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Diagnostic and Prognostic Significance of Calretinin in Invasive Breast Carcinoma: A Retrospective Observational Study

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ABSTRACT

Background: Breast cancer is the most common cancer in women, with 2.3 million cases universal in 2020, and remains a leading cause of cancer-related death, especially in low-income regions. Prognosis and treatment depend on molecular markers, with luminal A and B subtypes having better survival rates than triple-negative BC. This study aims to evaluate the expression of Calretinin (CL) in invasive breast carcinoma (IBC) and its association with clinicopathological parameters.

Methods: This retrospective observational study aimed to analyse CL expression in IBC and its association with clinicopathological parameters and analytical significance. The study included 96 IBC cases analysed at a single institute over one year. Immunohistochemical analysis was performed for CL and ER, PR, Ki67, and Her-2 neu markers. CL expression was assessed using a collective scoring system, including the percentage of positive tumour cells and staining intensity.

Results: Cases were considered into low (score 0-2) and high (score 3-9) expression groups. Most cases (39%) had a CL score of 1-2, followed by 29% with a score of 0, 22% with a score of 3-6, and 10% with a score of 7-9. Higher CL scores were frequent in progressive tumour stages (T2-T3) and higher nodal contribution (N3). CL expression varied significantly across tumour grades (p=0.000), with higher scores in grade II and III tumours.

Conclusion: The study concluded that Calretinin expression relates significantly with tumor grade, stage, and nodal involvement, signifying its possibility as a prognostic marker. Higher CL expression is related to more aggressive tumor features, which could affect treatment strategies and risk assessment in breast cancer management.

Key-words: Invasive breast carcinoma, Calretinin, Immunohistochemistry, Prognostic marker, Clinicopathological parameters, Molecular subtypes, Tumour grade

INTRODUCTION

Breast cancer (BC) is among the most frequently diagnosed cancers and is the fifth most frequent cause of cancer death, with a total of around 2.3 million new BCs registered worldwide, according to data from GLOBOCAN 2020 [1]. The mortality rates from BC are much higher in developing countries like Melanesia, Western Africa, Micronesia/Polynesia, and the Caribbean, and are roughly 88% more than developed countries like Australia/New Zealand, Western Europe, Northern America, and Northern Europe [2].

Malignant neoplasms are the highest global disease burden in women and are estimated to cause 107.8 million Disability-Adjusted Life Years (DALYs), with 19.6 million DALYs contributed by BC [3]. BC is the most

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common cancer in women and had around 2.26 million United States, it is estimated to account for 29% of all new cancer cases in women [5]. The GLOBOCAN 2018 data reports a high positive correlation between rates of BC incidence and the Human Development Index (HDI) [6].

In addition to being most common, BC continues to be the cancer most responsible for cancer death among women, contributing to 684,996 fatalities (95% UI, 675,493–694,633) with an age-standardized rate of 13.6 per 100,000 worldwide [4]. While incidence rates are highest in developed nations, 63% of deaths due to BC in 2020 were in Asia and Africa [4]. While survival is good in high-income countries, women in low- and middle-income countries have much worse outcomes [7].

IBC comprises several histological subtypes, each with unique features. The most common is no special subtype (NST) in luminal IBC [8]. Classical invasive lobular (95% UI, 2.24–2.79 million) new cases in 2020 [4]. In the carcinoma, also in the luminal category, is characterised by discohesive growth and loss of E-cadherin expression [8]. Less frequent luminal subtypes are tubular, invasive cribriform, mucinous, and invasive micropapillary carcinomas [8]. Apocrine differentiation is most commonly found in breast carcinoma which usually belongs to the luminal androgen receptor (AR) type, and neuroendocrine neoplasms of the breast are exceptionally rare [8]. Prognosis and therapy depend heavily on classification according to molecular markers (ER, PR, HER2, Ki-67). Luminal A tumors, ER/PR positive, carry a 76% decreased risk of death versus triple-negative BC, and luminal B subtypes carry a 54% reduced risk (Fig. 1) [9].

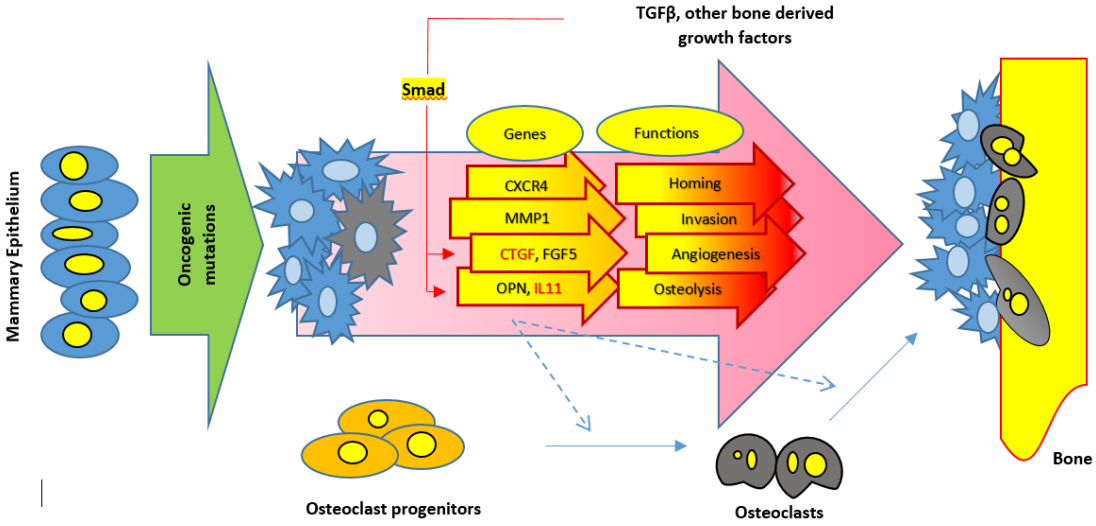

Fig. 1: Pathophysiology of Breast cancer (source: https://www.wikidoc.org/index.php/File:SoroushSeifirad,_Breast_Cancer.png)

HER2-positive cancers have a 47% decreased risk of death versus triple-negative BC, with the worst prognosis [9]. High Ki-67 levels are associated with a greater risk of mortality [9]. Well-established biomarkers ER, PR, HER2, and Ki-67 have excellent concordance between core biopsy and surgical resection, with ER reaching up to 99% and PR up to 95% [10]. Intratumoral heterogeneity is a limiting factor, with PR having more variability (coefficient of variation 0.26) than ER (0.08) [10]. New biomarker research has found 151 differentially expressed protein-coding genes about survival outcomes, out of which C3orf80, UGP2, and SPC25 are potential candidates in machine learning models [11].

CL, an EF-hand family calcium-binding protein, is involved in numerous cellular processes [12,13]. It is mainly found in the nervous system and mesothelial cells but also in some fibroblastic and myofibroblastic tumors, such as desmoid fibromatosis (75%), proliferative fasciitis (50%), and nodular fasciitis (23%) [12]. Functionally, CL is engaged in intracellular calcium buffering, message targeting, calcium signaling, cell cycle control, and modulation of apoptosis [12,13]. Clinically, it is an

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immunohistochemical marker for malignant mesothelioma and could be responsible for keeping cancer cells undifferentiated [12,13].

CL, conventionally identified as a marker for mesothelium, has become a diagnostic marker in IBC [14]. The protein is found in 55.1% of IBCs, with strong expression seen in 54.3% of basal-like carcinomas, 33.3% of HER2-positive carcinomas, and 30% of unclassified ones [15]. It is found to be strongly correlated with carcinomas that show features of medullary histology (p=0.014) and type II invasive ductal carcinoma of no special type (p<0.001) [14]. Prognostically, intense CL expression is associated with decreased overall survival (p=0.0096) and is an independent survival predictor when analysed multivariantially (p=0.0023) [15]. Its potent correlation with the aggressive tumor phenotype also indicates a possible clinical impact on BC prognosis and classification (Table 1) [15].

Table 1: Key Characteristics and Clinical Aspects of Invasive Breast Carcinoma

Categories	Details
Incidence & Prevalence	Accounts for the majority of BC cases; higher prevalence in postmenopausal women.
Risk Factors	Genetic predisposition (BRCA1/BRCA2 mutations), hormonal influences, obesity, lifestyle factors, and environmental exposure.
Molecular Subtyping	Divided into Luminal A, Luminal B, HER2-positive, and Basal-like (Triple-negative) based on gene expression and receptor status.
Histological Variants	Includes invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), mucinous carcinoma, and medullary carcinoma.
Clinical Presentation	Palpable lump, nipple discharge, skin changes, and lymph node involvement in advanced cases.
Diagnostic Modalities	Mammography, ultrasound, MRI, biopsy (core needle or excisional), and immunohistochemistry (IHC).
Therapeutic Approaches	Surgery (mastectomy/lumpectomy), chemotherapy, radiotherapy, endocrine therapy, targeted therapy (HER2 inhibitors, CDK4/6 inhibitors).
Prognostic Indicators	size, lymph node involvement, grade, receptor status, proliferation markers.
Emerging Biomarkers	CL, PD-L1, androgen receptor, and tumor-infiltrating lymphocytes (TILs) are being investigated for diagnostic and prognostic roles.

The purpose of this research is to analyse CL expression in invasive breast carcinoma and determine its relationship with clinicopathological parameters. Furthermore, its prognostic significance in the progression of disease and patient prognosis were evaluated, further improving our understanding of its potential role as a biomarker.

MATERIALS AND METHODS

Research Design- This observational cross-sectional study was conducted in the Department of Pathology at the Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun. It aimed to evaluate Calretinin expression in invasive breast carcinoma cases diagnosed within the institution over one year. The calculated sample size was 96.

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Clinical data, including patient demographics, complaints, examination findings, and radiological observations, were systematically recorded. Excisional biopsies and mastectomy specimens submitted by surgeons were processed for histopathological and immunohistochemical evaluation. Tissues were fixed in 10% buffered formalin—smaller biopsies overnight, mastectomy specimens for up to three days. Specimens were grossed following standard departmental protocols, documenting tumour tissue, surgical margins, and lymph nodes.

Tissue processing involved dehydration through graded alcohol concentrations, clearing in xylene, and embedding in paraffin. Microtome-generated sections (4-5µm thick) were stained with hematoxylin and eosin for morphological assessment. Immunohistochemical analysis was performed for Calretinin, ER, PR, Ki67, and Her-2 neu markers. The staining process included deparaffinisation, antigen retrieval via microwave, peroxidase blocking, and incubation with monoclonal antibodies. A polymer-based detection system with horseradish peroxidase and 3,3'-diaminobenzidine tetrahydrochloride was used, followed by counterstaining with hematoxylin. Calretinin expression was assessed based on nuclear/cytoplasmic staining using a combined scoring system (0-9). Cases were classified as low (score 0-2) or high (score 3-9) expression groups based on staining intensity and distribution.

Inclusion criteria- All patients diagnosed with invasive breast carcinoma at the institution were included in the study.

Exclusion criteria- Patients with benign, in situ/intraductal breast carcinoma. Cases that had acknowledged chemotherapy or radiotherapy before the study were excluded.

Statistical Analysis- Statistical analysis was performed using SPSS (version 23) and Microsoft Excel. Data were presented through tables, bar charts, and pie diagrams. Categorical variables were expressed as frequencies and analyzed using Pearson's chi-square test, while continuous data were represented as mean±standard deviation or median. A p-value <0.05 was considered statistically significant. The study aimed to identify relationships between Calretinin expression and various clinicopathological parameters.

Ethical clearance- Ethical clearance was obtained, and written informed consent was secured from all participants.

RESULTS

The breast-related conditions are most common in middle-aged individuals, with the highest prevalence in the 41-50 age group (34%), followed by the 61-70 age group (20%). The occurrence decreases suggestively in older individuals, with only 2% of cases in patients above 80. The majority of patients (88%) presented with a lump as their only complaint, while 9% had both pain and a lump, and 3% qualified a lump with nipple discharge. Most breast lumps are painless, which may delay early detection without regular screening. Regarding the location of breast lumps, the upper outer quadrant was the most affected (47%), followed by the upper inner quadrant (20%). The lower outer and inner quadrants accounted for 17% and 12% of cases, respectively, while the sub-areolar region and cases involving all quadrants were the least frequent. The prevalence of lumps in the upper outer quadrant parallels known breast cancer patterns, as this region contains a higher concentration of glandular tissue (Table 2).

Table 2: Age Distribution, Symptoms, and Quadrant Involvement in the pattern of Breast Lump

Age Group (in years)	Number of Patients	Percentage (%)
31 - 40	19	9%
41- 50	33	34%
51 - 60	18	18%
61 - 70	20	20%
71 - 80	4	4%

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>80	2	2%
Total	96	100%
Complaint		
Pain and Lump	9	9%
Lump and Nipple discharge	3	3%
Lump only	84	88%
Total	96	100
Quadrant of the breast		
Upper Outer	45	47
Upper Inner	19	20
Lower Outer	17	17
Lower Inner	11	12
Sub-aerolar	1	1
All quadrants	3	3
Total	96	100

In BIRADS III cases, the majority (50%) had a Calretinin score of 1-2, with 25% each falling in scores 0 and 3-6, and none in the highest category (7-9). For BIRADS IV, the highest proportion (38%) was in the 1-2 score range, followed by 30% in score 0, 23% in 3-6, and 10% in 7-9. Similarly, in BIRADS V cases, 40% had a score of 1-2, followed by 28% with a score of 0, 20% in 3-6, and 12% in 7-9. Overall, the majority of cases (39%) were in the 1-2 score range, followed by 29% in score 0, 22% in 3-6, and only 10% in 7-9. The higher Calretinin scores (7-9) are comparatively uncommon but are observed more regularly in the BIRADS IV and V categories (Table 3).

Table 3: Comparison between Calretinin Expression and Mammography BIRADS Classification

Mammography	**Calretinin**				
	Score 0	**Score 1-2**	**Score 3-6**	**Score 7-9**	**Grand Total**
BIRADS III	1 (25%)	2 (50%)	1 (25%)	0%	4
BIRADS IV	18 (30%)	23 (38%)	14 (23%)	6 (10%)	61
BIRADS V	7 (28%)	10 (40%)	5 (20%)	3 (12%)	25
Total	26 (29%)	35 (39%)	20 (22%)	9 (10%)	90

In Grade I tumours, the majority (60%) had a Calretinin score of 3-6, with 20% each in scores 0 and 1-2, and no cases in the highest category (7-9). Grade II tumours had a broader distribution, with the highest proportion (39%) in the 1-2 score range, followed by 33% in score 0, 18% in 3-6, and 10% in 7-9. Grade III tumours showed a comparatively even spread, with 44% in scores 1-2, 33% in 3-6, 11% in score 0, and 11% in 7-9. Overall, most cases (39%) fell within the 1-2 score range, followed by 30% in score 0, 22% in 3-6, and 9% in 7-9. The significant differences in $p(<0.001)$ correlation between histological grade and Calretinin expression represent that Calretinin levels vary significantly across tumour grades (Table 4).

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Table 4: Comparison between Calretinin Expression and Grade

Grade	Calretinin					
	Score 0	Score 1-2	Score 3-6	Score 7-9	Total	p-value
Grade I	1 (20%)	1 (20%)	3 (60%)	0 (0%)	5	p=0.000
Grade II	27 (33%)	32 (39%)	15 (18%)	8 (10%)	82	
Grade III	1 (11%)	4 (44%)	3 (33%)	1 (11%)	9	
Total	29 (30%)	37 (39%)	21 (22%)	9 (9%)	96	

For tumour (T) stages, in T1 cases, the majority (71%) had a Calretinin score of 0, with 29% in the 1-2 score range and no cases in higher scores. T2, which comprises 68% of cases, showed a more balanced distribution, with the highest proportion (38%) in the 1-2 range, followed by 29% in score 0, 24% in 3-6, and 10% in 7-9. In T3 cases, 35% had a score of 1-2, 30% had 3-6, 20% had 0, and 15% had 7-9. T4 cases were rare (2%) and had equal distribution in scores 0 and 1-2, with no cases in the higher scores. For nodal (N) involvement, N0 cases showed an even distribution across scores 0, 1-2, and 3-6 (each 30%), with 10% in 7-9. N1 cases had the highest proportions in scores 0 and 1-2 (both 41%), while scores 3-6 and 7-9 were less frequent (11% and 7%, respectively). In N2 cases, the majority (54%) had a score of 1-2, while 31% had a score of 0, and lower proportions were 3-6 and 7-9 (8% each). N3 cases exhibited the highest proportion in scores 3-6 (42%), followed by 33% in 1-2, 17% in 7-9, and 8% in score 0. These results suggest that lower Calretinin scores are more common in early tumour stages (T1), while higher scores (3-6 and 7-9) are more frequently observed in advanced stages (T2-T3) and higher nodal involvement (N3) (Table 5).

Table 5: Distribution of Calretinin Expression Across TNM Stages

TNM	Count	%	Score 0	Score 1-2	Score 3-6	Score 7-9
T1	7	8%	5 (71%)	2 (29%)	0 (0%)	0 (0%)
T2	63	68%	18(29%)	24(38%)	15(24%)	6 (10%)
T3	20	22%	4 (20%)	7 (35%)	6 (30%)	3 (15%)
T4	2	2%	1 (50%)	1 (50%)	0 (0%)	0 (0%)
N0	40	43%	12(30%)	12 (30%)	12(30%)	4 (10%)
N1	27	29%	11(41%)	11 (41%)	3 (11%)	2 (7%)
N2	13	14%	4 (31%)	7 (54%)	1 (8%)	1 (8%)
N3	12	13%	1 (8%)	4 (33%)	5 (42%)	2 (17%)

DISCUSSION

Powell *et al.* [16] conducted a study about CL expression present at variance in primary breast adenocarcinomas and analysed all the corresponding features of CL-expression tumors. In luminal findings, 53 primary breast adenocarcinomas were confirmed for CL by immunohistochemistry. In addition, immunostaining was performed for cytokeratin (CK)5/6 and epidermal growth factor receptor (EGFR) in CL-positive tumors. Tumors were classified as basal-like according to established morphological and immunohistochemical criteria. CL expression was seen in 15% of the cases. These included 88% of grade 3 tumors, as compared with 20% of CL-negative tumors ($p<0.001$). Furthermore, only 13% of CL-positive tumors were ER-positive, while 87% of CL-negative tumors were ER-positive ($p<0.001$). Basal-like subtype was detected in 11%, four of which were positive for CL, and two were negative ($p=0.003$). The results suggested that 15% of breast carcinomas are positive for CL and are more likely to be high-grade, ER-negative, and have a basal-like profile [16].

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Farrag *et al.* [17] carried out a study to evaluate the frequency of CL expression in invasive breast carcinoma and its relationship with clinicopathological features and prognostic value. Tissue microarrays were built using 225 breast carcinoma samples. Strong CR expression was strongly correlated with high tumor grade (p<0.0001), higher locoregional recurrence (p=0.005), negative hormone receptor status, and higher Ki-67 indices. Most CR-expressing tumors had a basal-like phenotype (p<0.0001), followed by HER2-positive and luminal B subtypes, with lower expression in luminal A and unclassified tumors. Moreover, CR-high expression was also associated with bad overall survival (p=0.03) but not with disease-free survival. These results indicated that CR may be a prognostic marker for predicting aggressive BC [17] (Table 6).

Table 6: Studies involving calretinin for diagnosis and prognosis of IBC

Author's Study	Study Design	Sample Size	Key Findings
A Fernandez-Flores [18]	Immunohistochemical analysis of calretinin in breast carcinoma	33 ductal breast carcinoma, 7 apocrine tumors	Calretinin expression not specific to breast carcinoma, especially in triple-negative cases.
Wieczorek *et al.* [19]	Immunohistochemical analysis of calretinin in mesothelioma	29 mesothelioma, 39 adenocarcinoma, 10 borderline tumors	Calretinin useful for diagnosing mesothelioma but not SBT.
Aboobacker & Saldanha [20]	Histopathological and immunohistochemical analysis in breast carcinoma	30 invasive breast carcinomas	High calretinin expression linked to aggressive tumor features (grade 3, larger size).
Venugopal *et al.* [21]	Observational study on calretinin in breast carcinoma subtypes	107 invasive breast carcinomas	High calretinin expression in basal-like subtype, correlates with poor prognosis.

CL is a major marker for mesothelial cells and malignant mesothelioma but also occurs in some breast carcinomas, most notably high-grade, ER-negative, basal-like types, and has the potential to cause diagnostic confusion. Although it is very important in the differential diagnosis of mesothelioma from adenocarcinoma, its occurrence in BC reduces its specificity, and an extensive diagnostic strategy is needed [14,15]. The presence of calretinin in BC, particularly in effusions, can be misleading as mesothelioma and highlights the importance of judicious pathological assessment. Because it is not specific to mesothelioma, being dependent only on calretinin is not sufficient, and the panel strategy using markers like mesothelin, cytokeratin 5/6, and WT1 is critical in making proper distinction [16,17]. This combination improves diagnostic accuracy in differentiating mesothelioma from adenocarcinoma and helps to identify basal-like BC, in which calretinin expression is more common [14-19].

Calretinin, a calcium-binding protein, is associated with aggressive BC subtypes, including high expression in basal-like tumors (54.3-70%) [15,17] and HER2-positive tumors (33.3-59.3%) [15,17], whereas it is lower in luminal A (9.5-11.1%) [15,17] and luminal B (12.7-33.3%) [15,17] subtypes. It is related to hormone receptor-negative status [17] and is often present in high-grade tumors (p<0.0001) [17]. Prognostically, calretinin is a predictor of unfavorable overall survival (p=0.034) [17] and is still an independent predictor of overall survival in multivariate analysis (p=0.0023) [15]. High-level expression of calretinin has been associated with inferior overall survival [15,17], high-grade tumors [17], and locoregional recurrence risk [17-21]. It is a consistent marker of adverse prognosis [17] and is highly correlated with the basal-like subtype (54.3-70%) and HER2-positive subtype (33.3-59.3%) [15,17]. While not explicitly mentioned, its association with particular molecular subtypes implies a possible role in informing targeted therapeutic approaches [15,17].

Future studies on calretinin as a biomarker should investigate the possible contribution of calretinin to BC invasion and metastasis and its potential for prognostic assessment, with special attention to basal-like tumors

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[15,22]. Molecular pathway analysis is required to investigate calretinin-dependent pro-invasive mechanisms such as p53 and MAPK pathways and their possible molecular targets for therapy. In addition, its value in the differentiation of metastatic BC from malignant mesothelioma is to be assessed. Subtype-specific investigations should accentuate the findings of calretinin on basal-like and HER2-positive BCs. At the same time, therapeutic studies should investigate its potential as a target for new treatment opportunities, especially concerning aggressive subtypes [15,22].

CONCLUSIONS

In conclusion, Calretinin expression shows a significant correlation with various factors such as BIRADS classification, tumor grade, and TNM stage. The majority of cases in the study displayed Calretinin scores in the 1-2 range, with higher scores (3-6 and 7-9) being more commonly associated with advanced stages and higher nodal involvement. The significant differences in Calretinin expression across histological grades, with Grade III tumors exhibiting varied scores, highlight its potential as a prognostic marker. Additionally, Calretinin expression tends to be lower in early tumor stages (T1) and increases in advanced stages (T2-T3) and higher nodal involvement (N3). These findings suggest that Calretinin may be a valuable biomarker for assessing the aggressiveness of breast cancer, aiding in prognosis and treatment decisions.

CONTRIBUTION OF AUTHORS

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