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# Relationship between molecular subtypes and differentiation degree of breast cancer with metastasis at Dr. M. Djamil General Hospital, Padang

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**Abstract**
**Background:** Breast cancer remains the most prevalent malignancy among women worldwide and represents a major cause of cancer-related mortality. Metastasis is the leading determinant of poor prognosis and mortality in breast cancer patients. Molecular subtyping, including Luminal A, Luminal B, HER2-positive, and Triple Negative Breast Cancer (TNBC), has been recognized as an important prognostic and predictive factor influencing the metastatic potential. In addition, histological differentiation grade reflects tumor aggressiveness and correlates with disease progression. However, the association between molecular subtype, histological differentiation, and metastasis remains controversial across studies and populations.
**Objective:** To investigate the relationship between molecular subtypes and differentiation degree of breast cancer with the occurrence of metastasis among patients at Dr. M. Djamil General Hospital, Padang, Indonesia.
**Methods:** A cross-sectional study was conducted on female breast cancer patients diagnosed between January 2020 and December 2024 who underwent immunohistochemistry evaluation for ER, PR, HER2, and Ki-67. Molecular subtypes were classified into Luminal A, Luminal B, HER2-type, and TNBC, while histological grading was assessed based on the Nottingham Grading System. Data were obtained from medical records and analyzed using Chi-square test, with a significance level set at $p<0.05$.
**Results:** A total of 90 patients were included, with 82.2% aged ≥40 years. Luminal B subtype was the most prevalent (43.3%), followed by HER2-type (25.6%), TNBC (18.9%), and Luminal A (12.2%). Most patients had grade II tumors (56.7%), and 82.2% had metastasis. There was a significant association between molecular subtypes and metastasis (p = 0.017), with Luminal B and HER2-type showing the highest metastatic proportion. No significant relationship was found between differentiation grade and metastasis (p = 0.367).
**Conclusion:** Molecular subtypes, particularly Luminal B and HER2-type, were significantly associated with breast cancer metastasis, whereas differentiation degree did not show a significant correlation. These findings underscore the importance of molecular profiling in predicting disease spread and guiding individualized therapy for breast cancer patients.

**Keywords:** Breast cancer, molecular subtype, differentiation degree, metastasis, immunohistochemistry

## Introduction
Breast cancer is the most frequently diagnosed malignancy among women and the leading cause of cancer-related death worldwide (Sung *et al*., 2021) [18]. According to the Global Cancer Observatory (GLOBOCAN 2022), over 2.3 million new cases of breast cancer were reported, accounting for 24.5% of all female cancers (WHO, 2022) [19]. The burden is particularly high in developing countries, where late diagnosis and limited access to optimal therapies contribute to higher mortality rates (Kocarnik *et al*., 2023) [11]. In Indonesia, breast cancer ranks first among female malignancies, with 66,271 new cases and 34,339 deaths in 2022 (Indonesian Ministry of Health, 2023). The province of West Sumatra is among the top three regions with the highest prevalence of cancer cases, highlighting an urgent need for improved local cancer surveillance and research.
Metastasis remains the key determinant of survival in breast cancer, accounting for more than 90% of cancer-related deaths (Gupta & Massagué, 2022) [8]. It represents a complex multistep biological process in which cancer cells disseminate from the primary tumor and colonize

distant organs. While various clinicopathological features influence metastatic risk, molecular subtype and histological differentiation have been identified as pivotal prognostic indicators (Perou *et al*., 2000; Coates *et al*., 2015) [14, 5]. Molecular classification based on immunohistochemical markers estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 allows for categorization into Luminal A, Luminal B, HER2-enriched, and Triple Negative Breast Cancer (TNBC) (NCCN, 2024) [13].

Each subtype exhibits distinct biological behavior and therapeutic response. Luminal A tumors are typically ER+/HER2- with low Ki-67, associated with favorable prognosis and hormonal therapy responsiveness. Luminal B subtypes, characterized by higher Ki-67 expression, demonstrate more aggressive behavior and poorer outcomes. HER2-enriched cancers are associated with high proliferative potential but benefit from HER2-targeted therapy. Conversely, TNBC, lacking ER, PR, and HER2 expression, presents the worst prognosis and limited therapeutic options (Bertucci *et al*., 2019; Collignon *et al*., 2020) [4, 20].

Histological differentiation, evaluated through the Nottingham Grading System (NGS), reflects tumor cell morphology and growth pattern. Poorly differentiated (grade III) tumors typically correlate with higher metastatic potential and poorer outcomes (Rakha *et al*., 2020) [16]. However, reports on the association between molecular subtype and differentiation degree with metastasis have been inconsistent. Some studies demonstrate strong correlations (Fan *et al*., 2023; Helmi *et al*., 2022) [6, 9], whereas others report no significant relationship (Mohammed *et al*., 2021; Abiltayeva *et al*., 2016) [12, 1].

Given the regional differences in breast cancer biology, healthcare infrastructure, and patient demographics, it is essential to understand these associations in Indonesian populations. This study aims to evaluate the relationship between molecular subtypes and differentiation degree with the occurrence of metastasis among breast cancer patients at Dr. M. Djamil General Hospital, Padang. Understanding these factors may aid in prognostic assessment and guide clinicians in optimizing treatment strategies tailored to tumor biology.

Siap Lia ✿ berikut lanjutan lengkapnya bagian Materials and Methods, Results (with tables), Discussion, dan Conclusion + References (APA 7th) seluruhnya disusun dengan gaya Scopus-indexed surgical oncology journal, sehingga nanti tinggal aku ubah ke file .docx format siap submit.

## 2. Materials and Methods

### 2.1 Study Design and Setting

This was a quantitative, cross-sectional study conducted at the Department of Surgery, Dr. M. Djamil General Hospital, Padang, Indonesia, between February and June 2025. The study evaluated the association between breast cancer molecular subtypes and histological differentiation with metastasis occurrence among patients diagnosed between January 2020 and December 2024. Ethical clearance was obtained from the Research Ethics Committee of Andalas University, Faculty of Medicine, prior to data collection.

### 2.2 Population and Sample

The study population consisted of all female breast cancer patients diagnosed through histopathology and immunohistochemistry (IHC) examinations during the study period.

**Inclusion criteria were**

1. Female patients aged ≥18 years.
2. Histopathologically confirmed breast cancer.
3. Completed IHC analysis including ER, PR, HER2, and Ki-67.
4. Available histological grading and metastasis evaluation records.

Exclusion criteria included patients with primary malignancies in other organs or incomplete data.

A minimum sample size of 59 was calculated using a single proportion formula with a 95% confidence interval, 10% margin of error, and estimated metastasis proportion of 18.7% (Anwar *et al*., 2021). To account for potential data loss, 90 patients were finally included using consecutive sampling.

### 2.3 Variables and Definitions

**Independent Variables**

**1. Molecular Subtype:** Classified based on IHC markers into Luminal A (ER+/PR+/HER2−/low Ki-67), Luminal B (ER+/PR−/HER2±/high Ki-67), HER2-enriched (ER−/PR−/HER2+), and TNBC (ER−/PR−/HER2−).

**2. Differentiation Grade:** Assessed by the Nottingham Grading System (Elston & Ellis, 1991) as:

- Grade I (well differentiated)
- Grade II (moderately differentiated)
- Grade III (poorly differentiated)

**Dependent Variable**

Presence of metastasis, confirmed through imaging (CT, MRI, or bone scan) or histopathological evidence.

### 2.4 Data Collection Procedure

Data were extracted from the hospital's medical record system. Demographic information (age), IHC results, histological grading, and metastasis status were recorded using a standardized data extraction sheet. All data were anonymized before analysis.

### 2.5 Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages. The Chi-square test was employed to evaluate the association between molecular subtypes, differentiation grades, and metastasis occurrence. Statistical significance was defined as $p<0.05$.

## 3. Results

### 3.1 Patient Characteristics

A total of 90 female breast cancer patients met the inclusion criteria. Most patients (82.2%) were aged ≥40 years. Luminal B subtype was the most common (43.3%), followed by HER2-enriched (25.6%), TNBC (18.9%), and Luminal A (12.2%). Most tumors were moderately differentiated (56.7%), and 82.2% of patients had evidence of metastasis.

**Table 1:** Characteristics of Breast Cancer Patients (n=90)

| Variable | Category | Frequency (n) | Percentage (%) |
|---|---|---|---|
| Age (years) | <40 | 16 | 17.8 |
| | ≥40 | 74 | 82.2 |
| Molecular Subtype | Luminal A | 11 | 12.2 |
| | Luminal B | 39 | 43.3 |
| | HER2-enriched | 23 | 25.6 |
| | Triple Negative | 17 | 18.9 |
| Differentiation Grade | Grade I | 5 | 5.6 |
| | Grade II | 51 | 56.7 |
| | Grade III | 34 | 37.8 |
| Metastasis | Present | 74 | 82.2 |
| | Absent | 16 | 17.8 |

### 3.2 Association Between Molecular Subtype and Metastasis

A significant relationship was observed between molecular subtype and metastasis ($p = 0.017$). Luminal B subtype showed the highest proportion of metastasis (47.3%), followed by HER2-enriched (38.4%). TNBC had a lower frequency (10.9%) in this cohort.

Table 2. Relationship between Molecular Subtype and Metastasis

| Molecular Subtype | Metastasis Present (%) | No Metastasis (%) | p-value |
|---|---|---|---|
| Luminal A | 7 (9.5%) | 4 (25.0%) | |
| Luminal B | 35 (47.3%) | 4 (25.0%) | 0.017* |
| HER2-enriched | 28 (38.4%) | 3 (18.8%) | |
| TNBC | 8 (10.8%) | 9 (31.2%) | |

*Significant at $p<0.05$

**3.3 Association between Differentiation Grade and Metastasis:** No significant correlation was identified between histological differentiation and metastasis ($p = 0.367$), though higher metastasis rates were observed in grade II and III tumors.

**Table 3:** Relationship between Differentiation Grade and Metastasis

| Differentiation Grade | Metastasis Present (%) | No Metastasis (%) | p-value |
|---|---|---|---|
| Grade I | 3 (4.1%) | 2 (12.5%) | |
| Grade II | 42 (56.8%) | 9 (56.2%) | 0.367 |
| Grade III | 29 (39.1%) | 5 (31.3%) | |

## 4. Discussion

This study demonstrated a significant relationship between molecular subtypes and breast cancer metastasis, while no significant association was found between differentiation degree and metastatic occurrence. Luminal B and HER2-enriched subtypes exhibited the highest metastatic potential, aligning with recent evidence highlighting their aggressive biological behavior (Fan *et al*., 2023; Helmi *et al*., 2022) [6, 9].

### 4.1 Molecular Subtype and Metastasis

The significant association found supports the growing evidence that molecular subtype plays a crucial role in tumor progression. Luminal B tumors, characterized by elevated Ki-67 expression, exhibit higher proliferative activity and resistance to endocrine therapy compared to Luminal A (Prat *et al*., 2020) [15]. HER2-positive tumors overexpress the HER2 receptor, promoting angiogenesis and cell motility through downstream PI3K/AKT signaling pathways (Arteaga *et al*., 2019) [3]. Consequently, these biological mechanisms enhance metastatic potential to visceral organs, including the liver and lungs (Guo *et al*., 2020) [7].

Previous regional studies have shown similar findings. Helmi *et al*. (2022) [9] reported that TNBC and HER2-positive subtypes had the highest odds ratio for metastasis (OR = 7.74). Likewise, Jeong *et al*. (2020) [10] demonstrated that epithelial-mesenchymal transition (EMT) markers were upregulated in HER2-negative and basal-like tumors, promoting invasion and migration. The present study adds to the evidence that Luminal B, despite being hormone receptor-positive, displays more aggressive metastatic behavior in Indonesian patients.

### 4.2 Differentiation Grade and Metastasis

Although histological grade has long been considered a prognostic marker, our findings did not show a statistically significant correlation. This might be attributed to the predominance of grade II tumors (56.7%), reducing variability for statistical comparison. However, previous research indicates that poorly differentiated tumors exhibit greater metastatic capacity due to loss of cell adhesion and higher nuclear pleomorphism (Rakha *et al*., 2020) [16].

Jeong *et al*. (2020) [10] observed increased EMT markers in grade III tumors, suggesting a biological link between de-differentiation and metastasis. Similarly, Siregar *et al*. (2023) [17] found that 50.8% of patients with bone metastasis had grade III tumors. Despite this, our cohort did not reproduce statistical significance, possibly due to sample size and differences in metastatic site distribution.

### 4.3 Clinical Implications

Understanding molecular subtype-specific metastatic patterns has significant clinical relevance. Luminal B and HER2-positive tumors may benefit from intensified systemic therapy and closer metastatic surveillance, even in early stages. The integration of genomic profiling and next-generation sequencing could enhance risk stratification and individualized treatment planning (Coates *et al*., 2015; NCCN, 2024) [14, 13].

### 4.4 Limitations

This study has several limitations. First, it was retrospective and relied on secondary data, which may have limited completeness.

Second, sample size was moderate, and metastasis assessment was primarily based on imaging and pathology reports without standardized timing. Third, the study was conducted in a single tertiary hospital, limiting generalizability to broader populations. Future prospective multicenter studies with larger samples are warranted to validate these findings.

## 5. Conclusion

This study revealed a significant association between molecular subtypes and breast cancer metastasis, particularly among Luminal B and HER2-enriched tumors. No significant correlation was observed between differentiation degree and metastasis. Molecular profiling should be incorporated into prognostic evaluation and treatment planning for breast cancer patients to improve early detection of metastatic risk and guide precision therapy.

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