pathologic Characteristics: Retrospective Analysis From an Argentine National Database. JCO Glob Oncol. 2020 Nov;6(6):639–46.

14. Zhang X, Yang J, Cui H, Ye Y. Young age is an independent adverse prognostic factor in early stage breast cancer: a population-based study. Cancer Manag Res. 2018;10:4005–18.

15. Bouchardy C, Fioretta G, Verkooijen HM, Vlastos G, Schaefer P, Delaloye JF, et al. Recent increase of breast cancer incidence among women under the age of forty. Br J Cancer. 2007 Jun;96(11):1743.

16. Dobi Á, Kelemen G, Kaizer L, Weiczner R, Thurzó L, Káhán Z. Breast cancer under 40 years of age: increasing number and worse prognosis. Pathol Oncol Res. 2011 Jun;17(2):425–8.

17. Zaheer S, Shah N, Maqbool SA, Soomro NM. Estimates of past and future time trends in age-specific breast cancer incidence among women in Karachi, Pakistan: 2004–2025. BMC Public Health.