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Histopathological Grading based on BI-RADS Mammography Category 4 and 5 in Breast Cancer

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ABSTRACT

Introduction: Breast cancer is the most common cancer worldwide. The diagnosis of breast cancer is established by a triple diagnostic, such as clinical examination, radiology (mammography), and histopathology. This study aimed to compare mammography breast imaging-reporting and data system (BI-RADS) category 4 and 5 with histopathological grading of breast cancer at Dr. Soetomo General Academic Hospital, Surabaya.

Methods: This was an observational, descriptive study with a comparative approach, utilizing secondary data from medical records of breast cancer patients at Dr. Soetomo General Hospital, Surabaya, from January 2017 to December 2021. There were 234 samples of patients who met the inclusion criteria. All statistical data were analyzed using the International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) version 26, with a $p<0.05$ regarded as statistically significant.

Results: The breast cancer patients were most prevalent in the 45-49 years old age group (20.9%). The highest distribution of the BI-RADS category was C-5 (85.9). The highest distribution of histopathological grading was grade III (53%). There was no difference in age intervals between BI-RADS C-4 and BI-RADS C-5 in breast cancer patients ($p=0.499$). There was no difference in histopathological grading between BI-RADS C-4 and C-5 in breast cancer patients ($p=0.592$).

Conclusion: There was no difference either in age interval or histopathological grading between BI-RADS category 4 and 5 in breast cancer patients.

Highlights:
1. Most breast cancer patients were in the 45-49 years old age group.
2. There was no difference in the age interval between BI-RADS C-4 and C-5 in breast cancer patients.
3. There was no difference in histopathological grading between BI-RADS C-4 and C-5 in breast cancer patients.

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Introduction

Breast cancer is the most common cancer worldwide. In 2020, globally, almost 2.3 million women were diagnosed with breast cancer, and 685,000 of them died.[1,2] In Indonesia, there were 65,858 new cases of breast cancer (16.6%) out of 396,914 new cancer cases in this country.[3] Several factors played role in this incident, including diagnosis at an advanced stage, unfavorable tumor characteristics, the lack of early detection and treatment, and also individual risk factors. Some of these risk factors include gender, aging, family history, reproductive factors, estrogen hormones, and lifestyle habits.[4]

The diagnosis of breast cancer is established through triple diagnostics, which includes clinical examination, radiology (mammography), and histopathology.[5,6] Mammography has a sensitivity up to 80% and a specificity up to 98%.[7] To standardize the assessment and reporting of mammography results, the American College of Radiology (ACR) has developed the BI-RADS (Breast Imaging-Reporting and Data System) assessment. BI-RADS has categories 1 to 6, which have different meanings. Category 4 (C-4) means suspicious for malignancy with a likelihood of malignancy > 2% but < 95%. Meanwhile, category 5 (C-5) means highly suggestive of malignancy with a likelihood of malignancy ≥ 95%.[8] According to the guidelines, if the results indicate BI-RADS categories 4 and 5, follow-up in the form of tissue sampling by needle biopsy is required.[8]

Biopsy is required for histopathological examination, which is the gold standard in establishing the breast cancer diagnosis.[8] Histopathological examination aims to determine the differentiation of normal cells into cancer cells.[9] One of the histopathological assessments includes grading from the Nottingham Grading System (NGS). NGS is a semi-quantitative assessment involving three components of tumor morphology, namely tubule/glandular formation, nuclear pleomorphism, and mitotic frequency. The grading assessment is divided into grade I/well-differentiated (score 3-5), grade II/moderately differentiated (score 6-7), and grade III/poorly differentiated (score 8-9). This assessment aims to evaluate the tumor's behavior and prognosis from a morphological perspective.[10,11]

Based on research conducted in Korea involving 31,691 patients, it was found that there were differences in histopathological grading between BI-RADS C-3-4 and BI-RADS C-5 in breast cancer patients.[12] Therefore, researchers are interested in comparing BI-RADS categories 4 and 5 with the histopathological grading of breast cancer at Dr. Soetomo General Hospital, Surabaya. This study can enhance the accuracy of mammography diagnosis by investigating whether tumor morphology, specifically grading, correlates with breast cancer imaging, particularly mammography.[12,13,14]

Methods

This type of research is observational descriptive with a comparative approach. The compared aspects are BI-RADS mammography and histopathological grading, which are parts of the triple diagnostics.[5,6] Retrieval of data using total sampling technique. This research is retrospective, using secondary data from medical records of breast cancer patients at Dr. Soetomo General Hospital, Surabaya, from January 2017 - December 2021. The research sample consists of all breast cancer patients at Dr. Soetomo General Hospital, Surabaya from January 2017 to December 2021 who meet the inclusion criteria, including 1). Breast cancer patients who have undergone mammography examinations on both breasts before surgery, and the results indicate BI-RADS assessment categories 4 and 5, 2). Breast cancer patients who have undergone tissue biopsy examinations and/or surgery, and the histopathological results indicate breast cancer. Exclusion criteria include: 1). Mammography results do not match the BI-RADS assessment 2013, 2). Histopathological results do not include/according to the histopathological grading based on NGS.

Out of a total of 452 patients who underwent diagnostic mammography, 234 patients met the inclusion criteria. Some of the data collected include patient age, BI-RADS category, and histopathological grading. Patient age is divided based on 5-year relative survival (< 40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, and ≥ 70 years old).[15] BI-RADS categories are divided into BI-RADS C-4 and C-5, while histopathological grading is divided into grades I, II, and III according to the NGS classification [12,13]. This research was conducted after obtaining approval from the Ethical Committee of Dr. Soetomo General Hospital, Surabaya (ethical clearance number 1136/LOE/301.4.2/XI/2022).

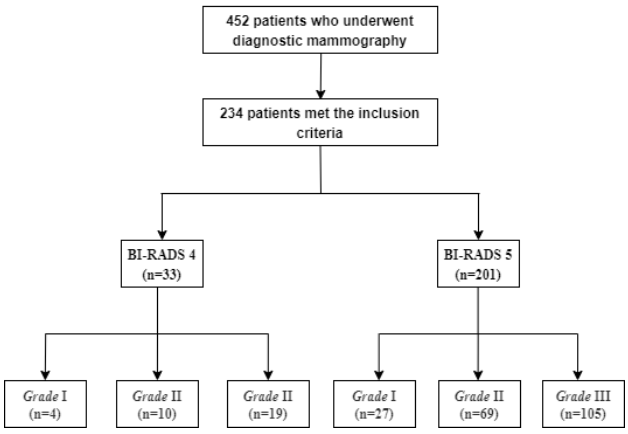

Figure 1. Flow diagram showing the patients selection and categorization process

Data Analysis

The data were collected and categorizes using Microsoft Excel 2021.[16] Data were analyzed and presented using crosstabulation, while the comparison, either between BI-RADS and age or BI-RADS and histopathological grading, were conducted using the Mann Whitney method. The research data were analyzed using International Business Machines Corporation (IBM)

Statistical Package for Social Sciences (SPSS) version 26.[17]

Results

The comparison between BI-RADS categories in mammography and histopathological grading is illustrated in Figure 1. The findings are summarized in terms of BI-RADS categories and compared with the related histopathological grading concerning behavior and prognosis.[18]

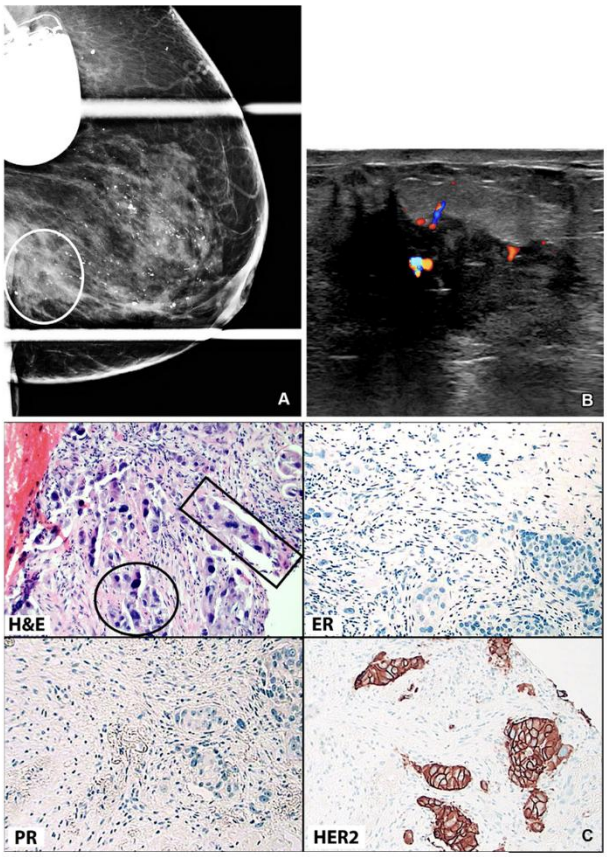

Figure 1. (A) The spot mediolateral oblique (MLO) mammogram on the left breast reveals an incidental oval mass with diffuse coarse calcifications throughout the breast, suggesting benign calcifications. (B) The color doppler ultrasound image of the left breast shows an irregular hypoechoic mass containing multiple echogenic foci, correlating with the calcifications observed in A, and exhibiting both peripheral and internal vascularity. (C) Photomicrographs of the left breast core needle biopsy (CNB) specimen display tumor cells arranged in nests (circle) and cords (rectangle), characterized by a high nuclear grade (3/3) (H&E staining). The immunohistochemical (IHC) findings indicate ER negative (ER−), PR negative (PR−), and HER2 positive (HER2+), consistent with ER−, PR−, HER2+ grade III invasive ductal carcinoma[18]

During January 2017 – December 2021 out of a total of 452 patients who underwent diagnostic mammography, 234 patients met the inclusion criteria. **Table 1** shows the distribution based on age intervals, BI-RADS categories, and histopathological grading. The most common age interval for breast cancer patients is 45-49 years, with 49 patients (20.9%). Meanwhile, the least common age interval for breast cancer patients is ≥ 70 years old, with 6 patients (2.6%). The mean age of breast cancer patients is 51.3 years. BI-RADS C-5 (85.9%) is more prevalent than BI-RADS C-4 (14.1%). Most histopathological grading is grade III (53%), followed by grade II and I, with 33.8% and 13.2%, respectively.

Table 1. Frequency distribution

Characteristic	N=234	Percentage (%)
Age (Years Old)		
<40	19	8.1
40-44	42	17.9
45-49	49	20.9
50-54	40	17.1
55-59	34	14.5
60-64	33	14.1
65-69	11	4.7
≥ 70	6	2.6
Breast Imaging Reporting and Data System Category		
C-4	33	14.1
C-5	201	85.9
Histopathological Grading		
Grade I	31	13.2
Grade II	79	33.8
Grade III	124	53

Source: Research data, processed

Table 2 shows the crosstabulation table and the results of the Mann Whitney test between BI-RADS categories with age and BI-RADS categories with histopathological grading. The distribution of BI-RADS categories by age shows that BI-RADS C-5 is consistently more common than BI-RADS C-4 in every age interval. The highest distribution of BI-RADS C-4 is in the 55-59 age interval, with 9 patients, while the lowest is in the 65-69 age interval, with 1 patient. The highest distribution of BI-RADS C-5 is in the 45-49 age interval, with 41 patients, and the lowest is in age interval ≥ 70 years old, with 4 patients. The comparison result of BI-RADS C-4 and C-5 with the age of breast cancer patients is 0.499. This means there is no difference in age intervals between BI-RADS C-4 and BIRADS C-5 in breast cancer patients at Dr. Soetomo General Hospital, Surabaya, from January 2017 to December 2021.

The distribution of BI-RADS categories by histopathological grading shows that BI-RADS C-5 is consistently more common than BI-RADS C-4 in grades I, II, and III. The highest distribution of BI-RADS C-4 is in grade III, with 19 patients (15.3%). Meanwhile, the highest distribution of BI-RADS C-5 is also in grade III, with 105 patients (84.7%). The comparison result of BI-RADS C-4 and C-5 with the histopathological grading of breast cancer is 0.592. This means there is no difference in histopathological grading between BI-RADS C-4 and BIRADS C-5 in breast cancer patients at Dr. Soetomo General Hospital, Surabaya, from January 2017 to December 2021.

Table 2. Comparison of age and histopathological grading according to BI-RADS category 4 and 5

Characteristic	BI-RADS Category		p-value
	C-4 (n=33)	C-5 (n=201)	
Age (Years Old)			
<40	2 (6.1%)	17 (8.5%)	0.499
40-44	4 (12.1%)	38 (18.9%)	
45-49	8 (24.2%)	41 (20.4%)	
50-54	5 (15.2%)	35 (17.4%)	
55-59	9 (27.3%)	25 (12.4%)	
60-64	2 (6.1%)	31 (15.4%)	
65-69	1 (3%)	10 (5%)	
≥ 70	2 (6.1%)	4 (2%)	
Histopathological Grading			
Grade I	4 (12.1%)	27 (13.4%)	0.592
Grade II	10 (30.3%)	69 (34.3%)	
Grade III	19 (57.6%)	105 (52.2%)	

BI-RADS: breast imaging reporting and data system
Source: Research data, processed

Discussion

This study result indicates that the breast cancer patients most frequent within the 45-49 age interval, while the least frequent distribution is found in ≥ 70 years old. These findings align with a study conducted in Malaysia involving 2166 breast cancer patients, where the majority of breast cancer patients were aged 40-59 years (54.4%).[19] Study in United States show that the incidence of breast cancer increases in the 20-49 age interval, with predominance in the 40-49 age interval.[20] Breast cancer incidence increases significantly with age, peaking at menopause, then declining gradually or remaining constant.[21] Breast cancer patients over 50 years demonstrate a lower survival rate.[9]

Based on the results of diagnostic mammography, BI-RADS C-5 is more prevalent than BI-RADS C-4. These findings indicate that most cases are highly suggestive of malignancy with a likelihood of malignancy ≥ 95% .This research aligns with a study in Korea involving 31,691 breast cancer patients, which reported BI-RADS C-5 (79.3%) is more prevalent than BI-RADS C-3-4 (20.7%).[12] However, another study indicates that the most prevalent distribution is BI-RADS C-4 (51.6%), followed by C-5 (42.9%) and C-3 (5.5%).[22]

Several criteria for categorizing as BI-RADS C-5 are correlated with malignancy occurrence. Some of these criteria include irregular mass, spiculated mass, pleomorphic calcifications, also linear and segmental calcifications.[22,23] A study also suggests a relationship between palpable breast masses and BI-RADS C-5.[12]

The histopathological results indicate that breast cancer patients are predominantly in grade III, followed by grade II, and the least in grade I. These findings suggest that most cases have poor tumor behavior and prognosis. This distribution is consistent with a study in the Netherlands involving 1,793 breast cancer patients over 10 years, which reported the following distribution in ascending order: grade III (43.6%), grade II (40.9%), and grade I (15.6%).[24]

Studies found that grading is an assessment of cancer cell morphology that is influenced by the predominant stromal type. This stroma has an impact on tumor growth, progression, and invasion. The fibroblast-dominated stroma has been shown to be significantly associated with grading, especially in high grade. Fibroblasts can cause physical changes in the basement membrane of cells, thereby facilitating cancer cell invasion. They not only promote the survival of cancer cells but also create a niche that causes resistance to treatments.[25,26]. Fibroblast influences tumor cell progression by regulating nutrient supply for these cells, altering the extracellular matrix to facilitate easier invasion by cancer cells, suppressing the body's defense mechanisms to prevent destruction by immune cells, and modulating both extracellular and intracellular signals to enhance cancer cell survival during chemotherapy.[27]

This study indicates no difference in age intervals between BI-RADS C-4 and BI-RADS C-5 in breast cancer patients (p = 0.499). Another study also indicates no significant relationship between BI-RADS categories and age (p = 0.517).[28] These results differ when compared to studies that divide BI-RADS categories into C-3-4 and C-5, and categorize patient age into < 50 years and ≥ 50 years. The comparison between BI-RADS 3-4 and 5 categories with age categories shows a difference (p < 0.001). BI-RADS C-3-4 is most prevalent in patients aged ≥ 50 years (50.8%), while BI-RADS C-5 is most prevalent in patients aged < 50 years (53.2%).[12] Age has a significant inverse relationship with breast density. Breast density is a risk factor for invasive breast cancer with ER-positive or ER-negative status, where the reduction in breast density occurs concurrently with increasing age.[21] ER (estrogen receptor) facilitates the action of estrogen in the body, which this hormone is also implicated in the risk of breast cancer. Hormonal status was significantly associated with the grading of invasive ductal carcinoma (IDC). If the hormonal status is positive then it tends to be high grade. Additionally, another study indicates that patients with positive hormonal status are three times more likely to develop metastases than patients with negative hormonal status.[29,30]

This study indicates no difference in histopathological grading between BI-RADS C-4 and BI-RADS C-5 in breast cancer patients (p = 0.592). These research findings differ from a study conducted in Korea involving 31,691 breast cancer patients. In this study, histopathological grading was divided into grade I-II and grade III. The distribution of BI-RADS C-3-4 and BI-RADS C-5 was most prevalent in grade I-II, at 69.2% and 63.4%, respectively. The comparison between BI-RADS C-3-4 and C-5 with the histopathological grading of breast cancer patients shows a difference (p = 0.019).[12] There are no current studies that provide a detailed explanation of their relationship. However, a study suggests that the criteria for determining BI-RADS, such as mass shape, margin, density, calcifications, focal asymmetry density, and architectural distortion, yield varying results based on histopathological grading. From several BI-RADS's component, only mass margin specifically spiculated was significantly associated with histopathological grading, which tends to indicate grade 1 or 2. Meanwhile, distinct mass, ill-defined mass, and calcification are not significantly related to histopathological grading.[12,13]

Strengths and Limitations

This research able to compare BI-RADS C-4 and C-5 with histopathological grading of breast cancer, which can enhance enhance the accuracy of mammography diagnosis by investigating whether tumor morphology, specifically grading, correlates with breast cancer imaging, particularly mammography. The limitation of this study did not list other clinicopathological variables, such as menopausal status, palpability mass, tumor staging, histological type, and immunohistochemistry results. So, further research on this topic is needed with a larger sample size and additional variables.

Conclusion

The breast cancer patients at Dr. Soetomo General Hospital, Surabaya, are predominantly in the middle age. Based on diagnostic mammography results, the most common is BI-RADS category-five, while based on histopathology results, most cases are classified as grade III. The study explains that there is no difference in age interval between BI-RADS category four and five in breast cancer patients, and there is also no difference in histopathological grading between BI-RADS category-four and five in breast cancer patients. This study indicates the triple assessments of breast cancer are inseparable and complementary.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This study had received ethical clearance from the Ethical Committee for Health Research Dr. Soetomo General Academic Hospital, Surabaya, (ethical clearance number 1136/LOE/301.4.2/XI/2022) on 17-11- 2022.

Authors' Contributions

FUR: design the study, handle the ethical clearance processing, data taking, data analysis, data interpretation, wrote the manuscript, revision. LM: design the study, data interpretation, advisor, and revision. EHK : design the study, advisor, and revision. HG: advisor, revision.

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