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Research Article

The Association between The Patient's Age Groups with Stage, Grading, and Molecular Subtype of Breast Cancer

Hubungan antara Kelompok Usia Pasien dengan Stadium, Derajat Diferensiasi dan Subtipe Molekuler Kanker Payudara

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Abstract

In 2020, Global Cancer Observatory reported breast cancer incidence was 11.7% and mortality was 6.9%, most presenting a late-stage and delaying diagnosis. The study aimed to assess the breast cancer clinicopathologic characteristics according to the age groups. The research was conducted on 98 Medical Records from Bethesda Hospital Yogyakarta. The variable data were analyzed by univariate and the association between variables were analyzed with binary logistic regression with odds ratio and 95% confidence interval. The presentation of age groups ≤ 30 years (1,02%), 31-40 years (12,24%), 41-50 years (25,51%), 51-60 years (46,94%), and ≥ 61 years (15,31%); right breast (48,98%) and left breast (51,02%); stage I (3,06%), II (28,57%), III (55,10%), dan IV (13,27%); ductal type of breast cancer (89,80%) and others (10,20%); molecular subtype luminal A (43,88%), luminal B (14,29%), HER-2 neu enriched (29,59%), and basal-like/triple-negative (12,24%). There wasn't any association between age groups and stages (p=0.368). There was an association between age groups and molecular subtype (p=0.013, OR 2.993 CI95% 1.239-7.230). Conclusions: The commonest clinicopathologic characteristic of breast cancer patients were in the age group 51-60 years, left breast, high stage, ductal type, and luminal A. Hormone receptors in breast cancer expressed more common in patients ≤50 years.

Keywords: *breast cancer; clinicopathology profiles; age group*

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Abstrak

Global Cancer Observatory tahun 2020 melaporkan insidensi kanker payudara sebesar 11,7% dengan kematian sebesar 6,9%, dan sebagian besar pasien sudah stadium lanjut dan ada keterlambatan diagnosis. Tujuan penelitian ini adalah untuk menilai karakteristik klinikopatologi penderita kanker payudara berdasarkan kelompok usia. Penelitian pada 98 Rekam Medik Rumah Sakit Bethesda Yogyakarta, data variabel diolah secara univariat dan bivariat dan hubungan antar variabel dianalisis menggunakan regresi logistic biner, disertai rasio odds dan konfiden interval 95%. Hasil: Presentasi kelompok usia ≤30 tahun (1,02%), 31-40 tahun (12,24%), 41-50 tahun (25,51%), 51-60 tahun (46,94%), dan ≥61 tahun (15,31%); payudara kanan (48,98%) dan kiri (51,02%); stadium I (3,06%), II (28,57%), III (55,10%), dan IV (13,27%); tipe histologi duktal (89,80%) dan non-duktal (10,20%); subtipe molekuler luminal A (43,88%), luminal B (14,29%), HER-2 positif (29,59%), dan *basal like/triple negative* (12,24%). Stadium kanker payudara tidak berbeda pada kelompok usia (p=0,368). Subtipe molekuler menunjukkan hubungan dengan kelompok usia, (p=0,013, OR 2,993 CI95% 1,239-7,230). Simpulan: Karakteristik klinikopatologi penderita kanker payudara terbanyak pada kelompok usia 51-60 tahun, sisi payudara kiri, stadium III, tipe histologi duktal, dan subtipe molekular luminal A. Pasien berusia ≤50 tahun lebih banyak menunjukkan ekspresi reseptor hormonal positif.

Kata kunci: kanker payudara; profil klinikopatologi; kelompok usia

Introduction

Cancer is a non-communicable disease characterized by unregulated cell growth. Breast cancer from unregulated breast parenchymal cells, mainly epithelial, growth.[1] Global Burden Disease Study (2019), there are 24.5 million incidents of cancer worldwide in 2017 and the odds of developing cancer during a lifetime (ages 0-79 years) were 1 in 3 in men and 1 in 4 in women.[2] Globocan data (2020) in International Agency for Research on Cancer WHO, globally the incidence of breast cancer according to Age-Specific Rate (ASR) in men and women (0-85 years) was 47.8 per 100.000 and the proportion in 5 years was 201,6% of all cancer excluding non-melanoma skin cancer.[3] In Indonesia breast cancer incidence is the highest among others cancer, with ASR 43.8 per 100.000 population, mortality ASR 9.4 per 100.000 population, and a proportion was 178.9 per 100.000 population.[3] The prevalence of all cancer in Yogyakarta was 4,1‰, the highest among other provinces in Indonesia, and breast cancer total cases in Yogyakarta was 4.325 cases.[4]

Breast cancer is one of the major health burdens in Indonesia. The burdens are different exposures to risk factors, economic settings, lifestyles, access to care and screening,[5] delay in seeking help and non-adherence [6], financial toxicity,[7,8], and Social Insurance Administration Organization reported that from 1,308,061 inpatient cancer cases treated in 2016, a total of 2.2 trillion rupiahs was spent, amounting to $486,960,633 in the US dollars (purchasing power

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parity 2016).[9] There are many breast cancer risk factors profiles studies,[10,11] pathologic profile of young age group[12], old age group.[13] This research is still important because the young age group patients increase with aggressive characteristics, in an older age group patients increase with a worse prognostic outcome, and the majority of breast cancer patients in Indonesia are diagnosed at a high stage,[12,14] and in Jogjakarta, almost half have delay presentation, and 64.7% experience delay in diagnosis.[15] The study aimed to assess the different clinicopathologic between the young age group and older age group, and this study could provide additional data for later epidemiological, clinical, biomedical studies and to make policies for breast cancer screening.

Methods

A cross-sectional study used secondary data from the Medical Records (MR) at Bethesda Hospital Yogyakarta, which included all women diagnosed with breast cancer from 1st January 2017 – to 31st December 2020. This research has ethical clearance from Bethesda Hospital Yogyakarta number 42/KEPK-RSB/V/21. Of the 98 Medical records, were collected clinical data including age, and breast cancer side. Using American Joint Commission on Cancer system Tumour Node Metastasis staging of breast cancer; pathologic data include the histological type and molecular subtype of breast cancer. Including criteria were all breast cancer patient records in Bethesda Hospital Medical Record, and the excluding criteria were not complete Medical Records.

The collected data were analysed by univariate statistics to describe the frequency and proportional percentage of clinicopathologic data. The significant difference between the dependent variable (age groups ≤ 50 years and > 50 years) and independent variables (low stage (I & II) - high stage (III & IV) and hormone receptors positive (Lumina A & Luminal B) – hormone receptors negative (HER-2/neu & Triple Negative Breast Cancer (TNBC)). The association between two variables was analysed by binary logistic regression.

Results

The 98 MR were included in the study. The clinicopathologic data is depicted in Table 1. Age-specific incidence rises steadily from age < 30 years, the highest rate was in the 51-60 years age group and declined after 60 years. The patients aged > 50 years are 62.23%, and 13.26% at the young age group (≤40 years), mean age 52.28 ± 0.944, youngest 24 years and oldest 78 years. Most of the histologic type of patients were invasive ductal carcinoma type (89.80%) rather than invasive lobular carcinoma type or other types. The high stage of cancer

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(III & IV) in this study was found in 67 patients (68.37%). Hormone-positive breast cancer (58.17%) was more than hormone-negative breast cancer (41.83%).

The significant differential analysis between low stage – high stage and hormone receptors positive and negative with age group ≤50 years and > 50 years, explained in Table 2. Percentage proportion of age group ≤ 50 years tend to show a higher risk for the advanced stage of breast cancer than age group > 50 years, although not statistically significant (p=0.368). Age group ≤ 50 years had hormone receptors positive, and the age group > 50 years had hormone receptors negative molecular subtype characteristic (p<0.05) in the odds 2.993 (CI 95% 1.239 – 7.230).

Table 1 Distribution of Age, Breast Cancer Side, Stage Histopathologic Type, Molecular Subtype

Variable		Frequency	%
Age	≤ 30 years	1	1,02%
	31-40 years	12	12,24%
	41-50 years	25	25,51%
	51-60 years	45	46,92%
	≥ 61 years	15	15,31%
Breast cancer side	Right	48	48,98%
	Left	50	51,02%
Stage	Stage 0	0	0,00%
	Stage I	3	3,06%
	Stage II	28	28,57%
	Stage III	54	55,10%
	Stage IV	13	13,27%
Histopathologic type	Invasive Ductal Ca.	88	89,80%
	Others	10	10,20%
Molecular Subtype	Luminal A	43	43,88%
	Luminal B	14	14,29%
	HER-2 positive	29	29,59%
	Basal-like / Triple-negative Breast Ca.	12	12,24%

Table 2 The Difference Between Age Groups with Stage and Molecular Subtype

Variable		Age groups		Significance
		≤50 years	>50 years	
Stage	Low	10 (32.3%)	21 (67.7%)	0.368
	High	28 (41.8%)	39 (58.2%)	
Molecular Subtype	Hormone receptor +	28 (49.1%)	29 (50.9%)	0.013
	Hormone receptor -	10 (24.4%)	31 (75.6%)	OR 2.993
				CI 95% 1.239 – 7.230

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Discussion

The incidence of breast cancer increases with age and decreases after age 60 years. A very young adult breast cancer patient in this study was at age of 24 years. Age group ≤ 50 years tend to have a high stage at diagnosis presentation (68.37%) and had hormone receptor-positive molecular subtype characteristic (58.17%).

In a study in Sardjito Hospital, the prevalent age of the patient was 46-50 years of age (22.4%), then 51-55 years of age (19.5%).[16] In a study at Kariadi Hospital Semarang (2016), there were 372 cases (83.4%) of breast cancer that occurred in age ≥ 40 years of totals 446 cases.[1] The study in RSUP Haji Adam Malik Medan (2021) show different results, age group 41 - 50 (38 cases of total 103 cases, 36.9%) was the highest rate of breast cancer,[2] and also in RSUP Sanglah Bali,[17,18] and RSUP Dr. R.D. Kandau Manado.[19] Increasing age is one of the breast cancer risk factors, but peaking age groups in one region to others are different. In Korea, the peaking incidence rate in the 45- 49year age group,[3] Japan 50-54year age group,[4] the United States 55-59 age group,[4] Australia 65-69 age group,[20] and in the world 49% 50-69 years age group.[21] The menopausal and postmenopausal are prevalent breast cancer patients in some regions but the other premenopausal patients are prevalent. Demographic differences with fewer old women in some regions and lower prevalence of risk factors of postmenopausal cancer are the most likely explanation for the lower mean age at diagnosis in those regions.[22]

In this study, the left lateralization of the right and left breast cancer was almost the same. In the study in St. Rita Medical Centre Ohio United States (2014), most patients had unilateral breast cancer in, the upper outer quadrant, and left breast side.[23] In the study at *Affiliated Hospital of Guangdong Medical University China* (2018), the left side of breast cancer was the dominant breast side in the≥ 40 year age group and the right side of breast cancer in the < 40 year age group.[24] Predominance lateralization on the left breast side could be explained by breast asymmetry in women, as measured on mammography, the left breast was noted to be larger than the right in 55% of healthy women. Breast hypertrophy was reported to be more common on the left side.[23]

In this study, stage III was the most of breast cancer stage. In a study conducted at RSUP Sanglah Bali (2020), most patients' stage presentation was stage III (64,06%),[17,18] and stage IV (63.6%) in RSUP Dr. RD. Kandau Manado.[19] The factors of delay in seeking treatment are caused by lacking breast cancer knowledge, the major cause, cost of treatment, culture and spiritual belief, and seeking complementary and alternative medicine (CAM).[17] In the study conducted at RSUP Prof. Dr. R.D. Kandau Manado (2018) and RSUP Sanglah Bali, the most histopathology type is invasive ductal carcinoma (96% and 84.7%).[18,19] Invasive Ductal

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Carcinoma No Specific Type (IDC NST) constitute 40-75% and invasive lobular carcinoma accounts for 10-15% of all breast cancers. The clinicopathologic presentations of IDC NST usually show a wide scope of morphological variation and clinical behaviors, such as tumor size, grade, the relative proportion of tumor cell and stroma, and types of margins. IDC NST shows heterogeneous growth, including diffuse sheets, nests, cords, or singly distributed cells with a variable amount of ductal differentiation.[25]

A molecular subtype of breast cancer is a determinant factor for overall survival (OS), favourable molecular subtypes (Luminal A and Luminal B) can expect an OS above 95% and a local recurrent rate of almost 100% above 5 years. On the other hand, the outcome of patients with HER-2/neu and TNBC subtype remains poor.[26] In this study hormonal receptor subtypes are predominant. In the study conducted in RSUP Sanglah Bali (2014), Luminal A and TNBC were the most molecular subtype,[27] in RSUP Dr. M. Djamil Padang (2016), Luminal B and TNBC were the most molecular subtype,[28] In RSUD Madiun (2021), Luminal B is the most molecular subtype than TNBC., Luminal A, and HER-2/neu.[29] Systematic Review study by Simbolon and Pohan (2021), molecular the subtype most molecular subtype was Luminal A (57.5%), Luminal B (17.7%), TNBC (14.3%), and Her-2/neu (10.1%). Luminal A subtype presents low histopathologic grade, special histologic type (tubular, mucinous, and lobular), low proliferation index, and low recurrent rate than other subtypes.[30]

Conclusion

Our study concluded that the 51-60 years age group was the most prevalent age group of breast cancer, and incidence declined after 60. Laterality of left breast side of breast cancer found almost the same with right breast side. Most patients presented a high stage of invasive ductal carcinoma. Hormone receptor-positive was the predominant subtype of breast cancer. Hormone receptor-positive subtypes were characteristic of patients ≤ 50 years old, 2.993 more prevalent than > 50 years, while hormone receptor-negative subtypes were characteristic of patients > 50 years old.

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