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ORIGINAL RESEARCH ARTICLE

Immunohistochemical Subtype Conversion and Pathological Response After Neoadjuvant Chemotherapy in Luminal B HER2-Negative Locally Advanced Breast Cancer: A Cross-Sectional Study

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ABSTRACT

Background: Luminal B HER2-negative breast cancer responds only modestly to neoadjuvant chemotherapy (NAC), and the receptor profile of its residual tumor may differ from that of the original biopsy.

Objective: To test whether subtype conversion after NAC is associated with pathological response.

Methods: This retrospective cross-sectional study included 49 consecutive women with stage IIIA–IIIB Luminal B HER2-negative cancer who received doxorubicin–cyclophosphamide or docetaxel–cyclophosphamide before mastectomy at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia (2024–2025). Conversion meant any change in immunohistochemical surrogate subtype between core biopsy and mastectomy. The outcomes were the Miller–Payne grade (primary) and the Residual Cancer Burden (RCB) class. Exact tests, proportional-odds and Firth logistic regression, and Holm correction were applied.

Results: Conversion occurred in 14 patients (28.6%; 95% CI 17.8–42.4), most often to Luminal B HER2-positive. Converted tumors had lower Miller–Payne grades (exact p = 0.027). None reached grade 4–5 (0/14 vs 9/35; p = 0.045). The adjusted cumulative odds ratio was 0.27 (95% CI 0.08–0.91). RCB-III was more frequent after conversion (78.6% vs 31.4%; adjusted OR 6.54, 95% CI 1.69–31.63). The association between conversion and the RCB class was the only one surviving Holm correction (p = 0.019), and the RCB-III association depended largely on eight HER2 gains defined by immunohistochemistry alone.

Conclusion: More than one in four Luminal B HER2-negative tumors changed surrogate subtype after NAC. Conversion, mostly HER2 gain, marked heavier residual disease. Before adjuvant therapy is chosen, receptors should be re-tested on residual tumor, with in situ hybridization to confirm HER2.

1. Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide, and it remains one of the leading causes of cancer death among them.[1] In Indonesia the burden depends as much on stage at presentation as on incidence: hospital series from referral centers describe cohorts in which stage IIIB is the commonest presentation and neoadjuvant chemotherapy (NAC) is used mainly to make the tumor operable, not to de-escalate surgery.[2] Current guidance regards the residual tumor after NAC as informative in its own right. Its extent and biology can alter the adjuvant plan.[3] For hormone receptor-positive disease the point is far from marginal. Population and trial data put the pathological complete response (pCR) rate of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative cancer after standard chemotherapy at roughly 6–18%, so pathologists and surgeons usually receive a residual tumor, not an empty tumor bed.[4–8]

Luminal B HER2-negative tumors form the proliferative, chemotherapy-eligible end of the luminal spectrum. They are estrogen receptor-positive and HER2-negative, with a high Ki-67 index or low progesterone receptor (PR) expression, and they are the luminal tumors most often offered NAC. Only a minority achieve pathological complete response; younger age and higher Ki-67 mark the patients who do.[9,10] Their response is also biologically heterogeneous. In the Penelope-B trial, longitudinal profiling of paired pre-treatment and post-treatment samples showed chemotherapy moving the intrinsic subtype of residual tumors from Luminal B towards Luminal A, and adaptive transcriptomic clusters defined by these shifts carried prognostic information beyond the baseline subtype.[11] Translational cohorts show that neoadjuvant therapy lowers estrogen

receptor (ER), PR and Ki-67 expression, down-regulates proliferation and luminal genes, and shifts HER2 immunohistochemistry (IHC) scores in both directions.[12,13] In a population-based Swedish cohort, the median Ki-67 index dropped from 40% before treatment to 12% in residual tumors. The post-treatment value was itself prognostic in ER-positive/HER2-negative disease.[14] On-treatment biopsies confirm that hormone receptor-positive/HER2-negative tumors retain invasive cells more often than any other subtype.[15] The immune microenvironment is remodeled at the same time.[16]

In routine pathology these dynamics appear as "receptor conversion" or "subtype conversion": a change, between the diagnostic core biopsy and the surgical specimen, in the IHC markers that define the surrogate subtype. Two meta-analyses published in 2025 quantified it. One pooled 24 studies and 5891 patients. It found conversion rates of 9.2% for ER, 15.1% for PR and 8.6% for HER2, and loss of hormone receptor positivity was linked to a lower pCR rate and worse disease-free survival.[17] The other pooled 22 studies and 5370 patients, with a hazard ratio for disease-free survival of 3.42 for hormone receptor loss and 1.89 for HER2 gain.[18] Single-center cohorts report a change of overall surrogate subtype in roughly one quarter to over one third of patients.[19–23] HER2 categories change in about 30% of residual tumors, whether the backbone was an anthracycline or a taxane–platinum regimen.[24] Part of this apparent change reflects measurement, not biology. Complete agreement between pathologists on HER2 IHC can be as low as 62%. Concordance differs between core biopsies and resections even without treatment. Current ASCO–College of American Pathologists guidance calls for in situ hybridization when HER2 results are equivocal.[25–27]

Response to NAC is graded on the same surgical specimen. The Miller–Payne system compares tumor cellularity before and after treatment on a five-grade scale, and in its original series of large and locally advanced cancers it was independently prognostic for survival.[28] Where pCR is rare, as in hormone receptor-positive/HER2-negative disease, intermediate Miller–Payne grades and composite definitions of "major pathological response" still separate patients by event-free survival.[5,29] The Residual Cancer Burden (RCB) index combines the residual tumor bed, cellularity and nodal disease; a pooled analysis of 5161 patients showed it to be prognostic within every subtype.[30] Conversion can be read only where residual tumor exists. The amount of residual tumor is exactly what response systems measure. The relation between the two is therefore clinically relevant but methodologically delicate. Most published series pool all subtypes, report conversion and response separately, or study survival without giving effect sizes for the response association, which makes it hard to know whether conversion within one luminal subtype tracks the depth of response.

Indonesian evidence on these questions is sparse. A Makassar cohort found a molecular subtype change in 43.2% of 44 patients, and change to triple-negative disease predicted worse progression-free survival.[31] A Jakarta series reported pCR in 8.3% and RCB class II–III in 90% of patients after NAC.[32] Studies from Jakarta, Makassar and Bali have linked immune infiltrates, HER2 and survivin expression to response to NAC.[33–35] None of these studies restricted the analysis to Luminal B HER2-negative disease, none related conversion to both the Miller–Payne grade and RCB in the same specimens, and none asked whether the anthracycline-based and taxane-based regimens used in Indonesian practice differ in either outcome. Dr. Hasan Sadikin General Hospital is the national referral hospital for West Java. It treats a large volume of locally advanced breast cancer with these regimens.

This study had three aims in women with locally advanced Luminal B HER2-negative breast cancer treated with NAC. The first was to describe how often, and in what pattern, the surrogate subtype changes after NAC. The second was to estimate the association between conversion and pathological response, measured by the Miller–Payne grade (primary outcome) and the RCB class (secondary outcome), with adjustment for regimen, histological grade, stage and age. The third, secondary and exploratory, was to examine whether the regimen (doxorubicin–cyclophosphamide vs docetaxel–cyclophosphamide) was associated with response or with conversion. The working hypothesis was that conversion would accompany poorer response.

2. Methods

Study design and reporting

This was a retrospective, single-center analytical study of a consecutive cohort treated with NAC. The exposure (subtype conversion) and the outcomes (Miller–Payne grade and RCB class) were both ascertained on the same mastectomy specimen. The analysis is therefore cross-sectional within the treated cohort. Associations are read as co-occurrence, not as temporal precedence. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies.

Ethical approval

The Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, approved the study protocol (Ethical Approval No. DP.04.03/D.XIV.6.5/200/2025; Reg. No. 05.25.200; 19 May 2025). Anonymized hospital records and archived pathology material were used, and individual informed consent was waived under institutional protocol. The study followed the Declaration of Helsinki. Study numbers replaced patient identifiers before analysis, and no identifiable information is reported.

Setting and participants

The study was conducted at Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia, using records from the Surgical Oncology Outpatient Clinic, the Asnawati Chemotherapy Unit and the Immunohistochemistry Laboratory of the Department of Anatomical Pathology. Patients who started NAC between January 2024 and January 2025 were eligible if they had histologically confirmed locally advanced breast cancer (clinical stage IIIA–IIIC, American Joint Committee on Cancer [AJCC] 8th edition; all included patients were stage IIIA or IIIB) of the Luminal B HER2-negative surrogate subtype on the diagnostic core biopsy, received an anthracycline-based or taxane-based NAC regimen and underwent mastectomy with immunohistochemical re-assessment of the surgical specimen. Patients with distant metastasis, diabetes mellitus, hypertension or another comorbidity that had caused complications, and patients who did not receive NAC, were excluded. All eligible patients in the period were included (consecutive sampling). Data were abstracted after ethical approval, between May and September 2025. Fifty-one records were identified; two medical record numbers each appeared twice, and one record per patient (the first entry) was retained, leaving 49 patients for the primary analysis. The flow of patients and the conversion pathways are shown in Figure 1.

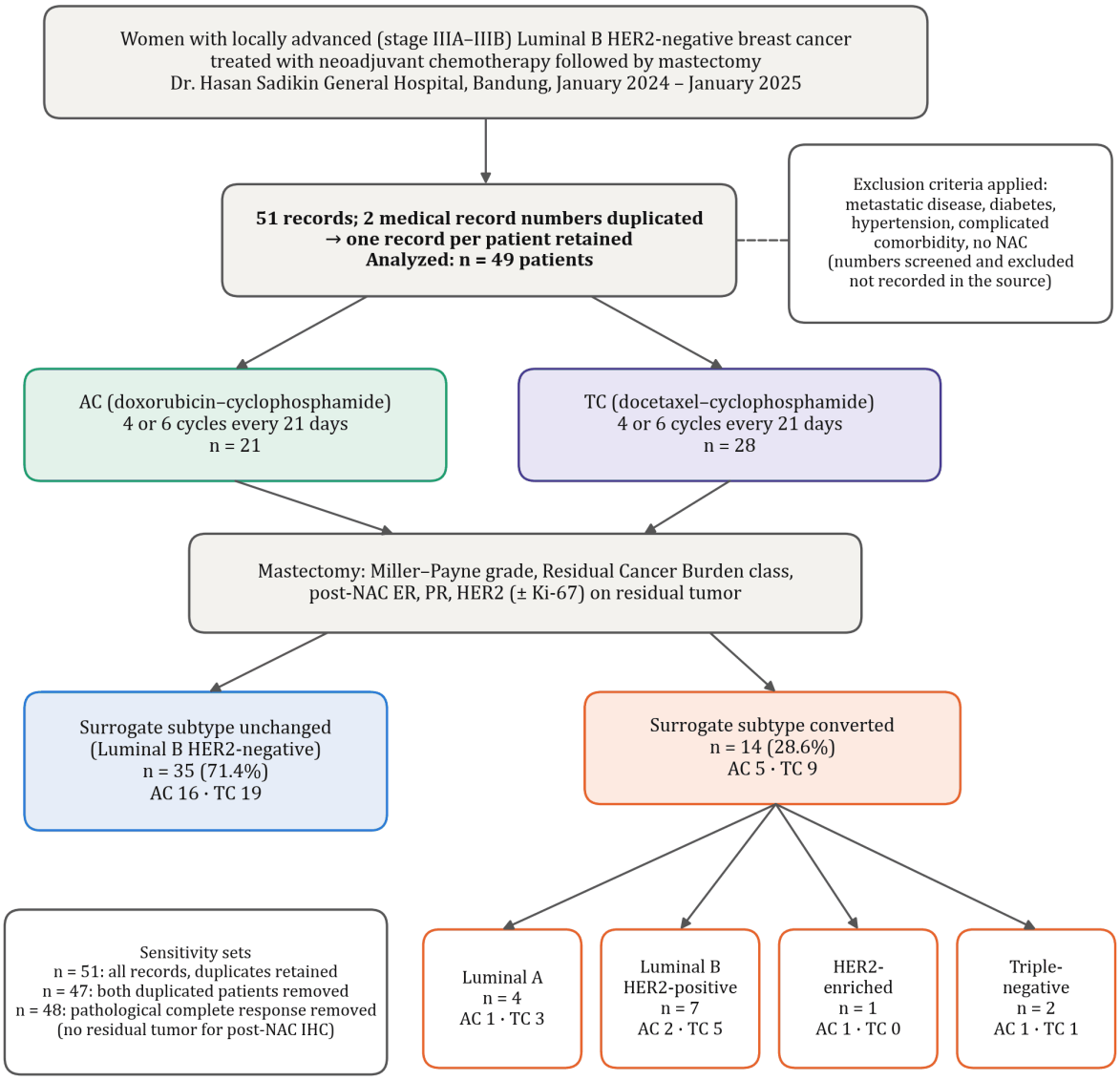


Figure 1. Study flow and post-neoadjuvant conversion pathways. Fifty-one records were identified; two medical record numbers occurred twice and one record per patient was retained, leaving 49 women with locally advanced Luminal B HER2-negative breast cancer who received AC (n = 21) or TC (n = 28) before mastectomy. The surrogate subtype was unchanged in 35 and converted in 14, most often to Luminal B HER2-positive (n = 7). Sensitivity sets are shown at the lower left. AC, doxorubicin–cyclophosphamide; TC, docetaxel–cyclophosphamide; IHC, immunohistochemistry; NAC, neoadjuvant chemotherapy.

Sample size

The target sample size was fixed a priori with Fisher's z formula, to detect a correlation of r = 0.40 between the exposure and the ordinal response ($\alpha = 0.05$, one-sided, Z = 1.64; power 0.90, Z = 1.28). This gave $n = (2.92 / 0.4236)^2 + 3 = 50.5$, rounded up to 51. After removal of duplicated records, 49 patients were

analyzed. All hypothesis tests were two-sided. A two-sided calculation with the same assumptions would have required 62 patients. The analysis that answers the study question is a two-group comparison of an ordinal outcome, so the minimum detectable effect of the achieved sample was also estimated by simulation (2000 replicates per scenario; two-sided α = 0.05; 35 vs 14 patients; Miller–Payne distribution of the unchanged group as reference). Power was 80% only for cumulative odds ratios of about 6 or more (0.17 or less in the protective direction). For a cumulative odds ratio of 3, power was 47%.

Treatment

Patients received either four or six three-weekly cycles of doxorubicin and cyclophosphamide (AC) or four or six three-weekly cycles of docetaxel and cyclophosphamide (TC), according to the multidisciplinary team's decision; no patient received a sequential anthracycline–taxane regimen. Regimen allocation was not randomized. After completion of NAC, all patients underwent mastectomy. Doses, the number of cycles actually delivered and dose intensity were not available for analysis.

Pathology, surrogate subtypes and response assessment

ER, PR, HER2 and Ki-67 were assessed by IHC on formalin-fixed, paraffin-embedded blocks. Blocks came from the diagnostic core biopsy and from the residual tumor in the mastectomy specimen, were retrieved from the archive of the Department of Anatomical Pathology, and were stained in the hospital's immunohistochemistry laboratory. ER and PR were called positive when at least 1% of tumor nuclei stained. A Ki-67 index above 20% was called high. HER2 status was determined by IHC without confirmatory in situ hybridization, so HER2 results are described as IHC-defined. The records did not document antibody clones, the number of reporting pathologists, or whether post-treatment scoring was blinded to the baseline result. Surrogate subtypes followed the St Gallen-based definitions used in the institution. Luminal A-like was ER-positive, PR-positive and HER2-negative with low Ki-67. Luminal B HER2-negative was ER-positive and HER2-negative with at least one of PR negative/low or Ki-67 high. Luminal B HER2-positive was ER-positive with any PR, HER2 overexpressed or amplified, and any Ki-67. HER2-enriched was ER-negative, PR-negative and HER2-positive. Triple-negative was ER-negative, PR-negative and HER2-negative. Subtype conversion was defined as any change of surrogate subtype between the core biopsy and the residual tumor, and the target subtype was recorded. Two marker-level groupings were derived. HER2 gain meant conversion to Luminal B HER2-positive or HER2-enriched; hormone receptor loss meant conversion to HER2-enriched or triple-negative.

The Miller–Payne grade was assigned by comparing tumor cellularity in the core biopsy and the surgical specimen: grade 1, no change or some alteration of individual cells without reduction in overall cellularity; grade 2, a minor loss of tumor cells (up to 30%); grade 3, a reduction of 30–90%; grade 4, a reduction of more than 90%, with only small clusters or widely dispersed individual cells remaining; and grade 5, no residual invasive carcinoma (ductal carcinoma in situ may be present).[28] Grades 4–5 were defined as major response, and grade 5 as pathological complete response in the breast. The RCB class (0, I, II or III) recorded for each specimen was analyzed as the secondary outcome.[30] Nottingham histological grade was also recorded. Anatomic clinical stage and the AJCC 8th edition clinical prognostic stage were recorded before NAC; the post-NAC prognostic stage in the institutional records re-applied the clinical prognostic staging to the pre-treatment TNM category with the post-NAC biomarkers and was therefore treated as a biomarker-driven re-assignment, not as a measure of disease progression.

Data collection and quality control

Data were abstracted from the medical and pathology records into a standard form, coded and checked for completeness. All frequencies were cross-checked against the original tabulation before analysis. Two medical record numbers each appeared twice. One pair differed only in histological grade; the other differed in age (by one year) and Miller–Payne grade. Each medical record number identifies one patient. The first record of each pair was therefore retained for the primary analysis (n = 49). One sensitivity analysis used all 51 records, and another removed both affected patients (n = 47). Post-NAC IHC cannot be performed when no invasive tumor remains, so the single patient with a Miller–Payne grade 5 response was classified as unchanged by default. A further sensitivity analysis excluded this patient (n = 48).

Statistical analysis

Categorical variables are reported as counts and percentages with Wilson score 95% confidence intervals (CIs). Age is reported as mean ± standard deviation and as median (interquartile range), after a Shapiro–Wilk test of normality. Groups were compared with Welch's t-test for age and Fisher's exact test for 2 × 2 tables. Larger tables used the Fisher–Freeman–Halton exact test: complete enumeration for 2 × k tables, otherwise Monte Carlo with 200,000 permutations and table-probability ordering. Ordinal outcomes were compared with the Mann–Whitney U test, which used the exact conditional distribution of the tied ranks, and with the exact Cochran–Armitage test for linear trend. Effect sizes were the rank-biserial correlation (rrb) with a percentile bootstrap 95% CI (5000 resamples), Cramér's V, Hedges' g, the risk difference with a Newcombe 95% CI, and the odds ratio (OR) with a Woolf 95% CI. A Haldane–Anscombe

correction was applied when a cell was zero. Agreement between the Miller–Payne grade and the RCB class was summarized with Spearman's ρ (Fisher-z 95% CI), Kendall's τ-b and Goodman–Kruskal γ.

Five cohort proportions were compared with published benchmarks using one-sample exact binomial tests with Cohen's h and Holm adjustment: overall subtype conversion (27.2%),[19] HER2 gain among residual HER2-negative tumors (10.1%),[36] hormone receptor loss (pooled ER conversion 9.2%),[17] pCR (7.3%)[5] and RCB class II–III (90.0%).[32] Where the comparator published exact counts, a two-sample Fisher's exact test was added.

Multivariable analysis used a proportional-odds (cumulative logit) model for the Miller–Payne grade, with grades 4 and 5 merged because grade 5 contained one patient. The covariates were fixed before the patient-level data were re-analyzed: conversion, regimen (AC vs TC), histological grade 3 vs 1–2, clinical stage IIIB vs IIIA and age per 10 years. Likelihood-ratio tests gave the p values, and the 95% CIs of the proportional-odds models are Wald intervals. The proportional-odds assumption was examined by fitting cut-point-specific Firth logistic models. Binary end points with few events were analyzed with Firth-penalized logistic regression: Miller–Payne 4–5 (9 events), RCB-III (22 events) and conversion itself (14 events). This method stays finite under the complete separation that zero cells produce, and it supplied profile penalized-likelihood 95% CIs and penalized likelihood-ratio tests. A proportional-odds model for the RCB class (0–I, II, III) served as a secondary model. Model performance was summarized by Nagelkerke R^2, the c-index or the area under the receiver operating characteristic curve (AUC) with a DeLong 95% CI, the Hosmer–Lemeshow test, the Brier score and an optimism-corrected AUC from 500 bootstrap resamples. Events per variable were low (3–8), so the multivariable estimates are presented as exploratory.

Five further analyses examined the structure of the main association. First, the comparison between converted and unchanged tumors was repeated within tumors of RCB class II–III and within RCB-III. This tested whether the association persisted among patients who all had considerable residual disease. Second, because HER2 was assessed without in situ hybridization, a misclassification analysis reclassified every HER2 gain as unchanged and, separately, excluded the HER2-gain tumors. Third, the conversion odds ratio of the proportional-odds model was re-estimated in a reduced model with only conversion and regimen, using 1000 bootstrap resamples (percentile 95% CI). Fourth, E-values quantified how strongly an unmeasured confounder would have to be associated, on the risk-ratio scale, with both conversion and the outcome to explain away the observed associations. Odds ratios were converted with the square-root approximation appropriate for common outcomes.[37] Fifth, baseline balance between the two regimens was tested with Welch's t-test and Fisher's exact test. The Hosmer–Lemeshow test has low power at this sample size, and it was interpreted accordingly.

The Holm procedure controlled multiplicity across six primary bivariate tests, defined before the patient-level data were re-analyzed: conversion with Miller–Payne grade and with RCB class; regimen with Miller–Payne grade and with conversion; and stage and histological grade with Miller–Payne grade. Robustness was examined with the three sensitivity datasets described above and by leave-one-out deletion of each patient. All tests were two-sided with $\alpha = 0.05$, and p values are reported to three decimals. Initial tabulation was done in IBM SPSS Statistics. All analyses reported here were performed in Python 3.14 with SciPy 1.18.1 and statsmodels 0.15.0, using purpose-written routines for the exact conditional tests and Firth regression (random seed 20251012).

3. Results

Patients

Forty-nine women were included (Figure 1). Their mean age was 52.0 ± 8.7 years (median 52, interquartile range 45.0–56.0; range 36–71), and 20 (40.8%; 95% CI 28.2–54.8) were younger than 50 years. Most tumors were clinical stage IIIB (40; 81.6%), most often T4b (25; 51.0%), and 31 (63.3%) were node-positive. Histological grade was 1 in 7 (14.3%), 2 in 20 (40.8%) and 3 in 22 (44.9%). Twenty-one patients (42.9%) received AC and 28 (57.1%) received TC. Baseline characteristics did not differ significantly between patients whose tumors later converted and those whose tumors did not (Table 1). Conversion was numerically more frequent in grade 1 tumors (4 of 7) than in grade 2 (6 of 20) or grade 3 tumors (4 of 22) and in node-positive than in node-negative disease (11 of 31 vs 3 of 18), but neither difference was statistically significant (p = 0.148 and p = 0.202).

Table 1. Baseline clinicopathological characteristics of the cohort, overall and by post-neoadjuvant subtype conversion status.

Characteristic	All (n = 49)	Unchanged (n = 35)	Converted (n = 14)	p	Effect size
Age, years, mean ± SD	52.0 ± 8.6	51.5 ± 9.2	53.3 ± 7.3	0.476	g = −0.20
Age, years, median (IQR)	52 (45.0–56.0)	51 (45.0–56.0)	53 (48.2–55.8)		
Regimen, n (%)				0.750	V = 0.09
AC	21 (42.9)	16 (45.7)	5 (35.7)		
TC	28 (57.1)	19 (54.3)	9 (64.3)		
Clinical stage, n (%)				0.702	V = 0.05

IIIA	9 (18.4)	6 (17.1)	3 (21.4)		
IIIB	40 (81.6)	29 (82.9)	11 (78.6)		
cT category, n (%)				0.904	V = 0.15
T3	9 (18.4)	6 (17.1)	3 (21.4)		
T4a	6 (12.2)	5 (14.3)	1 (7.1)		
T4b	25 (51.0)	17 (48.6)	8 (57.1)		
T4c	6 (12.2)	5 (14.3)	1 (7.1)		
T4d	3 (6.1)	2 (5.7)	1 (7.1)		
cN category, n (%)				0.184	V = 0.29
N0	18 (36.7)	15 (42.9)	3 (21.4)		
N1	28 (57.1)	17 (48.6)	11 (78.6)		
N2	3 (6.1)	3 (8.6)	0 (0.0)		
Histological grade, n (%)				0.148	V = 0.29
G1	7 (14.3)	3 (8.6)	4 (28.6)		
G2	20 (40.8)	14 (40.0)	6 (42.9)		
G3	22 (44.9)	18 (51.4)	4 (28.6)		
AJCC 8th clinical prognostic stage before NAC, n (%)				0.558	—
IIA	7 (14.3)	4 (11.4)	3 (21.4)		
IIIA	2 (4.1)	2 (5.7)	0 (0.0)		
IIIB	40 (81.6)	29 (82.9)	11 (78.6)		

Values are n (%) unless stated. p: Welch t-test for age; Fisher's exact test (2 × 2) or Fisher–Freeman–Halton exact test (larger tables; Monte Carlo, 200,000 permutations) for categorical variables. g, Hedges' g; V, Cramér's V. AC, doxorubicin–cyclophosphamide; TC, docetaxel–cyclophosphamide; AJCC, American Joint Committee on Cancer; IQR, interquartile range; NAC, neoadjuvant chemotherapy.

Surrogate-subtype conversion

The surrogate subtype changed in 14 patients (28.6%; 95% CI 17.8–42.4) and was unchanged in 35 (Table 2). The most frequent target was Luminal B HER2-positive (7 patients; 14.3% of the cohort and 50.0% of conversions), followed by Luminal A (4; 8.2%), triple-negative (2; 4.1%) and HER2-enriched (1; 2.0%). IHC-defined HER2 gain therefore occurred in 8 patients (16.3%; 95% CI 8.5–29.0) and hormone receptor loss in 3 (6.1%; 95% CI 2.1–16.5). Conversion occurred in 5 of 21 AC-treated patients (23.8%) and 9 of 28 TC-treated patients (32.1%; Fisher p = 0.750; OR 0.66, 95% CI 0.18–2.37). The re-assigned prognostic stage moved from IIIB to IIIA in three patients whose tumors became Luminal B HER2-positive and from IIIB to IIIC in the two whose tumors became triple-negative; the two triple-negative conversions had Miller–Payne grades 1 and 2.

Table 2. Post-neoadjuvant surrogate-subtype conversion profile and pathological response by conversion target.

Post-NAC surrogate subtype	n (% of 49) [95% CI]	% of converted	AC / TC	MP grade 1 / 2 / 3 / 4 / 5	RCB 0 / I / II / III	MP 4–5 / RCB-III
Luminal A	4 (8.2) [3.2–19.2]	28.6	1 / 3	0 / 2 / 2 / 0 / 0	0 / 0 / 1 / 3	0 / 3
Luminal B HER2-positive	7 (14.3) [7.1–26.7]	50.0	2 / 5	2 / 3 / 2 / 0 / 0	0 / 0 / 1 / 6	0 / 6
HER2-enriched	1 (2.0) [0.4–10.7]	7.1	1 / 0	0 / 0 / 1 / 0 / 0	0 / 0 / 0 / 1	0 / 1
Triple-negative	2 (4.1) [1.1–13.7]	14.3	1 / 1	1 / 1 / 0 / 0 / 0	0 / 0 / 1 / 1	0 / 1
Unchanged (reference)	35 (71.4) [57.6–82.2]	—	16 / 19	3 / 10 / 13 / 8 / 1	1 / 4 / 19 / 11	9 / 11
Any conversion	14 (28.6) [17.8–42.4]	100	5 / 9	3 / 6 / 5 / 0 / 0	0 / 0 / 3 / 11	0 / 11
HER2 gain (Luminal B HER2-positive or HER2-enriched)	8 (16.3) [8.5–29.0]	57.1	3 / 5	2 / 3 / 3 / 0 / 0	0 / 0 / 1 / 7	0 / 7
Hormone-receptor loss (HER2-enriched or triple-negative)	3 (6.1) [2.1–16.5]	21.4	2 / 1	1 / 1 / 1 / 0 / 0	0 / 0 / 1 / 2	0 / 2

All tumors were Luminal B HER2-negative on the pre-treatment core biopsy. 95% CI, Wilson score interval. HER2 gain and hormone-receptor loss are overlapping groupings derived from the target subtype (the HER2-enriched tumor belongs to both); HER2 status was determined by immunohistochemistry without in situ hybridization. Kruskal–Wallis test of Miller–Payne grade across the five categories: H = 7.37, p = 0.118, $\varepsilon^2 = 0.15$; Fisher–Freeman–Halton p = 0.628. MP, Miller–Payne; RCB, Residual Cancer Burden.

Pathological response and agreement between grading systems

Miller–Payne grades 1, 2, 3, 4 and 5 were recorded in 6 (12.2%), 16 (32.7%), 18 (36.7%), 8 (16.3%) and 1 (2.0%) patients, respectively; major response (grades 4–5) occurred in 9 patients (18.4%; 95% CI 10.0–31.4), and pathological complete response in the breast in 1 (2.0%; 95% CI 0.4–10.7). RCB classes 0, I, II and III were recorded in 1 (2.0%), 4 (8.2%), 22 (44.9%) and 22 (44.9%) patients. The two systems agreed moderately (Spearman ρ = −0.44, 95% CI −0.65 to −0.17; Kendall τ-b = −0.41; Goodman–Kruskal γ = −0.59; the negative signs reflect the opposite directions of the two scales; Figure 2). Disagreement concentrated in the middle of the Miller–Payne scale: 7 of 18 grade 3 tumors were classified as RCB-III, and 2 of 8 grade 4 tumors were RCB-III.

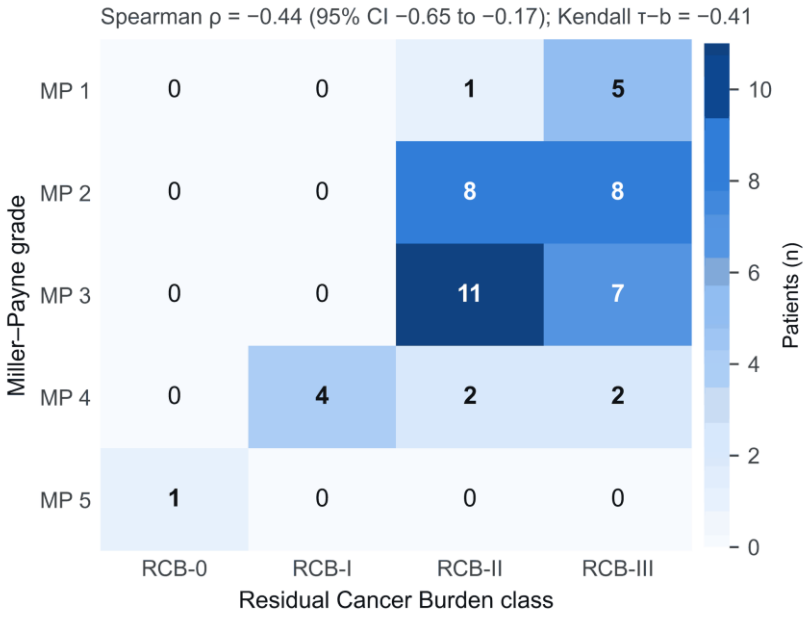


Figure 2. Concordance between the Miller–Payne grade and the Residual Cancer Burden (RCB) class in the 49 mastectomy specimens. Cells show patient counts; darker shading indicates more patients. Agreement was moderate (Spearman ρ = −0.44, 95% CI −0.65 to −0.17); 7 of 18 Miller–Payne grade 3 tumors were RCB-III.

Comparison with published benchmarks

None of the five cohort proportions differed significantly from its literature benchmark (Figure 3). The overall conversion rate (28.6%) was close to the 27.2% reported by Coiro et al. (exact p = 0.872; Cohen's h = 0.03). HER2 gain among tumors with residual disease (8 of 48; 16.7%) exceeded the 10.1% of Ma et al. by a small margin (p = 0.145; Holm p = 0.727; h = 0.19), hormone receptor loss (6.1%) was below the pooled ER conversion of 9.2% (p = 0.623), the pCR rate (2.0%) was below the 7.3% of Ji et al. (p = 0.263; h = −0.26) and the proportion with RCB class II–III (89.8%) matched the 90.0% reported in Jakarta (p = 1.000).

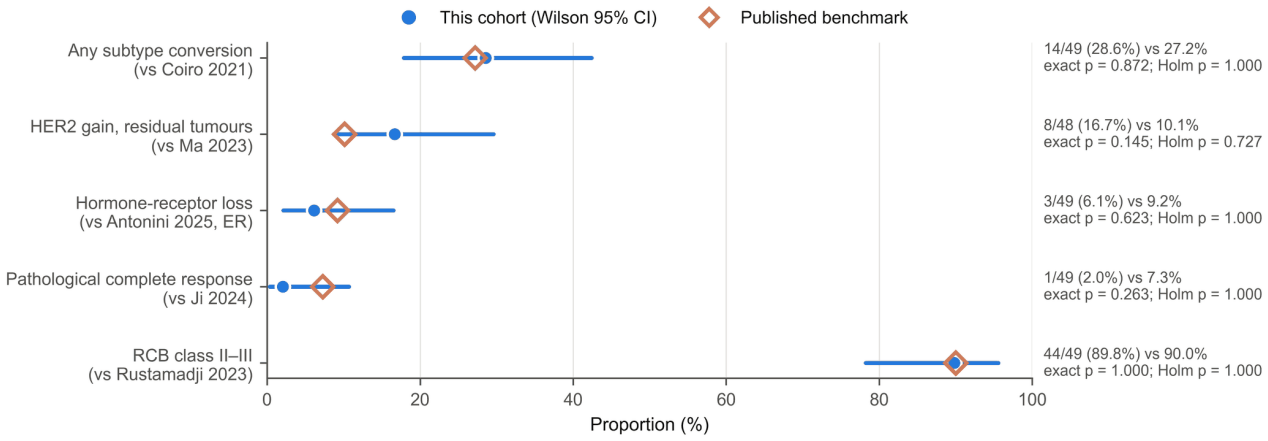


Figure 3. Cohort proportions compared with published benchmarks. Filled circles with horizontal bars show the observed proportion with its Wilson 95% confidence interval; open diamonds mark the benchmark value from the cited study. Exact binomial p values are shown with Holm adjustment across the five comparisons; none differed significantly. RCB, Residual Cancer Burden.

Pathological response by conversion status

Converted tumors had lower Miller–Payne grades than unchanged tumors (median 2 vs 3; mean 2.14 vs 2.83; exact Mann–Whitney p = 0.027; rrb = 0.39, 95% CI 0.10–0.66; Table 3). The ordered trend was significant (exact Cochran–Armitage p = 0.033), whereas the omnibus Fisher–Freeman–Halton test of the full 2 × 5 table was not (p = 0.188; Cramér's V = 0.34). No converted tumor reached Miller–Payne grade 4–5, compared with 9 of 35 unchanged tumors (25.7%; Fisher p = 0.045; risk difference 25.7 percentage points, 95% CI 1.3–42.1; Figure 4). The difference at the lower threshold of grade 3 or higher (35.7% vs 62.9%) was not significant (p = 0.116; Figure 5).

Table 3. Pathological response by subtype conversion status and by chemotherapy regimen.

Outcome	Group 1	Group 2	p	Effect size (95% CI)
By conversion status	Unchanged (n = 35)	Converted (n = 14)		
Miller–Payne grade, median (mean)	3 (2.83)	2 (2.14)	0.027[a]	rrb = 0.39 (0.10–0.66)
Distribution (FFH) / linear trend (Cochran–Armitage)			0.188 / 0.033	V = 0.34
Miller–Payne ≥ 3, n (%)	22 (62.9)	5 (35.7)	0.116	RD 27.1 pp
Miller–Payne 4–5, n (%)	9 (25.7)	0 (0.0)	0.045	RD 25.7 pp (1.3–42.1); ORHA 10.4 (0.56–191.81)
RCB class, median (mean)	2 (2.14)	3 (2.79)	0.003[a]	rrb = −0.50 (−0.73 to −0.23)
Distribution (FFH) / linear trend (Cochran–Armitage)			0.027 / 0.006	—
RCB 0–I, n (%)	5 (14.3)	0 (0.0)	0.303	RD 14.3 pp
RCB-III, n (%)	11 (31.4)	11 (78.6)	0.004	OR 8.00 (1.85–34.54); RD 47.1 pp; V = 0.43
By regimen	AC (n = 21)	TC (n = 28)		
Miller–Payne grade, median (mean)	3 (2.86)	2 (2.46)	0.086[a]	rrb = 0.28 (−0.03 to 0.58); FFH p = 0.041
Miller–Payne ≥ 3, n (%)	16 (76.2)	11 (39.3)	0.019	OR 4.95 (1.41–17.41)
Miller–Payne 4–5, n (%)	4 (19.0)	5 (17.9)	1.000	OR 1.08 (0.25–4.64)
RCB class, median (mean)	2 (2.24)	3 (2.39)	0.193[a]	rrb = −0.20 (−0.49 to 0.09)
RCB-III, n (%)	6 (28.6)	16 (57.1)	0.081	OR 0.30 (0.09–1.00)
Subtype conversion, n (%)	5 (23.8)	9 (32.1)	0.750	OR 0.66 (0.18–2.37)

[a]Exact (conditional) Mann–Whitney U test. Other p values: Fisher's exact test; FFH, Fisher–Freeman–Halton exact test. rrb, rank-biserial correlation (positive values = higher scores in group 1) with bootstrap 95% CI; RD, risk difference in percentage points (pp) with Newcombe 95% CI; ORHA, Haldane–Anscombe-corrected odds ratio (zero cell); V, Cramér's V. RCB, Residual Cancer Burden.

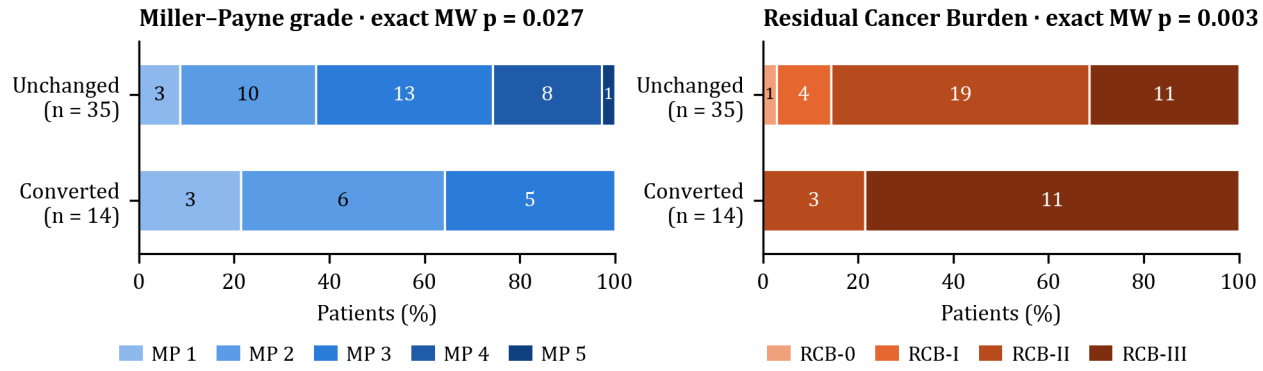


Figure 4. Distribution of the Miller–Payne grade (left) and Residual Cancer Burden class (right) by post-neoadjuvant subtype conversion status. Bars are 100% stacked; numbers inside segments are patient counts. No converted tumor reached Miller–Payne grade 4–5 or RCB 0–I, and 11 of 14 converted tumors were RCB-III. p values are exact Mann–Whitney tests. MW, Mann–Whitney; MP, Miller–Payne; RCB, Residual Cancer Burden.

The association with residual disease burden was stronger. Converted tumors had higher RCB classes (exact Mann–Whitney p = 0.003; rrb = −0.50, 95% CI −0.73 to −0.23; exact trend p = 0.006), 11 of 14 (78.6%) were RCB-III compared with 11 of 35 (31.4%) unchanged tumors (Fisher p = 0.004; OR 8.00, 95% CI 1.85–34.54; risk difference 47.1 percentage points), and none was RCB 0–I (0 vs 5 of 35; p = 0.303). Within the converted group, Miller–Payne grades did not differ by target subtype (Kruskal–Wallis p = 0.118); every Luminal B HER2-positive conversion except one was RCB-III, and three of the four Luminal A conversions were RCB-III (Table 2).

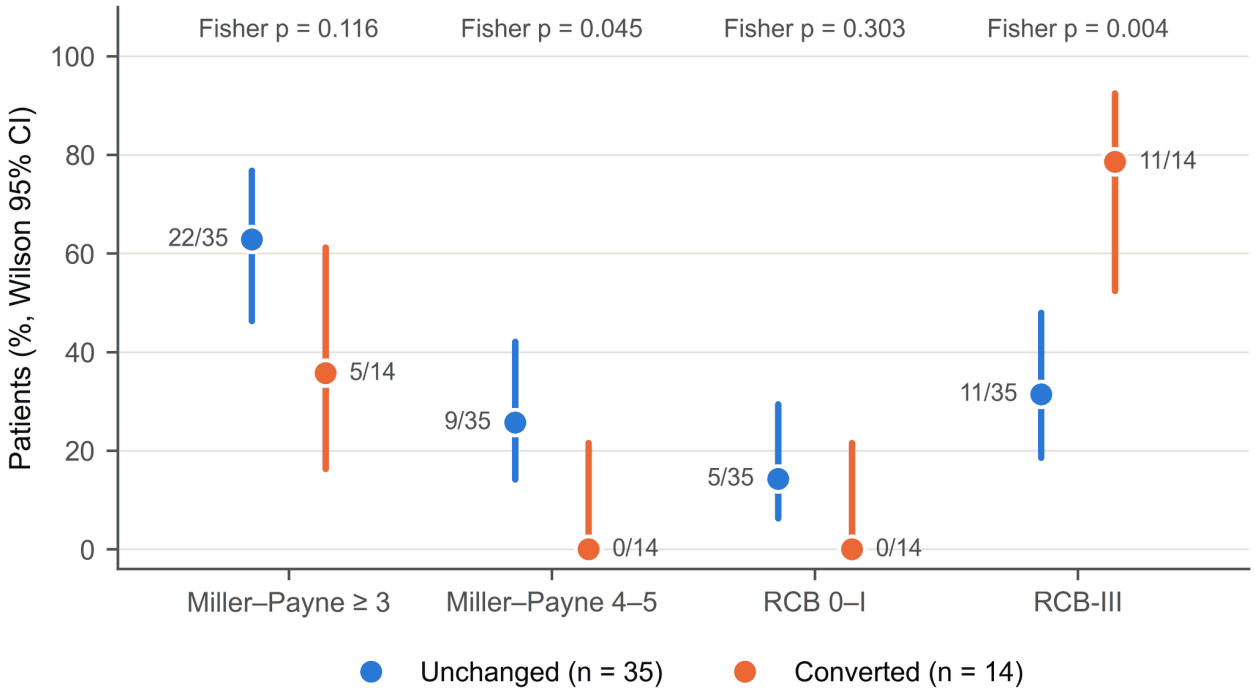


Figure 5. Response thresholds by subtype conversion status. Circles show the proportion of patients reaching each threshold and vertical bars the Wilson 95% confidence interval; labels give the count. Fisher's exact p values are printed above each pair. RCB, Residual Cancer Burden.

Pathological response by regimen and other characteristics

The two regimen groups were balanced at baseline: mean age was 50.5 ± 8.3 years with AC and 53.1 ± 8.9 years with TC (p = 0.285), and stage IIIB (17 of 21 vs 23 of 28; p = 1.000), histological grade 3 (11 of 21 vs 11 of 28; p = 0.398) and node-positive disease (14 of 21 vs 17 of 28; p = 0.769) were similarly distributed.

AC-treated tumors reached Miller–Payne grade 3 or higher more often than TC-treated tumors (16 of 21, 76.2%, vs 11 of 28, 39.3%; p = 0.019; OR 4.95, 95% CI 1.41–17.41), and the two Miller–Payne distributions differed (Fisher–Freeman–Halton p = 0.041). The rank shift, however, was not significant (median 3 vs 2; exact Mann–Whitney p = 0.086; rrb = 0.28, 95% CI −0.03 to 0.58; Table 3; Figure 6). Major response did not differ (19.0% vs 17.9%; p = 1.000), and the single pCR followed TC. Neither the RCB distribution (p = 0.193) nor the proportion with RCB-III (28.6% vs 57.1%; p = 0.081) differed significantly. The following showed no association with the Miller–Payne grade: clinical stage (p = 0.200), cT category (p = 0.353), cN category (p = 0.904), histological grade (p = 0.855), the pre-NAC prognostic stage (p = 0.240), the re-assigned post-NAC prognostic stage (p = 0.359) and age (Spearman ρ = −0.14; p = 0.344).

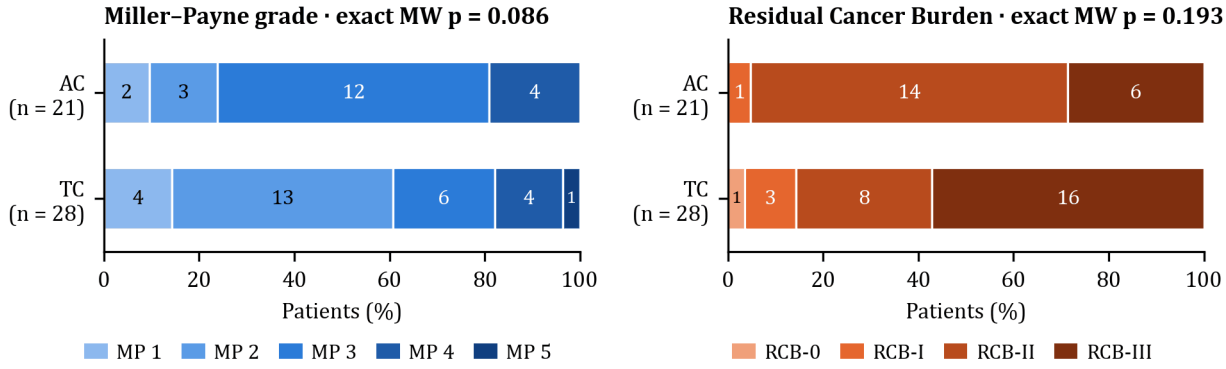


Figure 6. Miller–Payne grade (left) and Residual Cancer Burden class (right) by neoadjuvant regimen. Bars are 100% stacked with patient counts inside segments; p values are exact Mann–Whitney tests. AC was followed by more grade 3 responses but not by a significant shift in the Miller–Payne rank distribution, more major responses or a different RCB distribution. AC, doxorubicin–cyclophosphamide; TC, docetaxel–cyclophosphamide; MW, Mann–Whitney; MP, Miller–Payne; RCB, Residual Cancer Burden.

Multivariable analysis

In the proportional-odds model, conversion was associated with a lower Miller–Payne category after adjustment for regimen, histological grade, stage and age (cumulative OR 0.27, 95% CI 0.08–0.91; p = 0.031), whereas regimen was not (AC vs TC: OR 2.37, 95% CI 0.79–7.10; p = 0.121; Table 4). A reduced model containing only conversion and regimen gave a conversion OR of 0.30 (95% CI 0.09–0.96; p = 0.039). Across 999 bootstrap resamples its percentile 95% CI was 0.05–0.84, and 98.7% of estimates lay below 1. The model as a whole explained a modest share of variation (likelihood-ratio χ^2 = 9.98 on 5 df, p = 0.076; Nagelkerke R^2 = 0.20; c-index 0.69). Cut-point-specific models showed the conversion effect growing towards the major-response threshold (OR 0.38 for grade 2 or higher, 0.34 for grade 3 or higher and 0.08 for grade 4–5), so the proportional-odds assumption held only approximately. In the Firth model for major response, conversion was associated with lower odds of Miller–Payne grade 4–5 (OR 0.098, 95% CI 0.001–0.87; p = 0.034), with no regimen effect (OR 0.95; p = 0.948).

Table 4. Multivariable models of pathological response (n = 49).

Model and predictor	OR	95% CI	p
Model A — proportional-odds, higher Miller–Payne category (1, 2, 3, 4–5)			
Subtype conversion (yes vs no)	0.27	0.08–0.91	0.031
AC vs TC	2.36	0.79–7.10	0.121
Histological grade 3 vs 1–2	0.89	0.30–2.67	0.840
Clinical stage IIIB vs IIIA	0.34	0.08–1.39	0.129
Age, per 10 years	1.10	0.59–2.05	0.772
Fit: LR χ^2 = 9.98 (5 df), p = 0.076; Nagelkerke R^2 = 0.20; c-index = 0.69			
Reduced model (conversion and regimen only): conversion OR	0.30	0.09–0.96	0.039
Bootstrap percentile 95% CI for conversion OR (999 resamples; 98.7% of estimates < 1)		0.05–0.84	
Model B — Firth logistic, Miller–Payne 4–5 (9 events)			
Subtype conversion (yes vs no)	0.10	0.001–0.87	0.034
AC vs TC	0.95	0.21–4.10	0.948
Fit: AUC 0.68 (0.52–0.81), optimism-corrected 0.63; Hosmer–Lemeshow p = 0.836; Brier 0.137			
Model C — Firth logistic, RCB-III (22 events)			
Subtype conversion (yes vs no)	6.54	1.69–31.63	0.006
AC vs TC	0.32	0.08–1.11	0.073
Histological grade 3 vs 1–2	0.81	0.23–2.86	0.737
Fit: AUC 0.80 (0.65–0.90), optimism-corrected 0.76; Nagelkerke R^2 = 0.31; Hosmer–Lemeshow p = 0.780			
Model D — proportional-odds, higher RCB class (0–I, II, III)			
Subtype conversion (yes vs no)	8.02	1.77–36.27	0.003
AC vs TC	0.58	0.18–1.91	0.370
Histological grade 3 vs 1–2	0.67	0.20–2.25	0.515
Clinical stage IIIB vs IIIA	1.90	0.37–9.77	0.444
Age, per 10 years	0.92	0.44–1.90	0.815
Fit: LR χ^2 = 11.92 (5 df), p = 0.036; Nagelkerke R^2 = 0.25; c-index = 0.75			

Models A and D: cumulative (proportional-odds) logistic regression, odds ratio > 1 = higher category (better response in A, more residual disease in D); Wald 95% CI; likelihood-ratio p. Models B and C: Firth-penalized logistic regression with profile penalized-likelihood 95% CI and penalized likelihood-ratio p; optimism correction by 500 bootstrap resamples; the Hosmer–Lemeshow test has low power at this sample size. Cut-point-specific Firth logits for conversion in Model A: OR 0.38 (≥ grade 2), 0.34 (≥ grade 3) and 0.08 (≥ grade 4), indicating that the effect concentrates at the major-response threshold.

In the Firth model for RCB-III, conversion was associated with higher odds of extensive residual disease (OR 6.54, 95% CI 1.69–31.63; p = 0.006), independent of regimen (OR 0.32, 95% CI 0.08–1.11; p = 0.073) and histological grade. The corresponding proportional-odds model for the RCB class gave a conversion OR of 8.02 (95% CI 1.77–36.27; p = 0.003) and no regimen effect (p = 0.370). The direction of the conversion estimate was the same in every model (Figure 7, where Miller–Payne odds ratios are inverted so that values above 1 indicate a worse response). The RCB-III model discriminated well (AUC 0.80, 95% CI 0.65–0.90; optimism-corrected 0.76) and was adequately calibrated (Hosmer–Lemeshow p = 0.780). The major-response model discriminated less well (optimism-corrected AUC 0.63; Figure 8). No pre-treatment characteristic predicted conversion. In the Firth model for conversion, the ORs were 0.83 for AC, 0.42 for grade 3, 0.88 for stage IIIB and 1.28 per 10 years of age (all p ≥ 0.18; optimism-corrected AUC 0.55).

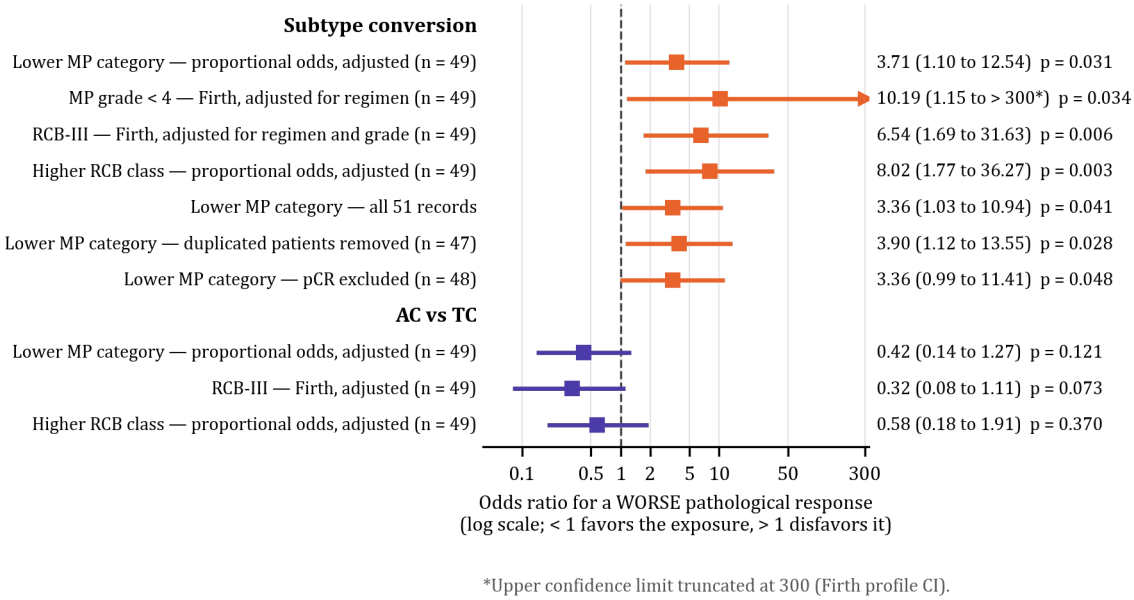


Figure 7. Adjusted odds ratios for a worse pathological response across models and sensitivity analyses. Squares are point estimates and horizontal bars 95% confidence intervals on a log scale; estimates for Miller–Payne outcomes were inverted so that values above 1 always indicate a worse response. Orange, subtype conversion (yes vs no); violet, AC vs TC. pCR, pathological complete response; MP, Miller–Payne; RCB, Residual Cancer Burden.

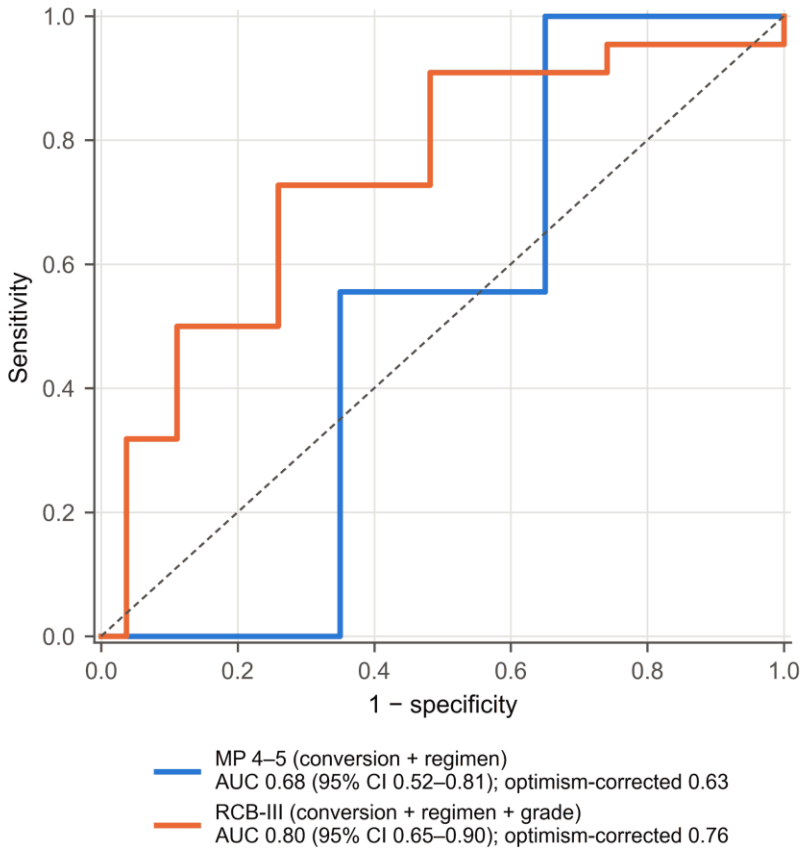


Figure 8. Receiver operating characteristic curves of the Firth-penalized models for Miller–Payne grade 4–5 (blue; predictors: conversion and regimen) and RCB-III (orange; predictors: conversion, regimen and histological grade). The legend gives the apparent AUC with its DeLong 95% confidence interval and the bootstrap optimism-corrected AUC (500 resamples). The dashed diagonal marks chance discrimination. AUC, area under the curve; RCB, Residual Cancer Burden.

Sensitivity analyses and multiplicity

The conversion–response association held whether duplicated records and the pCR patient were retained or removed (Table 5). With all 51 records the adjusted cumulative OR was 0.30 (95% CI 0.09–0.97; p = 0.041). With both duplicated patients removed (n = 47) it was 0.26 (95% CI 0.07–0.89; p = 0.028). With the pCR

patient excluded (n = 48) it was 0.30 (95% CI 0.09–1.01; p = 0.048). The RCB-III association had p ≤ 0.005 in every set. The Fisher p value for Miller–Payne grade 4–5 was 0.084 and 0.085 when both duplicated patients or the pCR patient were removed, respectively (Table 5). Across 49 leave-one-out deletions, the conversion OR ranged from 0.21 to 0.34 and never crossed 1. The regimen association with the Miller–Payne grade was significant only when all 51 records were used (exact p = 0.041) or when the pCR patient was excluded (p = 0.046). After Holm correction across the six primary tests, only the association between conversion and the RCB class remained significant (adjusted p = 0.019). The adjusted p values were 0.135 for conversion and the Miller–Payne grade, and 0.343 for regimen and the Miller–Payne grade.

The structure of the association was then examined. Among the 44 tumors with RCB class II–III, the Miller–Payne difference between converted and unchanged tumors attenuated (Mann–Whitney p = 0.107; rrb = 0.29), and no converted tumor reached grade 4–5 compared with 4 of 30 unchanged tumors (p = 0.290); within RCB-III (n = 22) the Miller–Payne grades of converted and unchanged tumors did not differ (p = 0.783). Conversion nevertheless remained associated with RCB-III rather than RCB-II among tumors with residual disease (11 of 14 vs 11 of 30; p = 0.022). In the misclassification analysis, reclassifying the eight HER2 gains as unchanged left six converted tumors and removed the association with both the Miller–Payne grade (p = 0.201) and RCB-III (4 of 6 vs 18 of 43; p = 0.388); excluding the HER2-gain tumors gave similar results (p = 0.118 and p = 0.168). The HER2-gain tumors alone were RCB-III in 7 of 8 cases, compared with 11 of 35 unchanged tumors (p = 0.006). The E-value for the RCB-III association was 4.55 (1.92 for the lower confidence limit), and that for the Miller–Payne association was 3.26 (1.27).

Table 5. Sensitivity analyses and correction for multiple testing.

Analysis	Conversion → MP: MW p	Conversion → MP: adjusted cumulative OR (95% CI); p	Conversion → MP 4–5: Fisher p	Conversion → RCB-III: Fisher p	AC vs TC → MP: MW exact p (Holm rows: raw → Holm-adjusted p)
Primary analysis, one record per patient (n = 49)	0.027	0.27 (0.08–0.91); 0.031	0.045	0.004	0.086
All 51 records, duplicates retained	0.033	0.30 (0.09–0.97); 0.041	0.045	0.005	0.041
Both duplicated patients removed (n = 47)	0.030	0.26 (0.07–0.89); 0.028	0.084	0.004	0.154
Pathological complete response removed (n = 48)	0.037	0.30 (0.09–1.01); 0.048	0.085	0.005	0.046
Leave-one-out (49 deletions)	—	range 0.21–0.34; all < 1	—	—	—
Restricted to RCB II–III (n = 44)	0.107[b]	—	0.290	0.022[c]	—
Restricted to RCB-III (n = 22)	0.783[b]	—	0.476	—	—
HER2 gains reclassified as unchanged (6 converted)	0.201[b]	—	—	0.388	—
HER2 gains excluded (n = 41; 6 converted)	0.118[b]	—	—	0.168	—
Holm family — Conversion × RCB class (exact MW)					raw 0.003 → Holm 0.019
Holm family — Conversion × Miller–Payne grade (exact MW)					raw 0.027 → Holm 0.135
Holm family — Regimen × Miller–Payne grade (exact MW)					raw 0.086 → Holm 0.343
Holm family — Clinical stage × Miller–Payne grade (FFH)					raw 0.200 → Holm 0.601
Holm family — Regimen × conversion (Fisher)					raw 0.750 → Holm 1.000
Holm family — Histological grade × Miller–Payne grade (Kruskal–Wallis)					raw 0.855 → Holm 1.000

Adjusted cumulative OR from Model A (Table 4; covariates regimen, grade, stage and age); OR < 1 = lower Miller–Payne category. The Holm family comprised the six primary bivariate tests. MW, Mann–Whitney U test; RCB, Residual Cancer Burden. [b]Asymptotic Mann–Whitney test. [c]RCB-III vs RCB-II among tumors with RCB II–III.

4. Discussion

Among 49 women treated for locally advanced Luminal B HER2-negative breast cancer at Dr. Hasan Sadikin General Hospital, the surrogate subtype changed after NAC in more than one in four tumors, and the change clustered in tumors with a poor pathological response. No converted tumor reached Miller–Payne grade 4–5 or RCB class 0–I. Almost four in five were RCB-III. The association with RCB was the strongest result and the only one to survive correction for multiple testing, yet it rested largely on HER2 gains defined by IHC alone. The association with the Miller–Payne grade pointed the same way in every model and sensitivity analysis, but it was modest, depended on the threshold, and did not survive correction. For the regimen comparison, AC was followed by more grade 3 responses than TC. The

Miller–Payne rank distribution did not differ significantly, however, and major response was similar.

The frequency of conversion lies well within the published range. The 28.6% observed here is close to the 27.2% reported by Coiro et al. in 265 tumors, the 28.7% in an Austrian cohort of 237 tumors and the 30.2% in 86 Brazilian patients. It is also similar to the 25.0% subtype change found among residual tumors in a Korean series.[19–22] Marker-level series give comparable figures. Hormone receptor status changed in 23.1% of 91 Saudi patients with locally advanced disease. ER and PR changed in 11.8% and 24.6% of 203 Turkish patients. Chinese and Indian series reported conversion rates of 4–17% for individual markers, with Ki-67 changing in about one third of tumors.[38–43] The higher rate of 43.2% from Makassar came from a smaller mixed-subtype cohort, which may explain part of the difference.[31] Most comparators included several subtypes. Agreement in overall rates is therefore indicative, not exact. The present study adds a subtype-restricted estimate, and the restriction matters. Every tumor began as Luminal B HER2-negative, so every conversion necessarily involved a change in PR, Ki-67, HER2 or ER. The pattern of targets can be read directly.

The dominant pattern was IHC-defined HER2 gain, seen in 8 patients and in 16.7% of tumors with residual disease. This proportion is higher than the 5.5% reported in the Saudi cohort and the 8.6% pooled HER2 conversion rate. Its excess over the 10.1% found by Ma et al. in 564 HER2-negative residual tumors, however, was small and not significant.[17,36,38] Ma et al. also found that hormone receptor-positive and HER2-low tumors were the most prone to HER2 gain, and Chen et al. showed that hormone receptor positivity tripled the odds of a HER2-zero tumor becoming HER2-low.[36,44] Luminal B HER2-negative tumors are exactly the population in which such shifts are expected. Two cautions apply. First, HER2 categories move in both directions, and often. At the Dana-Farber Brigham Cancer Center 29.5% of 1080 residual tumors changed HER2 category; in a Rochester series 39.9% of non-pCR tumors did, and in a Shanghai cohort of 2489 patients 39.5% of HER2-0 non-pCR tumors moved between HER2-0 and HER2-low.[24,45,46] Second, without in situ hybridization an IHC score of 2+ cannot be classified as HER2-positive. Interobserver and inter-assay agreement at the low end of the HER2 scale is only moderate: κ was about 0.6 for each of two assays, complete agreement reached only 62% of slides among nine pathologists, and substantial agreement only 72% of HER2-0 cases among six.[25,27,47,48] Some HER2 gains recorded here may therefore be equivocal results that in situ hybridization would have reclassified. The uncertainty carries clinical weight, because HER2 gain after NAC was associated with worse disease-free survival in the 2025 meta-analysis (HR 1.89).[18] The studies reviewed here did not establish a benefit of HER2-directed treatment for positivity acquired after NAC in tumors that were HER2-negative at diagnosis. The appropriate response to an IHC-defined gain is thus confirmatory in situ hybridization and multidisciplinary review, not automatic escalation.

The four conversions to Luminal A illustrate the opposite direction. In the Penelope-B trial, a shift from Luminal B to Luminal A in residual tumors was the most consistent transcriptomic finding, and it came with a broader move towards less proliferative adaptive clusters.[11] NEOENDO showed that both chemotherapy and endocrine therapy push hormone receptor-positive tumors towards Luminal A-like profiles.[12,13] A falling Ki-67 index is the likeliest immunohistochemical route to this change. Median Ki-67 fell from 40% to 12% in Swedish residual tumors.[14] Ki-67 also shows only moderate concordance between core biopsies and excisions, even before treatment (70–93%).[49] An anthracycline-treated cohort likewise found that Ki-67 change carried predictive information.[50] A Luminal A label on a post-treatment specimen therefore usually reflects proliferation arrest in surviving cells, not a more indolent tumor. It should not be used to de-escalate adjuvant endocrine therapy. Three of the four Luminal A conversions were RCB-III, which fits this reading. The rule that produced the Luminal A label (a fall in Ki-67 below 20%, a gain of PR, or both) could not be determined from the available records.

Hormone receptor loss was uncommon, affecting three patients, two of whom converted to triple-negative disease. Even so, it is the pattern with the clearest prognostic signal in the literature. In the meta-analysis by Dowling et al., hormone receptor loss carried hazard ratios of 3.42 for disease-free survival and 1.99 for overall survival, and Antonini et al. linked it to lower pCR rates and worse disease-free survival.[17,18] In Makassar, change to triple-negative disease was the subtype change that predicted worse progression-free survival.[31] Here, both triple-negative conversions had Miller–Payne grades of 1 or 2, and both were re-assigned from prognostic stage IIIB to IIIC. The numbers are too small for inference. Still, these observations point the same way and support routine re-testing of hormone receptors on residual tumors, since a patient whose residual disease has lost ER and PR expression is unlikely to gain the expected benefit from adjuvant endocrine therapy alone.

The central finding, that conversion co-occurs with poor response, has to be read through the design. Post-treatment IHC can be performed only where invasive tumor remains. Patients in whom conversion can be detected are therefore, by construction, those with residual disease. The amount of residual tumor sets both the opportunity for clonal selection and the quantity of tissue available for re-testing. The association with RCB was stronger than that with the Miller–Payne grade. This is probably because RCB integrates residual tumor size, cellularity and nodal disease, and so measures the residual burden in which selection and re-testing operate, whereas the Miller–

Payne grade measures only the proportional fall in cellularity.[28,30] Two observations fit that distinction: the moderate agreement between the two systems in this cohort (ρ = −0.44), and the seven Miller–Payne grade 3 tumors classified as RCB-III. They also fit the difficulty of measuring scattered residual disease after NAC, which changed the tumor size or ypT (post-treatment pathological tumor) category in just over half of re-measured specimens (53.7%) in one study.[51] The cut-point-specific models point the same way. The conversion effect was weak at the lower Miller–Payne thresholds. It was strong at the major-response threshold, where residual tumor becomes scant. Two interpretations follow, and the data cannot separate them. Conversion may mark a chemoresistant residuum of surviving subclones that were HER2-higher, hormone receptor-lower or less proliferative before treatment. Or it may be partly an artifact of re-testing larger residual tumors with imperfect assays (Figure 9). Either way, conversion is better understood as a marker of what remains after chemotherapy than as a cause of resistance.

The additional analyses sharpen this reading. Among tumors that all had considerable residual disease (RCB II–III), the Miller–Payne difference between converted and unchanged tumors attenuated. Within RCB-III it disappeared. The Miller–Payne association is thus largely a function of how much tumor remained. Conversion still separated RCB-III from RCB-II within the residual-disease stratum, as would be expected if conversion marks the most extensive residuum. The misclassification analysis identifies the weakest link: when the eight HER2 gains were treated as unchanged, no association remained, and the HER2-gain tumors alone carried most of it (RCB-III in 7 of 8). Whether the main finding is biological or partly an assay artifact therefore depends on whether in situ hybridization would confirm these IHC-defined gains. If the gains are genuine, an unmeasured confounder would need a risk ratio of about 4.6 with both conversion and RCB-III to explain the association away, and about 1.9 to move its confidence interval to the null. No measured covariate approached that strength.[37] The cut-point-specific models, with the conversion effect concentrated at the major-response threshold, support the same reading. Conversion separates patients with scant residual tumor from those with extensive residual disease better than it orders the intermediate grades.

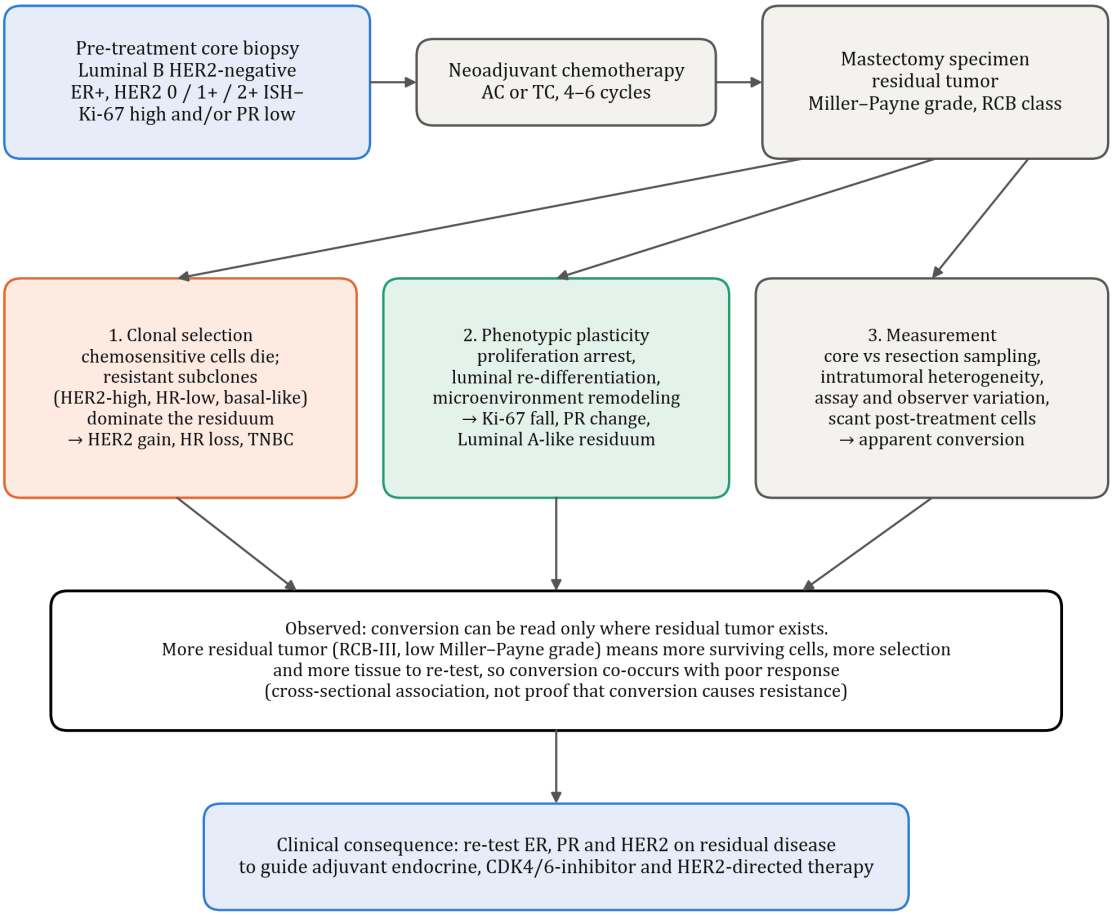


Figure 9. Conceptual model of post-neoadjuvant surrogate-subtype change in Luminal B HER2-negative breast cancer. Three non-exclusive pathways — clonal selection, phenotypic plasticity and measurement error — can each produce an apparent conversion, and all of them require residual tumor, which links conversion to poor pathological response in a cross-sectional design. The lowest box shows the clinical implication: re-test receptors on residual disease. AC, doxorubicin–cyclophosphamide; TC, docetaxel–cyclophosphamide; HR, hormone receptor; ISH, in situ hybridization; RCB, Residual Cancer Burden; TNBC, triple-negative breast cancer.

These results agree in direction with the wider literature, but not in every detail. Antonini et al. found that hormone receptor loss was associated with lower pCR and HER2 gain with improved pCR.[17] No HER2-gain tumor in this cohort reached a major response. The difference lies largely in the population. The pooled studies included HER2-positive tumors that received HER2-directed therapy alongside chemotherapy, so HER2 expression marked a treatment target. The present cohort was restricted to HER2-negative tumors treated with chemotherapy alone. A newly HER2-positive residuum had received no targeted treatment. In hormone receptor-positive/HER2-negative disease, the Miller–Payne grade and major pathological response remain prognostic when pCR is rare. One series reported five-year event-free survival of 87% after major response versus 68% without it, and another showed a similar separation by Miller–Payne grade combined with a 70-gene signature.[5,29] On-treatment biopsies show that residual tumor during chemotherapy almost precludes pCR in this subtype (3%).[15] The RCB-III rate of 44.9% in this cohort, together with conversion and RCB-III in 11 of 14 converted tumors, thus identifies a group with a high expected risk of recurrence.[30]

The regimen comparison requires particular caution. AC was followed by more grade 3 responses than TC, and the two Miller–Payne distributions differed. Yet the rank shift was not significant, major response and pCR did not differ, and the association with RCB-III did not reach significance in the adjusted model. The Miller–Payne difference was significant only in sensitivity sets that retained a duplicated record or excluded the pCR patient. Allocation was not randomized and probably reflected age, cardiac fitness, drug availability and clinician preference, and the number of cycles actually delivered was not available. A network meta-analysis of 17 randomized trials in hormone receptor-positive/HER2-negative disease found no difference in pCR between anthracycline-only backbones and alternative chemotherapy backbones,[52] and a Jakarta cohort reported that taxane chemotherapy predicted a lower RCB score.[32] Conversion itself was not associated with the regimen in this cohort (OR 0.66). This agrees with the similar HER2 change rates after anthracycline-based and taxane-based or platinum-based regimens in the Dana-Farber series.[24] The firmer inference is that both four-to-six-cycle doublets produced few major responses. The pCR rate of 2.0% was lower, though not significantly, than the 6–18% reported for hormone receptor-positive/HER2-negative or Luminal B-like disease in recent cohorts and trials, and far below the 26.3% reported for Luminal B tumors after six cycles of concurrent docetaxel, epirubicin and cyclophosphamide.[4–8,10] Newer strategies that combine chemotherapy with immune checkpoint inhibition have raised pCR in high-risk ER-positive disease (24.5% vs 13.8% with placebo).[6] HER2-low status does not appear to improve chemosensitivity (pooled OR for pCR 0.75 in hormone receptor-positive disease), so a newly HER2-low residual tumor should not be expected to behave differently under chemotherapy.[53]

The clinical implications follow from the frequency and direction of conversion. Guidance already recommends that the extent and biology of residual disease inform adjuvant treatment,[3] and conversion changed the adjuvant plan in 3.8% of tumors in the Italian series.[19] In this cohort, 10 of 49 patients (20.4%) had a residual tumor with an IHC-defined HER2 gain or a loss of hormone receptors. Such changes would prompt confirmatory testing and multidisciplinary review of the endocrine and HER2-directed plan. HER2 gains were frequent and in situ hybridization was not performed. The practical priority at institutional level is therefore a standard re-testing protocol for residual tumors. It would cover ER, PR, HER2 and Ki-67 on the mastectomy specimen whenever invasive tumor remains, reflex in situ hybridization for HER2 2+ results, reporting of HER2-0 and HER2-low categories, and routine RCB reporting alongside the Miller–Payne grade.[26,27] At national level, the same protocol would let Indonesian centers compare conversion rates. At present, measurement differences make published figures hard to pool.

The regional context sharpens these implications. Indonesian cohorts present predominantly at stage IIIB,[2] and response to NAC in Indonesian series has been modest: pCR was 8.3% and RCB class II–III 90% in Jakarta, pCR was 16.7% in triple-negative disease in Bali, and HER2 positivity and survivin expression predicted poor response in a prospective Makassar cohort of locally advanced cancers.[32,34,35] Immune infiltrates have been linked to the Miller–Payne response in Jakarta.[33] Against this background, the RCB class II–III rate of 89.8% in Bandung is unsurprising, and it means that most Indonesian patients treated with NAC will have a residual tumor available for re-testing. The Makassar finding that change to triple-negative disease predicted worse progression-free survival suggests that conversion is prognostic in Indonesian patients too,[31] but no Indonesian study has yet linked conversion to survival within a single subtype.

Several next steps can be specified. A prospective multicenter Indonesian cohort of patients with Luminal B HER2-negative cancer should pair core biopsies with residual tumors. It should include central re-testing of ER, PR (as continuous percentages), HER2 (IHC with reflex in situ hybridization) and Ki-67. RCB should be reported for every specimen, and stromal tumor-infiltrating lymphocytes scored in both samples. Based on the present estimates (about 28% conversion), about 120 patients would give 80% power to detect a cumulative odds ratio of 3 for the association between conversion and the Miller–Payne grade. About 280 would be needed for an odds ratio of 2. Estimating the

conversion rate to within ±5 percentage points would require about 314 patients. The same cohort should follow patients for disease-free and overall survival, so that the prognostic meaning of each conversion pattern (HER2 gain, hormone receptor loss and Luminal A-like change) can be estimated in Indonesian patients. A randomized or carefully matched comparison of anthracycline-based and taxane-based regimens of defined intensity, with RCB as the primary end point, would answer the regimen question that this retrospective cohort can only raise.

The study has several strengths. Complete patient-level data were available and were cross-checked against the original tabulation. Two variables often missing from retrospective series, the RCB class and the histological grade, could be included. The cohort was restricted to a single surrogate subtype, so each conversion can be interpreted as a change in specific markers. Response was measured with two validated systems. Their agreement was quantified. The analysis used exact tests, effect sizes with confidence intervals, penalized regression suited to small samples, correction for multiple testing, benchmarking against published rates and sensitivity analyses defined before re-analysis of the records. The strength of each finding can therefore be judged rather than assumed.

The limitations are equally specific. The study was retrospective and single-center, with 49 patients and 14 conversions, and it had adequate power only for large effects. The multivariable estimates rest on few events per variable. The number of patients screened and the reasons for exclusion were not recorded, so selection bias cannot be assessed. Conversion and response were measured on the same specimen, so the design cannot establish temporal order, and the single patient with a pCR could not be assessed for conversion. Two medical record numbers were duplicated. One record per patient was retained, and the conversion results did not depend on how the duplicates were handled. IHC was not centrally reviewed, and the antibody clones and blinding of post-treatment scoring were not documented. HER2 was assessed without confirmatory in situ hybridization, and the misclassification analysis showed that the main association depends on the HER2 calls. Continuous ER, PR and Ki-67 values were not available, so marker-level conversion and the exact rule that produced the four Luminal A conversions could not be analyzed. The a priori sample size used a one-sided α, whereas all analyses were two-sided. Regimen allocation was not randomized. The number of cycles delivered was not recorded, and no survival data were available. Finally, the post-NAC prognostic stage in the records is a derived quantity and was not used as an outcome.

5. Conclusion

In women with locally advanced Luminal B HER2-negative breast cancer treated with anthracycline-based or taxane-based NAC at a national referral hospital in West Java, the surrogate subtype changed in 28.6% of tumors (95% CI 17.8–42.4), most often through IHC-defined HER2 gain. This rate is in line with international series. Conversion was concentrated in tumors with poor response. None reached Miller–Payne grade 4–5, and 78.6% were RCB-III (adjusted OR 6.54, 95% CI 1.69–31.63). The association between conversion and the RCB class was the only one that survived correction for multiple testing. It depended largely on HER2 gains defined by IHC alone. Conversion is best regarded as a marker of extensive residual tumor, not a cause of resistance. Its biological meaning depends on confirming the HER2 gains by in situ hybridization. ER, PR and HER2 should be re-tested on every residual tumor, with reflex in situ hybridization for equivocal HER2 results and routine RCB reporting, before adjuvant therapy is chosen. Larger prospective work is needed. A multicenter Indonesian cohort of about 120–280 patients, with central re-testing and survival follow-up, would confirm these associations and establish the prognostic meaning of each conversion pattern.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung (Ethical Approval No. DP.04.03/D.XIV.6.5/200/2025; Reg. No. 05.25.200; 19 May 2025) and was conducted in accordance with the Declaration of Helsinki. The study used anonymized hospital records and archived pathology material, and individual informed consent was waived under institutional protocol.

Consent for publication

Not applicable. No identifiable individual information is reported.

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Competing interests

The authors declare no competing interests.

Author contributions

Contributions follow the CRediT taxonomy. S.A.P.: conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, writing – review & editing. K.A.R.: conceptualization, supervision, validation, writing – review & editing. B.S.H.: methodology, supervision, validation (pathology), writing – review & editing.

Data availability

The de-identified patient-level dataset (one record per patient, CSV format) and the analysis code are available from the corresponding author on reasonable request, subject to approval by the Research Ethics Committee of Dr. Hasan Sadikin General Hospital.

Generative AI disclosure

None. No generative artificial intelligence tools were used to prepare this manuscript.

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