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Cyclin D1 as emerging biomarker and its correlation with other biomarkers in intraductal carcinoma of breast

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Introduction

A biomarker is a feature that is objectively evaluated and measured for the study of pathologic process, normal biologic process and pharmacologic response to treatment. Many prognostic and predictive biomarkers have been investigated in the past for decades [1,2]. With progression of new gene expression profiling technique, it has been evaluated that in comparison to traditional markers, molecular markers have important role. The incidence of breast cancer is rising globally in women and the trend is rising in India too, figuring 27% among all cancers with annual mortality of 21.5% of all cancer related deaths [3,4].

Many investigative efforts have focused on a better understanding of IBC's (Invasive Breast Carcinoma) oncogenic pathways and the search for new breast cancer biomarkers, of prognostic and therapeutic predictive value [5,6].

Materials & methods

The consecutive 57 samples over a period of 18 months have been included for the study in a tertiary care set up of a centralized institute. The written informed consent has been obtained from the patients or their legal guardians. The study has been approved by institutional review board. The patients who were diagnosed as breast carcinoma clinically have submitted either mastectomy/lumpectomy specimen to the department have been included in the study and after screening confirmed Intraductal carcinoma cases are being analysed. The cases with presence of fixation artefact, other types of benign/malignant breast tumor besides invasive duct carcinoma, patients who have received any kind of chemotherapy/radiotherapy/contemporary treatment and the cases where the written informed consent could not be obtained are excluded from the study.

The primary outcome measure was to evaluate the correlation between Cyclin D1 status of IDC (Intraductal carcinoma) with different biomarkers of carcinoma of breast. As secondary outcome measures, the correlation with other variables e.g., Age, Tumour Grade, Tumour size, Nodal status, Laterality, Location with Molecular classification has been analysed. For statistical analysis data were entered and analysed by SPSS (Statistical Package for the Social Sciences) software (version 25.0; SPSS Inc., Chicago, IL, USA) [7].

Results

In Grade-1 Group, (n=3, 50.0%) patients were in 41-50 years, in Grade-2 Group, (n=6, 42.9%) patients were 41-50 years, in Grade-3 Group, (n=2, 50.0%) patients were 61-70 years, in Grade-4 Group, (n=11, 44.0%) patients were in 41-50 years and in Grade-5 Group, (n=4, 50.0%) patients were distributed 41-50 years age group. The association of Age in Years vs group was not statistically significant (p=0.0710) (Table 1, Figure 1)

In Grade-1 Group, (n=4, 66.7%) patients had 1 ER scoring, in Grade-2 Group, (n= 5,35.7%) patients had been found with 1 and 2 ER scoring, in Grade-3 Group, (n=1, 25.0%) patients had 1 ER, 2 Er, 3 ER and 4 ER scoring. In Grade-4 Group, (n=12, 48.0%) patients had 3 ER scoring, in Grade-5 Group, (n=4, 50.0%) patients had 2 ER scoring. The association of ER scoring vs group was not statistically significant (p=0.2227) (Table 2, Figure 2).

In Grade-1 Group, (n=4, 66.7%) patients had 2 ER Pos & Neg status, in Grade-2 Group, (n=10, 71.4%) patients had 1 ER Pos and Neg status, in Grade-3 Group, (n=3, 75.0%) patients had 1 ER Pos & Neg status and in Grade-4 Group, (n=17, 68.0%) patients had 1 ER Pos and Neg status and in Grade-5 Group, (n=5,62.5%) patients had 1 ER Pos & Neg status. The association of ER pos and Neg vs group was not statistically significant (p=0.5263). (Table 3, Figure 3).

In Grade-1 Group, (n=3, 50.0%) patients had 1 PR scoring, in Grade-2 Group, (n=7, 50.0%) patients had 3 PR scoring, in Grade-3 Group, (n=2, 50.0%) patients had 3 PR scoring and in Grade-4 Group, (n=7, 28.0%) patients had 5 PR scoring and in Grade-5 Group, (n=3, 37.5%) patients had 4 PR scoring. The association of PR scoring vs group was not statistically significant (p=0.3963) (Table 4, Figure 4).

In Grade-1 Group, (n=3, 50.0%) patients had 3Her2-Neu scoring, in Grade-2 Group, (n= 6, 42.9%) patients had 0 Her2-Neu scoring, in Grade-3 Group, (n= 2, 50.0%) patients had 2 Her2-Neu scoring, in Grade-4 Group, (n=16, 64.0%) patients had 3Her2-Neu scoring and in Grade-5 Group, (n= 4,50.0%) patients had 1 Her2-Neu scoring. The association of Her2-Neu scoring *vs* group was statistically significant (p=0.0359) (Table 5, Figure 5).

In Grade-1 Group, (n=4, 66.7%) patients had 2 PR Pos & Neg, in Grade-2 Group, (n=10, 71.4%) patients had 1 PR Pos & Neg, in Grade-3 Group, (n= 3, 75.0%) patients had 1 PR Pos & Neg, in Grade-4 Group, (n= 15, 60.0%) patients had 1 PR Pos & Neg and in Grade-5 Group, (n=4,50.0%) patients had both 1 PR Pos and Neg and 2 PR Pos and Neg status. The association of PR pos and Neg vs group was not statistically significant (p=0.5192). (Table 6, Figure 6).

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Table 1. Association between age in years: Cyclin D1 status

CYCLIN D1 STATUS						
Age in Years	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
<40						
n	0	3	0	4	1	8
%	0.0	21.4	0.0	16.0	12.5	14.0
41-50						
n	3	6	1	11	4	25
%	50.0	42.9	25.0	44.0	50.0	43.9
51-60						
n	1	3	1	8	3	16
%	16.7	21.4	25.0	32.0	37.5	28.1
61-70						
n	2	2	2	2	0	8
%	33.3	14.3	50.0	8.0	0.0	14.0
TOTAL	6	14	4	25	8	57
n	10.5	24.6	7.0	43.9	14.0	100.0
%	100.0	100.0	100.0	100.0	100.0	100.0

Table 2. Association between ER scoring: Cyclin D1 status

CYCLIN D1 STATUS						
ER scoring	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
1						
n	4	5	1	8	3	21
%	66.7	35.7	25.0	32.0	37.5	36.8
2						
n	0	5	1	4	4	14
%	0.0	35.7	25.0	16.0	50.0	24.6
3						
n	1	2	1	12	1	17
%	16.7	14.3	25.0	48.0	12.5	29.8
4						
n	1	2	1	1	0	5
%	16.7	14.3	25.0	4.0	0.0	8.8
TOTAL						
n	6	14	4	25	8	57
%	100.0	100.0	100.0	100.0	100.0	100.0

Table 3. Association between ER Pos & Neg: Cyclin D1 status

CYCLIN D1 STATUS						
ER pos & Neg	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
1						
n	2	10	3	17	5	37
%	33.3	71.4	75.0	68.0	62.5	64.9
2						
n	4	4	1	8	3	20
%	66.7	28.6	25.0	32.0	37.5	35.1
TOTAL						
n	6	14	4	25	8	57
%	100.0	100.0	100.0	100.0	100.0	100.0

In Grade-1 Group, (n=3, 50.0%) patients had 1 Her2 Status, in Grade-2 Group, (n=9, 64.3%) patients had 2 Her2 Status, in Grade-3 Group, (n=2, 50.0%) patients had 2 Her2 Status, in Grade-4 Group, (n=15, 60.0%) patients had 1 Her2 Status and in Grade-5 Group, (n=5, 62.5%) patients had 2 Her2 Status. The association of Her2 Status vs group was not statistically significant (p=0.2672). (Table 7, Figure 7).

In Grade-1 Group, (n=5, 83.3%) patients had High Ki-67 Status, in Grade-2 Group, (n=9, 64.3%) patients had Low Ki-67 Status, in Grade-3 Group, (n=3, 75.0%) patients had High Ki-67 Status, in Grade-4 Group, (n=22, 88.0%) patients had High Ki-67 Status and in Grade-5 Group, (n=8, 100.0%) patients had High Ki-67 Status. The association of Ki-67 Status vs group was statistically significant (p=0.0021) (Table 8, Figure 8).

In Grade-1 Group, both (n=3, 50.0%) patients had 2 TUMOR GRADE and 3 TUMOR GRADE, in Grade-2 Group, (n=10, 71.4%) patients had 2 TUMOR GRADE, in Grade-3 Group, (n=3, 75.0%) patients had 2 TUMOR GRADE, in Grade-4 Group, (n=15, 60.0%) patients and in Grade-5 Group, both (n=4, 50.0%) patients had 2 TUMOR GRADE and 3 TUMOR GRADE. The association of TUMOR GRADE vs group was not statistically significant (p=0.3514) (Table 9, Figure 9).

In Grade-1 Group, (n=4, 66.7%) patients had STAGE-2, in Grade-2 Group, (n=7, 50.0%) patients had STAGE-2, in Grade-3 Group, (n=2, 50.0%) patients had STAGE-2, in Grade-4 Group, (n=16, 64.0%) patients had STAGE-2 and in Grade-5 Group, (n=4, 50.0%) patients had STAGE-2. The association of STAGE-T vs group was not statistically significant (p=0.3587) (Table 10, Figure 10).

Table 4. Association between PR scoring: Cyclin D1 status

CYCLIN D1 STATUS						
PR scoring	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
0	1	1	0	3	2	7
n	16.7	7.1	0.0	12.0	25.0	12.3
%						
1	3	2	1	4	1	11
n	50.0	14.3	25.0	16.0	12.5	19.3
%						
2	1	0	0	2	0	3
n	16.7	0.0	0.0	8.0	0.0	5.3
%						
3	0	7	2	5	1	15
n	0.0	50.0	50.0	20.0	12.5	26.3
%						
4	1	1	1	4	3	10
n	16.7	7.1	25.0	16.0	37.5	17.5
%						
5	0	3	0	7	1	11
n	0.0	21.4	0.0	28.0	12.5	19.3
%						
TOTAL	6	14	4	25	8	57
n	100.0	100.0	100.0	100.0	100.0	100.0
%						

Table 5. Association between PR pos & Neg: Cyclin D1 status

CYCLIN D1 STATUS						
PR pos and Neg	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
1	2	10	3	15	4	34
n	33.3	71.4	75.0	60.0	50.0	59.6
%						
2	4	4	1	10	4	23
n	66.7	28.6	25.0	40.0	50.0	40.4
%						
TOTAL	6	14	4	25	8	57
n	100.0	100.0	100.0	100.0	100.0	100.0
%						

Table 6. Association between Her2-Neu scoring: Cyclin D1 status

CYCLIN D1 STATUS						
Her2-Neu scoring	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
0	2	6	1	4	2	15
n	33.3	42.9	25.0	16.0	25.0	26.3
%						
1	0	3	0	2	4	9
n	0.0	21.4	0.0	8.0	50.0	15.8
%						
2	1	3	2	3	1	10
n	16.7	21.4	50.0	12.0	12.5	17.5
%						
3	3	2	1	16	1	23
n	50.0	14.3	25.0	64.0	12.5	40.4
%						
TOTAL	6	14	4	25	8	57
n	100.0	100.0	100.0	100.0	100.0	100.0
%						

Table 7. Association between Her2 Status: Cyclin D1 status

CYCLIN D1 STATUS						
Her2 Status	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
1						
n	3	2	1	15	2	23
%	50.0	14.3	25.0	60.0	25.0	40.4
2						
n	2	9	2	8	5	26
%	33.3	64.3	50.0	32.0	62.5	45.6
3						
n	1	3	1	2	1	8
%	16.7	21.4	25.0	8.0	12.5	14.0
TOTAL						
n	6	14	4	25	8	57
%	100.0	100.0	100.0	100.0	100.0	100.0

Table 8. Association between Ki-67 Status: Cyclin D1 status

CYCLIN D1 STATUS						
Ki-67 Status	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
High						
n	5	5	3	22	8	43
%	83.3	35.7	75.0	88.0	100.0	75.4
Low						
n	1	9	1	3	0	14
%	16.7	64.3	25.0	12.0	0.0	24.6
TOTAL						
n	6	14	4	25	8	57
%	100.0	100.0	100.0	100.0	100.0	100.0

Table 9. Association between tumor grade: Cyclin D1 Status

CYCLIN D1 STATUS						
TUMOR GRADE	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
2	3	10	3	10	4	30
Row %						
Col %	50.0	71.4	75.0	40.0	50.0	52.6
3	3	4	1	15	4	27
Row %						
Col %	50.0	28.6	25.0	60.0	50.0	47.4
TOTAL	6	14	4	25	8	57
Row %	100.0	100.0	100.0	100.0	100.0	100.0
Col %						

Table 10. Association between STAGE-T: Cyclin D1 status

CYCLIN D1 STATUS						
STAGE-T	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
1						
n	0	5	1	2	0	8
%	0.0	35.7	25.0	8.0	0.0	14.0
2	4					
n	66.7	7	2	16	4	33
%		50.0	50.0	64.0	50.0	57.9
3						
n	2	1	1	4	2	10
%	33.3	7.1	25.0	16.0	25.0	17.5
4						
n	0	1	0	3	2	6
%	0.0	7.1	0.0	12.0	25.0	10.5
TOTAL						
n	6	14	4	25	8	57
%	100.0	100.0	100.0	100.0	100.0	100.0

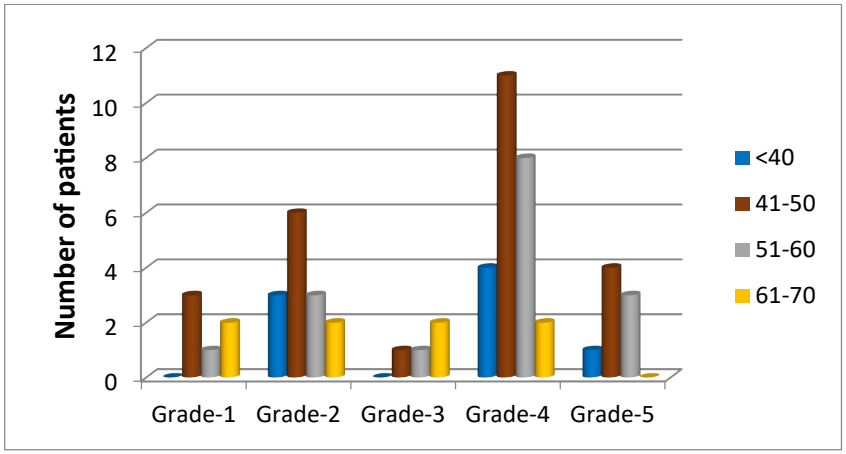

Figure 1. χ^2 **(Chi-square value):** 10.4321; **p-value:** 0.5781

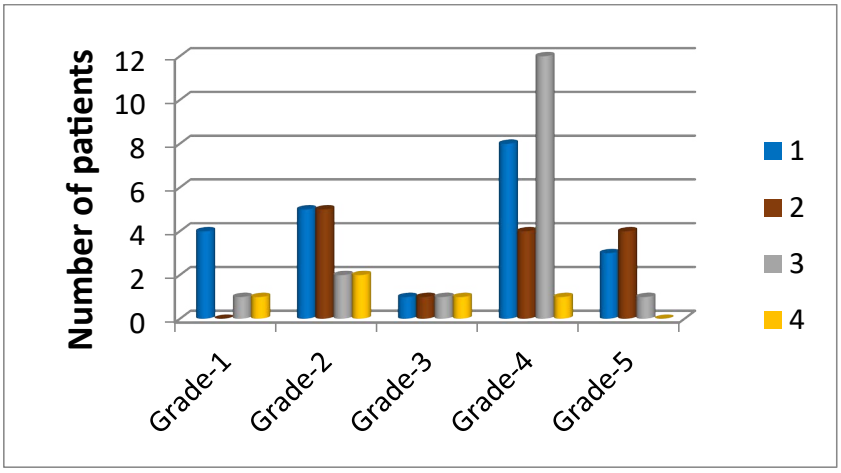

Figure 2. χ^2 **(Chi-square value):** 15.3528; **p-value:** 0.2227

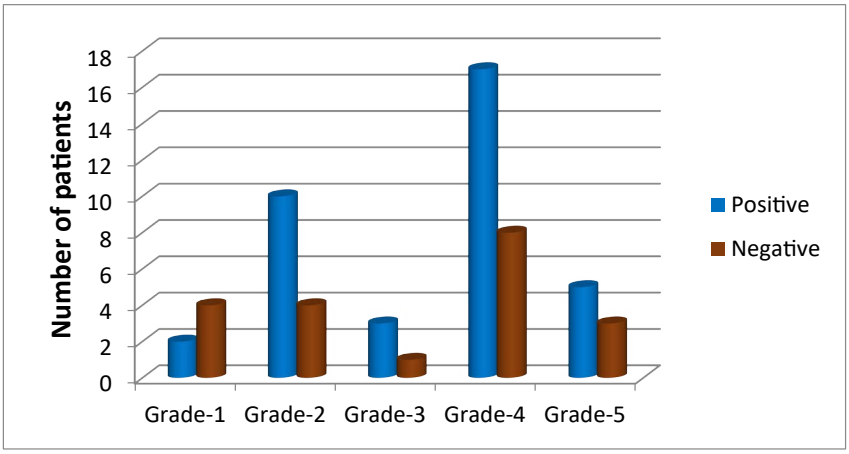

Figure 3. χ^2 **(Chi-square value):** 3.1918; **p-value:** 0.5263

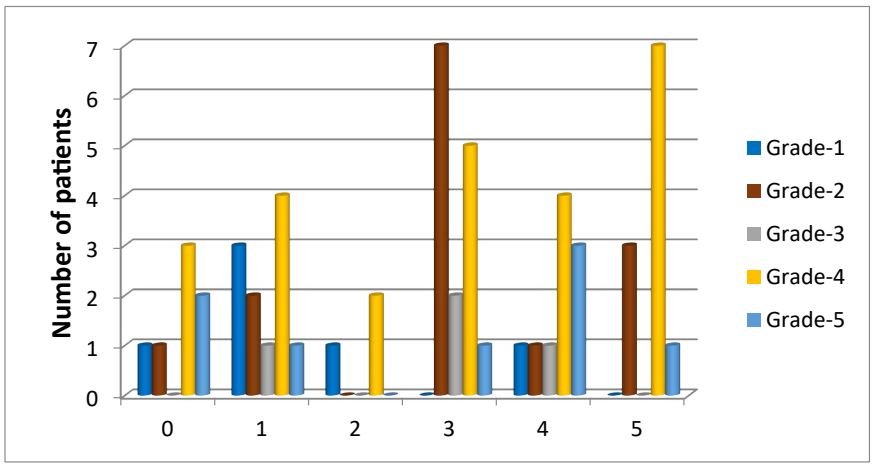

Figure 4. χ^2 **(Chi-square value):** 21.0140; **p-value:** 0.3963

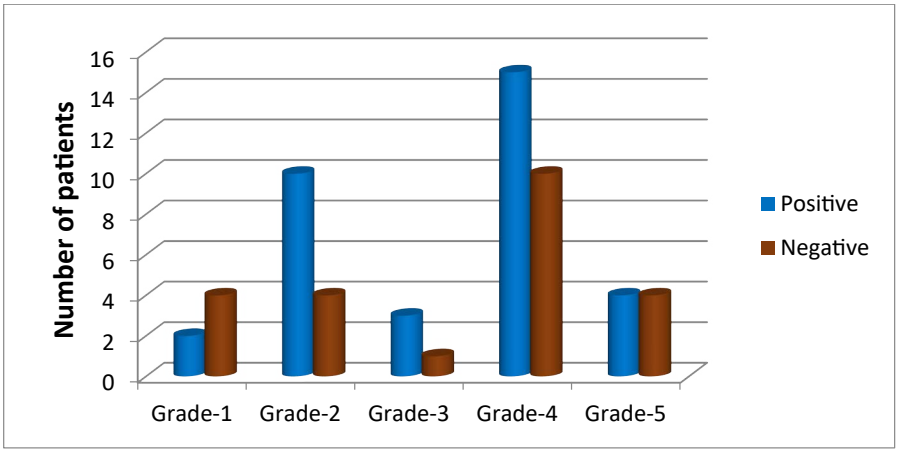

Figure 5. χ^2 **(Chi-square value):** 3.2358; **p-value:** 0.5192

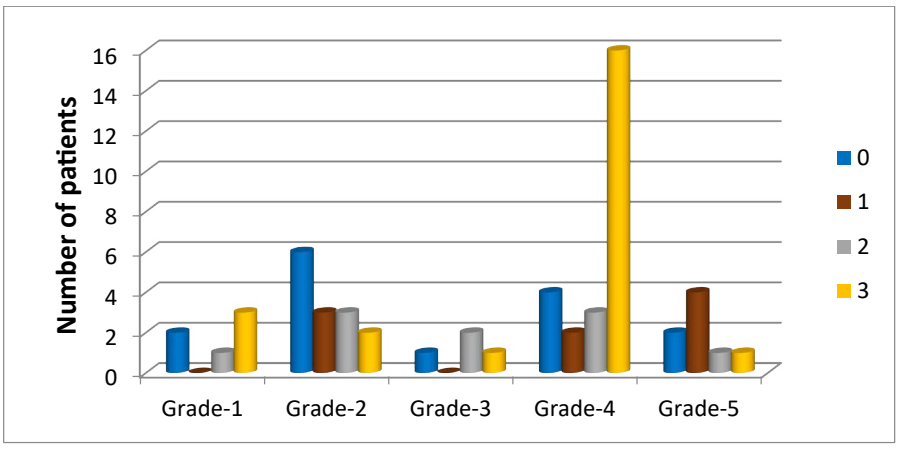

Figure 6. χ^2 **(Chi-square value):** 22.1492; **p-value:** 0.0359

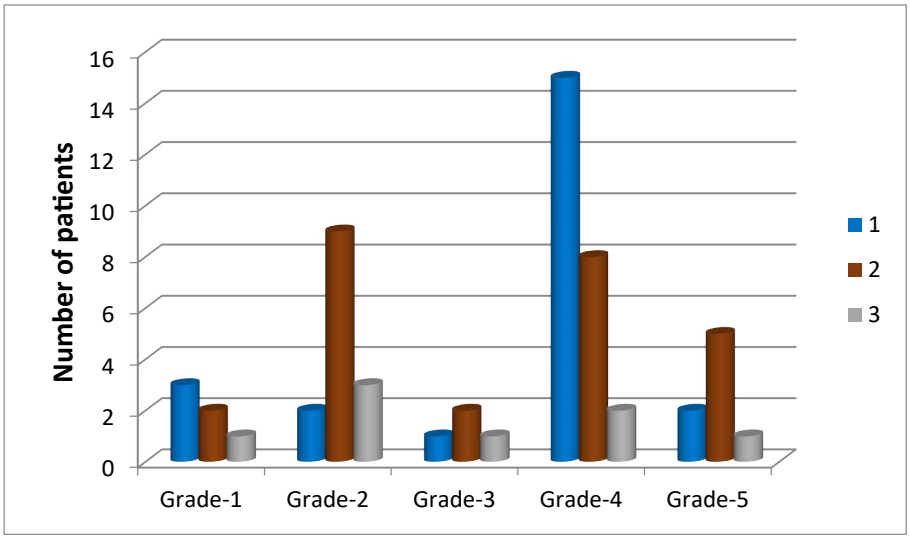

Figure 7. χ^2 **(Chi-square value):** 9.9694; **p-value:** 0.2672

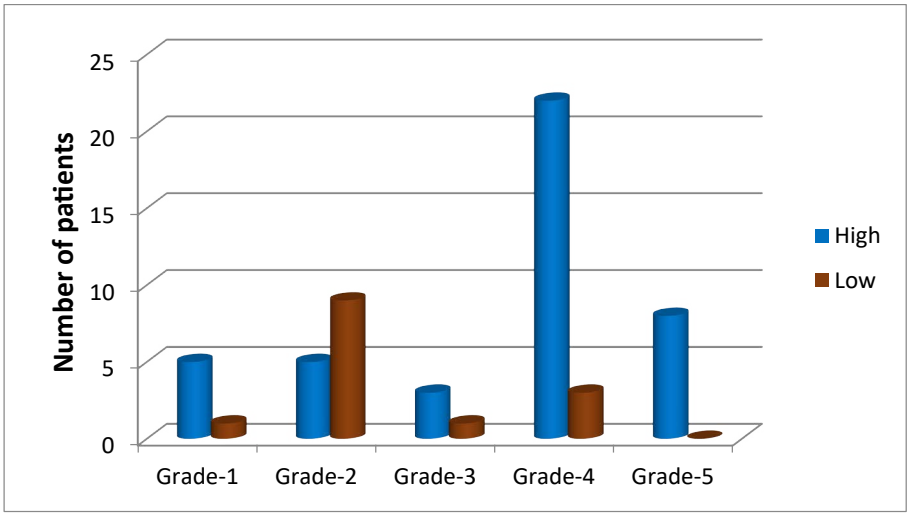

Figure 8. χ^2 **(Chi-square value):** 16.8591; **p-value:** 0.0021

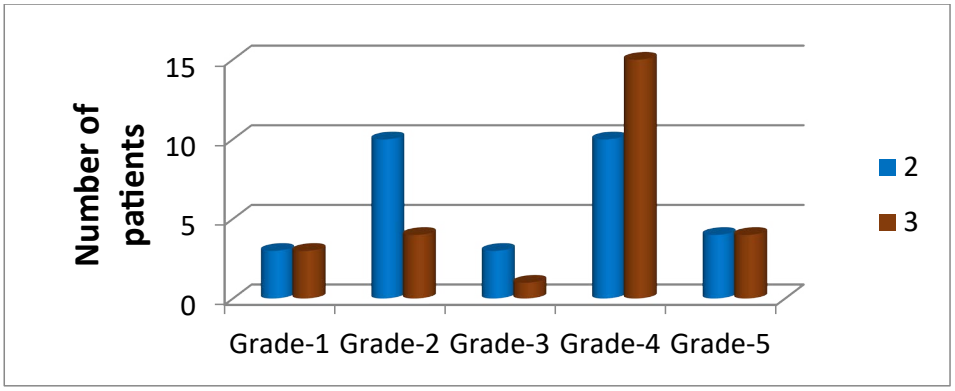

Figure 9. χ^2 **(Chi-square value):** 4.4258; **p-value:** 0.3514

In Grade-1 Group, (n=5, 83.3%) patients had N 1, in Grade-2 Group, (n=5, 35.7%) patients had N_0 and N_1, in Grade-3 Group, (n=2, 50.0%) patients had N_3, in Grade-4 Group, (n=9, 36.0%) patients had N_2, and in Grade-5 Group, (n=4, 50.0%) patients had N_2 lymph node status. The association of STAGE-N (lymph node status) vs group was not statistically significant, χ^2 (Chi-square value): 17.9009; (p=0.1187). (Table 11, Figure 11).

In Grade-1 Group, (n=5, 83.3%) patients had LL Laterality, in Grade-2 Group, (n=11, 78.6%) patients had LL Laterality, in Grade-3 Group, (n=4, 100.0%) patients had LL Laterality, in Grade-4 Group, (n=19, 76.0%) patients had LL Laterality and In Grade-5 Group, (n=6, 75.0%) patients had LL Laterality. It is evident that in all the grades LL (Left Lateral) laterality is predominant. The association of Laterality vs group was not statistically significant (p=0.8540) (Table 12, Figure 12).

In Grade-1 Group, (n=4, 66.7%) patients had UO (upper outer), in Grade-2 Group, (n=6,42.9%) patients had UI (upper inner), in Grade-3 Group, (n=2, 50.0%) patients had both UI and UO location, in Grade-4 Group, (n=12, 48.0%) patients had UI and in Grade-5 Group, (n=3, 37.5%) patients had UO location of the tumour. The association of LOCATION vs group was not statistically significant (p=0.7928) (Table 13, Figure 13).

In Grade-1 Group, (n=2, 33.3%) patients had each HER2, LB and TN molecular classification. In Grade-2 Group, (n=8, 57.1%) patients had LA, in Grade-3 Group, (n=2, 50.0%) patients had LB, in Grade-4 Group, (n=15, 60.0%) patients had LB and in Grade-5 Group, (n=4, 50.0%) patients had LB molecular classification. The association of Molecular Classification vs group was statistically significant (p=0.0165) (Table 14, Figure 14).

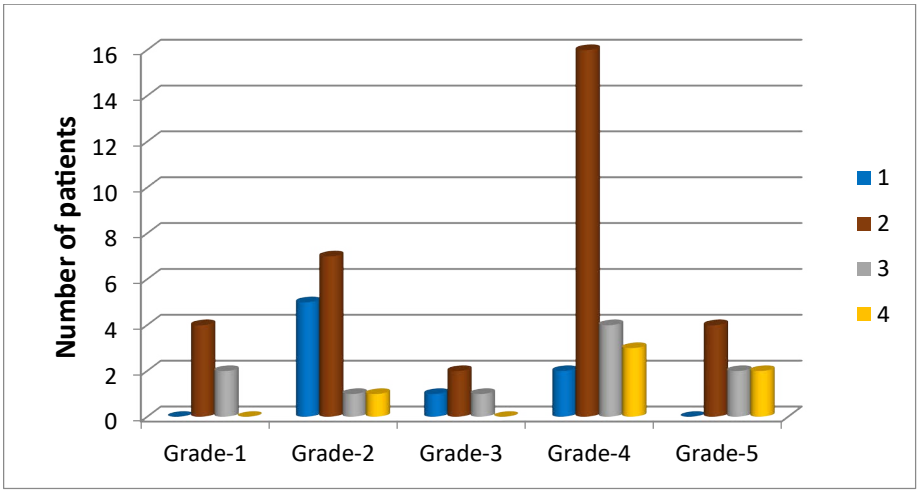

Figure 10. χ^2 **(Chi-square value):** 13.1438; **p-value:** 0.3587

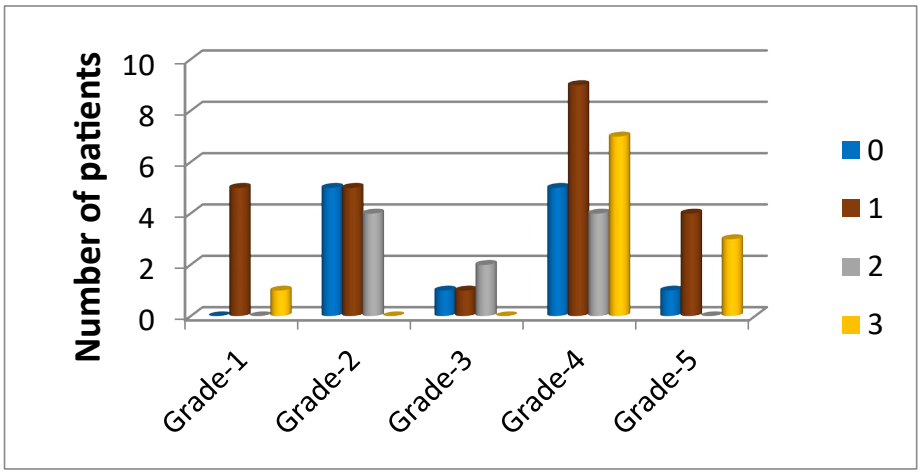

Figure 11. χ^2 **(Chi-square value):** 17.9009; **p-value:** 0.1187

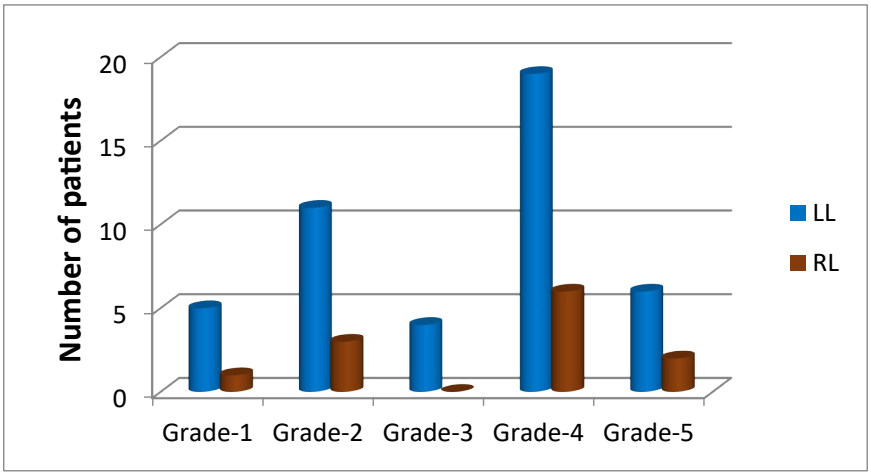

Figure 12. χ^2 **(Chi-square value):** 1.3430; **p-value:** 0.8540

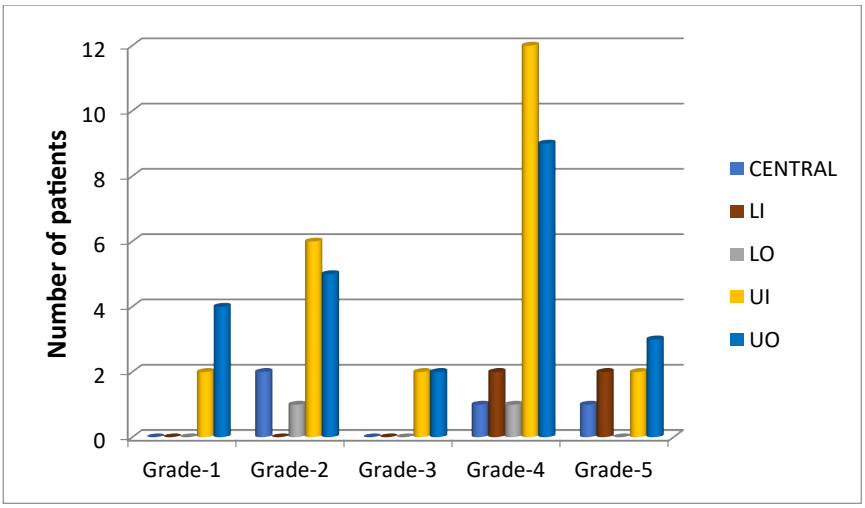

Figure 13. χ^2 **(Chi-square value):** 11.2664; **p-value:** 0.7928

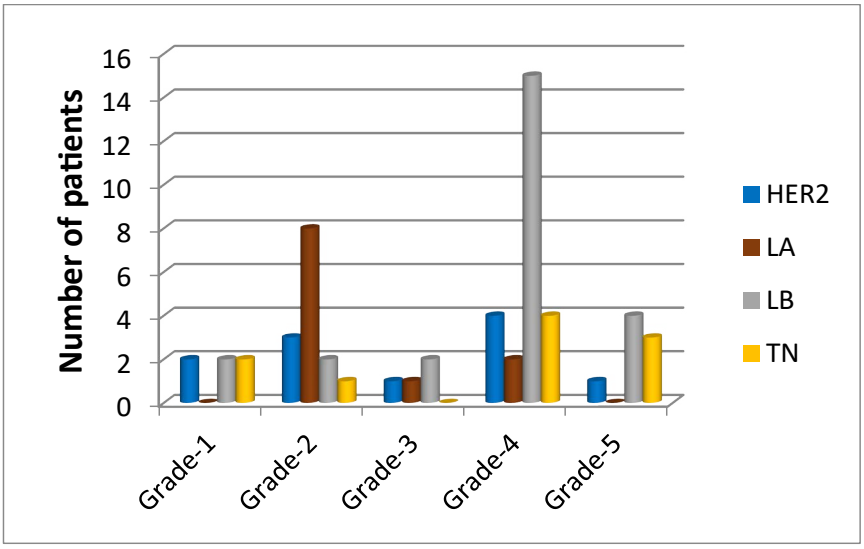

Figure 14. χ^2 **(Chi-square value):** 24.6572; **p-value:** 0.0165

Table 11. Association between STAGE-N: Cyclin D1 status

CYCLIN D1 STATUS						
STAGE-N	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
0						
n	0	5	1	5	1	12
%	0.0	35.7	25.0	20.0	12.5	21.1
1						
n	5	5	1	9	4	24
%	83.3	35.7	25.0	36.0	50.0	42.1
2						
n	0	4	2	4	0	1
%	0.0	28.6	50.0	16.0	0.0	17.5
3						
n	1	0	0	7	3	1
%	16.7	0.0	0.0	28.0	37.5	19.3
TOTAL						
n	6	14	4	25	8	57
%	100.0	100.0	100.0	100.0	100.0	100.0

Table 12. Association between laterality: Cyclin D1 status

CYCLIN D1 STATUS						
Laterality	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
LL						
n	5	11	4	19	6	45
%	83.3	78.6	100.0	76.0	75.0	78.9
RL						
n	1	3	0	6	2	12
%	16.7	21.4	0.0	24.0	25.0	21.1
TOTAL						
n	6	14	4	25	8	57
%	100.0	100.0	100.0	100.0	100.0	100.0

Table 13. Association between location: Cyclin D1 status

CYCLIN D1 STATUS						
LOCATION	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
CENTRAL						
n	0	2	0	1	1	4
%	0.0	14.3	0.0	4.0	12.5	7.0
LI						
n	0	0	0	2	2	4
%	0.0	0.0	0.0	8.0	25.0	7.0
LO						
n	0	1	0	1	0	2
%	0.0	7.1	0.0	4.0	0.0	3.5
UI						
n	2	6	2	12	2	24
%	33.3	42.9	50.0	48.0	25.0	42.1
UO						
n	4	5	2	9	3	23
%	66.7	35.7	50.0	36.0	37.5	40.4
TOTAL						
n	6	14	4	25	8	57
%	100.0	100.0	100.0	100.0	100.0	100.0

Table 14. Association between molecular classification: Cyclin D1 status

	CYCLIN D1 STATUS					
MOLECULAR CLASSIFICATION	**Grade-1**	**Grade-2**	**Grade-3**	**Grade-4**	**Grade-5**	**TOTAL**
HER2						
n	2	3	1	4	1	11
%	33.3	21.4	25.0	16.0	12.5	19.3
LA						
n	0	8	1	2	0	11
%	0.0	57.1	25.0	8.0	0.0	19.3
LB						
n	2	2	2	15	4	25
%	33.3	14.3	50.0	60.0	50.0	43.9
TN						
n	2	1	0	4	3	10
%	33.3	7.1	0.0	16.0	37.5	17.5
TOTAL						
n	6	14	4	25	8	57
%	100.0	100.0	100.0	100.0	100.0	100.0

Discussion

The oncogene encoding Cyclin D1 overexpression has been reported upto 50% of human breast cancers but its prognostic impact is still controversial. The inverse relationship between cyclin D1 overexpression and tumour grade and positive relationship between ER and PR scoring in IDC suggest that cyclin D1 may directly or indirectly responsible for maturation and differentiation for tumour cells [8,9].

Cyclin D1 regulates, cell cycle progression along G1 phase and oncogene CCND1 encoding cyclin D1 is amplified in parathyroid, colon, prostrate, breast carcinoma as well as in lymphoma and melanoma [10].

The clinical implications of Cyclin D1 protein can vary in different breast carcinoma subtype e.g., Luminal B subgroup is strongly ER positive with high level of Cyclin D1 protein whereas basal subgroup is ER negative and has low cyclin D1 expression. Most of the breast carcinoma cohorts (almost 70%) are luminal tumours. The relevance of Cyclin D1 in basal tumour is lost [11,12].

Cyclin D1 has been found to be correlated positively and negatively with Ki67 expression. Exploratory analysis is required to predict the clinical outcome if both these markers are elevated in breast tumours. In some studies the expression of Cyclin D1 is Her2 positive/negative and T1, T2 tumour size has been found to be significantly correlated [13,14].

The cell activity of proliferative biomarkers play an important role in development of neoplasia and metastasis and therefore clinically implicated with survival and prognosis of breast cancers [15,16].

Conclusion

The present study has some drawbacks. The other varieties of invasive breast carcinoma like lobular carcinoma, metaplastic, medullary carcinoma have not been studied. A follow up longitudinal study with higher sample size and more biomarkers will be helpful to extrapolate the findings of present study. Despite the above limitations, the present study is expected to generate the significant outcome which will be helpful for future research and will add scientific values with current understandings.

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