ABSTRACT

Introduction: Breast cancer in very young women showed varied clinicopathological data among studies. This study presented the clinicopathological features of very young Balinese women with breast cancer from the Cancer Registry in 2016-2021.

Methods: This study retrospectively studied the characteristic of Balinese women with breast cancer aged less than 35 years old that has been histopathology confirmed. The clinicopathologic parameters included were the age of menarche, parity, education, employment, family history, location and area of breast lump, histologic subtypes, grade, lymphovascular invasion, tumour infiltrating lymphocytes, and AJCC TNM-based breast cancer’s stage was recorded. Statistical analysis was performed using the SPSS 16.0 software.

Results: There were 100 Balinese women under 35 years of age (5.16% of the total population of women with breast cancer from 2016-2021) diagnosed with breast cancer in Bali from January 2016 to October 2021. The majority subjects had the age of menarche of 12-14 years old (66%), multiparity (56%), highest education of senior high school (50%), housewife (40%), no family history of breast cancer (92%), presented in advanced stage (68%), mostly in stage IIIB (26%), had histology type of non-special type of invasive carcinoma (81%), histological grade II (48%), no presence of lymphovascular invasion (33%), positive tumour-infiltrating lymphocytes (67%), and with luminal B (47%) subtype.

Conclusions: The clinicopathological features of very young female subjects with breast cancer in Bali were quite similar to others studies and the general population of breast cancer subjects.

KEYWORDS very young, breast cancer, clinicopathology
cancer in young women usually has a more aggressive nature, thus has a higher risk of death [4]. Breast cancer in young women requires special attention because of its specific morphological and prognostic characteristics and unique aspects, including its impact on family life and career. Thus, this study aimed to present the clinicopathological features of very young Balinese women with breast cancer from the Cancer Registry in 2016-2021.

Methods

Data sources

This was a descriptive study that used the Bali Cancer Registry Database from January 2016 to September 2021 to gather information on female breast cancer subjects who have been histopathologically confirmed. This study included all populations aged $\leq 35$ years old, taking the total sample. The exclusion criteria were missing data that cannot be retrieved through phone calls or electronic medical records. The Bali Cancer Registry is a local-based cancer registry jointly sponsored by The Indonesian Society of Surgical Oncology, which includes all breast cancers subjects treated in Bali, Indonesia. This registry was established in January 2016.

Data collection

The demographic features such as the age of menarche, parity, education, employment, and family history were recorded. The clinical features such as location and area of breast lump were recorded. The pathologic features such as histologic subtypes, grade, lymphovascular invasion, tumour-infiltrating lymphocytes, and AJCC TNM-based breast cancer’s stage were recorded.

All subjects included in this study have been histopathologically confirmed to have breast cancer. All histological slides were reviewed by one pathologist, and tumours were classified as invasive cancer of no special type, lobular carcinoma, mucinous, tubular, and signet-ring cell carcinoma. The histological grade was determined based on the Nottingham Grading System, classified as grades I, II, and III.

The molecular subtypes were determined based on the immunohistochemistry test, classified as luminal A (ER+ and/or PR+, HER-2-), luminal B (ER+ and/or PR+, HER-2-), luminal B HER2 (ER+ and/or PR+, HER-2+), HER-2+/HER- (ER-, PR-, and HER-2+), and triple-negative (ER-, PR-, HER-2). Immunohistochemistry was done on formalin-fixed, paraffin-embedded tissue sections at the Pathology Laboratory at Sanglah General Hospital. ER and PR were determined positive if $\geq 10\%$ nuclei were stained. HER-2 expression was measured also using the immunohistochemistry technique. HER2 status was evaluated with immunohistochemistry, and +3 was defined as positive; those with +2 were further evaluated by fluorescence in situ hybridization (FISH). A ratio of HER2 gene/chromosome 17 $\geq 2.0$ was considered positive. Ki67 was used to differentiate luminal A and B with the cut off value of 14%.

Data analysis

Data were collected and described. Data on clinicopathologic features as categorical data were presented as numbers and percentages. Statistical analysis was performed using the SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

Results

This study included all female patients with breast cancer who were treated at our institution, Sanglah General Hospital, from January 2016 to September 2021. There were 100 breast cancer patients under 35 years of age (5.16% of the total population of women with breast cancer from 2016-2021). From 2016 to 2020, the total cases of breast cancer patients under 35 years have almost the same incidence, around 4-6% of the total breast cancer patients of all ages. The median age of the subjects in this study was 32 years old (24-35 years old). There were 100 breast cancer patients aged 35 years old. 6% of patients were aged 20-25 years old, 28% were aged 26-30 years old, and 66% were aged 31-35 years old. The clinical and pathological characteristics can be seen in Table 1. In this study, the author also divides the table into female breast cancer subjects aged 30 years old and those 31-35 years old.

In demographic characteristics, the majority of very young patients aged under 30 years or 30-35 years had age of menarche of 12-14 years old (66%), multiparity (56%), highest education of senior high school (50%), has a profession as a housewife (40%), and no family history of breast cancer (92%). In clinical features, the group of very young age under 30 years old showed predilection of the breast lump at the left side of the breast, while the very young age group 31-35 years old showed predilection at the right side of the breast. However, both groups showed the same area of breast lump incidence in the upper outer quadrant (11% and 21%, respectively). In pathological features, both groups presented in advanced stage (68%), mainly in stage IIIB (26%). There were 20% total cases of distant metastases, with the most common metastases place found in the lung and multiple sites.

Almost all breast cancer cases in this study had histology type of non-special type of invasive carcinoma (total 81%). Four cases of a special type of breast cancer histology were found in the very young age group aged 31-35 years old. The majority observed histological grades were grade II (48%), no presence of lymphovascular invasion (33%), and positive tumour infiltrating lymphocytes (67%). In the molecular subtypes description, luminal B was the major case (47%), followed by TNBC (21%), HER2 type (14%), luminal HER2 (10%), and the least luminal A (8%). There was no luminal A case found in the population aged less than 30 years old.

Discussion

Breast cancer in young adults is defined by the National Cancer Institute as a diagnosis occurring among those aged 15 to 39 years. Most studies further classified subjects less than 30 years old as a very young age group [5]. Globally there is an increase in the incidence of breast cancer in adolescents and young women due to an increase in the young population, increased awareness of both patients and clinicians in diagnosing the disease, and increased case reporting [6]. For example, in Bali, there was a surge in breast cancer cases, both young and adult, diagnosed in 2016 with an affordable national health insurance system for people who increased awareness of going to the hospital. Breast cancer tends to be more aggressive in young women. Young breast cancer patients present with more advanced stages and have more adverse outcomes [2]. Breast cancer risk increases each 1.05 for every year younger at menarche [7]. In this study, the median age of diagnosis of very young age women with breast cancer was 32 years old. In this study, it was shown that the most menarche age was 12-14 years old and had no family
Table 1 Clinical and pathological characteristics of very young female patients with breast cancer.

| Clinicopathological features                  | <30 years old | 31-35 years old | Total |
|-----------------------------------------------|---------------|-----------------|-------|
| Age of menarche                               |               |                 |       |
| ≤ 11 years old                                | 6             | 4               | 10    |
| 12-14 years old                               | 18            | 48              | 66    |
| ≥ 15 years old                                | 10            | 14              | 24    |
| Parity                                        |               |                 |       |
| Nulliparity                                   | 9             | 12              | 21    |
| Primiparity                                   | 12            | 10              | 22    |
| Multiparity                                   | 13            | 43              | 56    |
| Grandemultiparity                             | 0             | 1               | 1     |
| Education                                     |               |                 |       |
| Junior high school                            | 3             | 7               | 10    |
| Senior high school                            | 12            | 38              | 50    |
| University                                    | 19            | 21              | 40    |
| Employment                                    |               |                 |       |
| Student                                       | 2             | 0               | 2     |
| Housewife                                     | 13            | 27              | 40    |
| Self-employed                                 | 7             | 13              | 20    |
| Employee                                      | 12            | 25              | 39    |
| Farmer                                        | 0             | 1               | 1     |
| Family history of breast cancer               |               |                 |       |
| No                                            | 31            | 61              | 92    |
| Yes                                           | 3             | 5               | 8     |
| Location of breast lump                       |               |                 |       |
| Left                                          | 20            | 27              | 47    |
| Right                                         | 14            | 38              | 52    |
| Bilateral                                     | 0             | 1               | 1     |
| Area                                          |               |                 |       |
| Central                                       | 8             | 15              | 23    |
| Upper outer quadrant                          | 11            | 21              | 33    |
| Upper inner quadrant                          | 5             | 15              | 20    |
| Lower outer quadrant                          | 2             | 0               | 2     |
| Lower inner quadrant                          | 8             | 15              | 23    |
| Stage                                         |               |                 |       |
| IIA                                           | 0             | 13              | 13    |
| IIB                                           | 6             | 13              | 19    |
| IIIA                                          | 7             | 12              | 19    |
| IIIIB                                         | 11            | 15              | 26    |
| IIIC                                          | 2             | 1               | 3     |
| IV                                            | 8             | 12              | 20    |
history. In Medan, out of 160 samples, 51% were aged 31-35 years. Most menarche age was found in the age group <12 years (65.5%), and 51.3% did not have a family history of 82 patients (51.3%) [8]. Although the risk of developing breast cancer at a young age is higher for women with a family history of the disease, most authors showed that in the population, the majority of subjects did not have these risk factors [9]. The majority of subjects in this study presented in the advanced stage (68%), and 20% of subjects have already had distant metastases. In a registry-based breast cancer population study by the authors in Bali from 2012-2019, subjects were mostly found in the advanced stage (65.4%), where 22.6% of subjects had distant metastases [10]. In Yogyakarta, Lukman et al. (2019) also showed that 64% of subjects were diagnosed in advanced stages, and metastasis was found in 16% at the time of diagnosis.

In the view of molecular subtypes, almost all studies showed that luminal B was the most commonly found, regardless of age. In this study, luminal B was found in 47% of patients, and only 8% of patients belonged to the luminal A subtype. In Jakarta, Ng et al. (2011) showed that 63% of breast cancer women at young age presented in stage III or IV and were mostly hormonal negative [11]. Anwar et al. (2019) showed that around 40% were hormone receptor-positive, 30.6% had HER2 receptor-positive, and 38.2% triple-negative [12]. Collins et al. revealed a lower proportion of luminal A disease (33% vs. 60-70%) and a higher proportion of luminal B disease (35% vs. 6-22%) in young women with breast cancer subjects compared to the total population with breast cancer [13]. In the molecular subtype of the Balinese female population with breast cancer, indeed luminal B dominates with a proportion of 36.5%. However, the proportion of patients who have luminal A is still quite large at 11.2%, and the rest are HER2 (16.3%), TNBC (17.6%), and luminal HER2. (17.8%). To further confirm the above clinical findings, Anders et al. showed that young patients had a lower expression of estrogen and progesterone receptors compared to the older population [14].

The clinicopathological features among studies of very young women with breast cancer were quite similar. The pathologi-
cal features of very young female subjects with breast cancer showed similar characteristics to the general population with breast cancer. Only the molecular hormonal subtype was lower in very young women with breast cancer compared to the older population.

However, the advanced stage at diagnosis of young-onset breast cancer indicates an urgent need for increased awareness of this disease. In addition, further research should investigate the new treatment strategies in young patients with breast carcinoma to help reverse the morbidity and mortality of this disease.

**Conclusion**

The clinicopathological features of very young female subjects with breast cancer in Bali were quite similar to others studies and the general population of breast cancer subjects.

**Conflicts of Interest**

The authors declare that there is no conflict of interest regarding the publication of this paper.

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