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TITLE AND ABSTRACT

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

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

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#25681 REVIEW

SUMMARY REVIEW EDITING

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PEER REVIEW

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Reviewer A

IMMUNOHISTOCHEMICAL PROFILE OF ER, PR, HER2, AND KI-67 IN BREAST CANCER PATIENTS

1. The introduction is unfocused and contains irrelevant information (e.g., detailed anatomy of the breast, nerve function, blood supply, and a lengthy, basic definition of immunology and immunohistochemistry that is not specific to breast cancer). This section must be drastically condensed.
2. The research problem is not clearly defined. It states the high incidence of breast cancer but does not establish *why* profiling IHC in *this specific cohort* is a necessary or valuable contribution to the literature.
3. Sharply focus the introduction on the clinical importance of the four biomarkers (ER, PR, HER2, Ki-67) in breast cancer classification, prognosis, and treatment selection. Clearly state the knowledge gap this study aims to fill (e.g., "While well-established, the distribution of these subtypes in the Indonesian population, particularly at a tertiary care center like ours, is not extensively documented.").
4. Critical Flaw: The methodology is severely under-described.
    a. Inclusion/Exclusion Criteria: Not mentioned. Were all breast cancer cases included? Did this include metastatic cases, recurrences, or only primary tumors? This must be specified.
    b. IHC Protocol: The antibodies (clones), dilution, and staining platform used for ER, PR, HER2, and Ki-67
    are mandatory information and are completely absent. The scoring criteria (e.g., Allred score for ER/PR, ASCO/CAP guidelines for HER2 and Ki-67) must be explicitly stated.
    c. ISH Testing: The method for resolving HER2 2+ cases (e.g., FISH, CISH, SISH) is not described.
5. Data Analysis: The analysis is purely descriptive (frequencies and percentages). For a cohort of this size, comparative statistics (e.g., Chi-square to test associations between age groups and molecular subtypes) are expected to add value.
6. Ethical Considerations: There is no mention of IRB/ethical committee approval for the use of patient data and archives. This is a mandatory requirement and must be obtained and stated.
7. Major Inconsistency: Table 2 reports HER2 results as Negative, 1+, 2+, 3+. However, the text and Table 3 subsequently categorize patients into molecular subtypes. The process for this categorization is not explained in the methods. How were HER2 2+ cases treated before ISH results were available? How was Ki-67 used to differentiate Luminal A from Luminal B? The criteria for subtype classification must be defined in the methods section.

8. Table 3 (Subtypes) has a confusing structure. The "Luminal B with HER2 (+)" and "with HER2 (-)" are listed awkwardly. "Not Available" should be clarified (e.g., "Cases with missing data for subtyping").
9. The discussion is largely a repetition of the results and contains general textbook knowledge about breast cancer subtypes.
10. It fails to interpret the specific findings in the context of existing literature. For example: How do the rates of ER+ (72.5%), HER2+ (23.7%), and high Ki-67 (82.9%) compare to other similar cohorts in the region or globally? Are the findings expected or unusual?
11. The discussion of the HER2 2+ group and the need for ISH is good but should be more critical (e.g., what percentage of 2+ cases were ISH-positive? This data is collected but not shown).
12. The statement that Luminal B HER2- is the most common subtype (43.7%) is a key finding that should be highlighted and discussed in depth.
13. Limitations: The retrospective design and lack of associated clinical data (tumor stage, grade, treatment, outcome) are major limitations that must be acknowledged and discussed transparently.
14. The conclusion is too generic. It should be specific to the study's findings (e.g., "In our cohort, we found a high prevalence of high-proliferation tumors and a Luminal B HER2- subtype. This reinforces the need for..."). Implications for local practice or policy should be suggested.
15. The writing requires significant editing for grammar, clarity, and academic tone. The flow is often disrupted by unnecessary information (e.g., the entire second paragraph of the introduction).
16. The structure is logical but sections need to be more concise and focused.
17. The references are a mix of relevant, up-to-date sources and some that are less directly relevant or outdated.
18. Formatting: Inconsistent. Authors must strictly adhere to the target journal's reference style guide (e.g., journal abbreviations, use of "et al.", punctuation). Examples: "Loganathan and Doss 2025" appears to be an in-press article; "Fu et al. 2025" is a future publication. Ensure all are correctly cited.
19. Reference more than 32 .

Reviewer B

IMMUNOHISTOCHEMICAL PROFILE OF ER, PR, HER2, AND KI-67 IN BREAST CANCER PATIENTS

Track Record Article Accepted: Published:	***Abstract*** *Breast cancer is a prevalent type of cancer in women and contributes to high cancer mortality worldwide. One of the strongest factors in the development of breast cancer is hormonal factors. The purpose of this study was to analyze the immunohistochemical profile of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 in patients with breast cancer at MRCCC Siloam Semanggi Hospital in 2022. This study was conducted with total sampling using anatomical pathology archives. There were 316 patient archives, and the largest age group was 40-49 years old. There were 229 patients (72.5%) who received positive estrogen receptor results. Based on progesterone receptor, 183 patients (57.9%) received positive results, and for human epidermal growth factor receptor 2 (HER2), 75 patients (23.7%) received positive results (3+). Additional testing, such as in situ hybridization (ISH), is required to confirm HER2 status if a positive result (2+) is obtained. The final result, Ki-67, was ≥ 20% in 262 patients (82.9%). Immunohistochemistry results can provide important insights into prognosis, diagnosis, targeted therapy, and response to chemotherapy.* ***Keyword: Breast Cancer, Immunohistochemistry, Estrogen Receptor (ER), HER2, Ki-67***

Recomendation:

a. Title: The title is concise, specific, and informative. No changes are required.
b. The abstract accurately summarizes the study's objectives, methods, and key findings.
c. Recommend adding a mention of the statistical methods used (e.g., Chi-square or t-tests) for clarity.
d. The introduction clearly defines the research problem and presents relevant background information.
e. Recommend identifying the gaps in current literature regarding the specific biomarkers studied and their clinical significance.
f. The literature review is comprehensive but could benefit from additional studies on the clinical implications of HER2 and Ki-67 in breast cancer treatment.

g. The study design is appropriate, and the sampling method is well-described.
h. Recommend expanding on how missing or incomplete data were handled in the analysis.
i. Clarify which statistical tests were performed to assess differences between groups.
j. The results are clearly presented, and the tables are informative.
k. Recommend providing more statistical analysis to assess relationships between biomarkers and clinical outcomes (e.g., treatment response).
l. The discussion meaningfully interprets the findings, but additional focus on the clinical implications for treatment decisions (e.g., targeted therapy) would be beneficial.
m. Recommend addressing limitations such as potential bias in using archived data and the inability to assess clinical outcomes.
n. The conclusions are well-supported by the results.
o. Recommend further elaborating on the clinical applications of these findings, particularly in low-resource settings.
p. The manuscript is well-organized and coherent.
q. Recommend a final review for grammatical clarity, particularly in the introduction and discussion sections.
r. Ethical considerations are mentioned, but more detail on how patient confidentiality was maintained would enhance transparency.
s. Citations are current and relevant, but adding recent studies on immunohistochemistry in breast cancer treatment would strengthen the manuscript.

Reviewer C

IMMUNOHISTOCHEMICAL PROFILE OF ER, PR, HER2, AND KI-67 IN BREAST CANCER PATIENTS

Track Record Article

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Abstract

Breast cancer is a prevalent type of cancer in women and contributes to high cancer mortality worldwide. One of the strongest factors in the development of breast cancer is hormonal factors. The purpose of this study was to analyze the immunohistochemical profile of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 in patients with breast cancer at MRCCC Siloam Semanggi Hospital in 2022. This study was conducted with total sampling using anatomical pathology archives. There were 316 patient archives, and the largest age group was 40-49 years old. There were 229 patients (72.5%) who received positive estrogen receptor results. Based on progesterone receptor, 183 patients (57.9%) received positive results, and for human epidermal growth factor receptor 2 (HER2), 75 patients (23.7%) received positive results (3+). Additional testing, such as in situ hybridization (ISH), is required to confirm HER2 status if a positive result (2+) is obtained. The final result, Ki-67, was ≥ 20% in 262 patients (82.9%). Immunohistochemistry results can provide important insights into prognosis, diagnosis, targeted therapy, and response to chemotherapy.

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

Commented [A1]: Abstracts should be concise, focusing on the main results and clinical implications.

INTRODUCTION

Commented [A2]: It's too long and covers a lot of breast anatomy and immunological fundamentals that aren't relevant to the research objectives. This makes the focus of the study unclear.

The development of abnormal cells in the breast can cause malignant tumors, which can lead to breast cancer. Most breast cancers occur in women and are rare in men (Ferlay et al. 2021; Loganathan and Doss 2025). The exact cause of breast cancer is unknown, but certain lifestyle factors, excessive stress, and lack of physical activity can increase the risk of breast cancer (Bellanger et al. 2018; Smolarz, Nowak, and Romanowicz 2022). Hormonal differences between men and women also significantly influence the development of breast cancer. The presence of estrogen and progesterone hormones, which play a role in breast development, makes hormonal factors the strongest factor in the development of breast cancer. 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).

One of the leading causes of death from cancer worldwide is breast cancer.4 GLOBOCAN (Global Burden of Cancer) data explains that breast cancer has topped the list as the most frequently diagnosed cancer, with an estimated 2.3 million new cases or around 11.7% (Sung et al. 2021). The Ministry of Health explains that around 70% of breast cancers will be detected in old age. In 2020, the World Health Organization (WHO) revealed that around 2.3 million women were diagnosed with breast cancer and 685,000 died globally.

Breasts are glandular organs located in the chest, found in both men and women, with different functions. The similarity in breast function in men and women is that they are both part of the sexual anatomy. They are considered part of the sexual anatomy because the nipples in both men and women contain nerves that can increase sexual arousal. 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, areola, and areola are part of the breast skin. 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. 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).

Immunohistochemistry 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 encompasses understanding the basic principles of immunity and developing diagnostics, therapeutics, and biomedical research. Immunohistochemistry is a scientific discipline that 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. 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.

Immunohistochemistry in breast cancer aims to characterize proteins or cell surfaces in all tissues. Proteins that can be examined 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)

The high incidence of breast cancer globally and nationally, coupled with the hormonal role, has led researchers to explore breast cancer as an interesting topic for further investigation into the immunohistochemical features of breast cancer in patients at the MRCCC Siloam Semanggi Hospital in 2022.

METHODS

Commented [A3]: The research design is called “descriptive retrospective”, but the explanation is still unclear.

This study used a retrospective descriptive method. Data collection consisted of secondary data, specifically medical records from the Anatomical Pathology Laboratory of Siloam MRCCC Semanggi Hospital, collected in 2022. The study was conducted at MRCCC Siloam Semanggi Hospital. The study period was from December 2023 to July 2024, with existing medical records collected from January to December 2022. The population of this study was all patients diagnosed with breast cancer at MRCCC Siloam Semanggi Hospital in 2022. Sampling was conducted using a total sampling technique, involving a sample of 316 participants who met the specified inclusion and exclusion criteria. The research instrument is secondary data in the form of archived Anatomical Pathology reports from patients with breast cancer in 2022 at MRCCC Siloam Semanggi Hospital. Data processing was carried out by entering complete data based on the collected Anatomical Pathology archives, and all data was edited using the SPSS (Statistical Package for the Social Sciences) computer application program. The completeness of all data entered is the result of editing.

Page PAGE * MERGEFORMAT 95

RESULTS

Commented [A4]: Tables 1–3 are fairly clear, but there is some inconsistency in the format.

Commented [A5R4]: Table 3 is less clear: there is a “Not Available” subtype but it doesn’t explain why.

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 Available	*14*	*4.4*

DISCUSSION

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Some comparisons with other studies are still descriptive, without explaining the differences or similarities in depth.

From the results of the study with a total of 316 patients who experienced breast cancer, the age category of 40-49 years was the highest, followed by the age of 50-59 years. The results for ages 40-49 and 50-59 are inversely proportional when adjusted to data according to the American Cancer Society. According to the results of the study for ages 40-49 years obtained 34.8% and 50-59 years was 28.5%. And according to the American Cancer Society for ages 40-49 years is 16% and for ages 50-59 years is 26% (Islami et al. 2024). There is a slight difference 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, comparing global data 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)

According to research conducted by Yaneva, et al that the distribution for positive estrogen receptors in breast cancer cases is the highest and is far compared to negative results. According to table 2 it is also shown that positive estrogen receptors with negative results are far compared (Yaneva et al. 2022). This data also agrees with research conducted by Rodrigues, et al 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 were 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 with negative have a fairly far comparison (Kamranzadeh et al. 2019).

According to the data in Table 2, the results are consistent with the study conducted by Yaneva et al., that positive progesterone receptor distribution has a higher result than negative results. The results of their study also indicate a small difference between positive and negative results. 20 In the study of Rodrigues et al., it was explained that positive progesterone receptor results are higher than negative results. Although the study was grouped into age groups of <45 years, 40-55 years, and >55 years, the positive results of these three age groups were the highest (Rodrigues et al. 2024). In the study conducted by Kamranzadeh et al., also conveyed a similar finding, namely that positive progesterone receptor characteristics have a higher value than negative ones. The difference between positive and negative results was also not too large (Kamranzadeh et al. 2019)

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). In 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 the in situ 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). According to Table 2, the most common results 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).

CONCLUSIONS

This study reveals that the majority of breast cancer patients at MRCCC Siloam Semanggi Hospital in 2022 exhibited positive expression of estrogen receptor (ER) and progesterone receptor (PR), at rates of 72.5% and 57.9%, respectively. Positive HER2 expression (3+) was found in 23.7% of patients, which emphasizes the importance of further examinations, such as in situ hybridization (ISH), for ambiguous HER2 results (2+). Additionally, 82.9% of patients exhibited Ki-67 values of≥20%, indicating high tumor cell proliferation. These findings emphasize that immunohistochemical examination of ER, PR, HER2, and Ki-67 is critical in determining the diagnosis, prognosis, and planning targeted therapy and chemotherapy in breast cancer patients.

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REFERENCE

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Ensure that only relevant references are used.

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Author Version

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 aimed 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 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.

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

INTRODUCTION

Breast cancer is one of the most prevalent malignancies among women worldwide and remains a major cause of cancer-related mortality despite advances in early detection and treatment. According to GLOBOCAN 2022, breast cancer accounts for approximately 2.3 million new cases and 685,000 deaths annually, representing a substantial global health burden (Sung et al., 2023). In Indonesia, breast cancer ranks as the most common type of cancer in women, with increasing incidence rates each year due to changes in lifestyle, hormonal factors, reproductive patterns, and improved screening programs (Kemenkes RI, 2022).

The development of abnormal cells in the breast can cause malignant tumors, which can lead to breast cancer. Most breast cancers occur in women and are rare in men (Ferlay et al. 2021;

Loganathan and Doss 2025). The exact cause of breast cancer is unknown, but certain lifestyle factors, excessive stress, and lack of physical activity can increase the risk of breast cancer (Bellanger et al. 2018; Smolarz, Nowak, and Romanowicz 2022). Hormonal differences between men and women also significantly influence the development of breast cancer. The presence of estrogen and progesterone hormones, which play a role in breast development, makes hormonal factors the strongest factor in the development of breast cancer. 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 located in the chest, found in both men and women, with different functions. The similarity in breast function in men and women is that they are both part of the sexual anatomy. They are considered part of the sexual anatomy because the nipples in both men and women contain nerves that can increase sexual arousal. 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, areola, and areola are part of the breast skin. 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. 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).

Immunohistochemistry 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 encompasses understanding the basic principles of immunity and developing diagnostics, therapeutics, and biomedical research. Immunohistochemistry is a scientific discipline that 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.

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.

Immunohistochemistry in breast cancer aims to characterize proteins or cell surfaces in all tissues. Proteins that can be examined 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)

The high incidence of breast cancer globally and nationally, coupled with the hormonal role, has led researchers to explore breast cancer as an interesting topic for further investigation into the 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. A retrospective approach was used because the study relied on existing patient data recorded prior to 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.

RESULTS

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*
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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

The predominance of breast cancer cases in the 40–49-year age group, followed by 50–59 years, differs from data 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. These findings highlight the need for earlier breast cancer awareness and screening strategies tailored to the Asian population, particularly targeting women below 50 years of age. According to the results of the study for ages 40-49 years obtained 34.8% and 50-59 years was 28.5%. And according to the American Cancer Society for ages 40-49 years is 16% and for ages 50-59 years is 26% (Islami et al. 2024). There is a slight difference 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, comparing global data 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. Importantly, PR expression provides additional prognostic value, as loss of PR in ER-positive tumors may indicate endocrine resistance and more aggressive tumor behavior.

According to research conducted by Yaneva, et al that the distribution for positive estrogen receptors in breast cancer cases is the highest and is far compared to negative results. According to table 2 it is also shown that positive estrogen receptors with negative results are far compared (Yaneva et al. 2022). This data also agrees with research conducted by Rodrigues, et al 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 were 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 with negative 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). In 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 the in situ 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). According to Table 2, the most common results 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).

Clinical Implications

Overall, these findings 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.

CONCLUSIONS

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. Collectively, 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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