Development of a Multi-Modal Artificial Intelligence (MMAI) Model for Predicting Distant Metastasis in HR+ Early-Stage Invasive Breast Cancer

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Background

- Accurately predicting the risk of distant metastasis (DM) in hormone receptor–positive (HR+) early-stage breast cancer (EBC) remains a key clinical challenge.
- Current prognostic tools often rely on limited clinical or genomic features.
- We developed and evaluated a pathology-based multimodal artificial intelligence (MMAI) prognostic biomarker that integrates clinical and histopathological data from six Phase III randomized trials to predict the risk of DM in HR+ EBC.

Objectives

- Developed a pathology-based MMAI model to predict distant metastasis (DM) risk in HR+/HER2– early breast cancer (EBC).
- MMAI model was locked prior to evaluation in two independent cohorts.

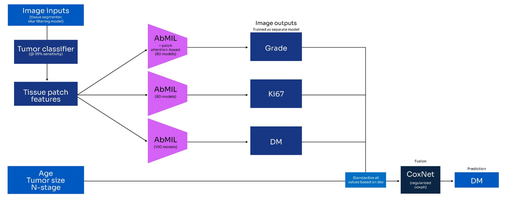


Figure 1. MMAI architecture of the breast model.

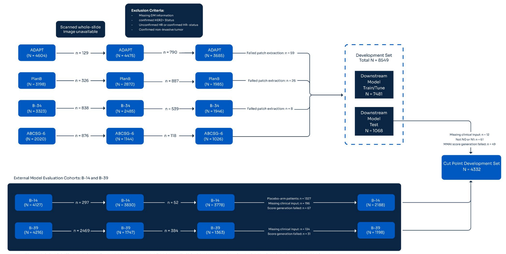


Figure 2. Flow diagram for model development, testing and evaluation data use

Methods and Materials

- **Patients –** The MMAI model was developed on 8616 patients from four trials: ADAPT, PlanB, B-34, and ABCSG 6. The prognostic ability of the continuous MMAI risk score was externally evaluated in HR+ B-14 (N = 2188) patients registered or randomized into the tamoxifen-only arm, and HR+ B-39 (N = 1198) patients with confirmed invasive disease **(Figure 2)**
- **Description of the Multimodal AI (MMAI) algorithm** - The MMAI model integrates deep learning-derived histopathology features with clinical variables (age, tumor size, nodal status) through a three-stage pipeline: (1) self-supervised feature extraction from H&E WSIs; (2) training of image-based submodels; and (3) fusion with clinical data in a regularized Cox model to predict DM risk **(Figure 1).**
- **Pathologist Interpretation of SSL Features** - 768-dimensional feature vectors were output from the model. UMAP grouped features into 40 clusters. A pathologist interpreted the 25 nearest-neighbor patches of the cluster centroids to identify histological patterns (**Figure 3**).
- **Endpoints –** Time to Distant Metastasis (DM)
- **Statistical Analysis –** The locked continuous MMAI score was validated in NSABP B-14 and B-39 cohorts. Performance was assessed using tdAUC, Cox regression, and Kaplan-Meier analysis, with a clinical model (age, tumor size, nodal status) as benchmark. Risk cut points were derived by maximizing 10-year DM restricted mean survival time across 4,332 pN0-1 patients from six held-out trials.

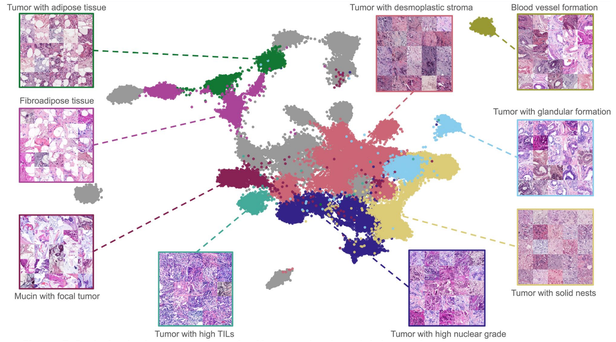


Figure 3. Pathologist interpretation of self-supervised model tissue clusters

Results

MMAI raw scores were generated for 2,188 patients in B-14, and 1,198 patients in B-39 with HR+ Stage I-II, EBC. The median follow-up time for B-14 was 17.6 years, and 9.4 years for B-39 **(Table 1).** MMAI demonstrated strong prognostic performance: in B-14, the locked MMAI showed a 10-year tdAUC of 0.71 [0.67-0.74] compared to the clinical comparator model (0.65 [0.62-0.69]); in B39, the 10-year tdAUC for MMAI was 0.72 [0.59-0.82] versus 0.69 [0.60-0.79] for the clinical comparator model **(Figure 3).** The MMAI raw score was significantly associated with risk of DM in both B-14 (HR [95%CI] = 2.06 [1.81-2.35]) and B-39 (HR [95%CI] = 2.31 [1.63-3.28]) **(Table 2).** The score remained significant after adjusting for age, tumor size, and pathological N stage in both B-14 (HR [95%CI] = 1.94 [1.68-2.25]) and B-39 (HR [95%CI] = 2.06 [1.36-3.11]) **(Table 2).** Subgroup analyses showed consistent prognostic performance across nodal status and menopausal status **(Table 3).** Using additional data as described, cut points were chosen to ensure sufficient sample sizes within risk categories, balancing statistical power for future validation and clinical interpretability. This resulted in 65.5% of patients being classified as low risk, 10.5% as intermediate risk, and 24.0% as high risk, with the corresponding 10-year DM-free rates of 95.5% (95%CI: 94.6% - 96.3%), 89.5% (95%CI: 86.2% - 92.4%), and 83.6% (95%CI: 81.1% - 86.0%), respectively **(Figure 4).**

Characteristic	NSABP B-14 N = 2,188[1]	NSABP B-39 N = 1,198[1]
Age (years)		
Mean (SD)	55 (10)	56 (11)
Menopausal Status, n (%)		
Pre- or Peri-menopausal	639 (29.2%)	478 (39.9%)
Post-menopausal	1,539 (70.3%)	720 (60.1%)
Unknown	10 (0.5%)	0 (0.0%)
Race, n (%)		
Black or African American	98 (4.5%)	44 (3.7%)
Other Race	2,090 (95.5%)	1,140 (95.2%)
Unknown	0 (0.0%)	14 (1.2%)
T-Stage, n (%)		
T1	1,401 (64.0%)	1,053 (87.9%)
T2	734 (33.5%)	145 (12.1%)
T3	53 (2.4%)	0 (0.0%)
Tumor Size (cm)		
Mean (SD)	2.1 (1.2)	1.3 (0.6)
N-Stage, n (%)		
N0	2,180 (99.6%)	998 (83.3%)
N1	8 (0.4%)	200 (16.7%)
Grading, n (%)		
1	0 (0.0%)	483 (40.3%)
2	0 (0.0%)	531 (44.3%)
3	0 (0.0%)	174 (14.5%)
Unknown	2,188 (100.0%)	10 (0.8%)
Systemic Therapy, n (%)		
Endocrine therapy only	2,188 (100.0%)	725 (60.5%)
Chemotherapy included	0 (0.0%)	374 (31.2%)
No systemic therapy or unknown	0 (0.0%)	99 (8.3%)

Table 1. Baseline characteristics.

UVA/MVA

		MVA		UVA	
Trial	Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
B-14	MMAI risk score	1.94 (1.68-2.25)	<0.001*	2.06 (1.81-2.35)	<0.001*
	Age	0.99 (0.98-1.01)	0.28	0.99 (0.98-1.00)	0.05
	Tumor Size	1.08 (0.97-1.20)	0.17	1.32 (1.23-1.42)	<0.001*
	Pathological N Stage (N1 v N0)	1.53 (0.38-6.15)	0.58	1.84 (0.46-7.41)	0.39
B-39	MMAI risk score	2.06 (1.36-3.11)	0.006*	2.31 (1.63-3.28)	<0.001*
	Age	1.03 (1.00-1.06)	0.08	1.02 (0.99-1.05)	0.26
	Tumor Size	1.44 (1.01-2.05)	0.05	1.88 (1.38-2.54)	<0.001*
	Pathological N Stage (N1 v N0)	0.57 (0.22-1.44)	0.23	1.27 (0.52-3.09)	0.59

Table 2. UVA and MVA (MVA; MMAI risk score + Age + Tumor Size + Pathological N Stage) analyses showing association between MMAI score and risk of DM in B-14 and B-39.

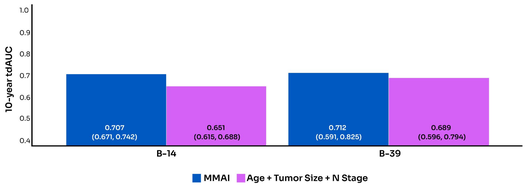


Figure 3. Prognostic Performance of the MMAI vs clinical comparator at 10-year tdAUC for DM in B-14 and B-39.

Cohort	Subgroup	Level	N (events)	HR (95% CI)
B-14	Menopausal Status	Pre- or Peri-menopausal	639 (88)	2.38 (1.89–3.00)
		Post-menopausal	1539 (199)	1.93 (1.65–2.25)
B-39	Menopausal Status	Pre- or Peri-menopausal	478 (11)	3.05 (1.62–5.72)
		Post-menopausal	720 (22)	2.06 (1.35–3.13)
	Pathgological N Stage	N0	998 (27)	2.31 (1.57–3.40)
		N1	200 (6)	3.35 (1.18–9.51)

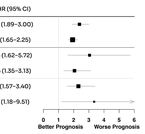


Table 3 Subgroup analyses in B-14 and B-39.

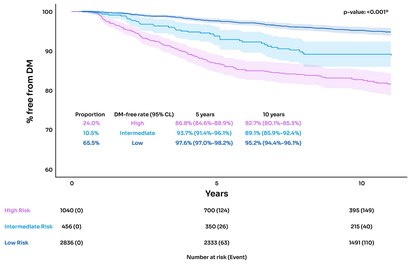


Figure 4 KM Curve of MMAI risk groups in cutpoint development cohort for DM

Conclusions

We have successfully developed and evaluated an MMAI model across six Phase III randomized breast cancer trials, demonstrating its utility as a prognostic biomarker for predicting risk of DM in HR+ EBC patients. This non-tissue destructive, faster turnaround technology is practical for real-world use and holds significant promise for personalizing patient care in breast cancer.

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