Original Article

Cyclin D1 Overexpression in Breast Carcinoma and Its Correlation with Standard Clinicopathological Parameters

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Abstract

Background: Breast cancer remains the most frequently diagnosed malignancy among women worldwide, with a significant disease burden in India where incidence is rising at younger ages. Conventional prognostic and predictive markers, including ER, PR, and HER2, play a central role in guiding management, yet outcomes remain variable. Cyclin D1, a cell cycle regulatory protein encoded by CCND1, is increasingly recognized as a potential biomarker in breast cancer due to its role in cell cycle control and interaction with hormone receptor pathways. Evaluating Cyclin D1 expression and its association with established prognostic markers may provide valuable insights into disease behavior and therapeutic response.

Materials and Methods: This study was carried out on 40 histologically confirmed cases of breast carcinoma. Expression of Cyclin D1, ER, PR, and HER2/neu was assessed using standard IHC protocols and scored according to Allred Score and ASCO/CAP guidelines. Statistical analysis was performed, with $p < 0.05$ considered significant.

Results: Cyclin D1 expression was detected in 23 (57.5%) out of 40 cases. Cyclin D1 expression showed a significant positive correlation with ER ($p < 0.001$) and PR ($p < 0.001$) status, but not with HER2/neu. Significant association was also observed between Cyclin D1 and molecular subtypes ($p < 0.001$), with positivity in all Luminal A and Luminal B cases, and negative correlation with TNBC.

Conclusion: Cyclin D1 expression was significantly associated with ER, PR, and Luminal A/B subtypes, but not with HER2, age, or nodal status, and showed negative correlation with TNBC. These findings suggest Cyclin D1 as a potential biomarker in hormone receptor–positive breast cancers, meriting validation in larger studies.

Keywords: Breast Cancer; Cyclin D1; Estrogen Receptor; Immunohistochemistry; Progesterone Receptor

Introduction

Breast cancer is the most common malignancy among women worldwide and the second most common cancer overall, with 2.3 million new cases reported in 2022. In India, it accounts for 13.6% of all cancers, 26.6% of cancers among women, and 10.7% of cancer-related deaths.[1] Alarmingly, one woman is diagnosed with breast cancer every three minutes in the country[1], with a rising incidence at younger ages.[2] Early detection through improved diagnostic modalities has the potential to reduce morbidity and mortality.

Prognostic evaluation typically includes clinical and pathological features such as tumor size, histological grade, lymph node status, and mitotic rate, while predictive markers include hormone receptors such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). These parameters serve as important indicators of disease progression and therapeutic response.[3]

Advances in molecular oncology have highlighted the role of novel biomarkers in breast cancer biology. Cyclin D1 has emerged as a potential biomarker which is essential for mammary gland development and regulates the transition from G1 to S phase by activating cyclin-dependent kinases (CDK4/6).[5] Dysregulation of Cyclin D1 has been observed in multiple malignancies, including breast cancer, where it promotes proliferation through Rb phosphorylation and E2F activation.[6, 4] Beyond its CDK-dependent functions, Cyclin D1 also interacts with nuclear receptors such as ERα and AR, along with co-activators and chromatin-modifying enzymes, thereby influencing transcriptional regulation and tumour progression.[6] Notably, Cyclin D1 overexpression enhances ERα activity even in the absence of estrogen, underscoring its potential role as an independent activator in breast carcinogenesis.[6, 7] Given its ability to modulate cell cycle progression and hormone receptor signalling, Cyclin D1 may serve as both a prognostic and predictive biomarker.[7] There have been a few studies on the clinicopathological correlation of Cyclin D1 expression in breast cancer in India.

The objective of present study was to investigate the expression of Cyclin D1 in breast cancer and its correlation with ER, PR, HER2/neu, and other clinicopathological parameters, with the aim of improving prognostic stratification and guiding therapeutic strategies.

Materials and Methods

This descriptive cross-sectional study was conducted over one year (August-2023 to July-2024) with the approval of Institutional Ethics Committee and included 40 histopathologically confirmed cases of invasive breast carcinoma. The sample size was calculated at 95% confidence level with prevalence of 84.6% based on previous study by Abdelnaby et al.[3]. Patients who had received neoadjuvant therapy or had benign breast lesions were excluded. Specimens from mastectomies, excisional, and tru-cut biopsies were processed routinely, sectioned at 3–4 µm, and stained with hematoxylin and eosin. Tumours were graded by the modified Scarff–Bloom–Richardson (SBR) system, and lymphovascular invasion was noted.

Immunohistochemistry (IHC) for ER, PR, HER2/neu, and Cyclin D1 was performed using standard heat-induced antigen retrieval, blocking, DAB chromogen visualization, and Mayer's hematoxylin counterstain. Tonsil tissue served as positive control for Cyclin D1, and omission of primary antibody was used as negative control. ER, PR and Cyclin D1 were interpreted by the Allred scoring system combining intensity (0–3) and proportion (0–5) scores, classified as negative (0–2), intermediate (3–5), or strong (6–8). (Table 1) and HER2/neu by ASCO/CAP guidelines (Table 2). [8, 9] Marker expression was correlated with clinicopathological parameters.

Table 1: Quantification of ER, PR and Cyclin D1 immunostaining.

Proportion Score	Positive Cells (%)	Intensity	Intensity Scores
0	0	None	0
1	<1	Weak	1
2	1-10	Intermediate	2
3	11-33	Strong	3
4	34-66		
5	>=67		

Table 2: Interpretation of HER2 immunostaining.

Result	Criteria
Negative (Score 0)	No staining observed or incomplete, faint/ barely perceptible membrane staining in <= 10% of invasive tumour cells.
Negative (Score 1+)	Incomplete, faint/barely perceptible membrane staining in <=10% of invasive tumour cells.
Equivocal (Score 2+)	Incomplete and/or weak to moderate circumferential membrane staining in > 10% of invasive tumour cells or, complete, intense, circumferential membrane staining in <=10% of invasive tumour cells.
Positive (Score 3+)	Complete, intense, circumferential membrane staining in >10% of invasive tumour cells.

Statistical analysis was performed using SPSS version 28. Associations between immunohistochemical expression and clinicopathological parameters were evaluated using the Chi-square test/Fisher's exact test, with $p < 0.05$ considered statistically significant.

Results

40 cases of invasive breast carcinomas were analysed. Patient age ranged from 29–76 years (mean 53.8 years), with most cases in the 41–60 year group.

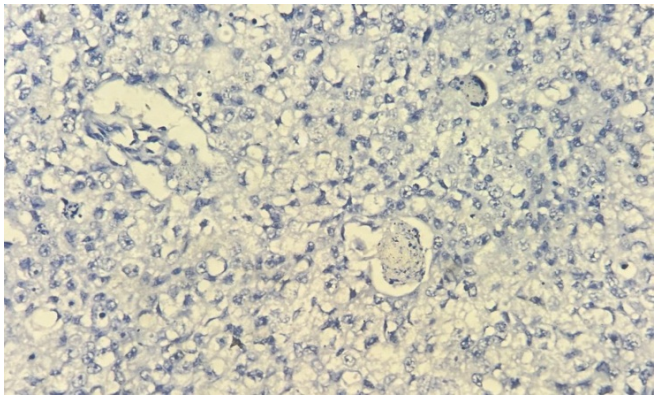

Figure 1: IHC showing negative staining for cyclin d1, grade III ductal carcinoma (400X).

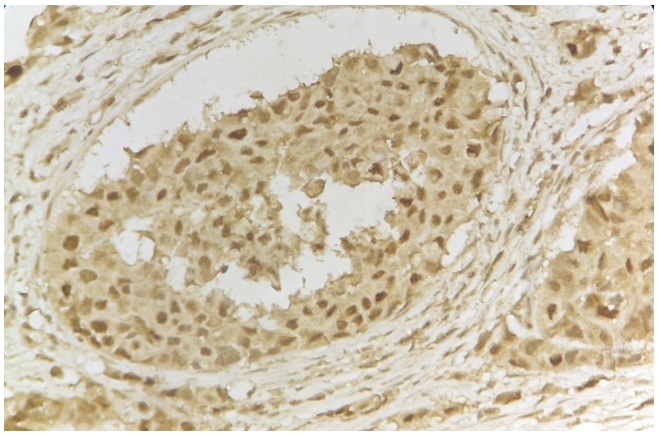

Figure 2: IHC showing intermediate positivity for cyclin d1, grade II ductal carcinoma (400X).

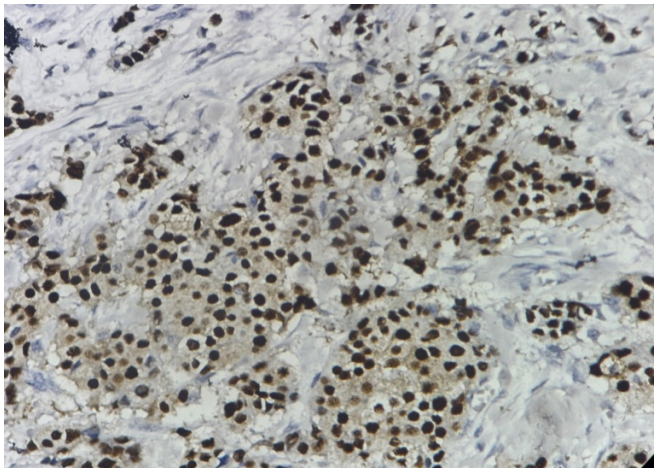

Figure 3: IHC showing strong positivity for cyclin d1, grade I ductal carcinoma (400X).

There was no significant association between Cyclin D1 expression and age group, tumour side, histological type, grade, lymph node status or LVI.(Table 3)

Cyclin D1 showed a significant positive association with ER expression (χ^2 = 32.860, p $<$ 0.001): all ER-positive tumours were Cyclin D1–positive, with ER staining intensity tracking Cyclin D1 intensity (5/5 intermediate ER paired with intermediate Cyclin D1; 7/10 strong ER paired with strong Cyclin D1). A similar significant positive association was observed with PR (χ^2 = 33.295, p $<$ 0.001): all PR-positive tumours were Cyclin D1–positive (9/11 intermediate PR paired with intermediate Cyclin D1; 4/4 strong PR paired with strong Cyclin D1). (Table 4)

No significant association was found between Cyclin D1 and HER2/neu status (χ^2 = 1.926, p = 0.452). (Table 4)

Across molecular subtypes, Cyclin D1 expression differed significantly overall (χ^2 = 21.987, p $<$ 0.001), being enriched in Luminal A (χ^2 = 9.167, p = 0.003) and Luminal B (χ^2 = 7.448, p = 0.016) and reduced in TNBC (χ^2 = 7.955, p = 0.021).

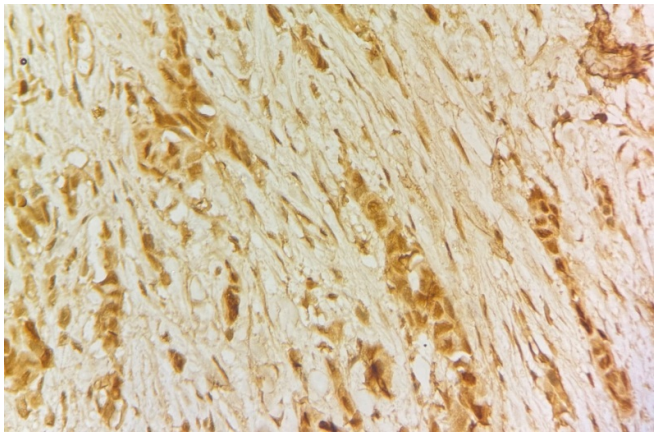

Figure 4: IHC showing cyclin d1 positivity for lobular carinoma (400X).

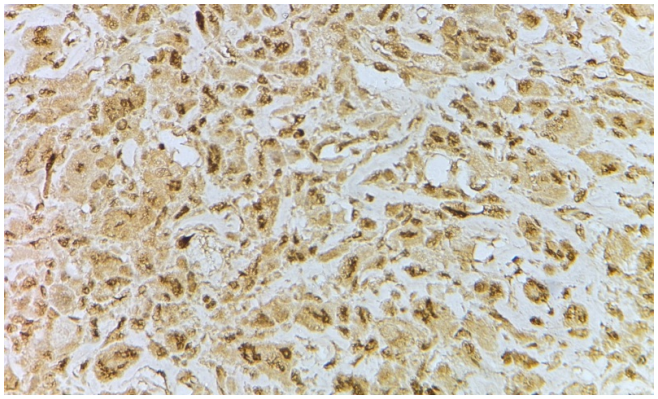

Figure 5: IHC showing cyclin d1 positivity for IDC with medullary features (400X).

Table 3: Correlation of Cyclin D1 expression with clinicopathological parameters.

Parameters	n	Cyclin D1 Expression			p value
		Negative(n = 17)	Intermediate(n = 15)	Strong(n = 8)	
Age Groups					0.497
20-40 Years	6	4 (23.5%)	1 (6.7%)	1 (12.5%)	
41-60 Years	23	9 (52.9%)	8 (53.3%)	6 (75.0%)	
>60 Years	11	4 (23.5%)	6 (40.0%)	1 (12.5%)	
Side					0.770
Right	18	7 (41.2%)	8 (53.3%)	3 (37.5%)	
Left	22	10 (58.8%)	7 (46.7%)	5 (62.5%)	
Carcinoma Type					0.499
Ductal	38	17 (100.0%)	13 (86.7%)	8 (100.0%)	
Lobular	1	0 (0.0%)	1 (6.7%)	0 (0.0%)	
Medulary	1	0 (0.0%)	1 (6.7%)	0 (0.0%)	
Grade					0.054
I	7	0 (0.0%)	5 (35.7%)	2 (25.0%)	
II	25	12 (70.6%)	8 (57.1%)	5 (62.5%)	
III	7	5 (29.4%)	1 (7.1%)	1 (12.5%)	
Lymphnode Involment					1.000
Yes	23	11 (64.7%)	8 (61.5%)	4 (66.7%)	
No	13	6 (35.3%)	5 (38.5%)	2 (33.3%)	
Lymphovascular Invasion					0.489
Yes	16	8 (47.1%)	4 (26.7%)	4 (50.0%)	
No	24	9 (52.9%)	11 (73.3%)	4 (50.0%)	

No significant association was noted with the HER2-enriched subtype. (Table 4)

Table 4: Correlation of Cyclin D1 expression with ER, PR and HER2 expression.

IHC Staining	n	Cyclin D1 Expression			p value
		Negative(n = 17)	Intermediate(n = 15)	Strong(n = 8)	
ER Expression					
Negative	25	17 (100.0%)	7 (46.7%)	1 (12.5%)	<0.001
Intermediate	5	0 (0.0%)	5 (33.3%)	0 (0.0%)	
Strong	10	0 (0.0%)	3 (20.0%)	7 (87.5%)	
PR Expression					
Negative	25	17 (100.0%)	6 (40.0%)	2 (25.0%)	<0.001
Intermediate	11	0 (0.0%)	9 (60.0%)	2 (25.0%)	
Strong	4	0 (0.0%)	0 (0.0%)	4 (50.0%)	
HER2/ neu Expression					
Negative	24	12 (70.5%)	7 (46.7%)	5 (62.5%)	0.452
Positive	16	5 (29.4%)	8 (53.3%)	3 (37.5%)	

Table 5: Correlation of Cyclin D1 expression with molecular subtypes.

Molecular Subtype	n	Cyclin D1 Expression			p value
		Negative(n = 17)	Intermediate(n = 15)	Strong(n = 8)	
Luminal A	8	0 (0.0%)	4 (26.7%)	4 (50.0%)	<0.001
Luminal B	8	0 (0.0%)	5 (33.3%)	3 (37.5%)	
HER2 Enriched	8	6 (35.3%)	2 (13.3%)	0 (0.0%)	
TNBC	16	11 (64.7%)	4 (26.7%)	1 (12.5%)	

Discussion

In this study, Cyclin D1 expression was observed in 57.5% of invasive breast carcinoma cases, which is comparatively lower than the positivity rates reported in earlier studies such as Mohammadizadeh et al., Ravikumar et al., Abdelnaby et al., Mehta et al. who reported Cyclin D1 expression in 60% to 93% of the cases.[3, 4, 10, 11] The relatively low rate of Cyclin D1 positivity in our cohort is likely attributable to a higher proportion of ER-negative tumours, triple-negative breast cancers (TNBC), and higher-grade malignancies in our sample set, as these features are known to be inversely correlated with Cyclin D1 expression.[12] Despite this lower overall expression rate, the distribution of Cyclin D1 across tumor subgroups exhibited patterns largely consistent with published literature.

When evaluated against demographic and clinicopathological parameters, no significant correlation of Cyclin D1 expression was observed with patient age, laterality of tumour, histological type, tumour grade, lymph node status, or lymphovascular invasion. These findings were consistent with the results of Mohammadizadeh et al., Sarkar et al., and Abdelnaby et al., who also reported no significant associations with these variables.[3, 4, 13] Nonetheless, a clear trend of higher Cyclin D1 expression in low-grade tumours was evident in our study, with Grade I tumours displaying higher average scores than Grade II and III tumours. This observation is biologically plausible and in agreement with Parvin et al. highlighting an inverse relationship between Cyclin D1 expression and tumour grade, suggesting that loss of Cyclin D1 may accompany dedifferentiation and tumour progression.[14]

Our study demonstrated a strong and statistically significant positive correlation between Cyclin D1 expression and hormone receptor status. All ER- and PR-positive tumours in our study also expressed Cyclin D1, with higher levels of Cyclin D1 expression in cases with stronger ER and PR expression. This robust association confirms the essential role of Cyclin D1 in luminal breast cancer biology and is consistent with previous studies by Parvin et al., Ravikumar et al., Abdelnaby et al., Mehta et al., and others, all of whom demonstrated a positive correlation between Cyclin D1 overexpression and ER/PR positivity.[3, 10, 11, 14, 13] From a mechanistic perspective, this relationship may be explained by the cross-regulatory role of Cyclin D1 in ER signaling, wherein Cyclin D1 functions as a co-regulator of ER-mediated transcription and is itself upregulated in response to estrogen signalling.[6] Taken together, this supports Cyclin D1 as a hallmark of hormone receptor–positive breast cancers.

In contrast, no statistically significant association was observed in our study between Cyclin D1 and HER2/neu expression. This finding is consistent with earlier studies of Mohammadizadeh et al., Sarkar et al., Parvin et al.,[4, 13, 14] but differs from studies of Guo et al., Li et al., Abdelnaby et al. that reported significant negative correlations.[3, 15, 16] The absence of a consistent relationship across studies suggests that the interplay between Cyclin D1 expression and HER2 signalling is complex, possibly influenced by additional genomic and epigenetic factors.

Analysis of molecular subtypes revealed distinctive patterns of Cyclin D1 distribution. Significantly higher expression was

found in Luminal A and Luminal B subtypes, whereas TNBC and HER2-enriched tumours exhibited markedly reduced expression. These findings are highly consistent with prior reports, Parvin et al., Abdelnaby et al., Mehta et al., which similarly documented Cyclin D1 overexpression in luminal subtypes and downregulation in TNBC.[3, 11, 14] These results suggest a potential role of Cyclin D1 as a surrogate biomarker for luminal differentiation and raise the possibility of incorporating Cyclin D1 into molecular panels for improved subtype characterization.

Beyond its diagnostic associations, Cyclin D1 has potential prognostic and therapeutic implications. Overexpression of Cyclin D1 has been linked to better differentiation, slower proliferative index, and favourable outcomes in hormone-responsive tumours. Importantly, Cyclin D1 is a key regulator of the cell cycle via CDK4/6 activation.[6] With the advent and widespread clinical adoption of CDK4/6 inhibitors (such as palbociclib, ribociclib, and abemaciclib), which are now standard of care in advanced ER-positive breast cancer, Cyclin D1 expression may have future implications in predicting treatment response. While our study did not address therapeutic outcomes, the strong correlation observed between Cyclin D1 and ER/PR positivity suggests that Cyclin D1 could serve as a predictive biomarker for selecting patients likely to benefit from CDK4/6 inhibitor therapy.

Study Limitation

This study has certain limitations. The sample size was modest (n=40), which may have limited statistical power for some subgroup analyses. Additionally, follow-up survival or therapeutic response data were not available, preventing prognostic analysis. Future multicentric studies with larger cohorts and integrated genomic analyses would help to validate and refine the role of Cyclin D1 in breast cancer classification, prognosis, and therapeutic decision-making.

Conclusion

Our findings demonstrate that Cyclin D1 is preferentially expressed in luminal breast cancer subtypes and shows a strong positive association with ER and PR expression. These results reaffirm the biological role of Cyclin D1 as a marker of hormone receptor–driven breast cancer, with potential utility as a biomarker in both classification and therapeutic stratification.

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Conflict of Interest: None

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