Immunohistochemical Profile of Er, Pr, Her2, and Ki-67 In Breast Cancer Patients

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Abstract

Breast cancer remains one of the leading causes of cancer-related mortality among women worldwide, with hormonal factors playing a critical role in tumor development and progression. This study aims to describe the immunohistochemical profile of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 in breast cancer patients at MRCCC Siloam Semanggi Hospital in 2022. A retrospective descriptive study was conducted using a total sampling of anatomical pathology archives, comprising 316 breast cancer cases. The most common age group was 40–49 years. ER positivity was observed in 229 patients (72.5%), while PR positivity was found in 183 patients (57.9%). HER2 overexpression (3+) was identified in 75 patients (23.7%); cases with equivocal HER2 (2+) required confirmation by in situ hybridization. High proliferative activity, indicated by Ki-67 ≥20%, was present in 262 patients (82.9%). These findings indicate a predominance of hormone receptor–positive tumors with high proliferative indices, highlighting the importance of immunohistochemical profiling in guiding prognosis assessment, therapeutic decision-making, and selection of targeted and systemic treatments in breast cancer management.

Keywords: Breast Cancer, Immunohistochemistry, Estrogen Receptor (ER), HER2, Ki-67

INTRODUCTION

Breast cancer is commonly found among women worldwide, and it is one of the biggest causes of death despite the advanced technology that has allowed us to detect and treat it. Every year, there are 2.3 million new cases, and 685,000 people die because of breast cancer (Sung et al. 2021). This number includes Indonesian citizens too, in that breast cancer is found to be the most common type of cancer in women. The increased number of people with breast cancer every year is caused by unhealthy lifestyles and reproductive patterns (Osborne, Adnani, and Ahinkorah 2025). How does breast cancer attack one's body? It is because of abnormal cells developing in the breasts, turning into tumors, leading to breast cancer. Breast cancer is commonly seen in women, but it does not mean that men cannot have it. Studies found that breast cancers mostly occurs in women, but is rare in men (Ferlay et al. 2021; Loganathan and Doss 2025).

Actually, the exact cause of breast cancer is still unknown; however, some studies explain that the risk of having breast cancer can be increased by bad lifestyle habits, excessive stress,

and lack of physical activity (Bellanger et al. 2018; Smolarz, Nowak, and Romanowicz 2022). Besides those factors, hormonal differences can also influence the development of breast cancer. For example, it can be affected by the presence of estrogen and progesterone hormones, which play a role in breast development. Surprisingly, when women experience menstrual cycles, pregnancy, or menopause, hormonal fluctuations can play a significant role in the development of breast cancer (Fujiki et al. 2024).

Breasts are glandular organs in the chest, found in both men and women witht different functions. Breasts in women can produce milk that is very good at supporting the baby's growth. Changes in breast size and shape are mediated by major changes in gene expression, so drastic modifications in the composition, structure, and life cycle pathways of the human gland significantly influence the development of breast tissue (Schusterman II and Rehnke 2023).

During puberty, female breasts elongate to varying sizes, depending on genetic makeup, race, and diet. The nipple typically contains 23 to 27 milk ducts, with a range of 11 to 48 per duct. The tubuloalveolar glands that make up the breast open into the nipple through narrow, narrowing openings. This is how a mother can produce milk to breastfeed her baby. Many cancer scientists are exploring breast anatomy to determine how cancer develops and spreads. The nipple is composed of easily movable muscle fibers and is richly innervated by sensory nerve endings and Meissner's corpuscles in the dermal papilla (Schusterman II and Rehnke 2023).

The breast receives blood from branches of the intercostal arteries and branches of the internal thoracic artery. The mammary artery, a branch of the lateral thoracic artery, is a crucial blood vessel that supplies the breast. All of these branches extend transversely to the nipple area and merge or anastomose with branches originating from the lateral thoracic artery (Schusterman II and Rehnke 2023).

Next, what we are discussing in this study is called immunohistochemistry which is a field of study that investigates the interactions between the immune system and various molecules to achieve specific goals. Focusing on antibodies and antigens, it is about understanding the basic principles of immunity and developing diagnostics, therapeutics, and biomedical research. Immunohistochemistry investigates the interactions between antibodies, antigens, and other immune molecules. It aims to decipher the language of the immune system and uncover the mechanisms of its interactions (Magaki et al. 2019).

Immunoglobulins, also known as antibodies, consist of four protein chains: two heavy chains and two light chains. A Y-shaped structure with varying regions represents a collection

of light and heavy chains. This Y structure binds explicitly to antigens. Several immune responses are initiated when an antigen binds to an antibody. This binding can activate the complement system, recruit immune cells, neutralize toxins or viruses, or facilitate phagocytosis (Ahmed 2024)

Immunohistochemistry in breast cancer characterizes proteins or cell surfaces in all tissues. Proteins in breast cancer help classify tumor subtypes, distinguish metastases from primary tumors, and predict response to therapy or evaluate residual tumor after treatment. Immunohistochemistry plays a crucial role in breast cancer by enabling the identification of histological subtypes and molecular phenotypes. Normal breast tissue consists of three cell types: luminal, basal, and myoepithelial, each expressing a distinct subset of proteins. Luminal cells express cytokeratins (CK 7, 8, 18, 19), estrogen receptors (ER), and progesterone receptors (PR). Myoepithelial cells express basal cell type CK and specific markers such as smooth muscle actin, calponin, S100, and p63. Immunohistochemical examination, in addition to determining the presence of estrogen receptors, progesterone receptors, and Ki-67, also plays a crucial role in determining the status of Human epidermal growth factor receptor two or HER2 because until now, there are only two examinations that can determine its status, namely immunohistochemistry and fluorescence in situ hybridization (FISH) (Van Asten et al. 2019; Zaha 2014). With the highest number of people affected by breast cancer in Indonesia and other countries motivates the researchers to explore this topic further to investigate immunohistochemical features of breast cancer in patients at the MRCCC Siloam Semanggi Hospital in 2022.

METHODS

This study employed a retrospective descriptive study design, aiming to describe the distribution of immunohistochemical markers without assessing causal relationships or treatment outcomes. This approach was used because the study relied on existing patient data recorded before the initiation of the research, while the descriptive nature focused on summarizing clinicopathological and immunohistochemical characteristics of breast cancer cases. Secondary data were obtained from medical records archived at the Anatomical Pathology Laboratory of MRCCC Siloam Semanggi Hospital, Jakarta. Data collection was conducted from December 2023 to July 2024, utilizing medical records from patients diagnosed with breast cancer between January and December 2022. The study population comprised all patients with a histopathological diagnosis of breast cancer at MRCCC Siloam Semanggi Hospital during the study period. Total sampling was applied, whereby all eligible

cases meeting the predefined inclusion and exclusion criteria were included, resulting in a total of 316 patient records. The research instrument consisted of secondary data extracted from archived Anatomical Pathology reports, including patient age and immunohistochemical results for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67. Data were collected using a standardized data extraction form to ensure consistency and completeness. Data processing involved data entry, coding, and verification to minimize errors. All collected data were edited and analyzed using the Statistical Package for the Social Sciences (SPSS) software. The analysis was limited to descriptive statistics, with results presented as frequencies and percentages to characterize the immunohistochemical profile of breast cancer patients.

RESULT

Table 1 presents participant characteristics based on age, obtained from data from patients with breast cancer in 2022. Data were recorded in the Anatomical Pathology Laboratory at Siloam Hospital MRCCC Semanggi, with 316 patients selected according to the inclusion criteria. The variables used in this study were age, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and Ki-67.

Table 1. Frequency Distribution of Age Groups in Patients with Breast Cancer in 2022

Age	Frequency	Percentage
20 – 29 years	3	0.9
30 – 39 years	32	10.1
40 – 49 years	110	34.8
50 – 59 years	90	28.5
60 – 69 years	48	15.2
70 – 74 years	24	7.6
≥ 75	9	2.8

Based on the table, the age groups diagnosed with breast cancer in 2022 at Siloam MRCCC Semanggi Cancer Specialist Hospital were 110 patients (34.8%) aged 40–49, followed by 90 patients (28.5%) aged 50–59. The 60–69 age group comprised 48 patients (15.2%), and the 30–39 age group consisted of 32 patients (10.1%). The next age group consisted of 24 patients (7.6%) aged 70–74, followed by nine patients (2.8%) aged 75 or older, and three patients (0.9%) aged 20–29.

Table 2 shows the distribution data for Estrogen Receptor frequency, Progesterone frequency, Human Epidermal Growth Factor Receptor 2 (HER2) frequency, and Ki-67 frequency in patients with breast cancer in 2022.

Table 2. Frequency Distribution of Estrogen Receptors, Progesterone, Human Epidermal Growth Factor Receptor 2 (HER2), and Ki-67 In Patients with Breast Cancer In 2022

Characteristics	Frequency	Percentage
Estrogen Receptors		
Positive	229	72.5
Negative	87	27.5
Progesterone		
Positive	183	57.9
Negative	113	42.1
Human Epidermal Growth Factor Receptor 2 (HER2)		
Negative	61	19.3
Positive (+1)	73	23.1
Positive (+2)	107	33.9
Positive (+3)	75	23.7
Ki-67		
< 20 %	54	17.1
≥ 20 %	262	82.9

Table 3. Breast Cancer Subtypes after In Situ Hybridization Examination in 2022

Subtypes	Frequency	Percentage
Luminal A	33	10.4
Luminal B		
with HER2 (+)	52	16.5
with HER2 (-)	138	43.7
HER2-enriched	36	11.4
Triple Negative	43	13.6
Not carrying out ISH (in situ hybridization) examination	14	4.4

DISCUSSION

Based on the findings, breast cancer cases are dominantly found in women aged 40 – 49 years old. This finding is different from what was reported by the American Cancer Society, where incidence peaks in older age groups. This discrepancy may reflect regional and ethnic differences, earlier exposure to hormonal risk factors, differences in reproductive patterns (such as younger age at menarche, delayed childbirth, or reduced parity), and varying screening practices. In many Asian countries, including Indonesia, breast cancer is often diagnosed at a younger age compared to Western populations, possibly due to genetic susceptibility, lifestyle transitions, and limited access to routine mammographic screening in older age groups. From this finding, it is crucial to increase young people's awareness of breast cancer, including the preventive strategies to avoid it.

According to the results of the study for ages 40-49 years obtained 34.8%, and 50-59 years was 28.5%. According to the American Cancer Society the age group 40-49 years is 16% and for ages 50-59 years is 26% (Islami et al. 2024). There is a slight difference in that the age range of 40-49 years and 50-59 years is the most common age for breast cancer diagnosis. According to the Global Burden of Cancer (GLOBOCAN) data on breast cancer in Asia, it was found that Asia has a higher risk of breast cancer incidence than Western countries. Globally, the 40-49 age group has the highest incidence of breast cancer, compared with Asian data. The 50-69 age group is considered to have a significant increase in breast cancer incidence, necessitating further public health interventions and research (DeSantis et al. 2015; Fu et al. 2025).

The high proportion of estrogen receptor (ER)–positive and progesterone receptor (PR)–positive tumors observed in this study aligns with previous reports from diverse populations. Rather than merely confirming existing data, this finding underscores the hormone-dependent nature of the majority of breast cancers in this cohort. The dominance of ER-positive tumors suggests that endocrine signaling plays a central role in tumorigenesis, supporting the continued prioritization of hormonal therapy as a cornerstone of treatment. Variations in ER and PR positivity rates across studies may be influenced by differences in laboratory techniques, antibody clones, interpretation thresholds, and population-specific tumor biology.

PR expression provides additional prognostic value, as loss of PR in ER-positive tumors may indicate endocrine resistance and more aggressive tumor behavior. Yaneva, et al reported that the distribution for positive estrogen receptors in breast cancer cases is the highest and is far higher compared to negative results. Table 2 also describes positive estrogen receptors with negative results are far compared (Yaneva et al. 2022). This data also agrees with research conducted by Rodrigues, who obtained 2223 breast cancer patients with positive estrogen receptors 1851 (83.3%) and for negative results 372 (16.7%) (Rodrigues et al. 2024). Research conducted by Kamranzadeh, et al there were 165 breast cancer patients with positive estrogen receptor results, 107 patients (64.85%), and for negative were 58 patients (35.15%), this shows also in accordance with the data in Table 2, which shows that positive results have a fairly far comparison (Kamranzadeh et al. 2019).

The predominance of HER2 equivocal (2+) results emphasizes a critical diagnostic challenge in routine practice. HER2 status is not only prognostic but also predictive of response to targeted therapy. The ASCO/CAP guideline–mandated use of in situ hybridization (ISH) for HER2 2+ cases is essential to avoid misclassification and inappropriate treatment decisions.

The need for ISH confirmation has significant clinical implications, as patients with confirmed HER2 amplification benefit substantially from anti-HER2 targeted therapies. Variability in HER2 positivity rates across studies may reflect differences in testing algorithms, access to ISH, and interobserver variability, particularly in resource-limited settings. For HER2 (2+) is the highest.

According to the American Society of Clinical Oncology and the College of American Pathologists, established guidelines that have been implemented in 2007, 2013, 2018, and most recently in 2023, for HER2 with (2+) is a questionable result, so to confirm it, a test is needed, namely ISH (in situ hybridization). HER2-negative and positive (1+) are categorized as negative, but must be accompanied by an explanation. Meanwhile, for HER2 positive (3+) is confirmed positive and no further test is needed, namely ISH (Honma et al. 2024; Wolff et al. 2023). The importance of hybridization examination in patients with HER2 positive (2+) is to determine the therapy or treatment. Patients with HER2 positive (2+) with positive ISH and HER2 positive (+3) are already eligible to receive anti-HER2 targeted therapy (Sajjadi et al. 2022).

The proliferation rate of Ki-67 is a key parameter for distinguishing between luminal A and luminal B, which are types of breast cancer. Several journals state different ranges of values for Ki-67, so researchers determined the range of values in this study to be <20% and ≥20% (Maranta et al. 2020). For example, in 2011 the St. Gallen Expert Consensus set the range of values at 14%, and in 2013 the range was 20%. Then Davey, et al., conveyed in their research that the range of values was also set at 20% (Davey et al. 2021). According to research conducted by Ma, et al., the range of Ki-67 values was 22.5% (Ma et al. 2024). Examination to assess Ki-67 is also useful for determining the therapeutic dose used for patients (Zaha 2014). The main determinant of prognosis and response to chemotherapy in breast cancer is the proliferation rate (Penault-Llorca and Radosevic-Robin 2017). A high proliferation rate indicates a better response to adjuvant or neoadjuvant chemotherapy (Finkelman et al. 2023).
Of the total 316 patients, 14 did not undergo ISH (in situ hybridization) examination, resulting in a total of 302 patients who underwent the examination. According to the American Cancer Society, most breast cancer subtypes are associated with positive hormone receptor status, namely positive estrogen receptor and/or positive progesterone receptor, and negative human epidermal growth factor receptor 2 (HER2).

In Table 2, the most common results seen are luminal B with negative HER2 status, and luminal A can also meet the criteria with positive hormone receptor status and negative human epidermal growth factor receptor 2 (HER2) (Islami et al. 2024). Luminal A is confirmed

by positive estrogen receptor and progesterone receptor status, negative human epidermal growth factor receptor 2 (HER2), and the proliferation rate of Ki-67 is <20%. Patients with estrogen receptor positivity, progesterone receptor negativity, human epidermal growth factor receptor two negativity, and varying Ki-67 proliferation rates can be classified as luminal B with HER2 negativity. Luminal B with HER2 positivity must have estrogen receptor positivity, progesterone receptor positivity or negativity, human epidermal growth factor receptor two positivity, and varying Ki-67 proliferation rates. HER2-enriched is defined as estrogen receptor and progesterone receptor negativity, but HER2 is positive.

If estrogen receptor, progesterone receptor, and HER2 are negative, it can be categorized as triple-negative breast cancer (Luengo et al. 2019). The importance of immunohistochemical examination and further examination, namely in situ hybridization, is to include the category of breast cancer in patients. One of the differences that can be assessed is that luminal A has a better prognosis and has a good response to hormonal therapy compared to luminal B (Rajc et al. 2018). Subtypes other than luminal A and B are human epidermal growth factor receptor 2 (HER2)-enriched and triple-negative breast cancer. HER2-enriched and triple-negative breast cancer subtypes have a worse prognosis compared to luminal A and luminal B subtypes.

Although luminal B subtypes with negative estrogen receptors or progesterone receptors also have a poor prognosis (Ahn et al. 2020). In situ hybridization examination is needed as a follow-up examination for patients with HER2 positive 2+ status, so that patients receive appropriate therapy. (Ferrando-Díez et al. 2022). Anti-HER2 targeted therapy can be given to patients with HER2 positive 3+ and positive 2+ status who undergo ISH examination and get positive results. The breast cancer subtype with the worst prognosis is triple-negative breast cancer. In a study conducted by Zagami and Carey, triple-negative breast cancer accounts for 15-20% of all breast cancer subtypes and is one of the breast cancer subtypes that does not have targeted therapy. This subtype is considered the worst because of its aggressive tumors, high proliferation rate, and minimal treatment options. Early outcomes for the triple-negative breast cancer subtype have improved due to improvements in polychemotherapy and the addition of immunotherapy. (Zagami and Carey 2022).

The findings of this study highlight the central role of comprehensive immunohistochemical evaluation in breast cancer classification, prognostication, and treatment selection. Accurate assessment of ER, PR, HER2, and Ki-67, supported by confirmatory ISH when indicated ensures appropriate subtype classification and optimizes therapeutic strategies. In settings with diverse patient populations and variable access to advanced diagnostics,

standardized testing, and adherence to international guidelines are essential to improving breast cancer outcomes.

CONCLUSION

This study demonstrates that breast cancer cases at MRCCC Siloam Semanggi Hospital in 2022 were predominantly hormone receptor–positive with a high proliferative index, reflecting a tumor biology that has important implications for patient management. The high prevalence of ER and PR positivity supports the central role of endocrine pathways in breast cancer pathogenesis in this population and reinforces the clinical value of hormonal therapy as a primary treatment modality. Meanwhile, the presence of HER2 overexpression in a substantial proportion of cases highlights the necessity of accurate HER2 assessment, including confirmatory in situ hybridization for equivocal results, to ensure appropriate selection of targeted therapy. The predominance of elevated Ki-67 further underscores the need for careful risk stratification, as tumor proliferation significantly influences prognosis and chemotherapy responsiveness. These findings contribute local epidemiological and biological evidence that supports standardized immunohistochemical evaluation as an essential component of breast cancer diagnosis and personalized treatment planning, particularly in referral hospital settings in Indonesia.

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