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Correlation of Clinicopathologic Features of Filipino Primary Breast Cancer Patients with HER2 Subgroups Classified according to the ASCO/CAP 2018 Breast Cancer HER2 Testing Guidelines

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ABSTRACT

Background. Guidelines for testing human epidermal growth factor receptor 2 (HER2) in breast cancer using fluorescence in situ hybridization (FISH) were released in 2018. These guidelines were jointly developed by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) to achieve a clearer designation of breast cancer HER2 status. Clinical correlation with other factors was also considered appropriate, especially for those cases classified under ISH groups 2, 3, and 4.

Objective. In this study, we examined clinicopathologic features among Filipino breast cancer patients whose HER2 status was reclassified based on the 2018 ASCO/CAP guidelines.

Methodology. One hundred and thirty-two (132) breast cancer cases with immunohistochemistry (IHC) equivocal results in the Medical City were enrolled from January 2017 up to December 2020. HER2 FISH results classified under groups 2, 3, and 4 were then re-evaluated for HER2-IHC status in accordance with the 2018 ASCO/CAP guidelines. The relationship between clinicopathologic features and HER2 status was analyzed using the Fisher exact test.

Results. Significant differences were found in histologic type, nuclear pleomorphism, mitotic rate, progesterone receptor (PR) status, and regional lymph node involvement among the reclassified ISH groups. In the conv+ group, the tumor cells did not involve the regional lymph nodes as compared to group 5, where the tumor cells were involved. The conv- group had a higher grade for nuclear pleomorphism, mitotic count, and overall Nottingham Histologic Grade than group 5. There was a significant association between progesterone receptors among the conv- group and group 1.

Conclusion. Filipino breast cancer cases whose HER2 status was reclassified to negative following the 2018 ASCO/CAP guidelines had statistically different clinicopathologic features from those classified as group 5.

Key words: breast cancer, ASCO/CAP, HER2, fluorescence in situ hybridization, immunohistochemistry

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INTRODUCTION

Breast cancer is the most common cancer in women and also one of the leading causes of cancer-related deaths worldwide.[1,2] Although Western countries generally have higher incidence rates compared to Asian countries, the Philippines is an exception, with a high incidence rate of 17.7% among Filipino women.[3] Despite being the most vulnerable population in Southeast Asia, there are only a few published studies on breast cancer in the Philippines, most of which are about risk factors.[4-6] There are limited data available on the clinicopathologic details of breast cancer in the country.[7]

Breast cancer is a disease that has different subtypes and is characterized by genetic and clinical heterogeneity.[8] One study was conducted in the Philippines to identify the gene expression profile of breast cancers in different molecular subgroups, such as luminal A, luminal B, HER2, basal, and normal breast-like. Among 36 female participants, luminal A was found to be the most common profile for Filipino women, accounting for 52.8% of cases. The HER2 profile, which is associated with aggressive disease

and poor survival outcomes,[9] was found to be the third most common subgroup, accounting for 8.3% of cases.[10] The Department of Health (DOH) Breast Cancer Control Program has reported a HER2-positivity rate of 23.17% nationwide, with approximately 80% of cases diagnosed early.[11]

HER2 IHC and/or ISH are commonly used in clinical practice to determine the responsiveness to therapies that target the HER2 protein. Guidelines such as those published by the ASCO/CAP are paramount for the performance and accuracy of HER2 testing. However, on the 2007 and 2013 ASCO/CAP guidelines, while a HER2-positive or negative result is straightforward, the inclusion of "equivocal" results in ISH has been a dilemma in clinical decision-making. On the updated 2018 guidelines, the ASCO/CAP HER2 testing Expert Panel overcame this by emphasizing the use of concomitant IHC to guide the interpretation of those previously labeled as equivocal.[12] The recommendations made in the 2018 guidelines were reaffirmed in 2023.[13]

Five categories (ISH groups 1, 2, 3, 4, & 5) have been established based on the HER2/CEP17 ratio and average HER2 copy number. Group 1 is HER2 positive, while group 5 is HER2 negative.[12,13] Cases in group 1 show a higher grade, more frequent occurrence of negative estrogen and progesterone receptor results, and a higher Ki-67 index than group 5.[14] HER2 ISH results that fall under groups 2, 3, and 4 are reported to be approximately only 5% of a large-scale population.[1] Due to the rarity of cases, data regarding groups 2, 3, and 4 are still considered inadequate, especially after reclassifying to either HER2 positive or negative. Limited publications have also been made about the association of clinicopathologic features of groups 2 to 4. And none have been published yet with Filipino breast cancer patients as their population.

The main objective of this study is to compare the clinicopathologic features of converted HER2 status among breast cancer patients with those classified as group 1 and group 5 according to the ASCO/CAP 2018 breast cancer HER-2 testing guidelines. Clinical correlation with other factors is crucial for better treatment management of any patient.

METHODOLOGY

Population and sample

This retrospective study is composed of all patients of either sex in all age groups, with a histopathologic diagnosis of primary invasive breast carcinoma and subsequently underwent IHC testing for ER, PR, and HER2, and FISH testing for HER2 between January 2017 and December 2020 at The Medical City.

Inclusion and exclusion criteria

Included are those with surgically resected specimens from definitive breast cancer surgeries: core needle biopsy with subsequent definitive surgery; excision biopsy with subsequent definitive surgery; total mastectomy with either sentinel lymph node biopsy with or without axillary lymph node dissection; modified radical mastectomy; and partial mastectomy with sentinel lymph node biopsy and intraoperative radiotherapy. Excluded in this study are those who only underwent core needle breast biopsy with no subsequent definitive surgery.

The minimum number of patients is determined based on the assumed proportion of GROUP 5 patients among primary breast cancer patients to be approximately 60% of the preliminary census acquired. The calculation is detailed below:

$$n = \frac{N * \frac{(Z_{\alpha/2})^2 * p(1-p)}{E^2}}{\frac{(Z_{\alpha/2})^2 * p(1-p)}{E^2} + N - 1}$$

where $Z_{\alpha/2}$ is the critical value of the normal distribution at α/2 (e.g., for a confidence level of 95%, α is 0.05 and the critical value is 1.96), E is the margin of error, p is the anticipated sample proportion, and N is the population size. Assuming N = 10,000, p = 60%, α = 0.05 and E = 7%, the recommended minimum sample size was 185.

Data collection

Histopathologic and IHC results were collected from the Laboratory Information System (LIS) at the Anatomic Pathology Department, while the HER2 FISH results were collected from the Institute of Personalized Molecular Medicine (IPMM). Clinical data of the patients was collected through the computerized health care information system ORION, Medical Information Documentation and Access System (MIDAS), and Strategic Hospital and Medical Automation on Net (SHAMAN) of The Medical City. Data collection forms were used (Table 1) for data organization. Patients' results included in this study were anonymized and assigned a unique numeric identifier. Investigators involved in data analysis were blinded to patient identity. Accrued data was strictly limited to the primary investigator.

Grouping was based on the HER2/CEP17 ratio and average HER2 copy number (Figure 1). A concomitant IHC review was done for those classified as groups 2, 3, and 4, with a recounting of the ISH test by a second reviewer if IHC 2+, as stated by the updated 2018 ASCO/CAP recommendations (Figures 2 to 4).

- Group 1 – Tumors with HER2/CEP17 ratio ≥2.0 and average HER2 copy number ≥4.0 signals per cell and a final status designation of HER2 positive.
- Conv+ group – Tumors with:
  - HER2/CEP17 ratio ≥2.0 and average HER2 copy number <4.0 signals per cell (group 2), concurrent IHC 3+ and a final status designation of HER2 positive;
  - HER2/CEP17 ratio <2.0 and average HER2 copy number ≥6.0 signals per cell (group 3), concurrent IHC 2+ or 3+ and a final status designation of HER2 positive; and
  - HER2/CEP17 ratio <2.0 and average HER2 copy number ≥4.0 and <6.0 signals per cell (group 4), concurrent IHC 3+ and a final status designation of HER2 positive.

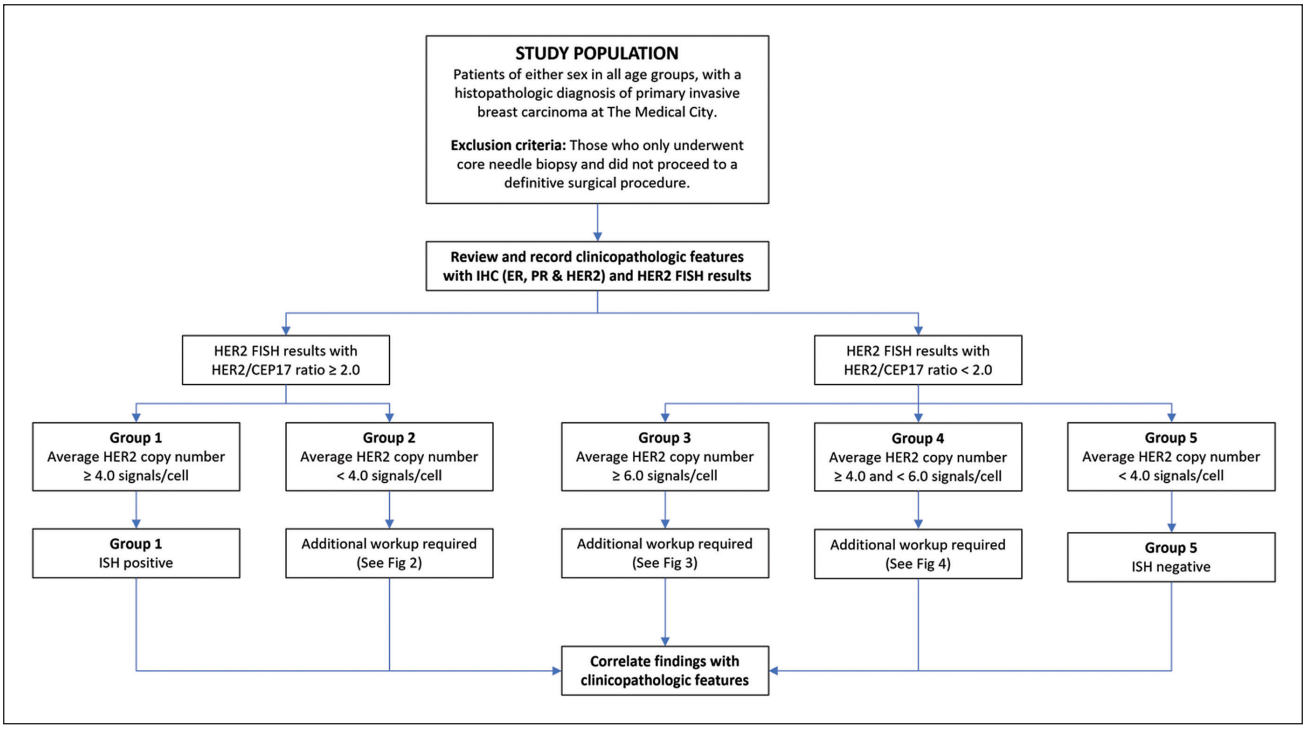

Figure 1. Diagrammatic workflow.

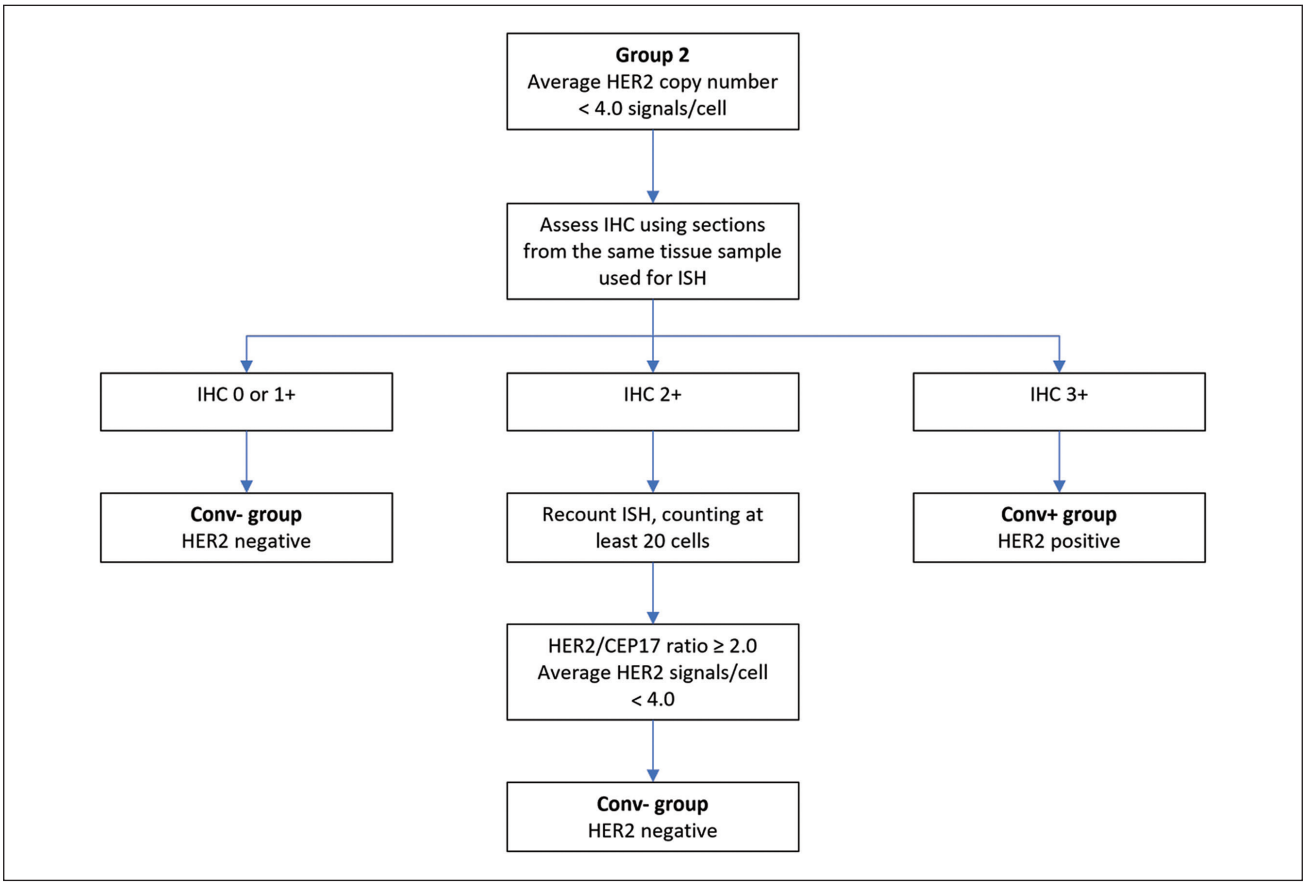

Figure 2. Additional workup to cases classified initially as group 2.

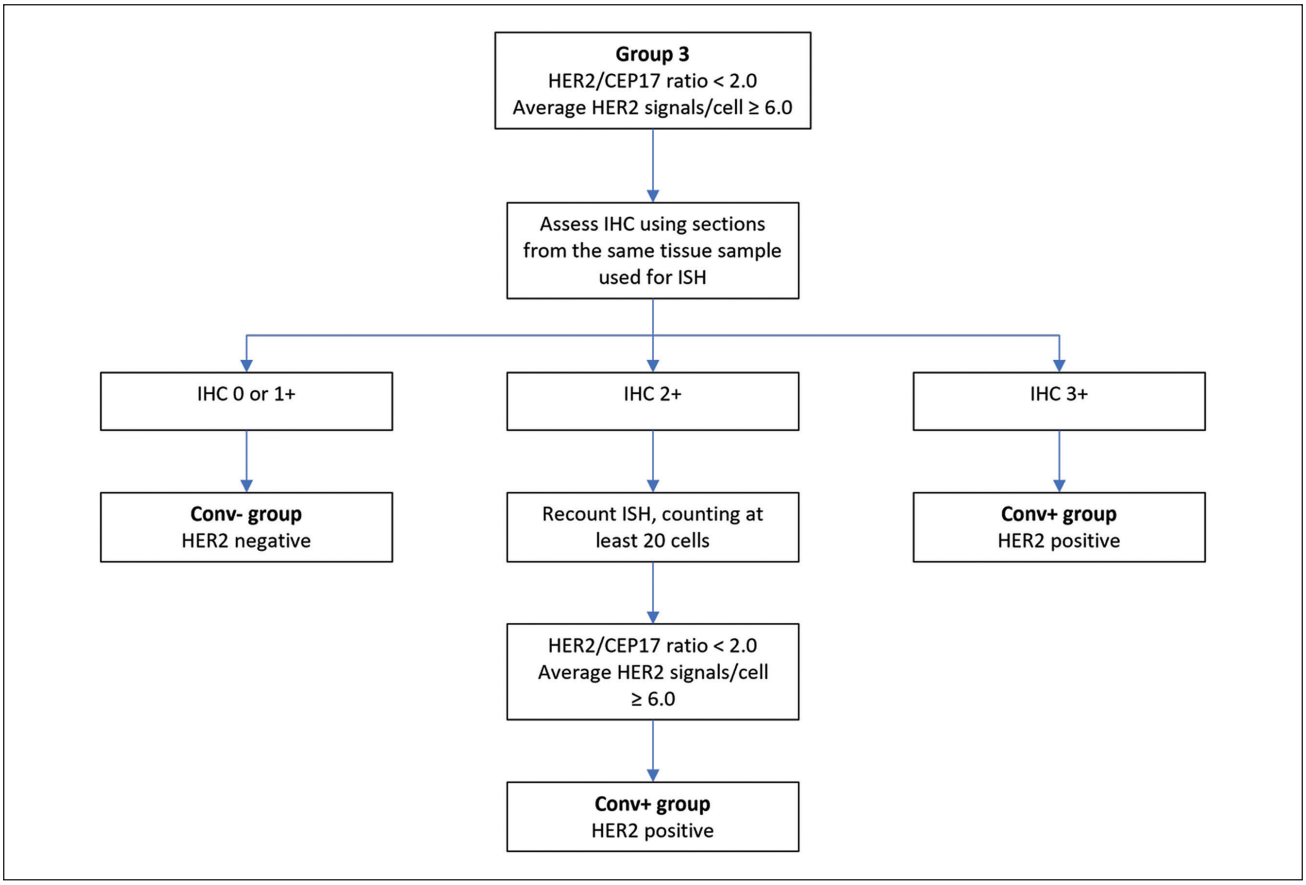

Figure 3. Additional workup to cases classified initially as group 3.

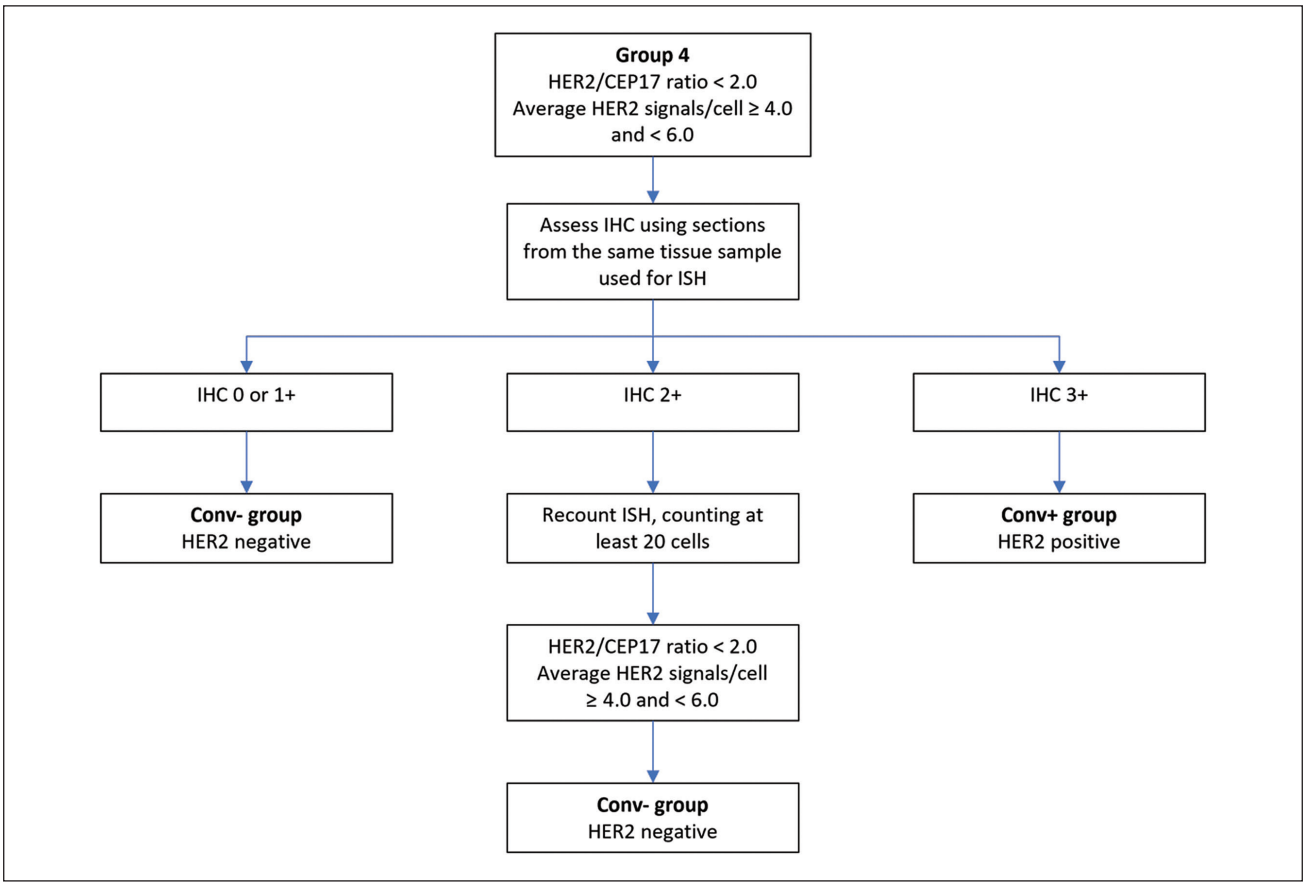

Figure 4. Additional workup to cases classified initially as group 4.

- Conv- group – Tumors with:
  - HER2/CEP17 ratio ≥2.0 and average HER2 copy number <4.0 signals per cell (group 2), concurrent IHC 0, 1+, or 2+ and a final status designation of HER2 negative;
  - HER2/CEP17 ratio <2.0 and average HER2 copy number ≥6.0 signals per cell (group 3), concurrent IHC 0 or 1+ and a final status designation of HER2 negative; and
  - HER2/CEP17 ratio <2.0 and average HER2 copy number ≥4.0 and <6.0 signals per cell (group 4), concurrent IHC 0, 1+, or 2+, and a final status designation of HER2 negative.
- Group 5 – Tumors with HER2/CEP17 ratio <2.0 and average HER2 copy number <4.0 signals per cell and a final status designation of HER2 negative.

HER2 IHC status reading was done at the Anatomic Pathology section of The Medical City. The recounting of ISH was done at the Institute of Personalized Molecular Medicine (IPMM) of the same institution.

Data analysis

Demographic characteristics and clinical features of patients were collected using the data collection form and summarized using frequencies and percentages. Contingency tables were generated to examine the relationship between clinicopathologic features and HER2 status. The clinicopathologic features include the following: age, sex, histologic type, histologic grade, presence or absence of ductal carcinoma in situ (DCIS), involvement of skin, nipple and/or skeletal muscle, regional lymph node involvement, lymphovascular space invasion, pathologic stage (pT and pN), and breast biomarkers (ER and PR). Associations between categorical variables were tested using the Fisher exact test. All tests were performed at a 5% level of significance.

RESULTS

Between January 2017 and December 2020, 226 patients underwent HER2 FISH testing at The Medical City. After applying inclusion and exclusion criteria, 132 patients ranging from 25 to 86 years of age were selected. Tables 1, 2 and 3 summarize the clinicopathologic characteristics of the breast cancer patients included in the study. Based on the 2018 ASCO/CAP update and reclassification used in this study, there were 28 group 1 cases, 4 conv+ cases, 19 conv- cases, and 86 group 5 cases. Most patients were over 50 years old (64.2%), and almost all were female (99.3%). The most common histological type was invasive carcinoma of no special type (ductal, NOS), with 101 cases (73.7%) and a Nottingham Histologic Grade of 2 (56.2%).

Significant differences were found in histologic type, nuclear pleomorphism, mitotic rate, PR, and regional lymph node involvement. Regarding conv+ samples, no tumor cells were present in the regional lymph nodes, while group 5 showed tumor cell involvement ($p = 0.048$). Conversely, conv- samples showed a significant difference in histologic type ($p = 0.001$), nuclear pleomorphism ($p = 0.025$), mitotic rate (p=0.010), and overall Nottingham Histologic Grade ($p = 0.005$) compared to group 5. The conv- group was more likely to have invasive ductal carcinoma, NOS, while group 5 was associated with invasive carcinoma with lobular and other features (e.g., micropapillary). Group 5 had a lower grade of nuclear pleomorphism (nuclear grade 1) compared to an intermediate grade (nuclear grade 2) in the conv- group. Conv- (score of 2) had a higher mitotic count than group 5 (score of 1). Finally, the overall Nottingham histologic grade was higher for conv- (grade 2) than for group 5 (grade 1).

There was a significant association between progesterone receptors in Group 1 and conv- ($p = 0.003$), with the former showing mostly negative results and the latter showing positive results.

Twenty-three FISH samples were categorized into groups 3 (4.35%) and 4 (95.65%), as shown in Table 4. Following this, the IHC staining degree of the samples was re-evaluated, leading to the classification of the samples as either conv+ or conv-. One sample under group 3 was reclassified to conv-. Out of the remaining twenty-two group 4 samples, four were reclassified to the conv+ group, while the remaining sixteen were classified as conv-.

DISCUSSION

The study reclassified samples in ISH groups 3 and 4 as either ISH-HER2 positive or negative and correlated clinicopathologic features with groups 1 and 5.

Table 1. Comparison of Clinicopathologic Features Across Classified Groups (Group 1, Conv+, Conv-, and Group 5) Based on 2018 ASCO Guidelines

	All (137)	Group1 (28)	Conv+ group (4)	Conv- group (19)	Group 5 (86)	$p^{\#}$			
						Conv+ vs Group 1	Conv+ vs Group 5	Conv- vs Group 1	Conv- vs Group 5
Age, years									
≤50	49 (35.8)	10 (35.7)	2 (50.0)	8 (42.1)	29 (33.7)	0.485	0.427	0.444	0.330
>50	88 (64.2)	18 (64.3)	2 (50.0)	11 (57.9)	57 (66.3)				
Sex									
Female	136 (99.3)	28 (100.0)	4 (100.0)	19 (100.0)	85 (98.8)	1.000	0.956	1.000	0.819
Male	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)				
Surgical procedure done									
Partial mastectomy with axillary contents	15 (10.9)	4 (14.3)	0 (0.0)	4 (21.1)	7 (8.1)				
Partial mastectomy without axillary contents	9 (6.6)	2 (7.1)	1 (25.0)	2 (10.5)	4 (4.7)	0.404	0.354	0.515	**0.025**
Total mastectomy with axillary contents	56 (40.9)	10 (35.7)	2 (50.0)	3 (15.8)	41 (47.7)				
Modified radical mastectomy	57 (41.6)	12 (42.9)	1 (25.0)	10 (52.6)	34 (39.5)				

#Fisher-exact test

Table 2. Comparison of Clinicopathologic Features Across Classified Groups (Group 1, Conv+, Conv-, and Group 5) Based on 2018 ASCO Guidelines *(continued)*

	All (137)	Group1 (28)	Conv+ group (4)	Conv- group (19)	Group 5 (86)	p#			
						Conv+ vs Group 1	Conv+ vs Group 5	Conv- vs Group 1	Conv- vs Group 5
Histologic type									
Ductal, NOS	101 (73.7)	26 (92.9)	4 (100.0)	19 (100.0)	52 (60.5)				
Invasive CA with lobular features/ lobular CA	15 (10.9)	2 (7.1)	0 (0.0)	0 (0.0)	13 (15.1)	1.000	0.608	0.508	**0.001**
Invasive CA with other features/ non-ductal	21 (15.3)	0 (0.0)	0 (0.0)	0 (0.0)	21 (24.4)				
Histologic grade (Nottingham histologic score)									
Glandular differentiation									
1	14 (10.2)	1 (3.6)	0 (0.0)	2 (10.5)	11 (12.8)	0.606	0.746	0.319	0.585
2	96 (70.1)	20 (71.4)	4 (100.0)	15 (78.9)	57 (66.3)				
3	27 (19.7)	7 (25.0)	0 (0.0)	2 (10.5)	18 (20.9)				
Nuclear pleomorphism									
1	22 (16.1)	3 (10.7)	1 (25.0)	0 (0.0)	18 (20.9)	0.540	0.999	0.382	**0.025**
2	90 (65.7)	19 (67.9)	3 (75.0)	13 (68.4)	55 (64.0)				
3	25 (18.2)	6 (21.4)	0 (0.0)	6 (31.6)	13 (15.1)				
Mitotic rate									
1	63 (46.0)	10 (35.7)	1 (25.0)	4 (21.1)	48 (55.8)	0.999	0.327	0.366	**0.010**
2	72 (52.6)	16 (57.1)	3 (75.0)	15 (78.9)	38 (44.2)				
3	2 (1.5)	2 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)				
Overall grade									
1	51 (37.2)	7 (25.0)	1 (25.0)	2 (10.5)	41 (47.7)	1.000	0.696	0.424	**0.005**
2	77 (56.2)	18 (64.3)	3 (75.0)	16 (84.2)	40 (46.5)				
3	9 (6.6)	3 (10.7)	0 (0.0)	1 (5.3)	5 (5.8)				
Tumor focality									
Single focus	123 (89.8)	27 (96.4)	4 (100.0)	18 (94.7)	74 (86.0)	0.875	0.558	0.650	0.270
Multiple foci	14 (10.2)	1 (3.6)	0 (0.0)	1 (5.3)	12 (14.0)				
Ductal carcinoma in-situ									
Not identified	51 (37.2)	7 (25.0)	3 (75.0)	6 (31.6)	35 (40.7)	0.181	0.516	0.684	0.671
Present: negative for EIC	60 (43.8)	13 (46.4)	1 (25.0)	10 (52.6)	36 (41.9)				
Present: positive for EIC	26 (19.0)	8 (28.6)	0 (0.0)	3 (15.8)	15 (17.4)				
DCIS architectural patterns									
Comedo	56 (40.9)	13 (46.4)	1 (25.0)	9 (47.4)	33 (38.4)				
Cribriform	68 (49.6)	18 (64.3)	1 (25.0)	11 (57.9)	38 (44.2)	0.999	0.999	0.883	0.966
Micropapillary/ Papillary	19 (13.9)	4 (14.3)	0 (0.0)	4 (21.1)	11 (12.8)				
Solid	62 (45.3)	17 (60.7)	1 (25.0)	9 (47.4)	35 (40.7)				
DCIS nuclear grade									
I	9 (6.6)	1 (3.6)	0 (0.0)	3 (15.8)	5 (5.8)	0.999	0.999	0.308	0.333
II	71 (51.8)	18 (64.3)	1 (25.0)	9 (47.4)	43 (50.0)				
III	6 (4.4)	2 (7.1)	0 (0.0)	1 (5.3)	3 (3.5)				
Skin, nipple and/or skeletal muscle involvement									
Not identified	125 (91.2)	26 (92.9)	3 (75.0)	15 (78.9)	81 (94.2)	0.339	0.245	0.169	0.054
Present	12 (8.8)	2 (7.1)	1 (25.0)	4 (21.1)	5 (5.8)				
Regional lymph node involvement									
No lymph nodes submitted or found	6 (4.4)	1 (3.6)	1 (25.0)	1 (5.3)	3 (3.5)	0.084	**0.048**	0.609	0.744
Uninvolved by tumor cells	69 (50.4)	16 (57.1)	3 (75.0)	8 (42.1)	42 (48.8)				
Involved by tumor cells	62 (45.3)	11 (39.3)	0 (0.0)	10 (52.6)	41 (47.7)				
Lymphovascular space invasion									
Not identified	59 (43.1)	13 (46.4)	1 (25.0)	10 (52.6)	35 (40.7)	0.402	0.473	0.452	0.243
Present	78 (56.9)	15 (53.6)	3 (75.0)	9 (47.4)	51 (59.3)				

#Fisher-exact test

Most of the group 4 samples were still classified as HER2 negative status (conv-) (81.82%) than HER2 positive status (conv+) (18.18%), which is consistent with the findings of a similar study by Yang et al. The study included samples with complete records of both IHC and FISH tests between January 2010 and August 2018 at West China Hospital. Of the 401 samples classified under group 4, 94.3% were HER2 negative, and 5.7% were HER2 positive.[14]

The clinicopathologic features of the conv- group are significantly different from those classified as group 5. The present study found that the histologic type, nuclear pleomorphism, mitotic rate, and overall Nottingham Histologic Grade were statistically different from group 5. Other studies by Woo et al.[15] and Yang et al.[14] support these findings, with the conv- group showing more aggressive clinicopathologic features. Woo et al. reported that their samples categorized as HER2 ISH-negative tumors in ISH group 4 showed significant associations with high T stage, lymph node metastasis, high histologic grade, lymphovascular invasion, high Ki-67 proliferation index, equivocal HER2 IHC, and CEP17 copy number gain compared to those in ISH group 5.[15] Yang et al., also reported that their conv- group had a higher histological grade, histological subtype, and Ki67 index than group 5.[14] These findings suggest that HER2-converted negative tumors, especially those classified from ISH group 4, are biologically different from those in group 5, which may be partly explained by a CEP17 copy number gain that reflects chromosomal instability.[16,17]

Table 3. Comparison of Clinicopathologic Features Across Classified Groups (Group 1, Conv+, Conv-, and Group 5) Based on 2018 ASCO Guidelines *(continued)*

	All (137)	Group1 (28)	Conv+ group (4)	Conv- group (19)	Group 5 (86)	p#			
						Conv+ vs Group 1	Conv+ vs Group 5	Conv- vs Group 1	Conv- vs Group 5
Primary tumor (pT)									
pT1	56 (40.9)	8 (28.6)	3 (75.0)	8 (42.1)	37 (43.0)				
pT2	63 (46.0)	18 (64.3)	1 (25.0)	6 (31.6)	38 (44.2)	0.230	0.774	0.067	0.234
PT3	14 (10.2)	2 (7.1)	0 (0.0)	3 (15.8)	9 (10.5)				
PT4	4 (2.9)	0 (0.0)	0 (0.0)	2 (10.5)	2 (2.3)				
Regional lymph nodes (pN)									
pN0	73 (55.3)	17 (60.7)	3 (100.0)	8 (47.1)	45 (53.6)				
pN1	35 (26.5)	6 (21.4)	0 (0.0)	8 (47.1)	21 (25.0)	0.999	0.777	0.280	0.292
pN2	16 (12.1)	3 (10.7)	0 (0.0)	1 (5.9)	12 (14.3)				
pN3	8 (6.1)	2 (7.1)	0 (0.0)	0 (0.0)	6 (7.1)				
Breast biomarkers									
Estrogen receptor (ER)									
Negative	16 (12.0)	4 (14.3)	0 (0.0)	2 (11.1)	10 (12.0)	0.569	0.607	0.563	0.637
Positive	117 (88.0)	24 (85.7)	4 (100.0)	16 (88.9)	73 (88.0)				
Progesterone receptor (PR)									
Negative	31 (23.3)	13 (46.4)	0 (0.0)	1 (5.6)	17 (20.5)	0.108	0.412	**0.003**	0.118
Positive	102 (76.7)	15 (53.6)	4 (100.0)	17 (94.4)	66 (79.5)				

#Fisher-exact test

Table 4. HER2 FISH status according to 2018 guidelines

ISH category (2018 guidelines)	n (%)	Conv- group	Conv+ group
3	1 (4.35)	1 (100)	0 (0)
4	22 (95.65)	18 (81.82)	4 (18.18)

For the present study, samples classified under group 1 or conv- were not statistically different from conv+. One reason for this discordance may be attributed to the small sample size (n = 4, 17.4%). Only metastasis to axillary lymph nodes within the conv+ group significantly differed from cases under group 5. The conv- had more involved nodes. The positive nodal status of conv- corresponded with larger tumor sizes and more ductal tumors.[14]

When comparing ER and PR status, cases classified under conv- showed a statistical difference to those under group 1. Conv- was disposed to a positive PR result than group 1 (PR negative result). Although this is inferred by one study that HER2 converted negative cases were not significantly different from HER2 negative cases (group 5), no study concluded a statistically significant difference with group 1.[14]

Limitations and recommendations

Due to the rarity of cases with unusual ISH classifications, data regarding it are still considered inadequate. Researchers could not meet the minimum sample size, predominantly due to the imposed strict exclusion criteria and the limited study samples in a single institution. This may be the reason for the discordance and ambiguity of the study in most publications. A multi-institutional study may be considered in the future to obtain the most appropriate sample size. Correlation with HER2/CEP17 ratio and CEP17 copy number may also be beneficial as one of the variables for future studies.

CONCLUSION

In conclusion, our study focused on the clinicopathologic characteristics of breast cancer in ISH groups 3 and 4. Although the sample size was limited, the study revealed that Filipino patients with breast cancer who converted to HER2 ISH-negative status had more aggressive clinicopathologic features than the traditional HER2-negative tumors in ISH group 5.

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STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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