Research Article

Association between p53 Status and Breast Cancer Molecular Subtypes in the Academic Hospital of Universitas Gadjah Mada

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Received 21 November 2024; Accepted 2 May 2025
https://doi.org/10.23886/ejki.13.964.59

Abstract

Breast cancer is the most common form of cancer and the leading cause of mortality in women. The p53 pathway is crucial for cell cycle regulation and tumor development. Alterations in the p53 are associated with increased aggressiveness of cancer cells. This cross-sectional study explored the association between p53 status and the molecular subtypes of invasive breast cancer in patients at the Academic Hospital of Universitas Gadjah Mada from 2016 to 2024. Immunohistochemical analysis was conducted to evaluate the presence of mutant p53 in primary tumor specimens. Of the p53-negative tumors in this study, 4 patients were triple-negative breast cancer. No association was observed between p53 expression and molecular subtype, with p-values of 0.16 and 0.224. In contrast, a significant correlation was noted between p53 and Ki67 expression, resulting in a coefficient of 0.513 (p=0.009). Additionally, a notable correlation of 0.531 was found between p53 expression and tumor size (p=0.006). In conclusion, tumor size is a crucial parameter for determining patient prognosis; specifically, as tumor size increases, p53 expression also rises, leading to a worse prognosis.
Keywords: *p53 status, primary tumor, molecular subtype, invasive breast cancer.*

Hubungan antara Status p53 dengan Subtipe Molekular Kanker Payudara Invasif di Rumah Sakit Akademik Universitas Gadjah Mada

Abstrak

Kanker payudara merupakan keganasan paling sering dan penyebab kematian utama pada perempuan. Jalur p53 memegang peranan penting dalam mengontrol siklus sel dan tumorigenesis pada kanker payudara. Adanya mutasi yang terjadi pada p53 menyebabkan agresifitas sel kanker. Studi ini bertujuan untuk menentukan korelasi status p53 dengan subtipe molekular kanker payudara invasif. Penelitian potong lintang ini menggunakan data pasien kanker payudara invasif di Rumah Sakit Akademik Universitas Gadjah Mada tahun 2016-2024. Pemeriksaan imunohistokimia p53 mutan pada tumor primer dilakukan. Hasil menunjukkan empat pasien dengan tumor p53 negatif adalah kanker payudara subtipe triple-negative. Tidak terdapat hubungan antara ekspresi p53 dan subtipe molekuler (p=0,16 dan p=0,224). Namun, terdapat korelasi antara ekspresi p53 dan ekspresi Ki67, dengan koefisien korelasi 0,513 (p=0,009). Selain itu, terdapat juga korelasi 0,531 antara ekspresi p53 dan ukuran tumor (p=0,006). Dapat disimpulkan bahwa ukuran tumor merupakan parameter penting untuk menentukan prognosis pasien; terutama, seiring dengan bertambahnya ukuran tumor, ekspresi p53 juga meningkat, menyebabkan prognosis yang lebih buruk.
Kata kunci*: status p53, tumor primer, subtipe molekular kanker payudara invasif.*

Introduction

Breast cancer constitutes the most frequently diagnosed malignancy and has arisen as the predominant cause of cancer-related mortality among women globally.[1] According to Globocan in 2020, the global breast cancer incidence reached 2,261,419 cases (24.5%), while in Indonesia, 65,858 cases (16.6%) were reported, with over 22,430 fatalities (9.6%).[2,3] Data from the 2018 Riskesdas report highlights that cervical and breast cancers are the two most common cancer types in Indonesia, with the prevalence rate in Yogyakarta surpassing the national average at 4.1 cases per 1,000 population.[4] In comparison to high-income countries, the 5-year survival rate for breast cancer patients in Indonesia is significantly lower, with a prior study indicating a survival rate of 81% among Indonesian patients with triple-negative breast carcinoma (TNBC).[5] The prognosis of patients is mostly determined by clinicopathological variables. In invasive breast cancer, the greatest and most commonly agreed prognostic indication is lymph node metastases.[6,7] Other parameters, such as tumor size and age at diagnosis, have shown variable prognostic significance across studies. For instance, a study by Lismawati et al[8] demonstrated no discernible correlation between tumor size, vascular invasion, lymph node metastases, and mutant p53 expression.[8] In contrast, Gonzalez Sistal et al[9] demonstrated a substantial correlation between tumor growth and p53 expression.

It is widely recognized that the p53 gene is an essential tumor suppressor. By preserving genomic stability, p53 prevents angiogenesis, metastasis, and the growth of cancer cells.[8] Mutations in the p53 gene impair these critical functions, leading to uncontrolled cell growth and an increased likelihood of metastasis. Mutant p53 loses its tumor-suppressive capacity and can gain oncogenic properties that promote tumor progression.[10] In the event of DNA damage, p53 is triggered to regulate the cell cycle's transition from the G1 to the S phase and from the G2 to the M phase. Additionally, p53 is instrumental in stimulating apoptosis.[11] Targeted therapies under development aim to restore mutant p53 to its wild-type functionality or promote its degradation through reactivation, immunotherapy, or gene therapy approaches.

Understanding the relationship between mutant p53 expression and these clinical features holds considerable importance for prognosis and the development of treatment strategies, particularly in the context of p53-targeted therapies. Moreover, given the absence of a comprehensive national cancer registry in Indonesia, this study seeks to fill critical knowledge gaps and inform data-driven healthcare strategies tailored to the local population. The objective of this study is to evaluate the association between p53 expression and the molecular subtypes of breast cancer, and analyzing its correlation with clinicopathological parameters.

Methods

This study utilized cross-sectional design conducted at Academic Hospital of Gadjah Mada University between March and October 2024. The study population included all breast cancer patients who had undergone surgical intervention and histopathological evaluation from January 2016 to June 2024. Due to limited funding, only 25 individuals were selected from the population per established inclusion and exclusion criteria.

The inclusion criteria for this study encompassed patients diagnosed with breast cancer and registered at the Academic Hospital of Gadjah Mada University who had previously undergone either mastectomy or lumpectomy. Eligible patients were required to have surgical specimens that had been subjected to histopathological examination and immunohistochemical profiling for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67. Additionally, complete medical records, particularly those documenting age, sex, and anatomical histopathology findings, were necessary for inclusion. The exclusion criteria included patients suspected of having breast cancer but with a benign histopathological diagnosis, as well as patients who had previously received chemotherapy, hormonal therapy, or antibody therapy.

The p53 status, which serves as the independent variable, is determined by the immunohistochemical examination of mutant p53 on PPFE paraffin blocks. The classification of p53 is determined by the extent of staining observed in tumor cell nuclei. It is regarded as negative when there is either an absence of staining or when less than 10% of the tumor cell nuclei exhibit positive staining. Conversely, p53 is classified as positive when more than 10% of the tumor cell nuclei demonstrate positive staining.

The invasive breast cancer molecular subtype, the dependent variable, is determined based on the molecular classification using ER, PR, HER2, and Ki67 statuses. This classification encompasses luminal A, luminal B (HER2-negative), luminal B (HER2-positive), HER2-enriched, and triple- negative subtypes.

The research procedure involves immunohistochemical testing for *p53* on primary tumor paraffin blocks. The required materials include xylene, graded ethanol (absolute, 90%, 80%, 70%), sterile distilled water, antigen retrieval (citrate buffer, pH 6.0), phosphate buffer saline (PBS), endogenous peroxidase blocking (3% H2O2 in methanol), blocking buffer, primary antibody for mutant p53, secondary antibody (biotin conjugate), streptavidin horseradish peroxidase (SA-HRP), diaminobenzidine (DAB) chromogen, Mayer's hematoxylin counterstain, and entellan.

IBM SPSS Statistics version 29.0 was used to analyze the data. Bivariate analysis exploring the relationship between *p53* expression and various clinicopathological characteristics, including molecular subtypes, was conducted using either the chi-square or Fisher's exact test. As these tests require a 2x2 contingency table, clinicopathological parameters were categorized into two groups. Age at diagnosis was divided into two categories: under 60 years and 60 years or older, based on the United Nations' definition of elderly individuals. Tumor size was categorized into two groups using a 5 cm threshold, based on findings by Kim et al[12] which demonstrated that tumors larger than 5 cm are associated with poorer prognosis. The Kruskal-Wallis test was used to identify statistically significant differences in T classification, N classification, and molecular subtypes across the groups. For continuous variables that were not normally distributed, the Spearman correlation test was applied. A p-value of less than 0.05 was considered statistically significant.

This study utilized paraffin block samples from patients while strictly adhering to ethical considerations, specifically ensuring patient confidentiality. Patient identification data, including names, medical record numbers, addresses, and anatomical pathology examination code numbers, were kept confidential by excluding names, numbers, or original patient codes from the study.

Ethical approval for this research has been granted by the Research Ethics Committee at the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada. The ethics clearance number is KE/FK/0681/EC/2024 granted on May 15, 2024.

Results

A total of 25 samples that fulfilled the predetermined inclusion and exclusion criteria were included in the analysis. The patients ranged in age from 29 to 77 years, with an average age of 57.16±11.323 years (Table 1). Among the total

Table 1. Characteristics of Breast Cancer Patients from January 2016 to June 2024

Characteristic	n (%)
Age	
Maen±SD	57.16 ±11.3
<60	12
≥60	13
T classification	
1	5
2	6
3	3
4	11
N classification	
0	8
1	8
2	7
3	2
Tumor size	
<5	6
≥5	7
Metastasis (X)	25
Tumor size (cm)	
Median	3
<5	16
≥5	9
Molecular subtype	
Luminal A	5
Luminal B HER2 negative	5
Luminal B HER2 positive	5
HER2 enriched	5
Triple negative	5
p53 expression	
Maen±SD	24.48±27.7
Positive	13
Negative	12

participants, 52% were aged ≥60 years. The TNM classification data in this study indicate that the majority of patients (n=11) presented with advanced tumor size (T4), followed by smaller proportions in T2 (n=6), T1 (n=5), and T3 (n=3). Lymph node involvement was most frequently classified as N0 (n=8) and N1 (n=8), followed by N2 (n=7) and N3 (n=2). Regarding metastasis, all patients were classified as Mx, indicating that pathological staging could not assess the presence of distant metastasis due to a lack of pathological evidence. Additionally, the data reveal that 64% of patients had tumors smaller than 5 cm, while only 36% had tumors measuring 5 cm or larger. Notably, among the eight samples with tumors smaller than 5 cm, ulceration contributed to their classification as T4b, despite their small size. The presence of ulceration plays a significant role in advancing the tumor stage, overshadowing the smaller tumor dimensions. The smallest tumor measured 1.1 cm, while the largest reached 13 cm.

Table 2 shows that the triple-negative subtype has the highest proportion of negative p53 expression (n=4) compared to other subtypes. Conversely, both luminal B HER2 Negative and luminal B HER2 Positive subtypes exhibit identical proportions of positive p53 expression (n=4). The luminal A and HER2 Enriched subtypes demonstrate a more balanced distribution between positive and negative p53 expression.

The majority of breast cancer samples with positive p53 expression were from patients aged under 60 years (n=8), with higher T staging, specifically T3 or T4 (n=9), and tumors that were 5 cm or larger (=7). The results in Table 3 indicate no significant difference between the molecular subtypes of breast cancer and p53 expression. Additionally, no relationship between p53 expression and other characteristics, including age, T and N classifications, tumor size, ER, PR, and HER2 status.

Further analysis using the Spearman correlation test revealed a significant and strong correlation between p53 and Ki67 expression, with a coefficient of 0.513 (p=0.009). A strong correlation of 0.531 was found between p53 expression and tumor size (p=0.006). The results indicate that elevated expression levels of p53 correlate with enhanced Ki67 expression and increased tumor size. The Kruskal-Wallis test evaluated the relationship between p53 expression and various clinicopathological characteristics. The results indicated that no associations were identified.

Table 2. P53 Expression of Each Molecular Subtype

Molecular Subtype	p53 Expression	
	Positive (n=13)	Negative (n=12)
Luminal A	2	3
Luminal B HER2 negative	4	1
Luminal B HER2 positive	4	1
HER2 enriched	2	3
Triple negative	1	4
Luminal A	2	3

Discussion

The p53 gene is the most frequently mutated gene observed in breast cancer, as well as in cancer overall, accounting for around 30% of breast cancer cases. It plays a vital role in several cellular processes, including regulating the cell cycle, metabolism, angiogenesis, and DNA repair mechanisms.

Table 3. Characteristics of the Study Population by p53 Expression

Characteristic	p53 Expression		p
	Positive (n=13)	Negative (n=12)	
Age			
<60	8	4	0.238
≥60	5	8	
T classification			
1/2	4	7	0.165
3/4	9	5	
N classification			
0	5	3	0.673
1/2/3	8	9	
Tumor size (cm)			
<5	6	10	0.097
≥5	7	2	
Molecular subtype			
Triple negative	1	4	0.160
Non-triple negative	12	8	
ER			
Positive	6	4	0.688
Negative	7	8	
PR			
Positive	4	6	0.428
Negative	8	6	
HER2			
Positive	8	7	1.000
Negative	5	5	

Referred to as the "guardian of the genome," the p53 protein prevents the proliferation of cells with genetic abnormalities, particularly those harboring oncogenic mutations. This protein is vital in responding to cellular stress, such as DNA damage, oncogenic signals, and oxidative stress, effectively suppressing tumor development. When *p53* is mutated, its protective function is lost, allowing tumor growth. Mutations in the *p53* are linked to more aggressive forms of breast cancer. Higher tumor grades and stages, increased lymph node metastasis, elevated proliferation indices, and a poorer prognosis characterize these forms.[13,14]

Based on gene expression profiles, breast cancer can be classified into five distinct molecular subgroups. The subtype with the lowest prevalence of *p53* mutations is luminal A. Meanwhile, the triple-negative breast cancer subtype constitutes to 15% of all breast cancer diagnoses and is characterized by the lack of ER, PR, and HER2 expression.[15] The lack of these receptors makes TNBC unresponsive to endocrine therapy and HER2-targeted treatments, significantly limiting therapeutic options for affected patients and contributing to poorer outcomes compared to other subtypes. Recent research highlights that p53 mutations, known for promoting genomic instability and aggressive tumor phenotypes, are present in approximately 80% of TNBC cases, suggesting that mutant p53 may serve as a potential therapeutic target in managing this disease.[16]

In immunohistochemical (IHC) analysis, various thresholds have been proposed to define p53-positive tumors. A large-scale study in China with a p53-positive threshold of ≥1% found that 53% of breast cancer tumors were p53-positive.[13] Another study at the Fourth Hospital of Hebei Medical University reported a p53-positive expression rate of 58.6% within their cohort, using a p53-positive threshold of ≥10%.[17] The lack of standardization in p53 scoring complicates direct comparisons between studies and may contribute to varying prevalence rates. In our study, we defined p53 positivity with a cut-off of ≥10%, identifying thirteen tumors as p53-positive, which aligns with these findings. Despite similar overall positivity rates, our study diverges from others regarding the distribution of p53 expression among molecular subtypes. A study in China examining p53 expression across different subtypes found that the proportion of p53-positive tumors was lowest in the luminal A subtype (46%), followed by HER2-negative luminal B (58%), HER2-positive luminal B (60%), triple-negative (61%), and highest in the HER2-enriched subtype (63%).[13] Among our study's thirteen p53-positive tumor cases, eight were luminal B tumors, while only one was triple-negative. Among the luminal B tumors, both HER2-negative and HER2-positive, eight were p53-positive. In contrast, among the five triple- negative tumors, only one was p53-positive. These discrepancies may be due to our limited sample size, which restricts generalizability, or reflect regional biological variability in breast cancer subtypes.

Age at diagnosis is a crucial factor influencing breast cancer prognosis. Most current literature indicates that younger age correlates with poorer outcomes due to a higher prevalence of aggressive and invasive diseases within this demographic. Among our 13 p53-positive tumors, 12 of patients were found under 60 years old. This finding is supported by previous studies from Brazil reporting a higher mutation rate of p53 (53%) in early-onset breast cancer patients aged below 44 years compared to 35% in those over 44 years old.[18] Another research from China also noted that 79.2% of p53-positive tumors occurred in patients under 60 years old.[13] The high frequency of p53 positivity in luminal B tumors observed in our study could relate to age-related factors. Luminal B tumors are more common in younger patients, as shown in a study from East Kalimantan, Indonesia, where this subtype predominated among patients under 35.[19] Moreover, within the luminal A subtype, younger age at diagnosis has been associated with higher p53 expression and worse prognosis.[20] Consistent with these findings, the average age of luminal breast cancer patients in our study was 53, compared to 62 for non-luminal cases, indicating a younger age distribution within the luminal subset. Notably, the youngest patient in our study, aged 29, was part of the luminal breast cancer group.

Genetic predispositions, including mutations in TP53, are more common in early-onset cases, contributing to heightened invasiveness and resistance to certain therapies.[21] Beyond genetic factors, lifestyle, and environmental risk factors may play a substantial role in the increasing incidence of breast cancer among younger women. Rising obesity rates, hormonal imbalances related to delayed childbearing, and greater exposure to endocrine-disrupting

chemicals have all been implicated.[22,23] Turkoz et al[22] have reported that women with two or more children had a significantly lower risk of luminal breast cancer compared to nulliparous women. Similarly, nulliparity compared to early first full-term pregnancy (<30 years) was associated with a higher risk.[22] Interestingly, these significant associations between lifestyle factors and breast cancer risk were confined to the luminal subtypes, suggesting that distinct, lifestyle-mediated pathways may underlie luminal tumor development in younger populations.

In breast cancer, tumor size is a known prognostic indicator, where larger tumors are typically correlated with a greater probability of metastasis, recurrence, and lower overall survival rate.[24] Studies consistently demonstrate that increasing tumor size correlates with more advanced disease and poorer outcomes. In addition to more aggressive biological behavior, larger tumors are more likely to exhibit axillary lymph node involvement and distant metastases, all of which are key factors that influence staging, prognosis, and treatment strategies.[9] There was no apparent distinction in the prevalence of p53-positive tumors smaller than 5 cm and greater than 5 cm in our study. However, among p53-negative tumors, 10 patients measured less than 5 cm. This finding contrasts with a study in China that categorized tumor sizes into <2 cm, 2–5 cm, and >5 cm revealing a significant relationship (p=0.002) between tumor size categories and p53 expression.[13] Additionally, a study at Monte del Naranco Hospital in Spain showed a relationship (p=0.006) between tumor size and p53 expression through immunohistochemistry.[9] Our data analysis did not find a statistically significant correlation between p53 expression and tumor size groups; however, a strong Spearman correlation of 0.531 (p=0.006) was observed between ungrouped, continuous tumor size and the percentage of p53 expression.

This study also analyzed the relationship between p53 and Ki67 expression, a nuclear protein commonly associated with cell proliferation and frequently used as a prognostic indicator in breast cancer. The Spearman test in this study revealed a strong correlation between p53 and Ki67 of 0.513 (p=0.009). While several available studies found no relationship between p53 and Ki67, a meta- analysis involving 12,155 patients showed that high Ki67 expression is associated with a worse prognosis.[16,25,26] Furthermore, Ki67 expression highly depends on the molecular subtype. luminal A breast tumors typically exhibit reduced Ki67 expression, indicative of lower proliferation rates. In contrast, triple-negative breast cancers are characterized by elevated Ki67 levels, correlating with their more aggressive nature and poorer overall prognosis.[18] No significant association was found between p53 expression and other clinicopathological characteristics, such as age and lymph node metastasis.

The primary drawback of our study is the small sample size, which may increase the likelihood of type II errors, potentially obscuring true associations. Additionally, the small cohort limits the diversity of clinical and molecular characteristics, preventing a comprehensive and representative representation of the broader breast cancer population. This impacts the generalizability of our findings, as our conclusions may not fully reflect patterns observed in larger or more diverse populations across different molecular subtypes. Furthermore, the small sample size hinders the ability to conduct detailed subgroup analyses that could have provided deeper insights into the relationships between p53 expression, the various clinicopathological parameters, and breast cancer subtypes. Another potential limitation of our study is its retrospective design, which may lead to selection bias and restrict our ability to establish causal relationships. Furthermore, the lack of detailed follow-up data on patient outcomes makes it difficult to correlate p53 expression with long-term survival, disease progression, or treatment response. To address these limitations, future studies should focus on using larger, prospective cohorts that encompass a more diverse population. A multi-center approach could enhance external validity and contribute to a more comprehensive understanding of p53's prognostic significance in breast cancer.

Conclusion

We conclude that tumor dimensions are a crucial factor in predicting the prognosis of patients; more specifically, a larger tumor results in elevated p53 expression, and thus a worse prognosis. Additionally, there is a strong correlation involving high Ki67 expression and p53 overexpression, suggesting more significant cell proliferation and poorer results.

Conflict of Interest

The authors declared no conflicts of interest.

Acknowledgments

The authors thank the Academic Hospital of Universitas Gadjah Mada for providing the research grant that supported this study.

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