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Research Article

The Relationship Between Molecular Subtypes and Histological Grade of Nottingham Breast Carcinoma at dr. H. Jusuf SK Regional General Hospital

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Abstract: Breast carcinoma is a biologically heterogeneous malignancy characterized by variations in molecular subtype and histological grade, both of which influence prognosis and therapeutic strategy. Although molecular classification using immunohistochemistry has become a standard component of breast cancer management, data regarding its correlation with histological grade in secondary healthcare facilities remain limited. This study aimed to analyze the relationship between molecular subtypes and histological grade of Nottingham breast carcinoma at dr. H. Jusuf SK Regional General Hospital. This retrospective analytical cross-sectional study included breast carcinoma patients diagnosed between January 2023 and September 2025. Only cases with complete immunohistochemical data (ER, PR, HER2, and Ki-67) were included in the analysis. Molecular subtypes were classified as Luminal A, Luminal B, HER2-enriched, and Triple-negative, while histological grading was determined using the Nottingham Histologic Score system (Grade I–III). The association between molecular subtype and histological grade was analyzed using Fisher's Exact test, with statistical significance set at $p < 0.05$. A total of 51 patients met the inclusion criteria. Luminal B was the most frequent subtype (39.2%), followed by Luminal A (27.5%), HER2-enriched (25.5%), and Triple-negative (7.8%). Grade III tumors accounted for 51.0% of cases. HER2-enriched (69.2%) and Triple-negative (75.0%) subtypes were predominantly associated with Grade III tumors, whereas Luminal A tumors were more frequently associated with Grade II (57.1%) and lower-grade tumors. Statistical analysis demonstrated a significant association between molecular subtype and histological grade (Fisher's Exact test, $p < 0.05$). These findings indicate a statistically significant relationship between molecular subtype and histological grade in Nottingham breast carcinoma. More aggressive molecular subtypes, particularly HER2-enriched and Triple-negative, are strongly associated with higher histological grade. This result highlights the biological concordance between molecular behavior and tumor differentiation and underscores the importance of comprehensive immunohistochemical evaluation in breast cancer management.

Keywords: Breast Carcinoma; Molecular Subtype; Nottingham Grade; Immunohistochemistry; Tumor Differentiation

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1. Introduction

Breast cancer remains the most common malignancy among women worldwide and represents a major public health burden in Indonesia. According to the Ministry of Health of the Republic of Indonesia, breast cancer accounts for 40.3 cases per 100,000 women and contributes significantly to cancer-related mortality nationally (Kementerian Kesehatan RI, 2025). Globally, GLOBOCAN 2020 reported breast cancer as the leading cause of cancer incidence among women, emphasizing its growing epidemiological impact (Sung et al., 2021). The projected increase in cancer burden underscores the urgency of strengthening diagnostic and therapeutic strategies, particularly in resource-limited and secondary healthcare facilities.

Breast carcinoma is a biologically heterogeneous disease characterized by substantial variability in morphology, molecular profile, clinical behavior, and therapeutic response (Łukasiewicz et al., 2021). Traditionally, histopathological grading using the Nottingham Histologic Score system has been an essential prognostic indicator. This system evaluates tubule formation, nuclear pleomorphism, and mitotic activity to classify tumors into Grade I, II, or III, reflecting increasing biological aggressiveness (Rakha et al., 2018; WHO, 2019). Higher histological grade is consistently associated with poorer prognosis, increased proliferative activity, and higher risk of recurrence (Sung et al., 2021).

In contemporary oncology practice, molecular classification based on immunohistochemical evaluation of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 has become fundamental in breast cancer stratification (Prat & Perou, 2010). This approach categorizes tumors into Luminal A, Luminal B, HER2-enriched, and Triple-negative subtypes. Each subtype exhibits distinct biological behavior, proliferation rate, and therapeutic responsiveness (Łukasiewicz et al., 2021; Prat & Perou, 2010). For example, Luminal A tumors are typically low proliferative and associated with favorable prognosis, whereas HER2-enriched and Triple-negative subtypes are often linked to aggressive clinical behavior and poorer outcomes (Łukasiewicz et al., 2021).

Several Indonesian studies have reported variation in the distribution of molecular subtypes across different institutions. Research conducted in South Sumatra demonstrated a predominance of Luminal B subtype and reported a significant correlation between Ki-67 expression and tumor grade (Harist et al., 2021). A national review by Nurmayeni and Windarti also highlighted heterogeneity in subtype distribution across Indonesian hospitals, emphasizing the need for institution-based epidemiological data (Nurmayeni & Windarti, 2022). These findings suggest that molecular subtype patterns may differ regionally and may correlate with histopathological characteristics.

Although histological grade and molecular subtype are independently recognized as important prognostic parameters, their biological interrelationship remains a critical area of investigation. Theoretically, tumors with higher proliferative molecular profiles are expected to demonstrate higher histological grades, reflecting concordance between molecular aggressiveness and morphological differentiation. Understanding this relationship is clinically relevant because it strengthens prognostic stratification and supports precision-based therapeutic decision-making.

At dr. H. Jusuf SK Regional General Hospital, data regarding the relationship between molecular subtype and histological grade have not previously been analyzed. Given the limited availability of institution-based analytical data in secondary healthcare settings, evaluating this association is important to better understand local tumor biology and to support evidence-based oncology service planning. Therefore, this study aims to analyze the relationship between molecular subtypes and histological grade of Nottingham breast carcinoma at dr. H. Jusuf SK Regional General Hospital during the period January 2023 to September 2025.

3. Materials and Method

Study Design and Setting

This study was a retrospective analytical cross-sectional study conducted at dr. H. Jusuf SK Regional General Hospital. The research was carried out in the Medical Records Unit and the Anatomical Pathology Laboratory. The data analyzed included breast carcinoma cases diagnosed between January 2023 and September 2025. An analytical cross-sectional approach was used to evaluate the association between molecular subtype and histological grade at a single point of assessment based on archived pathological data.

A similar approach has also been used in previous studies analyzing the relationship between molecular subtypes of breast cancer and histopathological characteristics, including histological grade (Devadass et al., 2023; Setyawati et al., 2018).

Population and Sample

The target population consisted of all patients diagnosed with breast carcinoma at dr. H. Jusuf SK Regional General Hospital during the study period. A total sampling method was initially applied to identify all eligible cases. However, for the analytical phase, only patients with complete immunohistochemical examination results, including estrogen receptor (ER),

progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 expression, were included in the final analysis. Cases without complete molecular subtype data were excluded from the association analysis. Based on these criteria, 51 patients were eligible and included in the analytical dataset.

Patients were included if they had a histopathologically confirmed diagnosis of invasive breast carcinoma, a documented Nottingham histological grade, complete immunohistochemical results for ER, PR, HER2, and Ki-67, and legible medical record documentation. Cases were excluded if histopathological reports were incomplete, immunohistochemical data were missing, or tissue preparations were damaged or uninterpretable, potentially compromising diagnostic accuracy. A similar approach has been applied in previous studies, where only breast cancer cases with complete immunohistochemical data (ER, PR, HER2, and Ki-67) were included in the final analysis to determine molecular subtypes and tumor characteristics (Kakudji et al., 2021).

Study Variables and Operational Definitions

The independent variable in this study was molecular subtype, which was classified based on immunohistochemical evaluation according to the recommendations of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP). Tumors were categorized as Luminal A when estrogen receptor (ER) and/or progesterone receptor (PR) were positive, HER2 was negative, and the Ki-67 proliferation index was low. Luminal B tumors were defined as ER and/or PR positive with either HER2 negativity or positivity accompanied by a high Ki-67 index. The HER2-enriched subtype included tumors that were ER and PR negative but HER2 positive, whereas Triple-negative tumors were defined as ER, PR, and HER2 negative. This classification of molecular subtypes based on immunohistochemical markers is widely used to describe the biological characteristics and therapeutic response of breast cancer (Allison et al., 2020; Yersal & Barutca, 2014).

The dependent variable was histological grade, determined using the Nottingham Histologic Score (NHS) system. This grading system evaluates three morphological components, namely tubule formation, nuclear pleomorphism, and mitotic count. Based on the cumulative score, tumors were classified into Grade I (well differentiated), Grade II (moderately differentiated), or Grade III (poorly differentiated).

Data Collection Procedure

Data were obtained from archived histopathology reports and immunohistochemistry results maintained in the Anatomical Pathology Laboratory database. A standardized data extraction form was used to ensure systematic and consistent collection of relevant variables. All extracted data were reviewed for completeness and subsequently entered into statistical software for analysis. A similar approach has been used in retrospective pathology-based studies, where clinical and histopathological data are systematically extracted from archived laboratory reports for research analysis (Liza et al., 2022).

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS). Descriptive statistics were used to summarize the distribution of molecular subtypes and histological grades. Cross-tabulation analysis was conducted to evaluate the distribution of histological grade across different molecular subtypes. Because several cells in the contingency table had expected frequencies less than five, the association between molecular subtype and histological grade was analyzed using Fisher's Exact Test. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

This study received ethical approval from the Research Ethics Committee of dr. H. Jusuf SK Regional General Hospital. All patient data were anonymized and handled confidentially in accordance with the principles of the Declaration of Helsinki. No personal identifiers were included in the data analysis.

4. Results and Discussion

A total of 51 breast carcinoma patients with complete immunohistochemical data were included in the analytical phase of this study. These cases were selected from the overall diagnosed cases during the study period based on the availability of complete molecular subtype evaluation.

Distribution of Molecular Subtypes

Among the 51 patients analyzed, Luminal B was the most frequently identified molecular subtype, accounting for 20 cases (39.2%). Luminal A was observed in 14 cases (27.5%), HER2-enriched in 13 cases (25.5%), and Triple-negative in 4 cases (7.8%). This distribution indicates that hormone receptor–positive subtypes constituted the majority of tumors in the analytical cohort.

Distribution of Histological Grade

Regarding histological grading based on the Nottingham Histologic Score system, Grade III tumors were the most common, representing 26 cases (51.0%). Grade II tumors accounted for 20 cases (39.2%), while Grade I tumors were the least frequent, observed in 5 cases (9.8%). These findings demonstrate that more than half of the analyzed tumors exhibited poor differentiation.

Table 1. Basic Characteristics of Breast Carcinoma Patients with Immunohistochemistry Data (n = 51).

Variable	n	%
Age (years)		
Mean ± SD	48.0 ± 8.9	–
Median (min–max)	47 (32–68)	–
< 40 years	9	17.6
40–59 years	36	70.6
≥ 60 years	6	11.8
Histopathological Type		
Invasive Carcinoma of No Special Type (IDC-NST)	48	94.1
Invasive Lobular Carcinoma	2	3.9
Mucinous Carcinoma	1	2.0
Histological Grade (Nottingham)		
Grade I	5	9.8
Grade II	20	39.2
Grade III	26	51.0
Molecular Subtype		
Luminal A	14	27.5
Luminal B	20	39.2
HER2-enriched	13	25.5
Triple-negative	4	7.8

Association Between Molecular Subtype and Histological Grade

Cross-tabulation analysis demonstrated variability in histological grade distribution across molecular subtypes.

Luminal A tumors were predominantly classified as Grade II (8 of 14 cases; 57.1%), with 4 cases (28.6%) classified as Grade III and 2 cases (14.3%) as Grade I. Luminal B tumors showed a broader distribution across grades; however, Grade III was the most frequent category (10 of 20 cases; 50.0%), followed by Grade II (35.0%) and Grade I (15.0%).

In contrast, HER2-enriched tumors demonstrated a clear predominance of high-grade morphology, with 9 of 13 cases (69.2%) classified as Grade III and the remaining 4 cases (30.8%) as Grade II. No HER2-enriched tumors were classified as Grade I. Similarly, Triple-negative tumors were predominantly Grade III, accounting for 3 of 4 cases (75.0%), with 1 case (25.0%) classified as Grade II and none classified as Grade I.

Overall, high-grade tumors (Grade III) were proportionally more common in HER2-enriched and Triple-negative subtypes compared to Luminal A and Luminal B subtypes.

Because several cells in the contingency table had expected counts below five, Fisher's Exact Test was used to assess the association between molecular subtype and histological grade. Statistical analysis demonstrated a significant association between molecular subtype and histological grade ($p < 0.05$).

These findings indicate that more biologically aggressive molecular subtypes, particularly HER2-enriched and Triple-negative tumors, are significantly associated with higher histological grade in this patient population.

Table 2. Association Between Molecular Subtype and Histological Grade of Nottingham Breast Carcinoma.

Molecular Subtype	Grade I n (%)	Grade II n (%)	Grade III n (%)	Total n (%)
Luminal A (n=14)	2 (14.3)	8 (57.1)	4 (28.6)	14 (27.5)
Luminal B (n=20)	3 (15.0)	7 (35.0)	10 (50.0)	20 (39.2)
HER2-enriched (n=13)	0 (0.0)	4 (30.8)	9 (69.2)	13 (25.5)
Triple-negative (n=4)	0 (0.0)	1 (25.0)	3 (75.0)	4 (7.8)
Total (n=51)	5 (9.8)	20 (39.2)	26 (51.0)	51 (100)

Discussion

This study demonstrated a statistically significant association between molecular subtype and histological grade in breast carcinoma patients at dr. H. Jusuf SK Regional General Hospital. High-grade tumors (Grade III) were proportionally more frequent in HER2-enriched and Triple-negative subtypes, whereas Luminal A tumors were more commonly associated with lower histological grades. These findings support the biological concordance between molecular behavior and morphological differentiation.

Histological grading using the Nottingham Histologic Score system remains one of the most established prognostic indicators in breast carcinoma. This system evaluates tubule formation, nuclear pleomorphism, and mitotic count to classify tumors into three grades reflecting increasing biological aggressiveness (Rakha et al., 2018; WHO, 2019). Numerous global studies have confirmed that higher histological grade correlates with poorer prognosis and increased proliferative activity (Sung et al., 2021). In the present study, more than half of the tumors were classified as Grade III, indicating a substantial burden of poorly differentiated carcinoma in this hospital-based population.

Molecular classification based on immunohistochemical evaluation has further refined prognostic stratification in breast cancer[2]. Luminal A tumors are generally characterized by low proliferation index and favorable prognosis, whereas Luminal B tumors exhibit higher proliferative activity. HER2-enriched and Triple-negative subtypes are widely recognized as biologically aggressive entities with higher recurrence rates and poorer clinical outcomes (Łukasiewicz et al., 2021). The predominance of Grade III tumors among HER2-enriched and Triple-negative cases in this study aligns with this biological framework.

Our findings are consistent with Indonesian studies that have reported a relationship between proliferative markers and histopathological characteristics. Research conducted in South Sumatra demonstrated a significant correlation between Ki-67 expression and tumor grade[7], suggesting that tumors with higher proliferative activity tend to exhibit poorer differentiation. Similarly, the predominance of Luminal B subtype reported in several Indonesian hospital-based studies (Nurmayeni & Windarti, 2022; Widiana & Irawan, 2020) may reflect higher Ki-67 expression in Asian populations, contributing to intermediate-to-high grade morphology. The present study reinforces this pattern by demonstrating that Luminal B tumors showed a considerable proportion of Grade III cases, although not as marked as in HER2-enriched and Triple-negative subtypes.

The strong predominance of high-grade morphology in HER2-enriched tumors observed in this study is biologically plausible. HER2 overexpression is associated with increased cellular proliferation, genomic instability, and aggressive tumor behavior(Prat & Perou, 2010),[10]. Similarly, Triple-negative breast cancer lacks hormone receptor expression and HER2 amplification, and is frequently associated with high mitotic index and poor differentiation[10]. The finding that 75% of Triple-negative tumors were Grade III in this cohort supports existing literature describing this subtype as an aggressive pathological entity.

Interestingly, Luminal A tumors in this study were more frequently associated with Grade II and lower-grade morphology. This is consistent with global evidence indicating that Luminal A tumors generally exhibit lower proliferative activity and better differentiation (Łukasiewicz et al., 2021; Prat & Perou, 2010). The morphological–molecular concordance observed in this study strengthens the validity of immunohistochemical classification as a reflection of underlying tumor biology.

From a clinical perspective, understanding the relationship between molecular subtype and histological grade enhances prognostic assessment and therapeutic planning. Histological grade provides morphological insight, while molecular subtype guides systemic therapy decisions, including hormonal therapy and anti-HER2 targeted therapy (Prat & Perou, 2010). The significant association observed in this study suggests that tumors with aggressive molecular profiles are also morphologically less differentiated, reinforcing the integrated role of pathology in precision oncology.

This study also highlights contextual challenges in secondary healthcare facilities. As reported in the previous descriptive phase, a substantial proportion of patients did not undergo immunohistochemical evaluation. Although the present analysis was limited to patients with complete biomarker data, the findings underscore the importance of expanding immunohistochemical coverage to enable comprehensive molecular stratification. Improving diagnostic capacity is essential to ensure appropriate therapeutic selection and optimize patient outcomes.

Several limitations should be acknowledged. First, the sample size of the analytical cohort was relatively small, particularly for the Triple-negative subgroup. Second, this was a single-center retrospective study, which may limit generalizability. Third, potential confounding variables such as tumor size, lymph node status, and clinical stage were not included in the analysis. Future prospective studies with larger sample sizes and multivariable analysis are recommended to further elucidate the prognostic interaction between molecular subtype and histological grade.

Despite these limitations, this study provides valuable institution-based analytical data demonstrating a significant association between molecular subtype and histological grade in a secondary hospital setting. The findings contribute to the growing body of Indonesian literature on breast cancer biology and support the integration of morphological and molecular evaluation in routine clinical practice.

5. Conclusion

This study demonstrates a statistically significant association between molecular subtype and histological grade in Nottingham breast carcinoma at dr. H. Jusuf SK Regional General Hospital. More biologically aggressive molecular subtypes, particularly HER2-enriched and Triple-negative tumors, were predominantly associated with high histological grade (Grade III), whereas Luminal A tumors were more frequently associated with lower or intermediate grades.

These findings support the biological concordance between molecular characteristics and morphological differentiation in breast carcinoma. The integration of immunohistochemical molecular classification with histological grading strengthens prognostic stratification and supports more precise therapeutic decision-making in clinical practice.

Although limited by sample size and retrospective design, this study provides important institution-based analytical evidence in a secondary healthcare setting. Expansion of immunohistochemical diagnostic capacity is essential to ensure comprehensive molecular evaluation and optimize evidence-based breast cancer management.

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