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Evaluation of Sensitivity to Endocrine Therapy (SET) as a Prognostic Biomarker in the Latin American Breast Cancer Cohort Study

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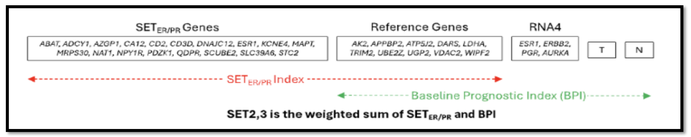
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Background

- The SET2,3 index, which combines the $SET_{ER/PR}$ index—a measure of transcriptional activity related to estrogen and progesterone receptor (ER, PR) —with the baseline prognostic index (BPI), has been validated as prognostic and predict endocrine treatment sensitivity in hormone receptor-positive (HR+) breast cancers from U.S. and European patients [1,2] .
- Prognostic utility remains to be determined in Latin American (LA) breast cancer patients, who possess a unique and diverse genetic admixture.

Methods

- Clinical and pathological retrospective data were collected from a multi-country LA cohort of breast cancer patients, the Molecular Profile of Breast Cancer Study (MPBCS). Tumor subtypes were previously characterized using PAM50 classification, Ki67%, and immunohistochemical analysis for ER, PR, and Human Epidermal Growth Factor Receptor 2 (HER2) status [3].
- SET2,3 index measures endocrine transcriptional activity ($SET_{ER/PR}$) adjusted for the baseline prognostic index (BPI). BPI was calculated using the pathological tumor stage (n=186), or the clinical tumor stage when node status were not available (n=71). The resulting SET2,3 measure was named “combined SET2,3”



- The SET2,3 index was measured using the QuantiGene Plex Assay on archival tumor tissue samples from the HR+/HER2 Negative (-) cancers, blinded to clinical outcomes.
- Patients were classified as **high SET2,3** if SET2,3 index ≥ 2.1, and **low SET2,3** if SET2,3 index < 2.1
- Disease-free survival (DFS) was compared across patient subgroups using the log-rank test, and hazard ratios (HRs) were estimated through Cox proportional hazards models.

Results

Table 1. Clinical and pathological characteristics of hormone-dependent tumors of the Molecular Profile of Breast Cancer Study (MPBCS), a Latin American Cohort of Breast Cancer Patients

Variable	n	Category/Range	N (%)
Country	291	Argentina	93 (32%)
		Brazil	36 (12.4%)
		Chile	63 (21.6%)
		Mexico-Guadalajara	71 (24.4%)
		Uruguay	28 (9.6%)
First Treatment	291	Neoadjuvant Chemotherapy	8 (2.7%)
		Primary Surgery	283 (97.3%)
Age group	291	50–70	141 (48.5%)
		<50	85 (29.2%)
		>70	65 (22.3%)
Histological Grade	287	1	55 (19.2%)
		2	140 (48.8%)
		3	92 (32.1%)
Menopausal Status	262	Postmenopausal	188 (71.8%)
		Premenopausal	74 (28.2%)
PAM50 Subtypes	275	Basal	14 (5.1%)
		Her2	6 (2.2%)
		LumA	182 (66.2%)
		LumB	72 (26.2%)
		Normal	1 (0.4%)
Ki67 category (%)	291	<5%	14 (4.8%)
		5-30%	174 (59.8 %)
		≥30%	103 (35.4%)
cT Stage	287	cT0	1 (0.3%)
		cT1	18 (6.3%)
		cT2	237 (82.6%)
		cT3	26 (9.1%)
		cT4	5 (1.7%)
cN Stage	287	cN0	181 (63.1%)
		cN1	100 (34.8%)
		cN2	5 (1.7%)
		cN3	1 (0.3%)
pT Stage	276	pT0	1 (0.4%)
		pT1	73 (26.4%)
		pT2	184 (66.7%)
		pT3	17 (6.2%)
		pT4	1 (0.4%)
pN Stage	277	pN0	163 (58.8%)
		pN1	74 (26.7%)
		pN2	30 (10.8%)
		pN3	10 (3.6%)
Adjuvant Chemotherapy	280	No	111 (39.6%)
		Yes	169 (60.4%)
Adjuvant Endocrine Therapy	289	No	66 (22.8%)
		Yes	223 (77.2%)
Vital status at 5 yr	283	Alive	247 (87.3%)
		Dead	36 (12.7%)

Figure 1. Consort diagram of the cases of the study

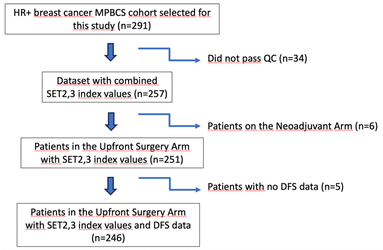
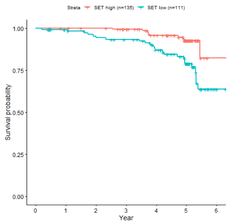


Table 2. Performance of SET2,3 class in multivariate Cox models of disease-free survival
Combined SET2,3 was used as a categorical variable

Multivariate Cox Model		(N = 246; 34 events)		
Variables	n	**HR**	**95% CI**	**p value**
Combined SET2,3 (Ref=High SET2,3)	246	3.20	1.48–6.91	0.0031
+ adjuvant Endocrine therapy (ET) (Ref=yes)	244	3.39	1.57–7.33	0.0019
+ adjuvant ET + PAM50 (LumA (ref) vs non-LumA)	221	2.67	1.14-6.26	0.0241
+ adjuvant ET + PAM50 (LumA vs non-LumA) + country	221	4.06	1.55-10.6	0.0043

- Patients in the low SET2,3 class has more than three times higher risk of recurrence than those of the high SET2,3 class. The addition of the variable adjuvant ET to the model did not affect the prognostic power of the combined SET2,3
- The subsequent addition of the PAM50 term did not significantly affect the prognostic power of the combined SET2,3
- The addition of country as a potential confusor did not abrogate the combined SET2,3 prognostic power

Figure 2. Six-year DFS according to SET2,3 categories (high or low) (P=0.002)



Patients within the low SET2,3 class has a significantly worse disease-free survival than patients with high SET2,3

SET2,3 index also predicted outcomes for those receiving adjuvant chemotherapy or endocrine therapy

Figure 3. Six-year DFS for SET2,3 categories (high or low) within patients that received chemotherapy (P=0.01)

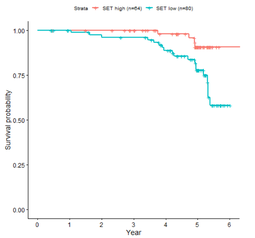


Figure 4. Six-year DFS for SET2,3 categories (high or low) within patients that received endocrine therapy (P=0.01)

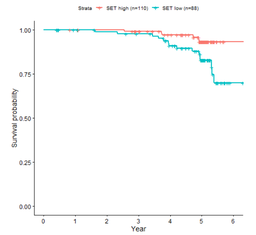
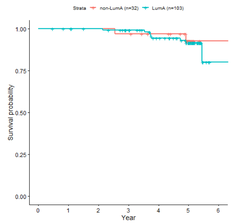
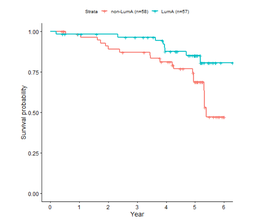


Figure 6. Six-year DFS for patients of the Luminal A or the non-Luminal A subtypes within the two SET2,3 categories – non-LumA patients with low SET2,3 patients have a significantly worse prognosis than LumA patients

SET2,3 high (P = 0.8)



SET2,3 low (P = 0.03)



Conclusions

The SET2,3 class is a strong predictor of disease-free survival in breast cancer of Latin American patients, with high SET2,3 index indicating longer DFS.

Limitations of this study:
- Small sample size for some of the analysis
- The retrospective nature of the analysis
- Differences in endocrine therapy usage among countries

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