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Clinical and Histopathological Profile of Breast Cancer Based on HER2 Stratification ASCO/CAP 2018: Analysis of HER2-Positive, Negative, Low, and Ultralow

Novasari[1]*, Citra Dewi[1,2], Sandria[1], Nora Ramkita[1,3]
[1]Department of Anatomical Pathology, Faculty of Medicine, Universitas Sriwijaya, Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia
[2]Department of Anatomical Pathology, Ministry of Health of the Republic of Indonesia, Sitanala General Hospital, Tangerang, Banten, Indonesia
[3]Department of Anatomical Pathology, Ministry of Health of the Republic of Indonesia, Dr. Rivai Abdullah General Hospital, Banyuasin, South Sumatra, Indonesia

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Corresponding author:
Novasari
E-mail address:
jandi_sabrina@yahoo.co.id

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ABSTRACT

Introduction. The emerging classification of HER2-low and HER2-ultralow breast cancer subtypes has important treatment implications, especially after the introduction of trastuzumab deruxtecan, which is effective in tumors exhibiting low levels of HER2 expression. However, data from Indonesia are still limited. This study aimed to characterize the clinicopathological features of Invasive Breast Cancer (IBC) according to the ASCO/CAP 2018 HER2 classification and to determine the proportion of HER2-negative patients who can be further categorized as HER2-low or HER2-ultralow. **Methods**. This retrospective descriptive-analytical study involved 50 patients diagnosed with IBC who underwent HER2 immunohistochemical evaluation at Mohammad Hoesin General Hospital, Palembang, in February 2023. The variables analyzed were age, ER/PR status, Ki-67 index, tumor-infiltrating lymphocytes (TILs), lymphovascular invasion (LVI), histological grade, and tumor subtype. **Results**. Of the 50 patients, 16 (32%) were categorized as HER2-positive and 34 (68%) were categorized as HER2-negative. Among the HER2-negative group, 10 patients (35.7%) were HER2-low and 5 patients (17.8%) were HER2-ultralow. The majority of patients were aged 40 years or older and ER-positive. A high Ki-67 index was observed in 84% of cases. Most tumors were grade II–III and of the NST subtype. No significant differences were observed between the HER2-low and HER2-ultralow groups ($p>0.05$). **Conclusion**. A considerable proportion of HER2-negative IBCs are categorized as HER2-low or HER2-ultralow. These findings highlight the importance of accurate HER2 assessment to identify patients who may benefit from antibody–drug conjugate therapy and to advance precision medicine in breast cancer management in Indonesia.

1. Introduction

Breast cancer is the most prevalent malignancy among women worldwide and continues to be a leading cause of morbidity and mortality. Recent advances in molecular pathology have refined our understanding of the biological heterogeneity of breast cancer, particularly with respect to Human Epidermal Growth Factor Receptor-2 (HER2) expression. Traditionally, breast cancers have been clinically categorized as either HER2-positive or HER2-negative, with only HER2-positive patients considered eligible for anti-HER2 targeted therapy. However, the emerging classifications of HER2-low and HER2-ultralow suggest that a considerable proportion of tumors previously classified as HER2-negative still exhibit low levels of HER2 expression. [1-3]

These developments are relevant to emerging therapeutic stratification through the introduction of antibody–drug conjugates such as trastuzumab deruxtecan, which has shown clinical benefit even in tumors with low HER2 expression.[4] As a result, patient groups that were previously ineligible for HER2-directed therapy may now be considered potential candidates for precision-based treatment. Nevertheless, accurate identification of HER2-low and HER2-ultralow tumors requires meticulous immunohistochemical interpretation and an appreciation of the biological variability in HER2 expression.

Currently, data describing the prevalence of HER2-low and HER2-ultralow breast cancers across diverse populations, including Indonesia, remains limited. Such information is needed to better characterize the clinicopathological features of affected patients and to determine the proportion of cases that shift classification when applying extended HER2 categories beyond the ASCO/CAP 2018 system.

In light of the increasing therapeutic relevance of HER2-directed strategies in these subgroups, establishing local epidemiological profiles has become increasingly important.

Therefore, this study aimed to determine the proportion and clinicopathological characteristics of Invasive Breast Cancer (IBC) patients based on the ASCO/CAP 2018 HER2 classification, and to identify the proportion of HER2-negative patients that fall within the HER2-low and HER2-ultralow categories. These findings are expected to contribute to the optimization of HER2 interpretation. and support the development of more precise therapeutic strategies in breast cancer care.

2. Methods

This study was an observational, analytical investigation with a retrospective design, utilizing medical records and anatomical pathology archives from patients diagnosed with IBC who had undergone HER2 immunohistochemistry (IHC) examination at Dr. Mohammad Hoesin General Hospital, Palembang. Data were obtained from the Department of Anatomical Pathology in August 2025 and included all patients who underwent HER2 testing in February 2023.

Collected variables included patient age at diagnosis, histological type, histological grade, and immunohistochemical profile comprising HER2 status, estrogen receptor (ER), progesterone receptor (PR), Ki-67 proliferation index, tumor-infiltrating lymphocytes (TILs), and lymphovascular invasion (LVI). HER2 status was classified based on the ASCO/CAP 2018 guidelines as HER2-positive or HER2-negative, and further subclassified into HER2-low and HER2-ultralow using IHC staining intensity and tumor cell proportion. A total sampling technique was used to include all patients meeting the inclusion and exclusion criteria.

HER2 IHC assessment was performed by certified anatomical pathologists using light microscopy. Re-evaluation was carried out for cases initially scored as 0 to confirm HER2-ultralow status, according to the presence of faint or incomplete membranous staining in a small proportion of tumor cells. All data were anonymized and recorded using standardized reporting formats.

HER2-low was characterized by an IHC score of 1+ or 2+ without HER2 gene amplification, in accordance with post-ASCO/CAP therapeutic stratification concepts. HER2-ultralow was characterized as an IHC score of 0 with faint, incomplete membranous staining in ≤10% of tumor cells, based on recent literature. It should be noted that HER2-low and HER2-ultralow are not official categories in ASCO/CAP 2018 but represent extended therapeutic classifications.

Re-evaluation of HER2 IHC slides was conducted independently by two experienced anatomical pathologists without prior access to the clinical data. In case of discrepancy, a consensus was reached through joint review.

The Ki-67 proliferation index represented the proportion of stained tumor nuclei and was grouped into low (<20%) and high (≥20%) categories based on St. Gallen criteria. The International TILs Working Group (2014) recommends averaging TILs on one 200–400× invasive tissue section (excluding necrosis/artifacts). Tumors with stromal tumor-infiltrating lymphocytes (TILs) involving more than 50% of the stromal area were categorized as TILs-dominant, while those with TILs involving 50% or less of the stromal area were categorized as TILs-non-dominant. LVI was assessed on hematoxylin–eosin stained sections.

Statistical analyses were completed using SPSS version 25. Results were presented as frequency distributions and tables. Categorical variables were analyzed using Fisher's exact test, and a p-value of <0.05 was regarded as statistically significant. Ethical approval for this study was obtained from the Institutional Review Board of Dr. Mohammad Hoesin General Hospital (No: 079/KEPK/2025) and did not involve direct patient intervention.

3. Results

This study analyzed 50 patients with IBC, consisting of 16 patients (32%) with HER2-positive status and 34 patients (68%) with HER2-negative status. Most patients were aged ≥40 years in both the HER2-positive and HER2-negative groups, and no significant association was found between age category and HER2 status (p=0.406).

Most patients showed positive hormonal receptor expression, with ER positivity in 68% and PR positivity in 60% of patients. In the HER2-positive group, ER positivity was observed in 75% of patients and PR positivity in 56.25%, while in the HER2-negative group, the corresponding values were 64.7% and 61.76%, respectively. However, neither ER nor PR status was significantly correlated with HER2 status (p=0.533 and p=0.763).

All patients demonstrated a positive Ki-67 proliferation index with predominance of the high category. High Ki-67 was identified in 87.5% of HER2-positive patients and 82.36% of HER2-negative patients, with no significant difference identified between the groups (p=1.000). Histologic grade was predominantly grade III in both groups, accounting for 87.5% of HER2-positive patients and 76.47% of HER2-negative patients, and no significant association was identified between histological grade and HER2 status (p=0.468).

Analysis of TILs showed that the non-dominant category was the most common pattern in both groups, comprising 81.25% of HER2-positive patients and 73.52% of HER2-negative patients, with no significant difference (p=0.728). LVI was identified in 37.5% of HER2-positive patients and 64.7% of HER2-negative patients; however, no statistically significant

difference was found (p=0.126). The most frequent histologic type in both groups was NST, with no significant difference observed (p=1.000).

Further analysis of HER2-negative patients identified 28 cases that were further classified into HER2-zero, HER2-ultralow, and HER2-low categories. Six patients did not meet the criteria and could not be clearly classified into further subclassification; therefore, to avoid bias, these cases were excluded. Most patients were classified as HER2-zero (46.4%), followed by HER2-low (35.7%) and HER2-ultralow (17.8%). Fifteen patients were included in the HER2-low and HER2-ultralow groups, with a greater proportion in the HER2-low group (66.7%).

Table 1. Baseline characteristics of invasive breast carcinoma patients based on HER2 ASCO/CAP 2018 classification

Variable	Category	HER2 Positive (%)	HER2 Negative (%)	n (%)	p-value
Age Category	<40 years	1 (6.35)	6 (17.64)	7 (14)	*0.406
	≥40 years	15 (93.75)	28 (82.36)	43 (86)	
ER Status	Positive	12 (75)	22 (64.7)	34 (68)	*0.533
	Negative	4 (25)	12 (35.3)	16 (32)	
PR Status	Positive	9 (56.25)	21 (61.76)	30 (60)	*0.763
	Negative	7 (43.75)	13 (38.24)	20 (40)	
Ki-67 Index	High	14 (87.5)	28 (82.36)	42 (84)	*1.000
	Low	2 (12.5)	6 (17.64)	8 (16)	
TILs	Dominant	3 (18.75)	9 (26.47)	12 (24)	*0.728
	Non-dominant	13 (81.25)	25 (73.52)	38 (76)	
LVI	Positive	6 (37.5)	22 (64.7)	28 (56)	*0.126
	Negative	10 (62.5)	12 (35.29)	22 (44)	
Histologic Grade	Grade I	0 (0)	1 (2.94)	1 (2)	*0.468
	Grade II	2 (12.5)	7 (20.58)	9 (18)	
	Grade III	14 (87.5)	26 (76.47)	40 (80)	
Histologic Type	NST	15 (93.75)	31 (91.17)	46 (92)	*1.000
	Non-NST	1 (6.25)	3 (8.82)	4 (8)	
Total		16	34	50 (100)	

Fisher's exact test; p-value considered significant if <0.05

Table 2. Distribution of HER2-zero, ultralow, and low patients

HER2 IHC Score Classification	N	Percentage (%)
0	13	46.4
0+	5	17.8
1+	10	35.7
Total	28	100

Table 3. Clinicopathological characteristics of patients based on HER2-low and ultralow

Variable	Category	HER2-Low (%)	HER2-Ultralow (%)	n (%)	p-value
Age Category	<40 years	2 (20)	2 (40)	4 (27)	*0.406
	≥40 years	8 (80)	3 (60)	11 (73)	
ER Status	Positive	9 (90)	3 (60)	12 (80)	*0.242
	Negative	1 (10)	2 (40)	3 (20)	
PR Status	Positive	8 (80)	3 (60)	11 (73)	*0.560
	Negative	2 (20)	2 (40)	4 (27)	
Ki-67 Index	High	8 (80)	4 (80)	12 (80)	*1.000
	Low	2 (20)	1 (20)	3 (20)	
TILs	Dominant	8 (80)	5 (100)	13 (87)	*0.524
	Non-dominant	2 (20)	0 (0)	2 (13)	
LVI	Positive	4 (40)	1 (20)	5 (33)	*0.600
	Negative	6 (60)	4 (80)	10 (67)	
Histologic Grade	Grade I	0 (0)	1 (20)	1 (6)	*0.600
	Grade II	4 (40)	0 (0)	4 (26)	
	Grade III	6 (60)	4 (80)	10 (67)	
Histologic Type	NST	9 (90)	4 (80)	13 (87)	*1.000
	Non-NST	1 (10)	1 (20)	2 (13)	
Total		10	5	15 (100)	

Fisher's exact test; p-value considered significant if <0.05

The distribution of clinicopathological characteristics among the HER2-low and HER2-

ultralow groups showed similar results. ER and PR positivity were more frequently observed in the HER2-low group compared with the HER2-ultralow group; however, no statistically significant differences were found. Ki-67 index, TILs, LVI, histologic grade, and histologic type also showed no statistically significant differences, with all p-values >0.05. Overall, no significant clinicopathological differences were found among the HER2-low and HER2-ultralow groups in this study population.

4. Discussion

As no statistically significant differences were observed, the following interpretations should be considered exploratory and hypothesis-generating rather than confirmatory. The lack of statistically significant associations in this study may be due to the limited sample size and low statistical power, particularly in subgroup analyses involving a small number of patients.

The majority of IBC patients in this study were aged ≥40 years in both HER2-positive and HER2-negative groups. This finding aligns with epidemiological evidence that breast cancer incidence increases with age, particularly after the fourth decade of life.[5] Although HER2-positive Tumors occurred more frequently in older patients in this cohort, no statistically significant association was observed between age and HER2 status, suggesting that age alone may not be a distinguishing factor in HER2 expression patterns in this population.

Hormone receptor positivity (ER and PR) was observed in most cases across both HER2 groups, with no statistically significant differences. This suggests that, within this study population, hormone receptor expression is relatively evenly distributed regardless of HER2 status. These findings are similar to those reported in previous studies reporting overlap between HER2 expression and hormone receptor positivity, particularly in luminal subtypes.[6,7] However, owing to the lack of a significant association, these results should be interpreted cautiously.

A high Ki-67 proliferation index was observed in the majority of patients (84%), indicating that most tumors in this cohort exhibit high proliferative activity. Despite this, no significant difference was detected between HER2-positive and HER2-negative groups. This suggests that high proliferative activity may be a common feature across different HER2 categories in this population, rather than being specifically associated with HER2 status.[8]

Histologic grade was predominantly grade III in both groups, further supporting the observation that many tumors in this cohort have aggressive histopathological features. However, similar to other variables, no statistically significant relationship was identified between histologic grade and HER2 status. This indicates that tumor differentiation in this study does not appear to be strongly influenced by HER2 classification alone.[9–11]

The analysis of TILs showed that most tumors were categorized as non-dominant, with no significant differences between HER2 groups. This finding suggests that the immune microenvironment, as reflected by TILs, may not differ substantially across HER2 categories in this cohort. Previous studies have reported variability in TILs distribution depending on tumor subtype, but such differences were not observed in this study, possibly due to the limited sample size.[12,13,14]

LVI was more commonly found in HER2-negative cases in comparison with HER2-positive cases, although the difference did not reach statistical significance. This finding may reflect heterogeneity within the HER2-negative group, which includes biologically diverse subtypes such as luminal and triple-negative tumors. However, without further subclassification and staging data, this observation remains descriptive.[15–19]

Additional categorization of HER2-negative tumors into HER2-zero, HER2-low, and HER2-ultralow revealed that a considerable proportion of cases fell into the HER2-low and HER2-ultralow categories. This supports the growing recognition that HER2-negative breast cancer is a heterogeneous group that may be further stratified based on low levels of HER2 expression.

When comparing HER2-low and HER2-ultralow groups, no significant differences were found across all clinicopathological variables, including age, hormone receptor status, Ki-67 index, TILs, LVI, histologic grade, and tumor type. This suggests that, within this study population, HER2-low and HER2-ultralow tumors share similar clinicopathological characteristics and may represent a closely related biological spectrum rather than distinct entities.[20, 21]

The lack of significant differences between these subgroups may also be influenced by the small sample size, particularly with only 15 patients included in the HER2-low and HER2-ultralow comparison. Therefore, these findings should be interpreted with caution and confirmed in larger cohorts.

This study presents several limitations. The relatively small sample size restricts statistical power and the ability to detect subtle differences between groups. In addition, the absence of tumor staging (TNM classification) limits the ability to fully interpret tumor aggressiveness. Furthermore, the retrospective design may contribute to selection bias and limit data completeness.

Despite these limitations, this study provides preliminary data on the distribution and clinicopathological characteristics of HER2-low and HER2-ultralow breast cancer in an Indonesian population. These findings may serve as a foundation for future studies exploring the clinical relevance of extended HER2 classification, particularly in relation to emerging therapeutic strategies.

Future studies with larger cohorts and prospective designs are needed to confirm these findings. Integration with clinical outcomes, including response to HER2-targeted therapies, including antibody–drug conjugates, will be essential to determine the clinical relevance of HER2-low and HER2-ultralow classifications.

5. Conclusion

This study demonstrates that most HER2-positive and HER2-negative breast cancer patients were aged ≥40 years, with a predominance of high Ki-67 expression and histologic grade III tumors. HER2-positive cancers were frequently hormone receptor–positive, reflecting biological interaction among HER2 and ER signaling pathways. Subclassification of HER2-negative tumors into HER2-low and HER2-ultralow revealed similar clinicopathological characteristics, with luminal dominance and high proliferative activity.

These findings emphasize the importance of comprehensive molecular evaluation in breast cancer for prognostic stratification and therapeutic decision-making. An individualized treatment approach based on HER2 and hormone receptor profiles is essential to optimize clinical outcomes in breast cancer patients.

Future studies with larger cohorts and prospective designs are needed to confirm these findings. Integration with clinical outcomes, including response to HER2-targeted therapies, including antibody–drug conjugates, will be essential to determine the clinical relevance of HER2-low and HER2-ultralow classifications.

6. Author Contribution

N. conducted the studies, collected the data samples, and composed the manuscript. C.D conceived the original idea and supervised the project. S. and N.R. provided assistance and guidance in the interpretation of the research results and specimens.

7. Acknowledgements

None to declare

8. References

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