ORIGINAL ARTICLE

HER2-negative breast cancer at a national hospital in Lima, Peru: retrospective analysis 2020–2024

Cáncer de mama HER2 bajo en un hospital nacional de Lima, Perú: análisis retrospectivo 2020–2024

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Ethical responsibilities: The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and institutional standards for research involving human subjects and the handling of biological samples. The authors are committed to scientific integrity and transparency in the presentation of results.

Data confidentiality: The information used was treated with absolute confidentiality. Clinical data and samples were anonymized to protect the identity of patients and were used solely for scientific research purposes.

Right to privacy and informed consent: In all cases, the rights of patients were respected. The images and data included do not allow the identification of the individuals involved, thus guaranteeing their privacy and dignity.

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ABSTRACT

Introduction: Breast cancer is the most common malignant neoplasm among women worldwide. Treatment has traditionally been guided by the expression of hormone receptors and other proteins related to cell proliferation, such as HER2 and Ki-67. HER2 status has been a key factor in therapeutic decision-making due to the availability of targeted therapies. However, recent studies have proposed the existence of a possible subgroup within HER2-negative tumors referred to as HER2-low that may benefit from new treatment options. Objective: To identify the proportion of breast cancer cases that could be classified as HER2-low in a national hospital in Peru. Methods: Observational, analytical, cross-sectional, and retrospective study. A total of 1,575 patients with a histopathological diagnosis of breast cancer were included, covering the period from 2020 to 2024. Results: Among all analyzed cases, the HER2-low subtype represented 37.6% of total breast cancer cases and 50.6% of those previously categorized as HER2-negative. Hormone receptor (HR) expression was more frequently observed in HER2-low tumors compared to HER2 0 and HER2-positive subtypes. Conclusions: HER2-low breast cancer accounts for a significant proportion of total cases, highlighting the importance of accurate molecular profiling. This subgroup could potentially benefit from newly emerging targeted therapies.
Key words: Breast Neoplasms; Receptor, ErbB-2; Immunohistochemistry; Molecular Targeted Therapy.

RESUMEN

Introducción: El cáncer de mama es la neoplasia maligna más frecuente en mujeres a nivel mundial. El tratamiento se ha basado históricamente en la expresión de receptores hormonales y de proteínas como HER2 y Ki-67. Determinar el estatus del HER2 ha sido crucial para definir esquemas terapéuticos debido a la existencia de tratamientos dirigidos. Sin embargo, investigaciones recientes proponen un subgrupo dentro de los casos HER2 negativos, denominado HER2 bajo, con potencial beneficio clínico ante nuevas terapias específicas. Objetivo: Determinar la proporción de casos de cáncer de mama clasificables como HER2 bajo en un hospital nacional del Perú. Métodos: Estudio observacional, analítico, transversal y retrospectivo. Se incluyeron 1575 pacientes con diagnóstico histopatológico de cáncer de mama atendidas entre los años 2020 y 2024. Resultados: El subtipo HER2 bajo representó el 37,6% del total de casos y el 50,6% entre los previamente categorizados como HER2 negativos. La expresión de receptores hormonales fue más frecuente en los casos HER2 bajo frente a los subtipos HER2 0 y HER2 positivo. Conclusiones: El subtipo HER2 bajo constituye una proporción significativa de los casos de cáncer de mama. Este hallazgo resalta la importancia de una clasificación molecular precisa, dado el potencial acceso a nuevas terapias dirigidas para este grupo emergente.
Palabras clave: Neoplasias de la Mama; Receptores ErbB-2; Inmunohistoquímica; Terapia Dirigida Molecularmente.

Introduction

Breast cancer represents the most prevalent malignant neoplasm among women globally. According to data from the Global Cancer Observatory (GLOBOCAN) 2022, it constitutes 19.9% of all neoplastic diagnoses in Peruvian women[(1)], thereby posing a significant public health concern that warrants priority attention.

Historically, breast cancer classification has relied primarily on histopathological criteria; however, these have demonstrated limited correlation with clinical outcomes and fail to adequately capture the intrinsic

biological heterogeneity of the tumor, a factor with substantial therapeutic and prognostic implications[2,3].

Within this framework, the characterization of the molecular profile of breast cancer has become an essential component of contemporary oncological practice. Accordingly, assessment of hormone receptor (HR) expression—including estrogen receptor (ER) and progesterone receptor (PR)—as well as human epidermal growth factor receptor 2 (HER2) status and the Ki-67 proliferation index in tumor tissue is required.

These molecular markers are determined using immunohistochemistry (IHC), a special staining procedure that uses antibodies to identify the presence of these antigens[4]. Although HER2 is naturally expressed in normal breast epithelium, its overexpression is recognized as a factor associated with poor prognosis and poor response to treatment[5].

According to the guidelines established by the American Society of Clinical Oncology and the American College of Pathologists (ASCO/CAP), HER2 status assessed by immunohistochemistry (IHC) is considered positive when protein expression meets the criteria for a score of 3+, and negative when the score is 0 or 1+. Cases assigned a score of 2+ are classified as equivocal, thereby requiring further evaluation of HER2 gene amplification through in situ hybridization (ISH), a method that is more specific, costly, and technically demanding, to definitively determine HER2 status[6].

In clinical practice, the determination of HER2 status has enabled the stratification of breast cancer into two principal therapeutic categories: HER2-positive and HER2-negative disease. Since 1998, patients with HER2-positive tumors have benefited from treatment with anti-HER2 monoclonal antibodies approved by the Food and Drug Administration (FDA), which have demonstrated significant improvements in survival outcomes[7].

Conversely, the HER2-negative subgroup, which comprises approximately 60% or more of breast cancer cases, lacked effective targeted therapeutic options until recently. In this context, findings from the DESTINY-Breast04 (DB-04) clinical trial introduced a novel therapeutic approach based on antibody–drug conjugates (ADCs), demonstrating clinical benefit in patients with metastatic breast cancer exhibiting low levels of HER2 expression[8–9].

Based on these findings, the term HER2-low breast cancer has been introduced to describe a subset of tumors previously categorized as HER2-negative[10], characterized by immunohistochemical expression scores of 1+ or 2+ in the absence of HER2 gene amplification as determined by ISH. This reclassification has generated new questions regarding both the magnitude of the therapeutic benefit associated with antibody–drug conjugates (ADCs) and the adequacy of current diagnostic methodologies for accurately assessing HER2 expression[11–13].

In response, the updated ASCO/CAP 2023 guidelines recommend the use of the term HER2-low in clinical practice, although they suggest that pathology reports continue to report HER2 status as 0, 1+, 2+, or 3+[14-15], so that oncologists can identify patients who are potential candidates for HER2-low targeted therapies (Table 1).

The objective of the present study is to determine the proportion of breast cancer cases that may be classified as HER2-low at a national hospital in Peru. These data may provide an estimate of the potential demand for this novel therapeutic approach among eligible patients and, additionally, contribute to the epidemiological foundation for future studies of greater scale and methodological complexity.

Methods

Study design and setting: This was an observational, analytical, cross-sectional, retrospective study based on a review of pathology reports issued by the Surgical Pathology Service of the Guillermo Almenara Irigoyen National Hospital (HNGAI), Lima, Peru, during the period from January 2020 to December 2024.

Population and sample: The population consisted of all patients diagnosed with invasive breast carcinoma at the HNGAI between January 2020 and December 2024. The sample was non-pro-

Table 1. Interpretation of HER2 immunohistochemical staining patterns according to the 2018 ASCO/CAP guidelines and the 2023 ESMO consensus for HER2-low breast cancer

Staining Pattern Description	Designation in the guide ASCO/CAP 2018	Conclusion of the 2023 review of the 2018 ASCO/CAP guidelines	Recommendations for clinical practice ESMO 2023
No staining	HER2-0	HER2 negative	HER2 null
Incomplete and/or faint staining in ≤10% of invasive tumor cells	HER2-0	HER2 negative	HER2 ultra-low
Incomplete and/or faint staining in >10% of invasive tumor cells	HER2 1+	HER2 negative	HER2 low
Weak to moderate complete membrane staining in >10% of invasive tumor cells (ISH negative)	HER2 2+, non-amplified	HER2 negative	HER2 low
Weak to moderate complete membrane staining in >10% of invasive tumor cells (ISH positive)	HER2 2+, amplified	HER2 positive	HER2 positive
Strong, complete membrane staining in >10% of invasive tumor cells	HER2 3+	HER2 positive	HER2 positive

Note. Summary of HER2 immunohistochemistry (IHC) interpretation based on the 2018 ASCO/CAP guidelines, the 2023 update, and the 2023 ESMO consensus. Low HER2 includes IHC 1+ or 2+ with a negative ISH result.
ASCO/CAP: American Society of Clinical Oncology and American College of Pathologists; ESMO: European Society for Medical Oncology; ISH: in situ hybridization.
Adapted from: Tarantino P, et al. ESMO expert consensus statements on the definition, diagnosis, and management of HER2-low breast cancer. Ann Oncol. 2023;34(8):645–659.

babilistic for convenience and included all cases that met the established inclusion criteria.

Inclusion criteria:

- Confirmed histopathological diagnosis of invasive breast cancer.
- Complete immunohistochemistry panel for breast cancer (ER, PR, HER2, and Ki-67).
- Availability of in situ hybridization (ISH) study in cases with HER2 2+ results.

Exclusion criteria:

- Incomplete immunohistochemistry panel or unevaluable results.
- Cases with ambiguous HER2 results without confirmation by ISH.

Variables analyzed: The following variables were analyzed:

Estrogen receptor (ER) and progesterone receptor (PR): These were evaluated using immunohistochemistry, applying the Allred scoring system. Cases with a score ≥ 3 points were considered positive[16].

HER2: Immunohistochemical evaluation was interpreted according to the recommendations of the ASCO/CAP 2023 guideline[14], considering the intensity of membrane staining and the percentage of positive tumor cells: 0 (no staining or incomplete weak staining in <10% of cells), 1+ (incomplete weak staining in >10%), 2+ (weak/moderate complete staining in >10% or strong staining in ≤10%), and 3+ (intense complete staining in >10% of tumor cells). Cases with a 2+ result were reevaluated by in situ hybridization (ISH) to determine gene amplification.

To determine HER2 expression, clone SP3 (Master Diagnóstics, Vitro, Spain) was used on the Dako Autostainer Link 48 platform during the period 2020–2023. From 2024 onwards, clone 4B5 (Ventana, Roche Diagnostics, Switzerland) was implemented on the Ventana BenchMark ULTRA automated platform.

Ki-67 proliferation index: a cutoff point of 20% was considered, according to the 2013 St. Gallen consensus[17], to differentiate between low- and high-proliferation tumors.

Clinical and demographic variables: age, histological type, and tumor grade, obtained from the pathological records.

Instruments and procedures: Histopathological diagnoses were made on samples obtained by core biopsy, lumpectomy, or mastectomy. These samples followed routine histological processing protocols.

Tissues fixed in 10% formalin were embedded in paraffin and sectioned at a thickness of 3 µm, then stained with hematoxylin and eosin (H&E) for histological evaluation.

Immunohistochemistry was performed with validated antibodies for ER, PR, HER2, and Ki-67, using external and internal positive controls.

Data analysis: A descriptive statistical analysis was performed using IBM SPSS Statistics® software, version 25. Absolute and relative frequencies were calculated for categorical variables. No inferential hypothesis tests were applied, given that the objective of the study was to characterize the distribution of breast cancer subtypes according to HER2 status and associated variables.

Ethical considerations: The study was approved by the Research Ethics Committee of the Guillermo Almenara Irigoyen National Hospital, under document number [LETTER No. 96 CIEI-OlyD-GRPA-ESSALUD-2025]. The confidentiality of the information was guaranteed in accordance with the ethical principles of the Declaration of Helsinki and national regulations on research involving human subjects.

Results

Of the 1,635 breast cancer cases diagnosed at the Guillermo Almenara National Hospital between 2020 and 2024, 60 were excluded for failure to meet the established inclusion criteria, resulting in a final study sample of 1,575 cases.

Tumors were first classified according to standard ASCO/CAP criteria as HER2-positive or HER2-negative. HER2-negative tumors were subsequently subclassified into HER2-0 and HER2-low. Overall, 579 tumors (36.8%) were classified as HER2-0, 593 (37.6%) as HER2-low, and 403 (25.6%) as HER2-positive. In turn, the HER2-low group represented 50.6% of tumors previously categorized as HER2-negative.

Within the low HER2 group, 515 cases (86.9%) were RH positive and 78 cases (13.1%) were RH negative. Regarding Ki-67 expression, 401 cases (67.6%) had a high index (≥20%), while 192 cases (32.4%) had a low index (<20%). The subgroup consisting of low HER2, RH-positive, and low Ki-67 tumors represented 184 cases, equivalent to 11.7% of the total sample.

In the HER2-negative group, 465 cases (80.3%) were RH-positive and 114 cases (19.7%) were RH-negative. Ki-67 expression was high in 369 cases (63.7%) and low in 210 cases (36.3%).

In HER2-positive tumors, 250 cases (62.0%) were RH-positive and 153 cases (38.0%) were RH-ne-

Table 2. Clinical and pathological characteristics of breast cancer patients according to HER2 status.

Variables	HER2-low	Her2-0	HER2-positive	Total
Age				
≤ 40 years	45 (7.6%)	50 (8.6%)	32 (7.9%)	127 (8.1%)
> 40 years	548 (92.4%)	529 (91.4%)	371 (92.1%)	1448 (91.9%)
Total	593	579	403	1575
Histological type				
Ductal	527 (88.9%)	497 (85.8%)	381 (94.5%)	1405 (89.2%)
Lobular	42 (7.1%)	52 (9.0%)	1 (0.2%)	95 (6.0%)
Micropapillary	10 (1.7%)	4 (0.7%)	17 (4.2%)	31 (2.0%)
Mucinous	5 (0.8%)	15 (2.6%)	3 (0.7%)	23 (1.5%)
Adenoid cystic	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Metaplastic	1 (0.2%)	0 (0.0%)	1 (0.2%)	2 (0.1%)
Papillary	7 (1.2%)	8 (1.4%)	0 (0.0%)	15 (1.0%)
Solid papillary	0 (0.0%)	2 (0.3%)	0 (0.0%)	2 (0.1%)
Tubular	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Total	593	579	403	1575
Hormone Receptors				
Positive	515 (86.8%)	465 (80.3%)	250 (62.0%)	1230 (78.1%)
Negative	78 (13.2%)	114 (19.7%)	153 (38.0%)	345 (21.9%)
Total	593	579	403	1575
Ki-67 Index				
<20% (Low)	192 (32.4%)	210 (36.3%)	41 (10.2%)	443 (28.1%)
≥20% (High)	401 (67.6%)	369 (63.7%)	362 (89.8%)	1132 (71.9%)
Total	593	579	403	1575

Note. Case counts are presented according to age group, histological type, hormone receptor (HR) expression, and Ki-67 cell proliferation index. Low HER2 includes tumors with immunohistochemistry 1+ or 2+ with negative ISH results. HR: hormone receptors; high Ki-67: ≥20%; low Ki-67: <20%.

gative. The proportion of cases with high Ki-67 was higher in this group, with 362 cases (89.8%), while 41 cases (10.2%) had low Ki-67.

Of the total cases studied, 192 were classified as triple negative (TN), of which 59.4% were HER2 negative and 40.6% were HER2 low.

Approximately 92% of cases corresponded to patients over 40 years of age at the time of diagnosis. In patients under 40 years of age, 35.4% had low HER2, 39.4% had HER2 negative, and 25.2% had HER2 positive, proportions comparable to those observed in women over 40 years of age.

The histological types identified in order of frequency were: ductal (89.2%); lobular (6%); and other less prevalent variants (4.7%) such as micropapillary, papillary, mucinous, adenoid cystic, and metaplastic (Table 2).

Discussion

The high proportion of low HER2 cases (37.6%) observed in this study confirms that this subtype constitutes a large segment of tumors initially considered HER2-negative. These results are consistent with the values found in international studies[18-19], and although the proportion of molecular subtypes of breast cancer varies according to ethnic group, our results are also consistent with those reported in other Latin American populations[20].

In Peru, there is a previous study by Gómez-Rázuri et al.[21] who reported that low HER2 in their population constituted only 18% of the total cases and 25% of those previously considered HER2-negative, values that differ from ours. These differences could be attributed not only to population factors or access to the health system, but also to technical variations, particularly the use of different antibody clones and immunohistochemistry platforms, which can influence the sensitivity to detect low levels of HER2 expression.

In terms of age, no significant differences were observed in the distribution of HER2 status between younger women (≤40 years) and older women. This contrasts with the greater biological aggressiveness described in breast cancers in younger women, which could be due to other molecular factors such as the presence of BRCA mutations or the basal-like genomic profile rather than HER2 status itself[22].

With regard to the histological subtypes of breast carcinoma, it was observed that the majority of HER2-positive cases (94.5%) are of the ductal subtype. Low HER2 and HER2-0 tumors show greater histological diversity, including special subtypes such as lobular and mucinous. This finding supports the idea that the low HER2 group shares more morphological similarities with HER2-negative than with HER2-positive.

In terms of hormone expression, the HER2-low group had a high proportion of tumors with positive hormone receptors (HR) (86.9%), which was higher than that observed in the HER2-0 group (80.3%) and significantly higher than in the HER2-positive group (62.0%). This finding supports the close association of the low HER2 phenotype with luminal tumors, characterized by their hormone dependence. However, when analyzing the cell proliferation index, it was found that 401 of the 593 low HER2 cases (67.6%) had elevated Ki-67 (≥20%).

Remarkably, even within the HER2-low and RH-positive subgroup, 331 of the 515 cases (64.3%) showed high proliferation, suggesting that, despite their positive hormonal profile, these tumors may have a more aggressive biological behavior than expected in classic luminal phenotypes. This trend contrasts with that reported in some international series, in which low HER2 tumors with a luminal profile showed lower or intermediate proliferation[23-24]. However, these findings support the idea that the HER2-low subtype constitutes a biologically heterogeneous group[25], and that the joint interpretation of Ki-67, hormone receptors, and HER2 remains essential for adequate prognostic and therapeutic stratification.

It should be noted that this study covered a period in which different antibodies were used to determine HER2: clone SP3 (Master Diagnostics, Vitro, Spain) between 2020 and 2023, and subsequently clone 4B5 (Ventana, Roche Diagnostics, Switzerland) from 2024 onwards. Although this methodological change allowed for greater diagnostic accuracy in the most recent stage, it may have influenced the relative

frequency of cases classified as HER2-low, given that the sensitivity of the two clones is not completely equivalent.

Study limitations: This study has limitations inherent to its retrospective, single-center design, which may restrict the generalizability of the results. In addition, different antibodies were used for HER2 determination during the 2020–2024 period (clones SP3 and 4B5 on the Ventana BenchMark ULTRA platform), which could have led to variations in the detection of cases with low HER2 expression[26]. However, all cases were reevaluated according to the ASCO/CAP 2023 guidelines[6,14], ensuring diagnostic consistency.

Conclusions

Classification of breast cancer according to HER2 status enables the identification of a substantial subgroup of tumors with low HER2 expression (HER2-low), which exhibit clinical and immunohistochemical features intermediate between HER2-negative and HER2-positive disease. This observation underscores the importance of maintaining rigorous standardization of immunohistochemical techniques and ensuring consistent use of validated antibodies, particularly for the accurate detection of the HER2-low subtype. The implementation of more sensitive methodologies, such as the use of the 4B5 antibody clone, facilitates improved identification of these cases and may carry significant therapeutic implications.

The results obtained provide valuable local evidence and lay the foundation for future prospective multicenter studies in the Peruvian context.

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