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The expression of Ki-67 and clinicohistopathological characteristics of breast cancer in Southern Sumatra, Indonesia

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ABSTRACT

Background: Breast cancer is the most frequently diagnosed cancer in the world, approximately 2.3 million new cases (11.7% of all cancer cases) per year in 2020. The Ki-67 expression is clinically used to classify molecular subtypes of breast cancer into luminal A and luminal B groups.
Objectives: This study aimed to investigate relationships between clinicohistopathological characteristics (ages, histopathological types, histopathological grades, molecular subtypes) of breast carcinoma patients and the Ki-67 proliferation index at dr. Moh. Hoesin General Hospital (RSMH) Palembang in 2019–2021.
Method: This study applied an observational analytic study with a cross-sectional approach. 521 samples were included in this study based on inclusion and exclusion criteria. The samples in this study included invasive breast carcinoma patients who underwent histopathological examination and immunohistochemistry (IHC), recorded in the medical records at RSMH Palembang for 2019–2021 period. Then a statistical analysis was performed by using the chi-square test, which was analysed in the SPSS application.
Results: The correlation between Ki-67 proliferation index and histopathological grades was statistically significant (p=0.018). The Ki-67 proliferation index was also statistically significantly associated with the molecular subtypes (p=0.000). Neither age (p=0.315) nor histopathological types (p=0.417) were significantly associated with the Ki-67 proliferation index.
Conclusion: The Ki-67 expression was significantly associated with histopathological value and molecular subtype in breast carcinoma patients at RSMH Palembang in 2019–2021. The Ki-67 expression was not associated with the clinic-histopathological characteristics of ages and histopathological types.

INTRODUCTION

Breast cancer is a significant global health challenge, particularly among the female population. Breast cancer starts in the mammary gland. Most of these are carcinomas.[1] In 2020, breast cancer was the most commonly diagnosed cancer in the globe, approximately 2.3 million new cases per year (11.7% of all cancer cases). This exceeds the new cases of lung cancer, which has been the leading cause of cancer worldwide over the past two decades. Its malignancy causes women to lose 19.6 million Disability-Adjusted Life Years (DALYs).[2] Breast cancer stands as the primary cause of mortality among women, resulting in 684,996 fatalities globally (95% CI 675,493–694,633). After accounting for ages, the

adjusted ratio of breast cancer-related deaths is 13.6 per 100,000 individuals. Notably, 63% of these deaths transpire in developing nations.[3] The mortality-to-incidence ratio (MIR) in 2020 as an indicator representing the global five-year survival rate was 0.30.[4]

Incidence and death rates of breast cancer have consistently risen worldwide over the last three decades. From 1990 to 2016, the number of cases of breast cancer had increased by over 100% in 60 nations, including Afghanistan, the Philippines, Brazil, and Argentina.[5] Additionally, the number of deaths caused by breast cancer also doubles in 43 countries, such as Yemen, Paraguay, Libya, and Saudi Arabia. According to the most recent forecasts, the number of new cases occurring all over the globe might have reached 2.7 million each year by the year 2030, with 0.87 million fatalities likely to occur.[4] The prevalence and death rates of breast cancer in various nations are influenced by economic advancement of countries, environmental variables, and ethnicity of populations. Environmental factors, breastfeeding, and lifestyle habits such as poor diets, lack of physical activities, alcohol and tobacco consumption are risk factors that heighten risks of breast cancer. Additional risk factors that contribute to the risks include factors related to reproduction and hormones. Genetic abnormalities in familial or hereditary instances significantly elevate the risks and have a crucial impact on the disease's progression.[6,7] In Indonesia, breast cancer is about 19.2% of 396,914 new cancer cases, making it the most common kind of cancer in the country. The number of fatalities caused by breast cancer in Indonesia is 22,000.[8]

Clinicopathological factors can help evaluate the prognosis and determine the most effective management strategy for breast cancer patients because of the heterogeneity of breast cancer. Therea are various clinicopathological factors of it, such as patients' ages, tumour sizes, histological types, histological grades, lymph node metastasis, hormonal receptor status (estrogen receptor [ER] and progesterone receptor [PR]), expression of human epidermal growth factor receptor 2 [HER2]), and Ki-67 expression.[9] Immunohistochemical markers are utilized more frequently than genetic testing to determine molecular subtypes in clinical practices due to cost and accessibility concerns.[10] The subtypes of breast cancer affect disease prognosis and are linked to endocrine therapy and chemotherapy responses.[11]

Cell proliferation is one of the most important prognostic factors and management determinants. Kiel-67 (Ki-67) is a nonhistone nuclear protein after the Gap 1(G1), Synthesis (S), Gap 2 (G2) and Mitosis (M) phases of cell cycles and is indicative of cell proliferation. Since the early 1980s, Ki-67 has been investigated.[12] Higher Ki-67 expression is also associated with a higher risk of relapse and a lower survival rate in breast cancer patients in the early stages.[13]

Numerous studies have found noteworthy correlations between Ki-67 and diverse clinicopathological variables. younger ages, between ≤50 years and <30 years old, are correlated with increased Ki-67 expression. This elevation, classified as high according to the Saint Gallen consensus (defined as >20%), indicates a more unfavourable prognosis. According to studies conducted by Nishit et al. and Liang et al., a notable correlation was found between Ki-67 and histological grades.[9,10] Aman and Hashmi et al. revealed that the histological type known as invasive breast carcinoma-ductal type of no special type (IBC-Ductal type NST) was the most commonly observed, accounting for 80.8% and 86.9% of cases, respectively. However, it was noted that other distinct subtypes, such as lobular and metaplastic with medullary groups, had higher Ki-67 values.[14,15] A substantial correlation was observed between elevated Ki-67 values and specific molecular subtypes of breast cancer linked with poorer prognoses.[14]

Other clinicopathological factors that have a significant association with high Ki-67 values were also found in various studies. A positive relationship between tumour size and Ki-67 is also demonstrated;[16] and a study by de Gregorio shows a positive relationship between lymph node status and Ki-67.[17] This current study is on the relationship between Ki-67 and clinicopathological factors at the Central General Hospital RSMH in Palembang. The dr. Mohammad Hoesin Central General Hospital in Palembang serves as a primary referral facility for the Southern Sumatra region. Most research in breast cancer clinicopathology focuses on general populations and often overlooks the unique characteristics and details specific to Southern Sumatra. This

glaring gap in the localized study is to enhance our understanding of the clinicopathological profile of breast cancer in this region, ultimately informing more tailored and effective clinical approaches. The clinicopathological features of breast cancer in Southern Sumatra have not been thoroughly investigated, resulting in a significant gap in the current study. The lack of focused studies on the specific characteristics of this disease in this geographical area highlights the necessity for additional studies. It is crucial to conduct comprehensive investigations to acquire a more nuanced understanding of breast cancer in Southern Sumatra. Consequently, the breast cancer patients receiving treatment at the general hospital are representative of the broader population of breast cancer patients in Southern Sumatra. This study focuses on the prognostic significance and treatment determination for breast cancer. It is the first investigation that aims to identify the correlation between Ki-67 expression and the clinicopathological characteristics of breast cancer at RSMH Palembang in 2019-2021 period.

METHOD

Research methods

This study applied an observational and analytical approach, using cross-sectional methodologies. It was conducted between August and October 2022 at the Anatomical Pathology Department of RSMH Palembang.

Population and samples

This study involved breast cancer patients who underwent histological examination and had their immunohistochemistry (IHC) recorded in the medical record at RSMH Palembang during a period from 2019 to 2021. A review was conducted on the medical records that were kept at RSMH Palembang. This study included patients diagnosed with invasive breast carcinoma and undergoing histopathological examination and breast carcinoma IHC by an anatomical pathology specialist. Additionally, patients completing information regarding their identity, diagnosis, results and interpretation of histopathological examination and breast carcinoma IHC were eligible to participate in this study. Patients with carcinoma in situ of the breast and patients with breast cancer who had distant metastases from other parts of the breast were not allowed to participate in this study. There were no exclusion criteria in this study, and all of the participants fulfilled the inclusion requirements that were given. To acquire the samples, a total sampling approach was implemented, and 521 samples were obtained.

Measurement parameters

The Ki-67 proliferation index was determined by calculating the proportion of tumour cells with Ki-67 cell nuclei stained by IHC staining, according to the Saint Gallen consensus. This index was then categorized as either high (≥20%) or low (<20%).[18] The subtypes of invasive breast carcinoma that were determined through histopathology were classified as invasive breast carcinoma of no special type (IBC-NST) and other types. This classification was based on the fifth edition of the World Health Organization (WHO)'s classification of breast cancer published in 2019. The tumour differentiation degree is determined by using the Nottingham Combined Histologic Grade System, specifically the Elston-Ellis Modification of Scarff and Bloom-Richardson Grading System.[19] The system categorizes tumours into three grades: grade 3 (poorly-differentiated), grade 2 (moderately-differentiated) and grade 1 (well-differentiated). The Saint Gallen consensus classifies breast carcinomas into different subtypes based on the expression of IHC markers (ER, PR, HER2, and Ki-67). This classification method is derived from the analysis of 50 gene expression signatures (PAM50). The classification has four primary subtypes (luminal A, luminal B, HER2-enriched, and basal-like), along with normal-like and claudin-low groupings (which contain the triple-negative subtypes in the future classification scheme). Luminal A and luminal B subtypes of breast cancer have estrogen receptor (ER) expression, whereas HER2-enriched and basal-like subtypes do not demonstrate ER expression. Luminal B HER2 positive breast cancer denotes hormone receptor-positive tumours with overexpression of HER2, while Luminal B HER2 negative represents hormone receptor-positive tumours without HER2 overexpression.[19–21]

Ethics

The current study obtained an ethical approval (Protocol No. 098-2022) in compliance with the

rules set by the Ethics Commission of the Faculty of Medicine at Universitas Sriwijaya.

Data analysis

The data were processed by Microsoft Excel and the Statistical Package for the Social Sciences (SPSS) version 24. Univariate analysis was applied to describe each variable that was investigated. The univariate analysis results demonstrated a frequency distribution. The Spearman test was performed to evaluate the Ki-67 proliferation index with ages, histological types, histopathological grades, and molecular subtypes of breast cancer.

RESULT

This study was conducted at dr. Moh. Hoesin Central General Hospital, the referral hospital in Southern Sumatra. This concludes that all breast cancer patients treated here represent breast cancer patients in Southern Sumatra. This study effectively included a total of 521 data of medical records. Table 1 provides an in-depth summary of the clinicohistopathological features. Most samples had a high category of Ki-67 proliferation index (74.7%). Samples taken from patients aged ≥50 years were comparable to samples from patients aged <50 years (235 [45.1%] versus 286 [54.9%] samples). IBC-NST was found as the majority of histopathological type (94.4%). The most frequently found histopathological grade was grade 3 (poorly differentiated) (67.6%). Regarding the molecular subtypes, Luminal B (HER2 negative) was found to be the most molecular subtype in breast cancer (52.4%).

Table 2 demonstrates the correlation that exists between the clinicohistopathological characteristics and the Ki-67 proliferation index. Patients with breast cancer who have a high Ki-67 proliferation index (more than 20%) are more likely to have a considerably higher histopathological grades than patients who have a low Ki-67; the Ki-67 proliferation index showed a significant association with histopathological grade (p=0.018). Additionally, there was a strong correlation between the molecular subtype and the Ki-67 proliferation index (p=0.000). Furthermore, there was no significant correlation between the Ki-67 proliferation index and either the ages of the patients (p=0.315) or the histological types

Table 1. Clinicohistopathological characteristics

Clinicohistopathological characteristics	Total (n)	Percentage (%)
Ki-67 Proliferation Index		
High	389	74.7
Low	132	25.3
Age		
≥50	235	45.1
<50	286	54.9
Histopathological type		
Invasive breast carcinoma of no special type (IBC-NST)	492	94.4
Other	29	5.6
Histopathological grade		
Stage 3 (poorly-differentiated)	352	67.6
Stage 2 (moderately-differentiated)	132	25.3
Stage 1 (well-differentiated)	37	7.1
Molecular subtype		
Triple-negative	41	7.9
HER-2 enriched	34	6.5
Luminal B (HER2 positive)	57	10.9
Luminal B (HER2 negative)	273	52.4
Luminal A	116	22.3

HER2: human epidermal growth factor receptor 2

Table 2. Clinicohistopathological characteristics and the Ki-67 proliferation index

Clinicohistopathological characteristics	Ki-67 Proliferation Index		p-value
	High (n [%])	Low (n [%])	
Age			
≥50	170 [72.3]	65 [27.7]	0.270
<50	219 [76.6]	67 [23.4]	
Histopathological type			
Invasive breast carcinoma of no special type (IBC-NST)	365 [74.2]	127 [25.8]	0.303
Other	24 [82.8]	5 [17.2]	
Histopathological grade			
Stage 3 (poorly-differentiated)	276 [78.4]	76 [21.6]	0.005*
Stage 2 (moderately-differentiated)	88 [66.7]	44 [33.3]	
Stage 1 (well-differentiated)	25 [74.7]	12 [25.3]	
Molecular subtype			
Triple-negative	33 [80.5]	8 [19.5]	0.000*
HER-2 enriched	30 [88.2]	4 [11.8]	
Luminal B (HER2 positive)	54 [94.7]	3 [5.3]	
Luminal B (HER2 negative)	266 [97.4]	7 [2.6]	
Luminal A	6 [5.2]	110 [94.8]	

Clinicohistopathological characteristics based on age, histopathological type, histopathological grade, and molecular subtypes of breast carcinoma are presented in frequency and percentage [n (%)]; *Significance is determined at $p < 0.05$ using Spearman test, HER2: human epidermal growth factor receptor 2.

of the patients (p=0.417).

DISCUSSION

This study indicates that most of the samples fall into the high category of the Ki-67 proliferation index. High category values are defined as being greater than 20%.[18] This high category was observed in 389 samples, accounting for 74.7% of the sample population. In Ragab et al.'s study, they found a similar percentage of samples with high Ki-67 levels. Specifically, of 89 samples, 56 samples (equivalent to 62.9%) had Ki-67 levels above 20%.22 This study cannot be directly compared to some contemporary studies due to variations in the Ki-67 cut-off value used to classify high/positive Ki-67 and the grouping of Ki-67 values into more than two categories. A study conducted by Kamranzadeh et al. revealed that 69.16% of the participants had positive results for Ki-67. Notably, its research subjects were split into two distinct groups based on a Ki-67 cutoff value of 10%.[23] According to a study conducted by Kanyılmaz et al., it was found that 50% of the participants exhibited elevated Ki-67 levels. Notably, its research subjects were categorized into three distinct groups based on Ki-67 cut-off values of 10% and 25%.[24] The values used in this current study were derived from the Saint Gallen consensus and adjusted to the RSMH laboratory reference values. This study differs from the studies by Kamranzadeh et al. and Kanyılmaz et al.

This study demonstrates a trend of breast cancer occurring in individuals of younger age. This aligns with a study conducted by Nishit et al., which examined the frequency distribution of those aged above 47 years compared to those aged 47 years or younger (49.62% vs 50.38%).[9] The prevalence of breast cancer in Asia and Africa among women under the age of 40 is considered to be high in

comparison to other global areas.[25] The presence of low educational and socioeconomic levels, along with insufficient health facilities in Asia, leads to delays in patients' ability to avoid risk factors and undertake screening. This phenomenon may be attributed to the higher incidence of breast cancer among young individuals in the Asian population compared to other areas.[26]

The findings of this study are likewise consistent with that of Aman et al.'s study, which indicated that the most prevalent histological type discovered was invasive breast carcinoma of no special types, accounting for 80.8% of all cases.[15] Hashmi's study also has the same conclusion, stating that ductal histology subtype breast cancer was present in 1,695 of the 1,951 individuals who participated in the study.[14] Invasive no special type of breast carcinoma is a broad and heterogeneous group of invasive breast carcinomas, including all types of invasive breast carcinoma that cannot be classified into any special histological type.[19]

The findings in this study regarding the histopathological grade are not in line with Mohammed's study which stated that the most frequent histopathological grade found was intermediate grade/2 with a total of 159 cases (50.6%) (compared to high grade/3 with a total of 144 cases [45.9%]).[27] The disparity between both studies may be due to the different settings in which the data were collected. This study's data were sourced from a central referral hospital, likely resulting in a higher proportion of more serious cases with a poorer prognosis. In contrast, Mohammed's study was conducted at a peripheral health institution affiliated with a university, which may see a broader range of cases, including less severe one.

The most frequently found breast cancer subtype in general was the luminal type (60–70% of total breast cancer, of which >50% were luminal A), followed by triple negative (approximately 20%) and HER2-enriched (10–15%) types. The worst to best prognosis are triple negative, HER2-enriched, luminal B, and luminal A subtypes respectively.[20,21] A study by Tan et al. showed a similar result to this current study that luminal B was the most common molecular subtype found.[28] A study using the Nurses' Health Study database ranging from the period 1976–2006, totalling 2,555 subjects, demonstrated contradictory results. The most common molecular subtype found was luminal A.[29]

Breast cancer patients with a high Ki-67 proliferation index (>20%) tended to have a significantly higher histopathological grade than patients with low Ki-67; the Ki-67 proliferation index had a significant relationship with histopathological grades. Shetty & Rao's study revealed similar results as the tumour grade in the high Ki-67 group (>10%) was more severe than that in the low Ki-67 group (≤10%), suggesting Ki-67 relationship with breast cancer tumour grade.[30] Another study also stated that there was a significant relationship between Ki-67 and histological grades in breast cancer patients, with a higher histopathologic grade in the high Ki-67 group than that in the low Ki-67 group.[10]

The Ki-67 proliferation index in this current was significantly associated with the molecular subtypes. This is in line with a study conducted in Ivory Coast, illustrating that the higher Ki-67 expression group had significantly more severe molecular subtypes than the lower Ki-67 expression group. The mean Ki-67 value correlated significantly with the correlated molecular subtypes in this study.[15] Another study by Elkablawy et al. also indicated the same; the Ki-67 proliferation index was significantly different between luminal A, luminal B, HER-2 neu (HER2-enriched), and basal-like (triple negative) subtypes.[16] This correlation is thought to be due to the presence of HER2 overexpression which is the basis for determining luminal B (HER2-positive) and HER2-enriched (non-luminal) subtypes, as well as non-expression of HER2 in luminal A, luminal B (HER2-negative), and triple-negative types; also Ki-67 is one of the many differentiators of luminal A and B subtypes. Higher Ki-67 expression is also known to be associated with a higher risk of recurrence and poorer survival in patients with early-stage breast cancer.[13]

Several variables were found not to be significantly associated with the Ki-67 proliferation index in this study. One of those variables was age. This is in line with a study in India, which showed that differences in ages (<40, 41–50, and >50 years) were not significantly related to Ki-67 with a median age value of 47 (26–84 years).[30] The opposite result was obtained in a study of Ragab et al., which found a significant relationship between ages and Ki-67.[22] This difference might occur due to the absence of exploring the onset

of complaints, risk factors, time of diagnosis, and details of diagnosis. The severity of breast cancer in subjects aged ≥ 50 years in this study means that there is a possibility that the cancer is more severe. However, on the one hand, breast carcinoma at a young age has a worse prognosis and is at greater risk of recurrence and distant metastases.[31]

The histopathological type variable was also not found to be significantly related to the Ki-67 proliferation index. A study by Shetty and Rao showed similar results as no significant relationship was found between the histopathological type and Ki-67 proliferation index.[30] The correlation between higher histologic grades and enhanced Ki67 expression may be attributed to their tight association with the proliferation rate of tumour cells. Ki67 serves as an indicator of cell proliferation, while histopathologic grades take into account not only cell proliferation but also other factors such as nuclear pleomorphism and tubule development.[32]

Various studies have been published on the significance of understanding the growth rate that takes place by assessing Ki-67 expression in breast cancer. For instance, Oncotype DX evaluates the degree of Ki-67 gene expression among 16 other genes. The Recurrence Score method considers the proliferation group, which is characterized by the Ki-67 marker, as a crucial factor.[33] The Ki-67 has long been recognized as a prognostic factor for breast cancer. Petrelli et al conducted a systematic review followed by a meta-analysis. This meta-analysis of 41 studies, including over 64,000 patients, demonstrated that increased Ki-67 percentages were independently associated with worse outcomes in breast cancer patients, despite variations in the studies' threshold levels.[34]

The Ki-67 also has the potential to serve as a prognostic indicator of the response to neoadjuvant and adjuvant therapy. Several studies have shown a substantial association between Ki-67 and the clinical or pathological response to neoadjuvant chemotherapy.[35,36] According to a comprehensive review conducted by Luporsi et al., Ki-67 has been classified as a level of evidence IIB in its ability to predict the response to neoadjuvant therapy.[37] The scientific data addressing the relevance of Ki-67 in predicting response to adjuvant treatment is very inconsistent. The International Breast Cancer Study Group (IBCSG) Trials VIII and IX found that Ki-67 does not have a predictive role in determining the response to chemotherapy compared to those not receiving chemotherapy.[38] Contrary to expectations, a study conducted by Denkert et al. revealed that higher levels of Ki-67 are linked to a worse prognosis and a more positive response to neoadjuvant treatment.[39]

The significant association observed in this study between the Ki-67 proliferation index, with a cut-off value of 20%, and histopathological grade, along with molecular subtypes, provides further evidence supporting the clinical relevance of the Ki-67 proliferation index at RSMH. This is particularly important for determining molecular subtypes, prognosis, and management, in line with the 2013 Saint Gallen consensus. The 2011 Saint Gallen consensus established that the threshold value for Ki-67 was first set at 15%, but then was amended to 20% and customized by individual laboratory settings.[40,41]

However, our study has several limitations. This study is subject to various constraints, and one of them is the use of secondary data. Consequently, there is a potential for human error, such as illegible handwriting or incomplete data records. Furthermore, this study was conducted exclusively at a single location, specifically a tertiary referral facility. As a result, the study's findings may not accurately represent the broader target population and may be skewed towards individuals with more severe illness patterns. This study did not investigate the initiation of symptoms, factors that increase the likelihood of developing breast carcinoma, the timing of diagnosis, or specific details regarding the severity of the breast cancer diagnosis.

CONCLUSION

The Ki-67 expression is strongly associated with the histopathological grades and molecular subtypes of breast cancer patients at RSMH Palembang from 2019 to 2021. The expression of Ki-67 was not associated with the clinicohistopathological variables of ages and histopathological types. Most breast cancer patients at RSMH Palembang between 2019 and 2021 exhibited a high Ki-67 proliferation index, were aged 50 years or older, and had similar characteristics to patients under 50 years of age. The most common histopathological type was IBC-NST, with most patients having grade 3 (poorly differentiated) tumours and belonging to

the luminal B molecular subtype. It is advisable to conduct more studies to examine the molecular processes that explain the observed associations and evaluate the predictive importance of Ki-67 expression in a wider and more varied group of individuals. Furthermore, given the high frequency of elevated Ki-67 expression in older patients, it may be necessary to develop customized treatment approaches and individualized interventions for this population. Additionally, further studies must investigate the possible impact of other molecular markers together with Ki-67 to improve the accuracy of prognostic evaluations in instances of breast cancer.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

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MH conceptualized the study; W and SF supervised the study; MH, NTP, and MRA created the methodology, wrote, reviewed, and edited the manuscript; MH wrote the original draft. All authors reviewed the results and approved the final version of the manuscript.

AUTHOR CONTRIBUTIONS

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LIST OF ABBREVIATIONS

RSMH: *Rumah Sakit Umum Pusat* dr. Moh. Hoesin Palembang/dr. Moh. Hoesin Central General Hospital; SPSS: Statistical Package for the Social Sciences; DALYs: Disability-Adjusted Life Years; MIR: mortality-to-incidence ratio; HER2: human epidermal growth factor receptor 2; IBC: invasive breast carcinoma; IHC: immunohistochemistry; IBC-NST: invasive breast carcinoma of no special type; ER: oestrogen receptor; PR: progesterone receptor; NST: no special type; IBCSG: International Breast Cancer Study Group; WHO: World Health Organization

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