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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, Indonesia.

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, Indonesia, from January 2017 to December 2021. There were 234 patient samples that 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 females 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.[1]

Several factors played a role in this incident, including diagnosis at an advanced stage, unfavorable tumor characteristics, the lack of early detection and treatment, and individual risk factors. Some of these risk factors include gender, aging, family history, reproductive factors, estrogen hormones, and lifestyle habits.[3]

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

A biopsy is required for histopathological examination, which is the gold standard in establishing the breast cancer diagnosis.[7] Histopathological examination aims to determine the differentiation of normal cells into cancer cells.[8] One of the histopathological assessments includes grading from the Nottingham Grading System (NGS). It 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 three grades: 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.[9,10]

A study conducted in Korea involving 31,691 patients found that there were differences in histopathological grading between BI-RADS C-3-4 and BI-RADS C-5 in breast cancer patients.[11] This study compared BI-RADS category 4 and 5 with the histopathological grading of breast cancer at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. This study can enhance the accuracy of mammography diagnosis by investigating whether tumor morphology, specifically grading, correlates with breast cancer imaging, particularly mammography.[11–13]

Methods

This was an observational descriptive study with a comparative approach. The compared aspects were BI-RADS mammography and histopathological grading, which were components of the triple diagnostic approach.[4,5] The retrieval of data employed the total sampling technique. This study used a retrospective design, utilizing secondary data from the medical records of breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2017 to December 2021. The research sample consisted of all breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2017 to December 2021 who met the inclusion criteria, including: 1) breast cancer patients who underwent mammography examinations on both breasts before surgery (the results indicated BI-RADS assessment category 4 and 5), and 2) breast cancer patients who underwent tissue biopsy examinations and/or surgery (the histopathological results indicated breast cancer). Exclusion criteria include: 1) mammography results did not match the BI-RADS assessment 2013, and 2) histopathological results did not include/were not 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 was categorized into 5-year relative survival groups (<40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, and ≥70 years old).[14] The categories of BI-RADS were divided into BI-RADS C-4 and C-5, while histopathological grading was divided into grade I, II, and III according to the NGS classification.[12,13] This study was conducted after obtaining approval from the Ethical Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (No.1136/LOE/301.4.2/XI/2022).

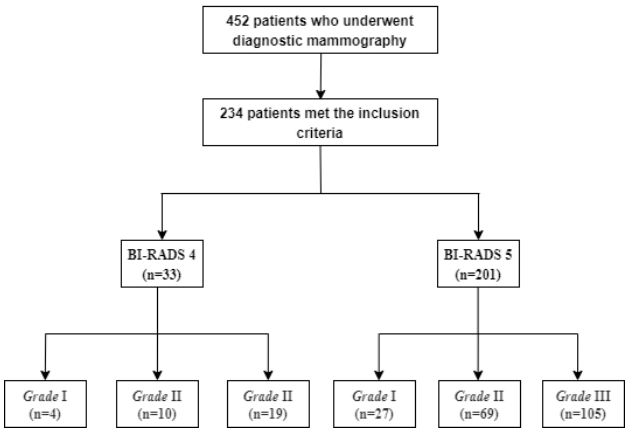

Figure 1. Flow diagram showing the patient selection and categorization process

Data Analysis

The data were collected and categorized using Microsoft Excel 2021.[15] The data were analyzed and presented using crosstabulation. Meanwhile, comparisons were conducted between BI-RADS and age, as well as between BI-RADS and histopathological grading, using the Mann-Whitney method. The data were analyzed using the

International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) version 26.[16]

Results

The comparison between BI-RADS categories in mammography and histopathological grading is illustrated in Figure 2. The findings are summarized in terms of BI-RADS categories and compared with the related histopathological grading in terms of behavior and prognosis.[17]

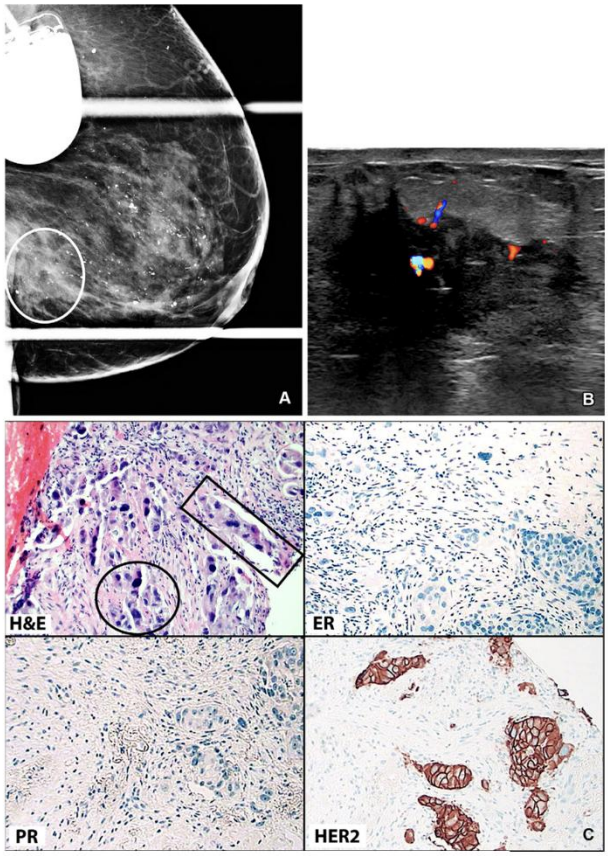

Figure 2. A) The spot mediolateral oblique mammogram on the left breast reveals an incidental oval mass with diffuse coarse calcifications throughout the breast, suggesting benign calcifications; B) The color doppler ultrasound image of the left breast shows an irregular hypoechoic mass containing multiple 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 specimen display tumor cells arranged in nests (circle) and cords (rectangle), characterized by a high nuclear grade (3/3) (hematoxylin and eosin staining). The immunohistochemical findings indicated that the tumor was estrogen receptor-negative (ER−), progesterone receptor-negative (PR−), and human epidermal growth factor receptor 2-positive (HER2+), consistent with an ER−, PR−, HER2+ grade III invasive ductal carcinoma.[17]

Between January 2017 and December 2021, a total of 452 patients underwent diagnostic mammography, and 234 patients met the inclusion criteria. Table 1 presents the distribution by age intervals, BI-RADS categories, and histopathological grading. The most common age interval for breast cancer patients was 45-49 years old, with 49 patients (20.9%). Meanwhile, the least common age interval for breast cancer patients was ≥70 years old, with six patients (2.6%). The mean age of breast cancer patients was 51.3 years old. Category 5 (85.9%) was more prevalent than C-4 (14.1%). Most histopathological grading was 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		
Category 4	33	14.1
Category 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 presents the crosstabulation table and the results of the Mann-Whitney test comparing BI-RADS categories by age and BI-RADS categories by histopathological grading. The distribution of BI-RADS categories by age shows that BI-RADS C-5 was consistently more common than BI-RADS C-4 in every age interval. The highest distribution of BI-RADS C-4 was in the 55-59 years old age interval, with nine patients, while the lowest was in the 65-69 years old age interval, with one patient. The highest distribution of BI-RADS C-5 was in the 45-49 years old age interval, with 41 patients, and the lowest was in the ≥70 years old age interval, with four patients. The comparison result of BI-RADS C-4 and C-5 with the age of breast cancer patients was 0.499. There was no difference in age intervals between BI-RADS C-4 and BI-RADS C-5 in breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2017 to December 2021.

The distribution of BI-RADS categories by histopathological grading showed that BI-RADS C-5 was consistently more common than BI-RADS C-4 in grade I, II, and III. The highest distribution of BI-RADS C-4 was in grade III, with 19 patients (15.3%). Meanwhile, the highest distribution of BI-RADS C-5 was 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 was 0.592. There was no difference in histopathological grading between BI-RADS C-4 and BI-RADS C-5 in breast cancer patients at Dr. Soetomo General Academic

Hospital, Surabaya, Indonesia, 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
	Category 4 (n=33)	Category 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 indicated that breast cancer patients were most frequent within the 45-49 years old age interval, while the least frequent distribution was found in ≥70 years old. These findings align with a study conducted in Malaysia involving 2,166 breast cancer patients, where the majority of breast cancer patients were aged 40-59 years old (54.4%).[18] A study in the United States (US) showed that the incidence of breast cancer increased in the 20-49 years old age interval, with predominance in the 40-49 years old age interval.[19] Breast cancer incidence increases significantly with age, peaking at menopause, then declining gradually or remaining constant.[20] Breast cancer patients over 50 years old demonstrate a lower survival rate.[8]

Based on the results of diagnostic mammography, BI-RADS C-5 was more prevalent than BI-RADS C-4. These findings suggested that most cases were highly suggestive of malignancy, with a likelihood of malignancy of 95% or greater. This aligns with a study in Korea involving 31,691 breast cancer patients, which reported that BI-RADS C-5 (79.3%) was more prevalent than BI-RADS C-3-4 (20.7%).[11] However, another study indicated that the most prevalent distribution was BI-RADS C-4 (51.6%), followed by C-5 (42.9%) and C-3 (5.5%).[21]

Several criteria for categorizing as BI-RADS C-5 are correlated with the occurrence of malignancy. Some of these criteria include irregular masses, spiculated masses, pleomorphic calcifications, as well as linear and segmental calcifications.[21,22] A study also suggested a relationship between palpable breast masses and a BI-RADS classification of C-5.[11]

The histopathological results indicated that breast cancer patients were predominantly in grade III, followed by grade II, and the least in grade I. These findings suggested that most cases had 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%).[23]

Studies have found that grading is an assessment of cancer cell morphology influenced by the predominant stromal type. This stroma has an impact on tumor growth, progression, and invasion. The fibroblast-dominated stroma is significantly associated with grading, particularly in high-grade tumors. Fibroblasts can induce physical changes in the basement membrane of cells, thereby facilitating the invasion of cancer cells. They not only promote the survival of cancer cells but also create a niche that causes resistance to treatments.[24,25] They influence tumor cell progression by regulating the 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.[26]

This study found 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 indicated no significant relationship between BI-RADS categories and age (p=0.517).[27] These results differ from those of studies that divide BI-RADS categories into C-3-4 and C-5, and categorize patient age into two groups: <50 years old and ≥50 years old. The comparison between BI-RADS category 3-4 and 5, along with age categories, revealed a significant difference (p<0.001). Category 3-4 was most prevalent in patients aged ≥50 years old (50.8%), while C-5 was most prevalent in patients aged <50 years old (53.2%).[11] Age has a significant inverse relationship with breast density. Breast density is a risk factor for invasive breast cancer with estrogen receptor-positive (ER+) or ER- status, where the reduction in breast density occurs concurrently with increasing age.[20] The estrogen receptor facilitates the action of estrogen in the body, which 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, it tends to be high-grade. Additionally, other studies indicated that patients with positive hormonal status were three times more likely to develop metastases than patients with negative hormonal status.[28,29]

This study found no difference in histopathological grading between BI-RADS C-4 and BI-RADS C-5 in breast cancer patients (p=0.592). These findings differ from a study conducted in Korea involving 31,691 breast cancer patients.[11] In this study, histopathological grading was divided into grade I-II and 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 revealed a significant difference (p=0.019).[11] There are no current studies that provide a detailed explanation of their relationship. However, a study suggested that the criteria for determining BI-RADS, such as mass shape, margin, density, calcifications, focal asymmetry, and architectural

distortion, yield varying results based on histopathological grading.[11,12] From several BI-RADS components, only the 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.[11,12]

Strengths and Limitations

This study compared BI-RADS C-4 and C-5 with histopathological grading of breast cancer, aiming to 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 was that it did not account for other clinicopathological variables, such as menopausal status, palpable mass, tumor staging, histological type, and immunohistochemistry results. Therefore, further research on this topic is necessary, utilizing a larger sample size and incorporating additional variables.

Conclusion

The breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, were predominantly middle-aged. Based on diagnostic mammography results, the most common was a BI-RADS category 5. Meanwhile, based on histopathology results, most cases were classified as grade III. There was no difference in age interval and histopathological grading between BI-RADS C-4 and C-5 in breast cancer patients. This study indicated that 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, Indonesia (No.1136/LOE/301.4.2/XI/2022) on 11/17/2022.

Authors' Contributions

Designed the study: FUR, LM, EHK. Handling the ethical clearance processing, data taking, data analysis, and writing the manuscript: FUR. Data interpretation: FUR, LM. Advisor: LM, EHK, HG. Revision: FUR, LM, EHK, HG.

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