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Original Research Paper

Characteristics of ER, PR, HER2 and Ki67 Expression in Invasive Breast Cancer Patients at RSUP Dr. Wahidin Sudirohusodo, Makassar 2021-2023

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ABSTRACT

Background: Invasive breast carcinoma is the most prevalent type of breast cancer among women worldwide and contributes significantly to cancer-related mortality. In Indonesia, it ranks first according to Globocan 2020 data. **Objective:** This study aimed to identify the expression of prognostic and predictive markers Estrogen Receptor (ER), Progesterone Receptor (PR), HER2, and Ki67 in breast cancer cases at RSUP Wahidin Sudirohusodo. **Methods:** A descriptive study was performed on 71 formalin-fixed, paraffin-embedded tissue samples collected from 2021 to 2023. The variables analyzed included patient age, histopathologic grade, and immunohistochemical expression of HER2, ER, PR, and Ki67. All samples were stained and reviewed microscopically, and data analysis was conducted using Chi-square tests in SPSS version 27. **Results:** Among the 71 samples, 47.89% were from patients under 50 years old, and 52.11% were from those aged 50 and above. Grade 2 tumors were predominant (59.15%). HER2 expression was negative in 59.15% of samples, ER was positive in 83.10%, PR in 67.61%, and Ki67 expression was low in 52.11%. **Conclusion:** The majority of breast cancer cases showed negative HER2 and positive ER/PR with low Ki67, emphasizing the prognostic and therapeutic relevance of these markers.

Introduction

Under normal conditions, cells in the human body can grow and divide to form new cells as needed by the body. However, cancer grows abnormally, uncontrollably, and can spread to nearby or distant organs[1].

Invasive breast carcinoma is a malignant neoplasm originating from the breast gland epithelium[2]. The incidence of breast carcinoma rises rapidly after the age of 30, with 75% of cases found in individuals over 50 years old and 5% in those aged 40. However, breast carcinoma can develop at any age, from childhood to old age. Breast carcinoma in men accounts for only 1% of cases compared to women[3].

Breast cancer in women is the most frequently diagnosed cancer and the leading cause of cancer-related death among women. It ranks as the fifth leading cause of cancer death, following lung cancer (first), colorectal cancer (second), liver cancer (third), and abdominal cancer (fourth)[4]. In Indonesia, breast carcinoma ranks first, with an incidence of 68.8 per 100,000 population and an average mortality rate of 22.4 per 100,000 population. Meanwhile, in Makassar, the total number of invasive breast carcinoma cases in the Pathology Anatomy Laboratory of RSUP Dr. Wahidin Sudirohusodo in 2022 was 181 cases.

Invasive breast cancer subtypes are classified into molecular subtypes for treatment

purposes based on Estrogen Receptor (ER) and ERBB2 (HER2) status: ER-positive, HER2-negative; ER-positive, HER2-positive; ER-negative, HER2-positive; and ER-negative, HER2-negative. These biomarker-defined subtypes exhibit differing outcomes and responses to therapy, along with variations in their global genomic and transcriptomic profiles[5].

Currently, for breast cancer screening in Indonesia, particularly at RSUP Wahidin Sudirohusodo, every patient diagnosed with invasive breast cancer undergoes immunohistochemical testing for Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2), and Ki67. This testing is conducted to determine the molecular subtype of breast cancer and serves as a predictive factor for therapy management. Breast cancer treatment has advanced significantly, encompassing not only chemotherapy, radiotherapy, and hormonal therapy but also extending to targeted molecular therapy. Consequently, research on invasive breast cancer is also expanding.

This study provides novel insights by examining the expression profiles of key prognostic and predictive markers ER, PR, HER2, and Ki67 in invasive breast cancer cases specific to RSUP Dr. Wahidin Sudirohusodo, Indonesia. While much research has been conducted globally on breast cancer biomarkers, this study uniquely focuses on the Indonesian population, contributing critical local epidemiological data. By analyzing molecular subtypes and their association with patient demographics, histopathological grades, and marker expression, the study aims to establish a tailored predictive and prognostic model for Indonesian breast cancer patients. This localized understanding is essential for enhancing therapeutic precision, addressing regional health disparities, and advancing targeted treatment strategies in a setting where breast cancer remains a leading health concern.

The purpose of our study is to examine the expression of prognostic and predictive markers ER, PR, HER2, and Ki67 in breast cancer cases at RSUP DR. Wahidin Sudirohusodo, contributing additional epidemiological data and aiding in the assessment of risk factors and prognosis for each breast cancer patient.

Materials and Methods

Study Design

This study used a descriptive, cross-sectional design conducted at RSUP Wahidin Sudirohusodo from May 2024 to July 2024.

Samples

The study included 71 samples of invasive breast cancer from patients diagnosed at the Pathology Anatomy Laboratory of RSUP Dr. Wahidin Sudirohusodo, meeting specific inclusion and exclusion criteria. Samples were stained with routine Hematoxylin-Eosin (HE) and immunohistochemistry for ER, PR, HER2, and Ki67.

Data Collection

Data collection involved reviewing patient medical records to obtain demographic information and immunohistochemical test results. Histopathological assessment was performed using a 400x light microscope. Tumor samples were graded by two pathologists using a semiquantitative scoring system based on tubular formation, nuclear pleomorphism, and mitotic count. Tubular structures were assessed across the tumor at low magnification, counting only central lumina structures surrounded by neoplastic cells. Nuclear pleomorphism was evaluated by comparing the size and shape of tumor cells to surrounding normal epithelial cells, scoring as follows: Score 1 for minimal pleomorphism with fine chromatin and invisible nucleoli, Score 2 for moderate enlargement (1.5–2x)

with small, indistinct nucleoli, and Score 3 for significantly larger cells (>2x) with vesicular chromatin and prominent nucleoli.

Table 1. Histological grading of invasive breast cancer (Rakha, Allison, Elis, et al, 2019)

Feature	Score
Tubule and gland formation	
Majority of tumour (> 75%)	1
Moderate degree (10-75%)	2
Little or none (< 10%)	3
Nuclear pleomorphism	
Small, regular, uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic count	
Dependent on microscope field area^2	1-3
Total Score	**Final grading**
Add the scores for gland formation, nuclear polymorphism, and mitotic count:	
3-5	Grade 1
6 or 7	Grade 2
8 or 9	Grade3

Data Analysis

Data analysis was performed using the Statistical Program for Social Science (SPSS) version 27 for Windows to evaluate and interpret findings.

Ethical Considerations

This study adhered to ethical standards for clinical research. Patient confidentiality was maintained, and data use was limited to research purposes in accordance with ethical approval obtained prior to study commencement.

The histological grading of invasive breast cancer was assessed using a semiquantitative method, evaluating tubular formation, nuclear pleomorphism, and mitotic count, as shown in Table 1 (Rakha, Allison, Ellis, et al., 2019)

Results

This study utilized 71 paraffin block samples of invasive breast carcinoma cases, specifically from patients who had previously undergone chemotherapy. The sample characteristics included patient age, and assessments of HER2, ER, PR, and Ki67 markers. Results showed that 34 samples (47.89%) were from patients under 50 years of age, while 37 samples (52.11%) were from those over 50. The most common histological grade was grade 2 with 42 samples (59.15%), followed by grade 3 with 25 samples (35.21%), and grade 1 with 4 samples (5.63%). HER2 testing showed 29 positive samples (40.85%) and 42 negative samples (59.15%). ER testing resulted in 59 positive samples (83.10%) and 12 negative samples (16.90%). For PR, 48 samples (67.61%) were positive and 23 samples (32.39%) were negative. Finally, Ki67 expression was low in 37 samples (52.11%) and high in 34 samples (47.89%).

Figure 1. Representative immunohistochemical staining images demonstrate the expression profiles of ER, PR, HER2, and Ki67 in invasive breast carcinoma. Panel A shows positive nuclear staining for Estrogen Receptor (ER), indicating ER-positive tumor cells. Panel B displays positive nuclear staining for Progesterone Receptor (PR), confirming PR expression in the tumor tissue. Panel C illustrates membrane staining for Human Epidermal Growth Factor Receptor 2 (HER2), highlighting HER2 overexpression in tumor cells. Panel D presents Ki67 immunostaining, revealing the proliferation index based on the proportion of tumor cells exhibiting nuclear Ki67 positivity. These markers collectively provide critical information for the molecular classification and prognostic assessment of invasive breast cancer.

Here is the table presenting the general characteristics of the samples and the expression of ER, PR, HER2, and Ki67 in invasive breast cancer.

Table 2 summarizes the distribution of age, tumor grade, and expression levels of ER, PR,

HER2, and Ki67 in the studied cohort of patients with invasive breast cancer.

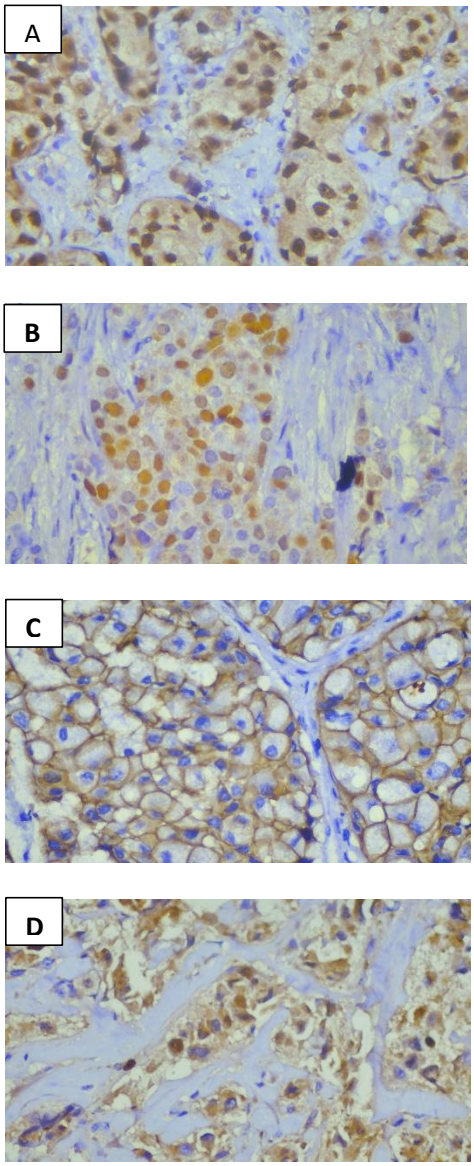

Figure 1. Expression of Immunohistochemical Markers in Invasive Breast Cancer

Discussion

Cancer arises when body cells undergo abnormal changes and multiply uncontrollably. This excessive growth allows cancer cells to invade and destroy surrounding healthy tissues. The process often begins with genetic mutations that disrupt normal cell function. Over time, these abnormal cells can form tumors and potentially spread to other parts of the body. Nearly every organ or tissue in the human body is susceptible to cancer[1,6].

Table 2. General Characteristics of Samples and Expression of ER, PR, HER2, and Ki67 in Invasive Breast Cancer

Characteristic	n	%
Age		
< 50 years	34	47.89
≥ 50 years	37	52.11
Grade		
Grade 1	4	5.63
Grade 2	42	59.15
Grade 3	25	35.21
ER		
Positive	59	83.10
Negative	12	16.90
PR		
Positive	48	67.61
Negative	23	32.39
HER2		
Positive	29	40.85
Negative	42	59.15
Ki67		
Low	37	52.11
High	34	47.89
Total	71	100.00

Breast cancer is a malignancy in breast tissue that can originate from the epithelial cells of the ducts or lobules. [7] It is the most common type of cancer among Indonesian women. This disease begins in the cells that form breast tissue and can grow rapidly. Data shows that an average of 12 out of 100,000 women in Indonesia are diagnosed with breast cancer each year, according to Pathological Based Registration. In Indonesia, breast cancer ranks first in frequency at 18.6% (Cancer Data in Indonesia Year 2010, according to histopathological data from the Indonesian Society of Pathology Specialists (IAPI) and the Indonesian Cancer Foundation (YKI)). The estimated incidence rate in Indonesia is 12 per 100,000 women[7].

In Indonesia, many breast cancer patients are diagnosed only after the disease has progressed to an advanced stage, making

treatment challenging. Therefore, it is essential to implement preventive measures, particularly for breast cancer, conduct early detection, and provide appropriate care—from treatment to recovery so that patients can receive the best management possible[7].

Several risk factors can contribute to the development of invasive breast cancer, including being female, advanced age, family history of mutations in genes such as BRCA1, BRCA2, ATM, or TP53, history of benign breast disease, irregular menstrual patterns, reproductive history, obesity, alcohol consumption, radiation exposure, and other environmental factors[7].

Women are at a higher risk of developing breast cancer, especially those over the age of 50[7]. In our study, the number of women diagnosed with invasive breast cancer was nearly equal, with 34 samples from patients under 50 years old and 37 samples from those aged 50 and above. This aligns with the research conducted by Agnes D et al., which included 80 samples and found that 37 samples (46.3%) were from women under 50 years and 43 samples (53.8%) were from women aged 50 and above. The increase in breast cancer incidence with age is closely related to the accumulation of carcinogens and cellular modifications over time[8].

Public awareness regarding self-examination when discovering a lump in the breast is still lacking, which impacts early cancer detection. According to a study by Yuni Purwati et al., 53.7% of the population had never performed a breast self-examination (SADARI), while only 46.3% had done so. Among the 53.7% who had performed SADARI, 40% were found to have breast cancer at an advanced stage, while 78.2% of those who had performed SADARI were still in the early stages. [9]

Based on histopathological grading, there were 42 samples (59.15%) with grade 2 and 25 samples (35.21%) with grade 3, and only 4 samples (5.63%) with grade 1. This is consistent with other studies (Agnes Diyah, histological grading) that show an increase in breast cancer grading when patients seek treatment. In Indonesia, many people only visit hospitals when their condition has already progressed significantly, and laboratory results often indicate a higher grading of the disease, specifically grade 2 and grade 3. This delay in seeking medical treatment is due to a tendency among the population to pursue alternative treatments before seeking conventional medical care[7,10].

For the treatment of invasive breast cancer, particularly for hormonal therapy, examinations of Estrogen Receptor (ER) and Progesterone Receptor (PR) are routinely conducted. These tests, along with HER2 and Ki67 assessments, are essential for evaluating the aggressiveness of the cancer[11,12].

HER2 is a transmembrane protein that plays a crucial role in cell growth regulation. Dysregulation of HER2 signaling is associated with various types of cancer, including breast cancer. Amplification of the HER2 gene promotes aggressive tumor growth and metastasis[13].

The expression of estrogen receptors (ER) and progesterone receptors (PR) in breast tumors has long been used as biomarkers to predict response to endocrine therapy and to classify tumor subtypes. The classifications of luminal A, luminal B, and other subtypes are based on the status of ER and PR. However, the clinical significance of differences in ER and PR expression among early-stage breast cancer patients with ER-positive and HER2-negative status is still not fully understood[12,14].

The expression of ER and PR influences the growth and development of breast cancer cells. Variations in the levels of ER and PR expression can indicate disruptions in the estrogen hormone signaling pathway. Differences between the levels of estrogen and progesterone in breast cancer cells have

significant clinical implications. Patients with substantial discrepancies in hormone levels tend to have more aggressive cancers and are less responsive to hormonal treatments. This information can be utilized to identify patients who may require additional therapy or who might be better suited for alternative treatment options[12,14].

This study shows that breast cancer patients with positive ER levels are more prevalent than those with negative levels, which tends to lead to delayed recurrence. This finding is consistent with previous research. Additionally, estrogen hormone levels in cancer cells can vary, even within a single patient or between primary tumors and metastatic cancer cells[12].

Positive ER status in breast cancer is associated with a good prognosis and a favorable response to hormonal therapy. However, the prognostic role of PR remains controversial. Some studies indicate that patients with PR-positive tumors have better survival rates. In contrast, low PR expression may indicate the activation of abnormal cell growth pathways, which is linked to resistance to hormonal therapy[12,15].

In our study, we found that the number of HER2-negative cases was greater than HER2-positive cases. HER2, as a member of the Erb receptor family, is a key factor in the transformation of normal cells into cancer cells. Overexpression of HER2 in approximately 25-30% of breast cancer cases correlates with poor prognosis. Trastuzumab, a monoclonal antibody targeting HER2, has become the first-line therapy for HER2-positive breast cancer, both in early and advanced stages. Adjuvant treatment with trastuzumab has been shown to significantly improve patient survival[12,16].

Ki-67 is a protein that marks cells that are actively dividing and is present in all active phases of the cell cycle. The greater the number of cancer cells that express the Ki-67 protein, the faster the growth of the cancer. In breast cancer, high Ki-67 levels are often associated with more aggressive cancer and a higher likelihood of recurrence[12,15].

Conclusion

The expression levels of ER, PR, HER2, and Ki67 in breast cancer can serve as significant prognostic factors for patients with invasive breast cancer at RSUP DR. Wahidin Sudirohusodo. To enhance the accuracy and reliability of the findings, it is recommended that this study be expanded to include a larger cohort of patients. This would provide a more comprehensive understanding of the relationships between these biomarkers and clinical outcomes, ultimately improving the prognostic assessment and management strategies for breast cancer patients.

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