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Prognostic Performance of MammaPrint in Patients with Small T1a, b, and c Node-Negative Early Breast Cancer

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Introduction

- The incidence of small, node-negative (T1a,b,c N0) early breast cancer (EBC) is increasing in mammography-screened populations¹.
- Although these tumors generally have favorable outcomes, a subset of patients still develops recurrence.
- Treatment decisions are often guided by tumor size, grade, and receptor status; however, these features may not fully capture the underlying tumor biology.
- Small node-negative breast cancers remain biologically heterogeneous, with some tumors exhibiting more aggressive behavior².
- MammaPrint® (MP), a 70 gene risk stratification assay, and Blueprint® (BP), an 80-gene molecular subtyping assay, provide additional insights for treatment decisions³.
- This study evaluates the prognostic performance of MammaPrint in patients with T1a, T1b, and T1c node-negative early breast cancer.

Methods

Study Cohort

- This analysis included 4,349 patients with T1N0 EBC enrolled in the FLEX Study.
- Patients received MammaPrint and Blueprint testing with 3.2 years median follow-up data.
- Tumor sizes were 414 T1a, 1,551 T1b, and 2,384 T1c.
- Clinical subtypes were 87% HR+HER2-, 5% HER2+, and 4% TNBC.

Statistics

- Recurrence-free survival (RFS) was evaluated using Kaplan-Meier (KM) and multivariable Cox proportional hazards models for all patients and the HR+HER2- subgroup.
- P-values of less than 0.05 were considered significant.

Results

Table 1. Clinical Characteristics of FLEX patients with T1N0 EBC.

	MammaPrint Category			Total (N=4349)	p value
	UL+Low (N=2568)	High1 (N=1359)	High2 (N=422)		
T1 category					< 0.001
T1a	278 (10.8%)	109 (8.0%)	27 (6.4%)	414 (9.5%)	
T1b	992 (38.6%)	443 (32.6%)	116 (27.5%)	1551 (35.7%)	
T1c	1298 (50.5%)	807 (59.4%)	279 (66.1%)	2384 (54.8%)	
Age					< 0.001
Median	63	63	60	63	
Mean (SD)	62.21 (10.85)	61.92 (11.78)	59.68 (11.93)	61.88 (11.27)	
Range	25.00 - 92.00	25.00 - 99.00	28.00 - 88.00	25.00 - 99.00	
Menopausal status					0.215
Pre-/Peri-	426 (16.6%)	239 (17.6%)	84 (19.9%)	749 (17.2%)	
Post-	2009 (78.2%)	1044 (76.8%)	316 (74.9%)	3369 (77.5%)	
NA	133 (5.2%)	76 (5.6%)	22 (5.2%)	231 (5.3%)	
Race/ethnicity					< 0.001
White	1998 (77.8%)	1004 (73.9%)	276 (65.4%)	3278 (75.4%)	
Black	170 (6.6%)	148 (10.9%)	77 (18.2%)	395 (9.1%)	
Latin American	202 (7.9%)	99 (7.3%)	32 (7.6%)	333 (7.7%)	
AAPI	56 (2.2%)	28 (2.1%)	11 (2.6%)	95 (2.2%)	
Other	18 (0.7%)	6 (0.4%)	3 (0.7%)	27 (0.6%)	
NA	124 (4.8%)	74 (5.4%)	23 (5.5%)	221 (5.1%)	
Clinical subtype					< 0.001
HR+HER2-	2427 (94.5%)	1132 (83.3%)	205 (48.6%)	3764 (86.5%)	
HER2+	42 (1.6%)	116 (8.5%)	67 (15.9%)	225 (5.2%)	
TNBC	11 (0.4%)	46 (3.4%)	133 (31.5%)	190 (4.4%)	
Other	5 (0.2%)	4 (0.3%)	3 (0.7%)	12 (0.3%)	
NA	83 (3.2%)	61 (4.5%)	14 (3.3%)	158 (3.6%)	
Histology					< 0.001
IDC	2013 (78.4%)	1138 (83.7%)	394 (93.4%)	3545 (81.5%)	
ILC	375 (14.6%)	135 (9.9%)	5 (1.2%)	515 (11.8%)	
Mixed_IDCILC	90 (3.5%)	32 (2.4%)	3 (0.7%)	125 (2.9%)	
Other	87 (3.4%)	52 (3.8%)	16 (3.8%)	155 (3.6%)	
NA	3 (0.1%)	2 (0.1%)	4 (0.9%)	9 (0.2%)	
Grade					< 0.001
G1	1221 (47.5%)	250 (18.4%)	16 (3.8%)	1487 (34.2%)	
G2	1152 (44.9%)	821 (60.4%)	101 (23.9%)	2074 (47.7%)	
G3	63 (2.5%)	221 (16.3%)	284 (67.3%)	568 (13.1%)	
NA	132 (5.1%)	67 (4.9%)	21 (5.0%)	220 (5.1%)	
Ki67 category					< 0.001
0-10	867 (33.8%)	183 (13.5%)	10 (2.4%)	1060 (24.4%)	
11-20	458 (17.8%)	239 (17.6%)	14 (3.3%)	711 (16.3%)	
>20	254 (9.9%)	414 (30.5%)	234 (55.5%)	902 (20.7%)	
NA	989 (38.5%)	523 (38.5%)	164 (38.9%)	1676 (38.5%)	
Blueprint					< 0.001
Luminal A	2505 (97.5%)	0 (0.0%)	0 (0.0%)	2505 (57.6%)	
Luminal B	0 (0.0%)	1225 (90.1%)	115 (27.3%)	1340 (30.8%)	
Basal	2 (0.1%)	43 (3.2%)	256 (60.7%)	301 (6.9%)	
HER2	2 (0.1%)	51 (3.8%)	44 (10.4%)	97 (2.2%)	
NA	59 (2.3%)	40 (2.9%)	7 (1.7%)	106 (2.4%)	
Treatment type					< 0.001
Adjuvant therapy	1959 (76.3%)	1020 (75.1%)	251 (59.5%)	3230 (74.3%)	
Neoadjuvant therapy	87 (3.4%)	88 (6.5%)	86 (20.4%)	261 (6.0%)	
Non-surgical	45 (1.8%)	15 (1.1%)	3 (0.7%)	63 (1.4%)	
NA	477 (18.6%)	236 (17.4%)	82 (19.4%)	795 (18.3%)	
Systemic therapy					< 0.001
ET only	1756 (68.4%)	346 (25.5%)	19 (4.5%)	2121 (48.8%)	
CT +/-	152 (5.9%)	731 (53.8%)	307 (72.7%)	1190 (27.4%)	
Other	98 (3.8%)	24 (1.8%)	11 (2.6%)	133 (3.1%)	
None	72 (2.8%)	19 (1.4%)	3 (0.7%)	94 (2.2%)	
NA	490 (19.1%)	239 (17.6%)	82 (19.4%)	811 (18.6%)	

Data presented as n (%); Non available (NA) were included in the table but excluded from the analysis; AAPI, Asian American and Pacific Islander; TNBC, Triple Negative Breast Cancer; IDC, Invasive Ductal Carcinoma; ILC, Invasive Lobular Carcinoma; ET, endocrine therapy; CT, chemotherapy. CT +/- refers to Chemotherapy alone (-) or Chemotherapy + Endocrine Therapy or Chemotherapy + Endocrine Therapy + Targeted Therapy.

Figure 1. Relapse-Free Survival (RFS) of (A) all patients with small tumor and node negative disease and (B) patients with HR+HER2- small tumor and node negative disease.

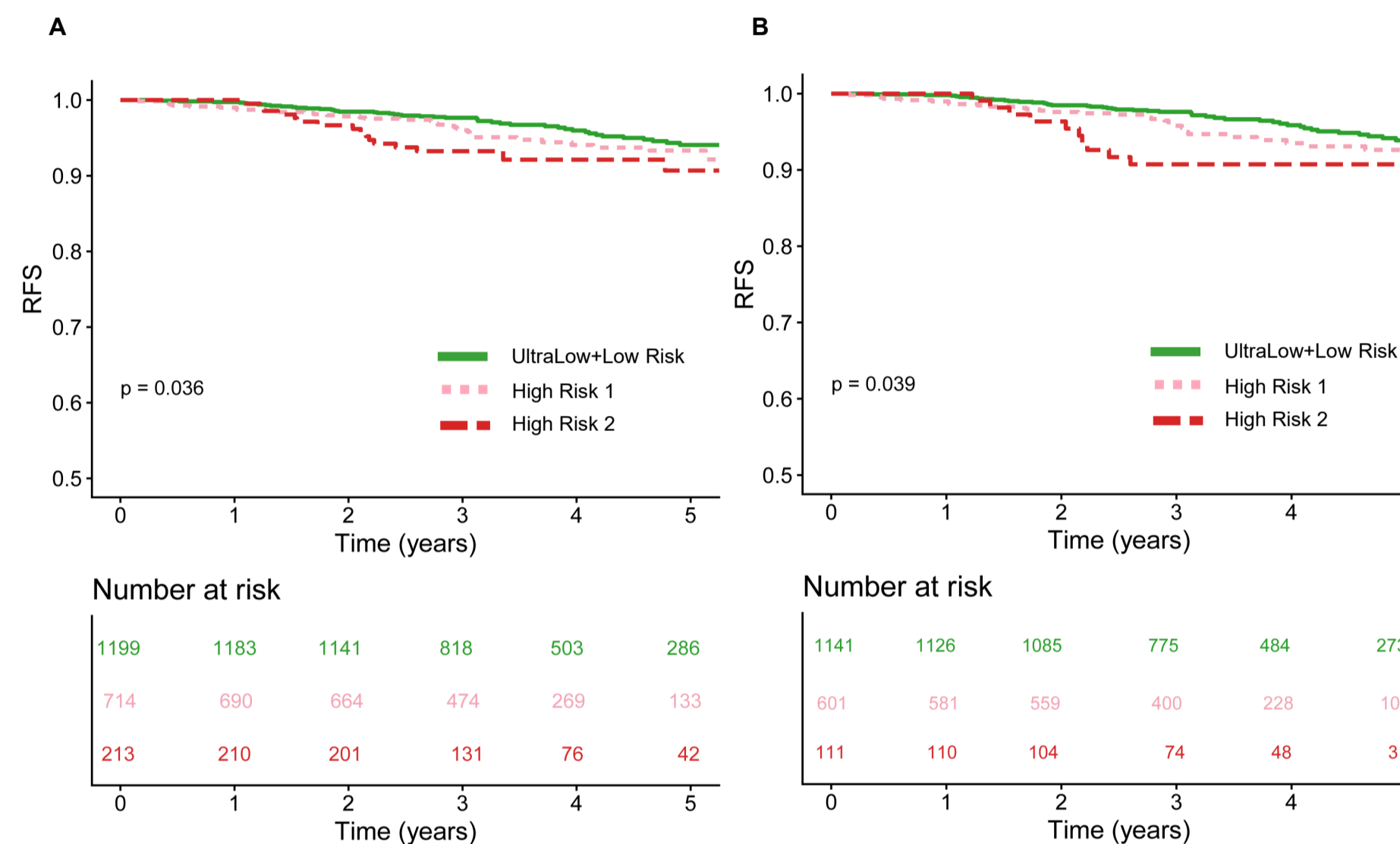


Table 2. Cox proportional hazards – Multivariable analysis

Patients with T1N0 EBC	MP Risk Group	3-Year RFS % (95% CI)	p-value	Multivariable HR (95% CI)	p-value
All patients	UL + LR	98 (97–99)		Reference	–
	H1	96 (95–98)	0.036	1.33 (0.86–2.05)	0.200
	H2	93 (90–97)		1.90 (1.07–3.36)	0.028
Patients with HR+HER2-	UL + LR	98 (97–99)		Reference	–
	H1	96 (94–98)	0.039	1.41 (0.91–2.21)	0.128
	H2	91 (85–96)		2.05 (1.03–4.07)	0.041

- Approximately 5% of patients with T1a-c, node-negative EBC – traditionally considered clinically low risk – exhibits a MammaPrint High Risk 2 genomic profile (Table 1).
- Blueprint subtyping revealed biologic heterogeneity within T1a-c node-negative tumors with MammaPrint H2 tumors more commonly classified as Luminal B rather than Luminal A (Table 1).

- Kaplan-Meier and multivariable analysis showed MammaPrint High Risk 2 was associated with significantly worse RFS among all patients. Same was observed in the HR+HER2- subgroup.
- In the overall cohort, patients with MammaPrint H2 had significantly higher risk of recurrence compared with UL+LR (HR= 1.9; p=0.028; Table 2), while H1 was not significantly different.
- In patients with HR+HER2- tumors MammaPrint H2 group remained associated with significantly decreased RFS (HR=2.05; p=0.041; Table 2), while H1 was not significantly different.
- Absolute 3-year RFS was lowest in MammaPrint H2 (91%).

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Conclusions

- MammaPrint identified a subset of patients with High Risk 2 (H2) tumors among clinically early-stage T1N0 EBC (10% overall; 5% in HR+HER2- disease).
- MammaPrint risk groups are prognostic in small, node negative EBC, with a more than two-fold chance of a RFS event in High 2 tumors compared to Low risk/Ultralow risk tumors.
- Our results highlight the limitations of risk stratification based solely on tumor size and nodal status.
- These findings demonstrate the prognostic value of MammaPrint beyond traditional clinical features and support further research into tailored strategies for genomically high risk early-stage tumors.