Postpartum breast cancer as a potential driver of increased 21-gene Recurrence Score® result (RS) and RS result category for node-positive HR+/HER2- breast cancer

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Introduction & Background

- The 21-gene Recurrence Score® result (RS) is widely used to guide adjuvant chemotherapy decisions in hormone receptor-positive (HR+) HER2-negative (HER2-) early breast cancer (BC).[1]
- In premenopausal women with node-positive disease, RS has limited utility in identifying low-risk individuals who may forgo chemotherapy.
- One understudied subgroup is postpartum BC (PPBC). PPBC is associated with higher rates of lymph node metastases, increased risk of distant recurrence, and worse overall prognosis, even after adjusting for traditional clinicopathologic factors.[3]
- As such, PPBC, particularly in women with nodal involvement, may confound RS interpretation.
- We aimed to evaluate whether PPBC is associated with higher RS in premenopausal women with node-positive HR+ HER2- BC compared to non-PPBC and nulliparous women and if this impacted outcomes.

Methods

- We identified women aged ≤45 years with HR+ HER2- BC with node positive disease who underwent RS testing at a single academic institution between 2011 and 2024.
- Reproductive and clinicopathologic data were collected through medical record review. Patients were stratified into three groups: nulliparous, PPBC (diagnosis ≤5 years postpartum), and non-PPBC (>5 years postpartum).
- Patients diagnosed with BC during pregnancy and patients with incomplete reproductive data were excluded.

Results

Table 1: Characteristics of the patient cohort

	Nulliparous (n = 27)	PPBC (n = 23)	Non-PPBC (n = 27)	p-value	Total (n = 77)
Age at Diagnosis	39.2 [33.2, 45.7]	40.5 [30.4, 45.6]	42.7 [32.7, 45.7]	0.002**	40.7 [30.4, 45.7]
Age at First Childbirth	NA	34.6 [36.4, 42.8]	29.3 [16.8, 40.1]	0.002**	31.6 [16.8, 42.8]
pT Stage				0.208	
0	0 (0%)	0 (0%)	0 (0%)		0 (0%)
1	12 (44.4%)	17 (73.9%)	15 (55.6%)		44 (57.1%)
2	13 (48.1%)	4 (17.4%)	11 (40.7%)		28 (36.4%)
3	2 (7.4%)	2 (8.7%)	1 (3.7%)		5 (6.5%)
pN Stage				0.073	
1	27 (100%)	29 (82.6%)	25 (92.6%)		71 (92.2%)
2 or 3	0 (0%)	4 (17.4%)	2 (7.4%)		6 (7.8%)
Ki67 category				0.305	
0 - 19%	13 (48.1%)	13 (56.5%)	19 (70.4%)		45 (58.4%)
≥20%	13 (48.1%)	10 (43.5%)	8 (29.6%)		31 (40.3%)
Missing	1 (3.7%)	0 (0%)	0 (0%)		1 (1.3%)
Received Chemotherapy	15 (55.6%)	17 (73.9%)	16 (59.3%)	0.377	48 (62.3%)
Adjuvant Radiation	22 (81.5%)	21 (91.3%)	22 (81.5%)	0.554	65 (84.4%)
Endocrine Therapy				0.177	
Yes	23 (85.2%)	23 (100%)	26 (96.3%)		72 (93.5%)
Missing	1 (3.7%)	0 (0%)	0 (0%)		1 (1.3%)
Ovarian Suppression				0.986	
Yes	21 (77.8%)	19 (82.6%)	22 (81.5%)		62 (80.5%)
Missing	1 (3.7%)	0 (0%)	0 (0%)		1 (1.3%)
CDK4/6 Inhibitors	7 (25.9%)	9 (39.1%)	9 (33.3%)	0.606	25 (32.5%)
Locoregional Recurrence	1 (3.7%)	0 (0%)	2 (7.4%)	0.402	3 (3.9%)
Distant Recurrence	1 (3.7%)	1 (4.3%)	2 (7.4%)	0.809	4 (5.2%)

Continuous variables summarized by mean [minimum, maximum]. Categorical variables summarized by count (percent).
*Increasing number of * represent statistical significance at alpha = 0.05, 0.01, 0.001;*
p-values from ANOVA if variable is continuous, chi-squared test if variable is categorical

Figure 1: Continuous RS result in lymph node positive patients by PPBC classification

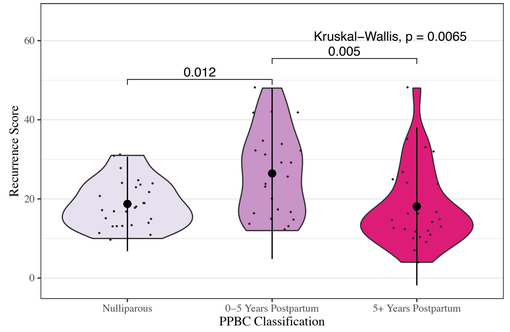
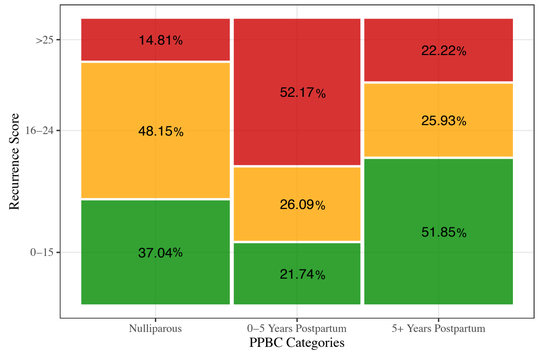
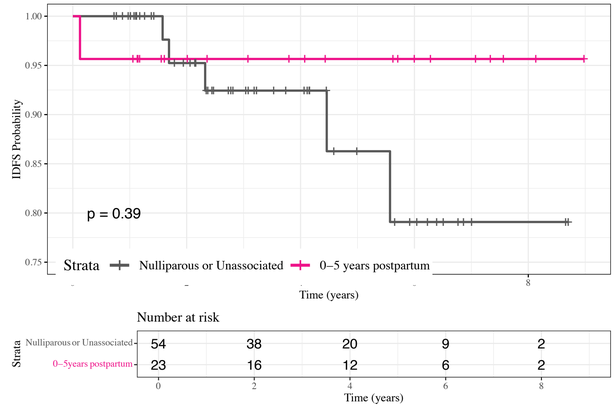


Figure 2: Categorical RS result in lymph node positive patients by PPBC category



- Women in the PPBC group had 3.78 times the odds of being classified in a higher RS category compared to nulliparous women (p = 0.016), and 3.87 times the odds compared to nulliparous and non-PPBC groups combined (p = 0.006). No significant difference in odds of higher RS category was observed in the non-PPBC group compared to nulliparous women (p=0.92). **Figure 2.**
- Among all 77 patients, 48 (62.3%) received chemotherapy and this increased with RS category: 41.3% (RS <16), 61.5% (16-25), and 90.9% (>25) (p=0.001).
- Median follow-up time of 3.07 years (range: 0.126, 8.977, IQR=4.01), and there were 6 recurrences (7.79%). **Figure 3.**

Figure 3: Invasive disease-free survival by cohort



- Five-year IDFS was 95.7% (95% CI: 87.7-100%) in PPBC patients and 86.3% (95% CI: 73.4-100%) in all others with a non-significant trend toward lower recurrence risk in non-PPBC and nulliparous patients compared to PPBC (p=0.39).
- Among the subgroup of patients who did receive chemotherapy (n=24), five-year IDFS was 94.1% (95% CI: 83.6-100%) in the PPBC group versus 81.5 (95% CI: 62.8-100%) in all other patients.

Conclusions and Discussion

- In this cohort of young women with HR+HER2- node-positive BC, PPBC was associated with higher RS and RS category than BC in nulliparous women.
- Larger studies with longer follow-up will be needed to evaluate whether distinguishing PPBC from nulliparous and non-PPBC can refine RS interpretation in the node-positive setting and enhance its utility in identifying premenopausal patients with biologically low-risk disease who may safely forgo chemotherapy.

References

1. Sparano et al. *NEJM* (2015). 2. Kalinsky et al. *NEJM* (2021). 3. Zhang, Z. *et al. JAMA Netw Open* (2022).

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