Prognostic Value of a Machine Learning Tool for Recurrence Risk Stratification in HR+/HER2- Early Breast Cancer: A Brazilian Cohort Analysis

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Purpose

Genomic assays are unavailable in Brazil's public health system and are not covered in the private sector, limiting risk stratification in early-stage HR+/HER2– breast cancer. Previous studies have developed machine learning tools to predict the 21-gene recurrence score directly from quantitative immunohistochemistry results and clinical factors. We evaluated this approach in a Brazilian cohort to determine the ability to predict prognosis and guide chemotherapy decisions in a resource-constrained setting without genomic testing.

Methods

We retrospectively analyzed HR+/HER2– breast cancer patients (stage I–III, ≤3 positive nodes) treated at the Instituto Nacional de Cancer, in Brazil (INCA) from 2016 - 2018. Age, grade, histologic subtype, and quantitative ER, PR, and Ki-67 expression were used to predict the 21-gene recurrence score with the previously published machine learning tool. Patients were separated into low-risk group and a high-risk group using a predefined threshold that achieves 90% sensitivity for recurrence score > 25. Disease free interval (DFI) and overall survival (OS) were estimated by Kaplan–Meier curves; hazard ratios were derived from Cox models to determine the prognostic difference of the low / high risk groups.

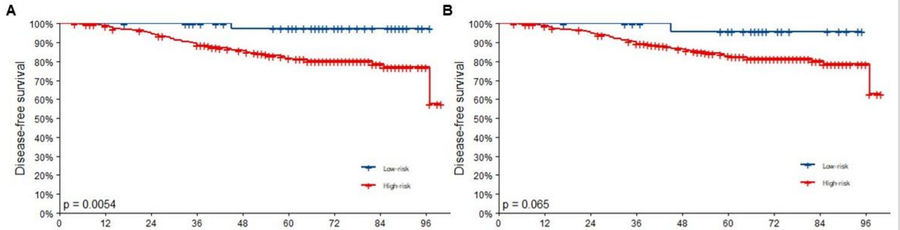
Results

We identified a sample of 299 cases for this analysis, with an average age of 59. 92 (31%) were PR negative, 212 (70%) had tumor sizer ≥ 2 cm, 163 (55%) had Ki-67 expression of 20% or higher, and 181 (61%) received chemotherapy. Median follow up was 73 months (95% CI, 71–75). Using the 90% sensitivity threshold, 15.4% of patients were low risk. Recurrence rates were 2.2% in low risk versus 19.4% in high-risk patients. Five-year DFI at 90% sensitivity was significantly better for low risk versus high risk (97.4% vs. 81.8%; long-rank p=0.0054). No significant differences in 5-year OS were observed. In multivariate analysis, stage III disease and Ki 67 ≥ 20% were also independent predictors of recurrence. Although chemotherapy was not associated with a reduction in disease free interval in either group, the excellent outcomes in the low-risk cohort with (recurrence rate 6.3%) or without (recurrent rate 0%) chemotherapy suggest this subgroup can safely forgo such treatment without genomic testing.

		all	HR (univariable)	HR (multivariable)
Age	Mean (SD)	59.2 (11.8)	0.97 (0.95-1.00, p=0.030)	-
Black/Brown vs White	Black/Brown	188 (62.9)	1.95 (1.03-3.69, p=0.039)	-
	White	111 (37.1)	-	-
90% Sensitivity	Low risk	46 (15.4)	-	-
	High risk	253 (84.6)	9.90 (1.35-70.99, p=0.024)	5.0 (0.66-38.84, p=0.120)
Stage	I	85 (28.4)	-	-
	II	179 (59.9)	2.02 (0.88-4.62, p=0.097)	1.45 (0.62-3.39, p=0.389)
	III	35 (11.7)	6.30 (2.57-15.47, p<0.001)	4.32 (1.72-10.81, p=0.002)
Chemotherapy	No	115 (38.5)	-	-
	Yes	184 (61.5)	2.09 (1.07-4.08, p=0.032)	-
Tumor size	< 2 cm	87 (29.1)	-	-
	≥ 2 cm	212 (70.9)	2.73 (1.22-3.71, p=0.008)	-
Node	No	196 (65.6)	-	-
	Yes	103 (34.4)	2.13 (1.22-3.71, p=0.008)	-
Ki67 expression	<20%	136 (45.5)	-	-
	≥20%	163 (54.5)	3.19 (1.63-6.23, p<0.001)	2.07 (1.02-4.18, p=0.044)
Grade	G1	45 (15.3)	-	-
	G2	212 (71.9)	2.56 (0.79-8.34, p=0.118)	-
	G3	38 (12.9)	5.13 (1.43-18.40, p=0.012)	-
Progesterone receptor	Negative	92 (30.9)	-	-
	Positive	206 (69.1)	0.51 (0.29-0.89, p=0.019)	-

Table 1. Multivariate Analysis for Disease-Free Survival (90% Sensibility)

Figure 1. DFS according to recurrence risk based on the UCMC tool

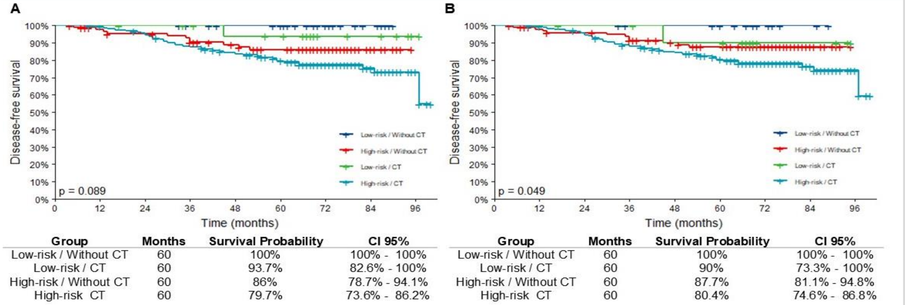


Group	Months	Survival Probability	CI 95%
Low risk	60	97,4%	92.6% - 100%
High risk	60	81.8%	77% - 86.9%

Group	Months	Survival Probability	CI 95%
Low risk	60	95.8%	88.2% - 100%
High risk	60	83%	78.5% - 87.8%

A.DFS curves at the 90% sensitivity threshold. B. DFS curves at the 95% sensitivity threshold.

Figure 2. DFS according to recurrence risk and chemotherapy use



Group	Months	Survival Probability	CI 95%
Low-risk / Without CT	60	100%	100% - 100%
Low-risk / CT	60	93.7%	82.6% - 100%
High-risk / Without CT	60	86%	78.7% - 94.1%
High-risk CT	60	79.7%	73.6% - 86.2%

Group	Months	Survival Probability	CI 95%
Low-risk / Without CT	60	100%	100% - 100%
Low-risk / CT	60	90%	73.3% - 100%
High-risk / Without CT	60	87.7%	81.1% - 94.8%
High-risk CT	60	80.4%	74.6% - 86.8%

A.DFS curves at the 90% sensitivity threshold. B. DFS curves at the 95% sensitivity threshold.

Conclusions

This machine learning prognostic tool demonstrated strong prognostic performance in a Brazilian cohort of HR+/HER2– early-stage breast cancer patients, identifying a low-risk subgroup with excellent DFI and no apparent benefit from chemotherapy, and is available for use online (rsncdb.cri.uchicago.edu). These findings support its use for therapy de escalation when genomic assays are unavailable. Further prospective studies are required to validate these findings.

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