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Performance of Prognostic Models After Neoadjuvant Therapy in Breast Cancer: A Retrospective Cohort Analysis of Residual Cancer Burden, Neo-Bioscore, and Pathologic Staging in a Latin American Population

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Research Article

Keywords: breast cancer, neoadjuvant chemotherapy, prognostic staging, locally advanced disease

Posted Date: May 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9696802/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

Accurate post-neoadjuvant risk stratification is essential for guiding breast cancer management. This study aimed to evaluate and compare the clinical utility and prognostic performance of the Neo-Bioscore (NB), residual cancer burden (RCB), and pathologic stage (PS) across breast cancer molecular subtypes, as their comparative superiority remains uncertain.

Methods

We retrospectively evaluated 850 consecutive patients with non-metastatic breast cancer treated with neoadjuvant chemotherapy and surgery in Mexico (2005–2020). The prognostic performance of clinical stage, PS, NB, and RCB was evaluated for 5- and 8-year disease-free and overall survival. Discrimination (time-dependent AUC), reclassification (integrated discrimination improvement [IDI]), calibration (Brier score), and clinical utility (decision curve analysis) were assessed overall and by subtype.

Results

Overall, 65.5% of patients presented with locally advanced disease. At an 83-month median follow-up, 31.6% recurred and 23.4% died. In luminal tumors, NB demonstrated superior 5-year discrimination (AUC 0.689), reclassification (IDI 6.76%), and net benefit; high NB categories predicted extremely poor outcomes. In triple-negative disease, RCB and PS achieved the highest discrimination (5-year AUCs 0.775 and 0.757) and reclassification improvements. In HER2-enriched tumors, RCB improved 5-year reclassification over clinical stage (IDI 6.39%). Stage migration analysis revealed substantial classification divergence between systems.

Conclusion

Post-neoadjuvant prognostic staging in breast cancer is highly subtype-dependent. Biologically integrated models like NB provide superior long-term risk prediction in luminal disease, whereas quantifying residual disease (RCB, PS) is critical in triple-negative and HER2-positive tumors. These findings support tailoring post-surgery risk estimation by subtype to optimize management.

Introduction

Breast cancer is the most common cancer in women worldwide and a leading cause of cancer-related mortality [1]. In Mexico and most of Latin America, patients are predominantly diagnosed in advanced stages [1, 2], in contrast with the presentation patterns reported in high income countries [3–5]. While neoadjuvant chemotherapy (NAC) is the standard of care for locally advanced disease to increase

breast-conserving surgery rates and evaluate in vivo tumor sensitivity, pathologic complete response (pCR) is an infrequent event [6, 7]. Because a significant proportion of patients (approximately 10% to 50%, depending on the molecular subtype [8, 9]) present with residual disease at surgery, relying on a binary outcome (pCR versus non-pCR) fails to reflect crucial prognostic heterogeneity. As therapeutic options expand, the possibility of tailoring adjuvant therapy based on the response to preoperative treatment demands the consideration of the complexities of residual disease [10]. Multiple tools have been developed to estimate risk in these scenarios, however, there is currently no consensus on which prognostic staging system is optimal in the post-neoadjuvant setting. The 8th edition of the American Joint Committee on Cancer (AJCC) classification system introduced the pathologic prognostic stage, integrating tumor biology with clinical characteristics [11]; however, this system excluded patients treated with NAC, limiting its use in this particular context. To address this limitation, classification systems such as the Neo-Bioscore (NB) were created by assigning scores to clinical and pathologic characteristics, including tumor grade, hormone receptor, and HER2 status to produce an index that reflects both tumor biology and response to treatment, classifying patients in eight different categories [12]. The residual cancer burden (RCB) index measures the amount of disease following NAC and considers residual tumor size, cellularity, and nodal involvement to classify patients in four different risk categories with long-term prognostic value [13, 14].

Current evidence regarding the comparative superiority of these tools remains contradictory, including in settings where late-stage disease is highly prevalent [15, 16]. Recent large-scale analyses suggest that the utility of these systems varies by biological subtype. In a pooled multicenter analysis of 5,161 patients, Yau et al. demonstrated that although RCB has prognostic value across all subtypes, the relationship between residual disease and recurrence risk is not uniform: it is linear in aggressive subtypes but non-linear in hormone receptor-positive (HR+), HER2-negative tumors, where the risk does not significantly increase until high RCB scores are reached [17]. Similarly, various cohort studies have confirmed that patients with triple-negative tumors and moderate to extensive residual disease (RCB categories II-III) face particularly poor outcomes, whereas in luminal subtypes, the association between RCB and survival is weaker [18, 19]. We hypothesize that the prognostic performance of these tools is phenotype-dependent due to intrinsic tumor resistance to chemotherapy. In luminal subtypes (HR+/HER2-), where sensitivity to NAC is low and pCR is uncommon, prognosis is influenced by the initial tumor burden, therefore, the use of pre-treatment factors may offer refined risk assessment by considering the "history" of the disease. Conversely, in highly chemosensitive and aggressive phenotypes such as HER2-enriched and triple-negative breast cancer, the extent of the pathological response could be useful for discriminating risks, even with low volumes of residual disease.

Additionally, there is a lack of data regarding the real-world applicability of these tools. Although these systems are used and have been validated in high-resource settings [20–23], few comparative results have been reported for Latin American populations [15, 24]. This lack of data has considerable implications, as these regions often present heterogeneous epidemiologic profiles, such as a higher prevalence of locally advanced disease and unique treatment scenarios that could impact on the real-world performance of prognostic models [25, 26]. The primary objective of this retrospective cohort

study was to evaluate and compare the prognostic performance of the AJCC pathologic stage (PS), NB, and RCB in predicting disease-free survival (DFS) and overall survival (OS) among breast cancer patients treated with NAC at a tertiary cancer center in Mexico. We conducted a comprehensive assessment of model performance by subtype, using time-dependent discrimination metrics, calibration indices, and decision curve analysis (DCA) to determine clinical utility. By validating the proposed hypothesis within this demographic, we aim to contribute towards an optimized use of prognostic models in regions where epidemiologic and treatment scenarios are similar.

Methods

Study Population

We conducted a retrospective cohort study including 850 consecutive Hispanic patients with non-metastatic breast cancer (BC) who received NAC and surgical treatment at Instituto Nacional de Cancerología in Mexico City from May 2005 to April 2020. Eligibility criteria included histologically confirmed invasive breast carcinoma, completion of a standard NAC regimen (anthracycline and/or taxane-based), and availability of baseline clinical staging, post-treatment pathologic staging, RCB index, and NB determination. Patients were excluded if follow-up information or biomarker data (ER, PR, HER2, Ki-67) were incomplete. Subtypes were defined using surrogate immunohistochemical markers according to the 2013 St. Gallen International Expert Consensus criteria: Luminal A (ER + and/or PR+, HER2–, Ki-67 < 20%), Luminal B (ER + and/or PR+, HER2–, Ki-67 ≥ 20%), HER2-enriched (HER2+, HR–), and triple-negative (ER–/PR–/HER2–) [27]. ER and PR positivity were defined as ≥ 1% staining according to ASCO/CAP guidelines [28]. The study was approved by the Institutional Review Board at Instituto Nacional de Cancerología. A STROBE-compliant diagram describing the patients included is shown in supplementary Fig. 1.

Baseline variables included age, clinical stage, tumor grade, hormone receptor status, HER2 status, and Ki-67 index. Clinical stage was defined according to the AJCC edition concurrent with diagnosis. PS was assigned according to the 8th edition of the AJCC Staging Manual [11]. The RCB score was calculated using the pathologic variables included in the web-based calculator (MD Anderson Cancer Center) [29], including residual primary tumor size, cellularity, and axillary nodal involvement, and categorized into RCB-0 (pCR), RCB-I, RCB-II, and RCB-III. pCR was defined as no residual invasive disease in the breast and no residual disease in axillary lymph nodes (ypT0/is, ypN0). NB was calculated as described by Mittendorf et al. [12], integrating PS, ER status, tumor grade, and HER2 status, with scores ranging from 0 to 7.

The primary outcome was disease-free survival (DFS), defined as the time from surgery to the first occurrence of local, regional, or distant recurrence, or death from any cause. The secondary endpoint was overall survival (OS), defined as the time from surgery to death from any cause. Survival analyses were performed using restricted mean survival time (RMST) to compare the prognostic performance of

the staging systems at 5 and 8 years. Patients alive and event-free at the time of last follow-up were censored.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Survival functions were estimated and plotted using Kaplan–Meier curves and compared using log-rank tests. To ensure the statistical stability of the models, risk categories with few patients were combined for survival analyses: PS IA was combined with IB (IA-IB), stage IIIB with stage IIIC (IIIB-IIIC), and NeoBioscore 0 was combined with score 1 (0–1). Survival outcomes were evaluated at 5 and 8 years using Cox proportional hazards regression to calculate hazard ratios (HRs) with 95% confidence intervals for clinical stage, pathological stage, RCB, and NB, both globally and stratified by subtype. The proportional hazards assumption was evaluated using Schoenfeld residuals. To reduce sparse-data bias in small subgroups, Firth's penalized maximum likelihood bias reduction for Cox regression was used.

The discriminatory performance for DFS and OS of each system was evaluated using a time-dependent area under the receiver operating characteristic curve (AUC-ROC), evaluating various timepoints from 12 to 96 months. The added predictive value of the models over the AJCC clinical stage (baseline model) for 5- and 8-year DFS and OS was quantified using the integrated discrimination improvement (IDI) index at months 12 to 96. Calibration for 8-year DFS was evaluated visually through calibration plots. Brier scores for DFS and OS were calculated from 12 to 96 months. Clinical utility for the prediction of 5-year recurrence risk was assessed through decision curve analysis (DCA), evaluating the net benefit of adding adjuvant therapy across a range of clinically relevant risk thresholds. All analyses were performed in R (version 4.4.0) [30] with the survival, timeROC, riskRegression, survIDINRI, dcurves, and CalibrationCurves packages. Two-sided p-values < 0.05 were considered statistically significant.

Results

A total of 850 patients with BC were treated with NAC from May 2005 to April 2020. The median age was 49 years (range 42–57). The majority of patients presented with T2 (n = 317, 37.3%) or T3 tumors (n = 284, 33.4%), and had involvement of 1–3 nodes (cN1, n = 374, 44%), with 557 patients (65.5%) presenting with clinical stage III breast cancer. Most tumors were grade 3 (n = 427, 50.2%); the most common subtype was luminal B (n = 455, 53.5%), followed by triple negative (n = 171, 20.1%), luminal A (n = 138, 16.2%), and HER2-enriched (n = 86, 10.1%). The most common surgery performed was mastectomy plus lymphadenectomy (n = 748, 88.0%). Of 593 ER/PR+ tumors (luminal A and B disease), 554 (93.4%) received adjuvant endocrine therapy, while 755 patients (88.8%, all subtypes) received adjuvant radiotherapy and 216 (98.6%) of patients with HER2-positive disease received targeted therapy. Additional baseline characteristics are described in Table 1. Regarding response to treatment, 263 (31.0%) patients achieved a pCR, with varying rates by subtype: 5.8% for luminal A, 31.0% for luminal B, 55.0% for HER2-enriched, and 40.0% for triple negative tumors. The median follow-up time was 83.0 months (IQR 53.0–110.0). During this period, 269 patients (31.6%) presented with recurrence (local: *n* = 39, 4.58%, distant: *n* = 230, 27.05%), and 199 (23.4%) died. Eight-year disease-free survival was estimated

using Kaplan-Meier curves by staging system (clinical, pathological, NB and RCB) and stratified by subtype (Fig. 1).

Survival Analysis and Subgroup Outcomes

Eight-year DFS and OS estimates for the overall cohort and by subtype were calculated using PS, RCB, and NB (Table 2). In the overall cohort, patients achieving a complete response (pCR/RCB-0) had an 8-year DFS and OS of 81.7% and 86.8%, respectively. Similarly, patients with NB scores 0–1 had an 8-year DFS of 75.0% and an OS of 86.8%. In contrast, the most advanced categories across all evaluated systems in the overall cohort were associated with a significantly increased risk of both recurrence and mortality (all $p < 0.001$). Patients with a NB score of 7 had an 8-year DFS of 0.0% (HR = 11.24, 95% CI: 3.62–34.93, $p < 0.001$) and an 8-year OS of 20.0% (HR = 40.34, 95% CI: 11.30–144.08, $p < 0.001$) compared to scores 0–1. Consistently, RCB-III correlated with an 8-year DFS of 48.5% (HR = 5.34, 95% CI: 3.56–8.00, $p < 0.001$) and an OS of 60.6% (HR = 5.91, 95% CI: 3.69–9.47, $p < 0.001$).

In luminal tumors, patients with NB scores 0–1 had an 8-year DFS of 77.8% and an 8-y OS of 90.7%. Conversely, scores of 6 or higher correlated to an 8-year DFS of 0% (HR = 11.78, 95% CI: 4.46–31.10, $p < 0.001$) and an OS of 42.3% (HR = 13.99, 95% CI: 3.74–52.27, $p < 0.001$) (supplementary table 1). In the HER2-enriched subgroup, patients with pCR had an 8-year DFS of 85.4% and an OS of 92.7%, while patients with RCB-III disease had an 8-year DFS and OS of 0.0%, with a HR for recurrence of 26.47 (95% CI: 7.19–97.42, $p < 0.001$) and a HR of 57.09 for death (95% CI: 12.90–252.65, $p < 0.001$) (supplementary table 2). In triple-negative disease, patients with pCR had an 8-year DFS of 85.2% and an OS of 85.5%; patients with RCB-I had an 8-year DFS of 58.5% (HR vs pCR = 2.64, 95% CI: 0.89–7.89, $p = 0.091$) and an OS of 52.8% (HR for death vs. pCR = 3.69, 95% CI: 1.35–10.04, $p = 0.013$). In this subgroup, patients with RCB-III disease had an 8-year DFS of 20.5% (HR = 10.73, 95% CI: 4.81–23.96, $p < 0.001$) and an OS of 33.1% (HR = 9.02, 95% CI: 3.95–20.61, $p < 0.001$) (supplementary table 3).

Staging System Performance Comparison

An alluvial plot was used to map stage migration between RCB, PS, and NB (supplementary Fig. 2). Time-dependent ROC, Brier score calculation and IDI analyses were performed for the overall cohort and stratified by molecular subtype (Fig. 2). Overall, all post-neoadjuvant systems outperformed the clinical stage for DFS. At 5 years, NB and PS achieved the highest discrimination (AUC = 0.712 and 0.704, respectively) and lowest prediction error (Brier = 0.148 and 0.149), contrasting with clinical stage (AUC = 0.612; Brier = 0.164). At 8 years, PS showed the highest discrimination (AUC = 0.671), followed by NB (AUC = 0.667), clinical stage (AUC = 0.648), and RCB (AUC = 0.636). Furthermore, RCB yielded the lowest 8-year prediction error (Brier = 0.201), followed by NB and PS (both 0.203), and clinical stage (0.210). In the overall cohort, 5-year IDI over clinical stage was highest for NB (7.51%), followed by PS (6.51%). At 8 years, NB maintained the highest IDI (5.70%), followed by PS (5.27%) (Table 3). These trends were consistent for 5- and 8-year OS, both overall and by subtype (supplementary tables 4–10).

Model Calibration and Clinical Utility

To evaluate model calibration for predicting 5-year DFS, we built a calibration curve, with predicted probabilities closely matching the observed Kaplan-Meier probabilities (supplementary Fig. 3). DCA for 5-year DFS revealed that the clinical utility of staging systems for guiding adjuvant therapy varied significantly by subtype (Fig. 3). In the overall cohort, post-neoadjuvant models provided a superior net benefit over "treat-all" or "treat-none" strategies across a range of clinically relevant risk thresholds (16% to 50%). In luminal disease, NB demonstrated the highest net benefit at intermediate-to-high risk thresholds (from 23% to 54%). In triple-negative tumors, PS and RCB had superior net benefit compared to both NB and clinical stage across decision thresholds (30% to 70%). Conversely, in HER2-enriched disease, model performance overlapped at lower thresholds (< 30%), while clinical stage maintained the highest net benefit across intermediate thresholds (32% to 65%). Notably, at high-risk thresholds (> 50%), NB had a net benefit that persisted up to the 74% threshold, outperforming post-neoadjuvant-focused metrics (RCB and PS).

Discussion

Our findings suggest that post-neoadjuvant prognostic stratification in breast cancer varies according to tumor subtype, which suggests against the use of a single staging system and instead supports a subtype-specific approach. In the overall cohort, NB achieved the highest reclassification improvement and discrimination for OS and DFS at both 5 and 8 years. However, subgroup analysis revealed that this was driven by luminal tumors, the most prevalent subtype in our population. In luminal disease, patients with NB scores ≥ 6 experienced poor long-term outcomes, with an 8-year DFS of 0% and an OS of 42.3%, highlighting the impact of baseline tumor biology and disease burden in HR+ disease. Given the pattern of late, endocrine-driven recurrence in these tumors, models that include pre-treatment characteristics appear to be more effective than metrics that focus on residual disease volume. In contrast, triple-negative breast cancer had a response-driven prognostic pattern, as RCB and PS had substantially higher discriminatory capacity and reclassification improvement, with IDI values for DFS ranging from 11% to 17% at both 5 and 8 years. Importantly, patients with RCB-III disease experienced 8-year DFS rates of 20.5%, reflecting considerable chemotherapy resistance. In this aggressive phenotype, the extent of residual disease after NAC appears to determine recurrence risk. These results reinforce the importance of systematically calculating RCB in pathology reports, as it provides prognostic information that can inform postoperative systemic escalation strategies. The HER2-enriched subgroup revealed a complex interaction between baseline tumor burden and treatment response. At 5 years, clinical stage had the highest net benefit across intermediate decision thresholds in DCA, even though RCB showed the highest discrimination (AUC = 0.776) and meaningful reclassification improvement (IDI = 6.39%). This could reflect the influence of initial tumor burden on early recurrence risk, even with high pCR rates (55% in this subgroup) and evolving anti-HER2 therapeutic strategies during the study period. Over longer follow-up, however, RCB and PS showed superior discriminatory performance for DFS (8-year AUC of 0.874 and 0.804, respectively), suggesting that residual disease volume reflects resistance and long-

term mortality risk. Our overall survival analysis directly confirmed this, as RCB showed an AUC for 8-year OS of 0.881 and a 23.78% reclassification improvement over clinical stage. These findings suggest that prognosis is time- and treatment-dependent in HER2-positive disease and that both baseline stage and residual disease contribute to risk stratification. In summary, these results suggest that subtype-specific staging can help clinicians identify patients that require treatment escalation or longer follow-up in the postoperative setting.

The alluvial plot analysis demonstrated substantial stage migration between NB, PS, and RCB, highlighting their lack of prognostic equivalence. Such differences have direct clinical implications, as the choice of staging system may influence decisions regarding adjuvant therapy escalation. DCA showed that for 5-year DFS, RCB and PS offered superior net benefit in triple-negative disease, whereas NB was superior in luminal tumors. These findings also suggest that staging selection should be adapted to tumor biology. This is particularly relevant in real-world practice, where locally advanced disease is common, as in our cohort, with 65.5% of patients presenting with clinical stage III disease. For populations similar to ours, relying on a unique staging system may omit important clinical and pathologic features. Instead, the use of accessible tools like NB and RCB allows to maximize the utility of pathology and tailor postoperative care without adding extra costs.

Our study has several limitations. First, its retrospective, single-center design may limit generalizability, although inclusion of consecutive patients and a large sample size reduce potential selection bias. Second, the inclusion period (2005–2020) includes therapeutic advances, particularly in anti-HER2 regimens, which could have influenced survival and may explain the temporal patterns observed in HER2-enriched tumors. Third, extreme prognostic categories (e.g., NB score 7) included relatively few patients, which required penalized regression to reduce sparse-data bias. Finally, external validation in contemporary, multi-institutional cohorts is needed to confirm the applicability of these findings across healthcare systems.

In summary, the present study demonstrates that commonly used post-neoadjuvant prognostic tools provide clinically useful risk stratification in a large Latin American cohort of breast cancer patients treated with NAC. Our findings indicate that the prognostic performance of these systems is highly influenced by tumor biology and molecular subtype. In our cohort, characterized by a high prevalence of locally advanced disease, NB was the best prognostic tool for luminal tumors, reflecting its ability to integrate baseline tumor burden with post-treatment pathological features and thereby capturing the risk of late recurrence and mortality. Conversely, in triple-negative and HER2-positive disease, prognosis was primarily driven by the volume of residual disease after therapy. Models that quantify residual disease, such as RCB and PS, provided superior discrimination and clinical utility in these subtypes. Overall, these findings reinforce the concept that post-neoadjuvant prognostic assessment should be interpreted within the biological context of each tumor subtype, and that these tools should be viewed as complementary rather than competing.

Table 1
Clinical and pathologic characteristics of the study population at diagnosis.

Characteristic	**N = 850**
Median age, years	49 (42, 57)
Clinical T Category	
T1	154 (18.12%)
T2	317 (37.29%)
T3	284 (33.41%)
T4	95 (11.18%)
Clinical N Category	
N0	216 (25.41%)
N1	374 (44.00%)
N2	176 (20.71%)
N3	84 (9.88%)
AJCC Clinical stage	
IA	5 (0.58%)
IB	1 (0.11%)
IIA	85 (10.0%)
IIB	202 (23.76%)
IIIA	295 (34.70%)
IIIB	211 (24.82%)
IIIC	51 (6.0%)
Radiotherapy	
No	95 (11.18%)
Yes	755 (88.82%)
Median Ki67 (IQR)	25 (15, 40)
Immunophenotype	
Luminal A	138 (16.24%)
Values are n (%) or Median (IQR).	

Characteristic	N = 850
Luminal B	455 (53.53%)
HER2-enriched	86 (10.12%)
Triple negative	171 (20.12%)
Grade	
1	132 (15.53%)
2	291 (34.24%)
3	427 (50.24%)
Surgery	
Breast conserving surgery	102 (12.0%)
Mastectomy + Lymphadenectomy	748 (88.0%)
Recurrence (local or distant)	
No	581 (68.35%)
Yes	269 (31.65%)
Vital status	
Alive	651 (76.59%)
Dead	199 (23.41%)
Median follow-up, months	83 (53, 110)
Chemotherapy regimen	
AC-T based	807 (94.94%)
Non-AC-T	43 (5.06%)
Values are n (%) or Median (IQR).	

Table 2
Eight-year disease-free and overall survival estimated by Cox regression with Firth's penalized likelihood.

		Disease-Free Survival			Overall Survival		
Staging System	Category	8-Year DFS	HR (95% CI)	P-value	8-Year OS	HR (95% CI)	P-value
Pathologic Prognostic Stage	0	81.7%	1.00 (Reference)	-	86.8%	1.00 (Reference)	-
	I A-I B	70.1%	1.92 (1.17–3.13)	0.011	74.2%	2.37 (1.37–4.11)	0.002
	II A	65.2%	1.91 (1.27–2.88)	0.002	67.2%	2.54 (1.61–4.03)	< 0.001
	II B	62.2%	2.85 (1.66–4.89)	< 0.001	67.7%	3.18 (1.74–5.82)	< 0.001
	III A	52.5%	3.30 (2.14–5.09)	< 0.001	66.1%	3.36 (2.01–5.60)	< 0.001
	III B-III C	24.3%	8.09 (5.26–12.42)	< 0.001	41.1%	8.09 (4.89–13.38)	< 0.001
Residual Cancer Burden	pCR	81.7%	1.00 (Reference)	-	86.8%	1.00 (Reference)	-
	RCB-I	65.1%	2.12 (1.28–3.50)	0.005	66.8%	2.97 (1.73–5.12)	< 0.001
	RCB-II	61.1%	2.92 (2.00–4.25)	< 0.001	67.5%	3.39 (2.19–5.25)	< 0.001
	RCB-III	48.5%	5.34 (3.56–8.00)	< 0.001	60.6%	5.91 (3.69–9.47)	< 0.001
Neo-Bioscore	0–1	75.0%	1.00 (Reference)	-	86.8%	1.00 (Reference)	-
	2	81.7%	0.67 (0.31–1.45)		86.5%	0.89 (0.33–2.37)	
	3	72.2%	0.99 (0.50–1.99)	0.984	80.3%	1.22 (0.50–3.00)	0.657
	4	66.1%	1.35 (0.68–2.69)	0.371	70.5%	1.99 (0.82–4.83)	0.091
	5	43.6%	3.22 (1.62–6.41)	< 0.001	48.3%	4.98 (2.06–12.05)	< 0.001
	6	22.1%	6.17 (2.89–13.20)	< 0.001	32.9%	8.35 (3.21–21.70)	< 0.001

	7	0.0%	11.24 (3.62–34.93)	< 0.001	20.0%	40.34 (11.30–144.08)	< 0.001

Table 3
Comparative prognostic accuracy and reclassification improvement of staging systems for DFS at 5 and 8 years, all subtypes.

Staging System	5-Year Performance			8-Year Performance		
	AUC	Brier Score	IDI (%)	AUC	Brier Score	IDI (%)
Clinical	0.612	0.164	Ref.	0.648	0.210	Ref.
Neo-Bioscore	0.712	0.148	7.51	0.667	0.203	5.70
Pathologic	0.704	0.149	6.51	0.671	0.203	5.27
RCB	0.661	0.147	1.35	0.636	0.201	-0.37
AUC, Area Under the Curve; IDI, Integrated Discrimination Improvement; RCB, Residual Cancer Burden. Clinical stage was used as the reference baseline model for IDI calculation.						

Declarations

Ethics approval and consent to participate: This retrospective study was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Ethics Committee of Instituto Nacional de Cancerología: CEI/1358/18. Due to its retrospective nature and the use of de-identified data, the requirement for informed consent to participate was waived.

Funding: The authors declare no conflicts of interest. No funding was received for this study.

Data availability: All data and code used in this article are available upon request to the corresponding author.

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Figures

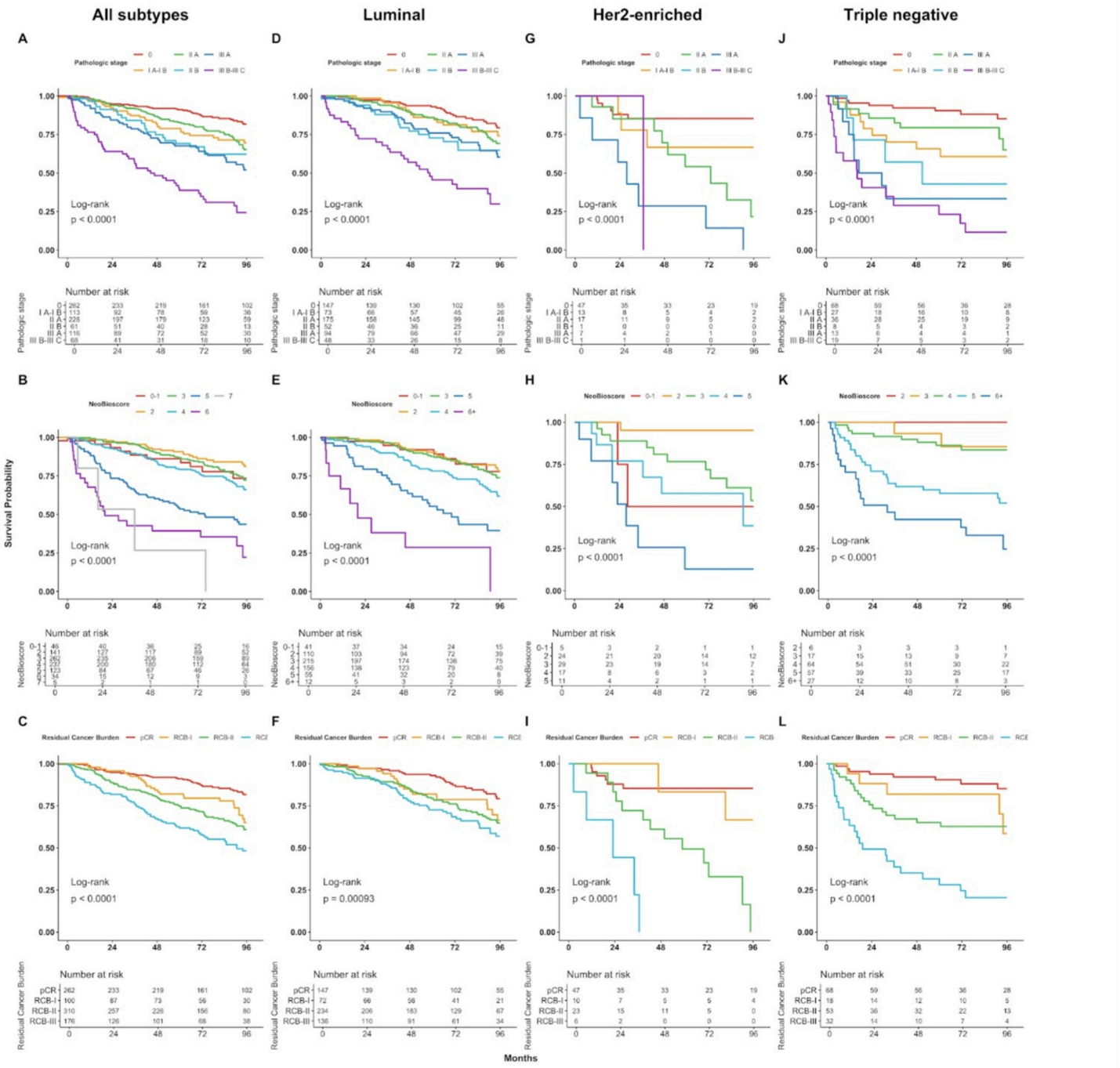


Figure 1

Kaplan-Meier curves of 8-year disease-free survival as estimated by AJCC pathologic prognostic stage, NB, and RCB, stratified by subtype.

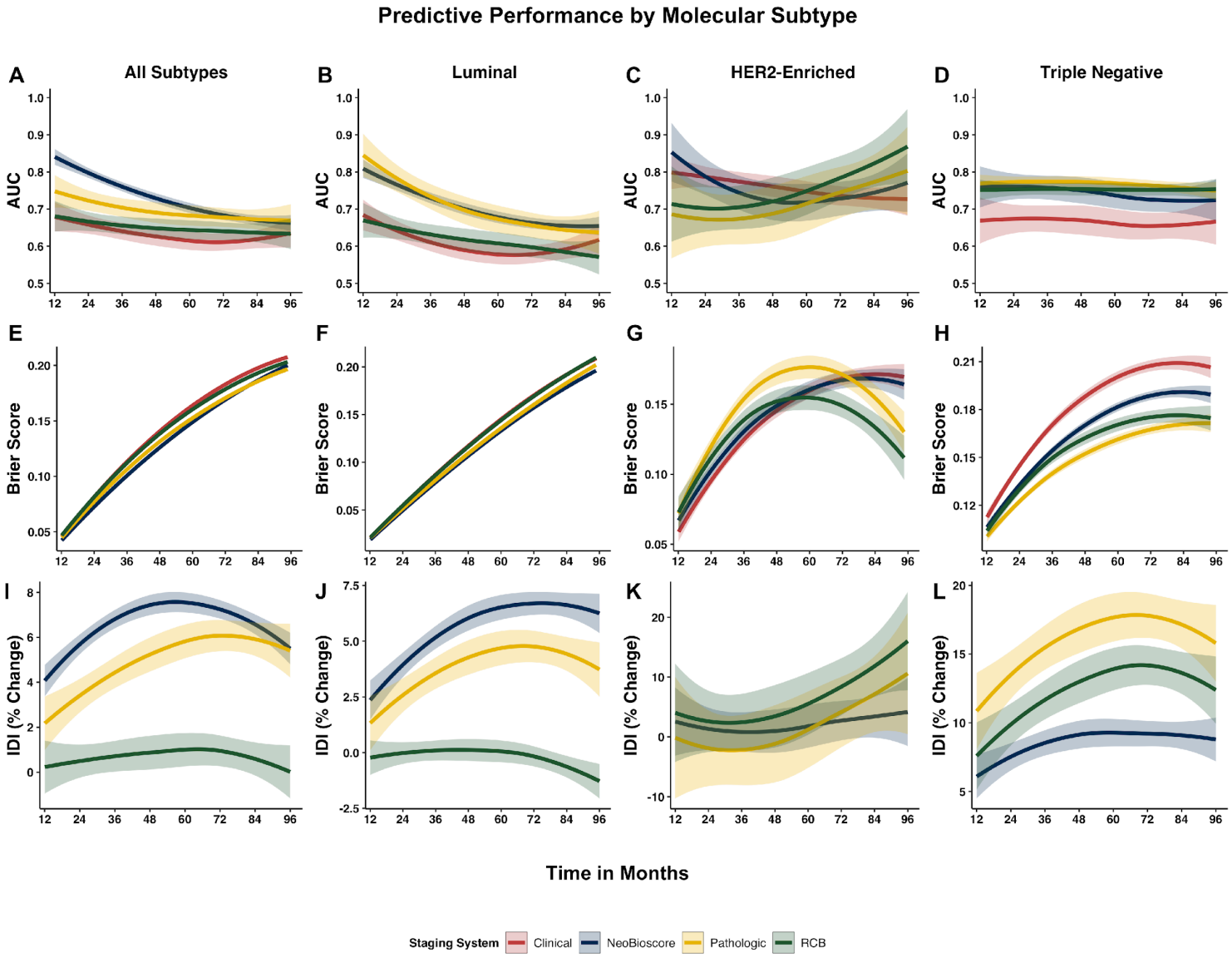


Figure 2

Time-dependent predictive performance of post-neoadjuvant staging systems for DFS by molecular subtype. Longitudinal prognostic accuracy of clinical stage, pathologic stage, RCB, and NB over an 8-year follow-up period are shown. (A-D) Time-dependent AUC demonstrating the discriminative ability for disease recurrence. (E-H) Time-dependent Brier scores, where lower values indicate superior overall model performance and calibration. (I-L) IDI curves, representing the continuous net improvement in patient reclassification provided by each system when compared to clinical stage. AUC, Area Under the Curve; IDI, Integrated Discrimination Improvement; RCB, Residual Cancer Burden. Shaded areas represent the 95% confidence interval for each metric.

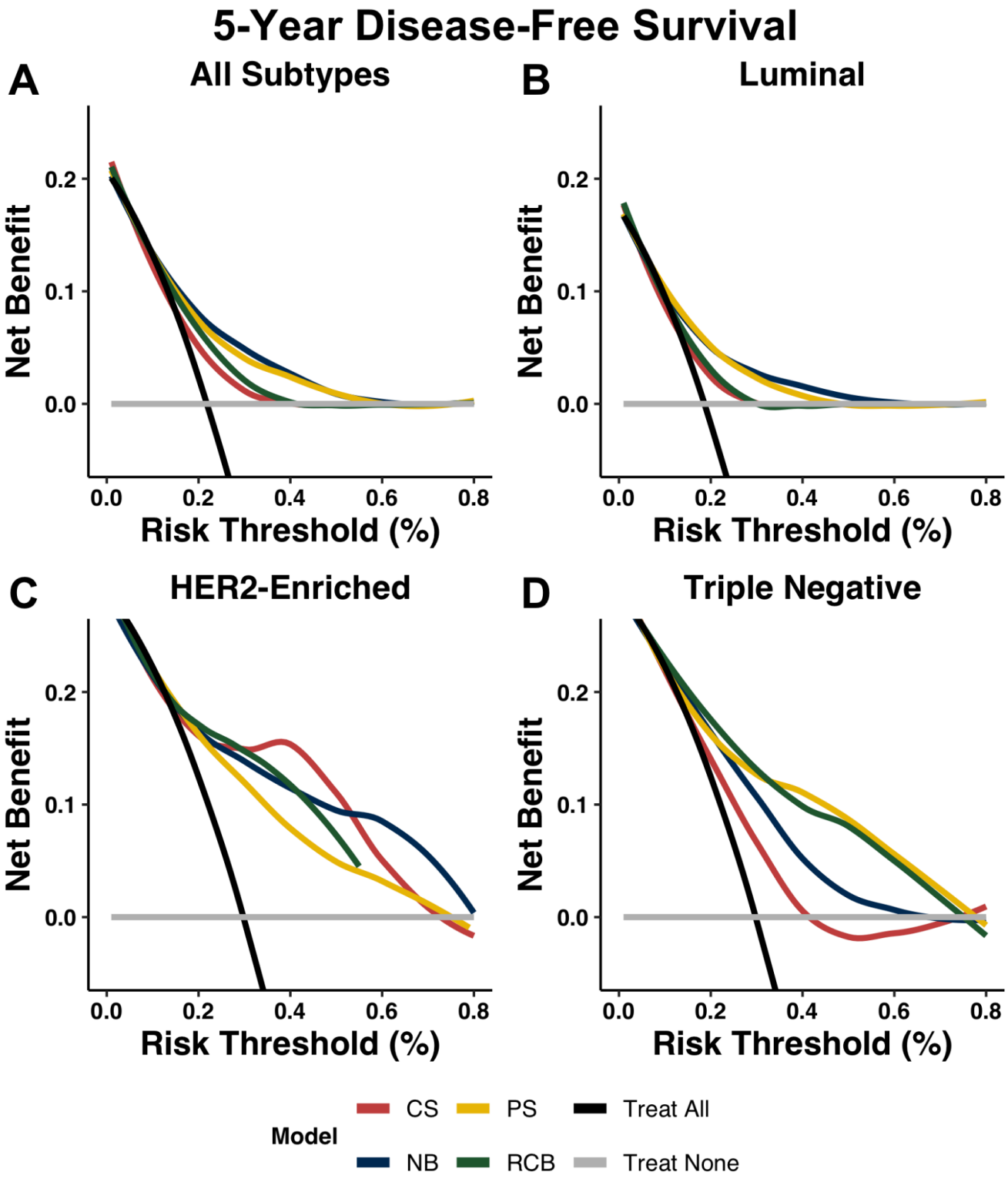


Figure 3

Decision curve analysis comparing the net benefit of each prognostic model. Models were evaluated at a 5-year endpoint for the overall cohort (A), luminal disease (B), HER2-enriched (C), and triple-negative disease (D). The highest curve at any given threshold probability represents the optimal staging system for guiding clinical decision-making. CS, clinical stage; NB, Neo-Bioscore; PS, pathologic stage; RCB, residual cancer burden.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryDataPPMBC2.docx