Original Article

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Pathology Section

Association of Poorly Differentiated Clusters with Clinicopathological Features and Tumour Budding Count in Invasive Breast Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Poorly Differentiated Clusters (PDC) and Tumour Budding Count (TBC) have emerged as potential histological markers of tumour aggressiveness. While their prognostic significance is well-documented in colorectal carcinoma, their role in invasive breast carcinoma remains underexplored.

Aim: To assess the frequency of PDCs in invasive breast carcinoma and to analyse their association with various clinicopathological factors, tumour budding and molecular profile.

Materials and Methods: This cross-sectional study was done from January 2022 to December 2025 at the Department of Pathology, Adichunchanagiri Institute of Medical Sciences, Karnataka, India. Clinicopathological details were noted down and PDC and TBC were assessed and graded on routine Haematoxylin and Eosin (H&E) slides. Further Immunohistochemistry (IHC) was done for Oestrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2), and Ki-67 for molecular classification of tumour. Statistical Package for the Social Sciences (SPSS) software version 25.0 was used to assess association between PDCs and TBC, clinicopathological features and molecular profile of tumour. Chi-square and multivariable logistic regression tests were done and p-value of <0.05 was considered significant.

Results: The study included 44 cases of invasive ductal carcinoma breast, no special type. Age of the patients ranged between 34 and 75 years. Majority of cases were of grade 2 (27 cases; 61.36%) and T2 stage (28 cases; 63.64%). PDC showed an association with tumour grade and tumour budding with a p-value of <0.05 and 0.02, respectively. There was no association with lymph node metastasis, lymphovascular invasion and tumour size. Similarly, hormone receptor, HER2 and Ki-67 expression did not show any association (p-value>0.05). On multivariate analysis, only TBC grade 1 showed a statistically significant association with PDC (OR=0.052, 95% CI: 0.003-0.864, p-value=0.039).

Conclusion: PDC evaluation is a simple and cost-effective morphological indicator of tumour aggressiveness on routine H&E section. It may compliment the conventional prognostic factors and aids in improved risk stratification.

Keywords: Invasive ductal carcinoma, Prognostic markers, Tumour aggressiveness

INTRODUCTION

Breast cancer is most common cancer diagnosed in women worldwide and a leading cause of cancer-related deaths [1]. Prognostic information is important in counselling the patients about their likely outcome and also it helps in deciding the treatment option. Traditional prognostic markers are histological grading, tumour size, lymph node status, and molecular classification [2]. However, patients with similar clinicopathological features display a different outcome of the disease. Hence, it is necessary to use additional markers of prognosis to supplement the traditional markers. Recent evidence underscores the importance of other newer morphological indicators of tumour aggressiveness like TBC and PDCs apart from traditional indicators [3]. TBC is defined as presence of single cancer cell or tiny clusters of ≤4 cells at the invasive tumour front and has been linked to aggressive behaviour and poor outcomes in breast cancer [4,5]. The PDCs is defined as clusters of five or more cancer cells lacking glandular formation, have been established as adverse prognostic indicators in colorectal, gastric, and other gastrointestinal cancers [6,7]. But their significance in breast cancer remains unclear. However, the presence of PDCs may reflect underlying tumour biology associated with epithelial–mesenchymal transition and invasiveness [4,6].

Both TBC and PDCs are believed to represent tumour de-differentiation and invasiveness, making them potentially valuable histological tools in routine diagnostic practice [4,6]. Tumour budding as a predictive marker has its own limits, as it can only be noticed in the active invasive front of the tumour and is hard to identify the single cancer cell or tiny cell clusters in routine histology sections [5]. In contrast to tumour budding, it is relatively easy to count larger clusters (≥5 cancer cells) in the entire tumour tissue stained with H&E. Studies have shown that PDC grading is more effective than tumour budding in assessing prognostic outcomes for colorectal cancer [8,9]. PDCs are well established prognostic marker in colorectal cancer, but their role in breast cancer is inconsistent. The tumour heterogeneity, hormone driven pathway and distinct stromal interaction are the reason for this difference in breast tumours [10]. Additionally, the breast cancer exhibits complex epithelial-stomal signalling and molecular heterogeneity which can influence the cluster formation invasion and metastatic potential [10,11]. Also, there is lack of standardised criteria and limited breast specific validation, which underscores the need of PDC evaluation in breast cancer [3,12]. Considering this paucity of studies on PDCs in breast cancer, the present study was undertaken to assess prognostic relevance of PDCs in breast cancer and their association with tumour budding, clinicopathological factors and molecular subtypes.

Objectives

- To assess the frequency of PDCs in invasive breast carcinoma.
- To evaluate the association of the PDCs with various clinicopathological factors such as tumour grade, lymph node status, lymphovascular invasion, TBC and molecular profile such as ER, PR, HER2 and Ki-67.

MATERIALS AND METHODS

This cross-sectional study was carried out in the Department of Pathology at Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Karnataka, India over a period of three years from January 2022-December 2025. Ethical approval from the Institutional Ethics Committee (IEC No: AIMS/IEC/05/2022) was obtained prior to initiation of the study. The study included a total of 44 cases of invasive breast cancer that met the predefined inclusion and exclusion criteria during the study period.

Inclusion criteria: Only the cases that underwent modified radical mastectomy with complete clinical details were included for the study.

Exclusion criteria: Lumpectomy and core biopsy cases and patients with prior neoadjuvant chemotherapy or radiotherapy were also excluded from the study.

Study Procedure

After receiving the surgical specimens, relevant clinical details were collected from patient records. Further gross examination was done to note the details like size, location, nipple retraction, and ulceration of skin. Further, tissues were fixed in formalin, processed, and embedded in paraffin blocks. Haematoxylin and Eosin (H&E) stained slides were prepared from 4 µm thick sections for microscopic examination. Histological diagnosis, tumour type, grade, and other variables such as tumour size, lymphovascular invasion, and lymph node status were noted. PDC and TBC were evaluated on H&E sections as follows.

Definition and Assessment of Variables

PDC: It is identified as cohesive groups of five or more tumour cells which lack the glandular differentiation. It was evaluated at the invasive front using a ×20 objective. The field showing the highest PDC count per ×20 was selected, and clusters were graded as Grade 1 (low, <5 clusters), Grade 2 (intermediate, 5-9 clusters), or Grade 3 (high, ≥10 clusters) [9].

Tumour Budding Count (TBC): It is defined isolated single cells or tiny clusters of up to four tumour cells. It was also evaluated at invasive front using a ×20 objective. The number of budding foci in one hotspot field was counted, and was graded as low (0-4 buds), intermediate (5-9 buds), or high (≥10 buds), using criteria adapted from the International Tumour Budding Consensus Conference (ITBCC) 2016 for use in colorectal carcinoma [13].

Further all the cases were subjected to IHC for ER, PR, HER2, Ki-67 under standard protocol. ER and PR were scored according to Allred score [14]. HER2 was evaluated according to ASCO/CAP criteria [15]. For Ki-67 index nuclear positivity percentage is used and count ≥20% was considered high [16]. Molecular subtypes were identified using IHC: Luminal A (ER/PR positive, HER2 negative, Ki-67 <20%), Luminal B (ER/PR positive, HER2 positive or negative, Ki-67 ≥20%), HER2-enriched (ER/PR negative, HER2 positive), and triple-negative (ER, PR, and HER2 negative) [17].

STATISTICAL ANALYSIS

Data were analysed using SPSS software version 25.0. Descriptive statistics were calculated in the form of frequency, percentages and mean. To assess the association between PDC and clinicopathological features, tumour budding and molecular profile, Chi-square test was used. Independent predictors of high PDC grade were evaluated using multivariable logistic regression model incorporating tumour grade and TBC grade. Odds ratios with 95% confidence intervals were calculated and p-value of <0.05 was considered significant.

RESULTS

The study included 44 cases of invasive ductal carcinoma, no special type. The age of the patients ranged between 34 and 75 years with mean age of 52.32±8.36 years. Majority of cases presented in the sixth decade of life (19 cases; 43.1%). The average tumour size was 3.6 cm (range: 1.5 to 7 cm). All the cases presented with lump in breast and only one case presented with ulceration. Left-side breast was most commonly involved (29 cases; 65.91%). Majority of cases were classified as T2 according to tumour size (28 cases; 63.64%). With respect to the Nottingham system of histological grading, Grade 2 tumour was predominant (27 cases; 61.36%). Lymphovascular invasion and lymph node metastasis was seen in 20 cases (45.45%) and 21 cases (47.73%) respectively. Hormone receptor and HER-2 positivity were seen in 30 cases (68.18%) and 18 cases (40.91%), respectively. Ki-67 expression was high in 27 cases (61.36%) [Table/Fig-1].

Variables	Category	n (%)
Age (years)	34-75	---
Tumour size (cm)	T1 (<2)	07 (15.91)
	T2 (2-5)	28 (63.64)
	T3 (≥5)	09 (20.45)
Tumour grade	Grade 1	08 (18.18)
	Grade 2	27 (61.36)
	Grade 3	09 (20.46)
Lymph node metastasis	Present	21 (47.73)
	Absent	23 (52.27)
Lymphovascular invasion	Present	20 (45.45)
	Absent	24 (54.55)
ER/PR	Positive	30 (68.18)
	Negative	14 (31.82)
HER2	Positive	18 (40.91)
	Negative	26 (59.09)
Ki-67	High	27 (61.36)
	Low	17 (38.64)

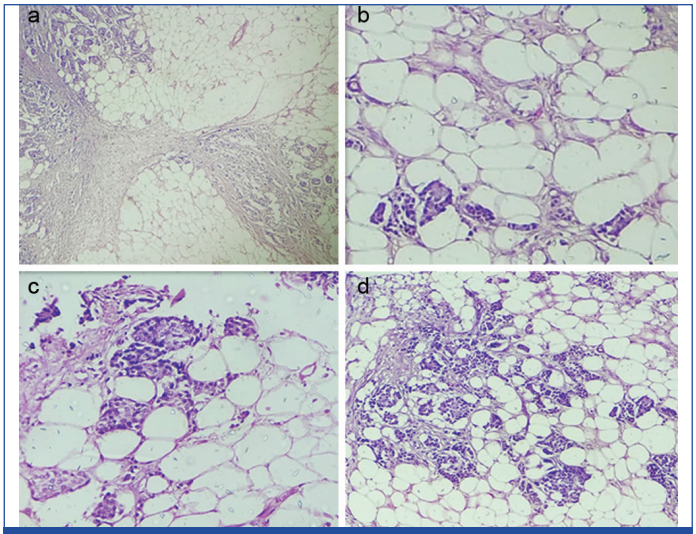
[Table/Fig-1]: Clinicopathological and immunohistochemical details of study population.

Based on molecular subtyping, Luminal A tumours were predominant (17 cases; 38.64%) followed by Luminal B (13 cases; 29.55%), Her2 enriched (9 cases; 20.45%) and triple negative tumour (5 cases; 11.36%). On grading the PDC, there were equal number of cases in grade1 PDC and grade 3 PDC (17 cases; 38.64%). With respect to TBC grading, grade 3 TBC was predominant (17 cases; 38.64%) followed by grade 1 TBC (15 cases; 34.09%) [Table/Fig-2,3].

Association of PDC with clinicopathological parameters: The PDC showed a statistically significant association with tumour grade, with PDC grade 3 increasing from 1 case (12.5%) in grade 1 tumour to 7 cases (77.8%) in grade 3 tumour (p-value=0.02). Similarly, TBC also showed a statistically significant association with

Grades	PDC n=44	TBC n=44
Grade-1	17 (38.64%)	15 (34.09%)
Grade-2	10 (22.72%)	12 (27.27%)
Grade-3	17 (38.64%)	17 (38.64%)

[Table/Fig-2]: Distribution of PDC and TBC in study population.



[Table/Fig-3]: a) Photomicrograph of invasive tumour front at scanner view (4x): b) PDC grade 1; c) PDC grade 2; (d) PDC grade 3 at 20x magnification.

the PDC grade 3, increasing from 1 case (6.6%) in low grade TBC to 11 cases (64.70%) in high-grade TBC (p-value<0.05). Although there was an increase in trend of PDC noted with higher tumour size, the results were not statistically significant whereas, lymph node metastasis and lymphovascular invasion did not show any significant association with a p-value of 0.71 and 0.81 respectively.

Hormone receptor positivity (ER/PR) was more frequent in lower PDC grade (14 cases; 46.7%) compared to higher grade (10 cases; 33.3%). However, results were not statistically significant. Similarly, HER2 expressions and Ki-67 expression also did not show any statistically significant results [Table/Fig-4].

Variable	PDC Grade 1	PDC Grade 2	PDC Grade 3	p-value
TBC				
Grade 1 (n=15)	13 (86.7%)	01 (6.7%)	01 (6.7%)	<0.05*
Grade 2 (n=12)	2 (16.7%)	5 (41.7%)	5 (41.7%)	
Grade 3 (n=17)	2 (11.8%)	4 (23.5%)	11 (64.7%)	
Tumour size				
Grade 1 (n=7)	3 (42.9%)	2 (28.5%)	2 (28.5%)	0.26
Grade 2 (n=28)	14 (50%)	5 (17.9%)	9 (32.1%)	
Grade 3 (n=9)	0	3 (33.3%)	6 (66.7%)	
Tumour grade				
Grade 1 (n=8)	5 (62.5%)	2 (25%)	01 (12.5%)	0.02*
Grade 2 (n=27)	11 (40.7%)	7 (25.9%)	9 (33.3%)	
Grade 3 (n=9)	1 (11.1%)	1 (11.1%)	7 (77.8%)	
Lymph node metastasis				
Positive (n=21)	9 (42.9%)	4 (19.0%)	8 (38.1%)	0.71
Negative (n=23)	8 (34.8%)	6 (26.1%)	9 (39.1%)	
LVI				
Positive (n=20)	7 (35%)	5 (25%)	8 (40%)	0.81
Negative (n=24)	10 (41.7%)	5 (20.8%)	9 (37.5%)	
ER/PR Status				
Positive (n=30)	14 (46.7%)	6 (20%)	10 (33.3%)	0.28
Negative (n=14)	3 (21.4%)	4 (28.6%)	7 (50%)	
HER2 Status				
Positive (n=18)	5 (27.8%)	6 (33.3%)	7 (38.9%)	0.39
Negative (n=26)	12 (46.1%)	4 (15.3%)	10 (38.4%)	
Ki-67 Index				
High (n=27)	8 (29.6%)	7 (25.9%)	12 (44.4%)	0.21
Low (n=17)	9 (52.9%)	3 (17.6%)	5 (29.4%)	

[Table/Fig-4]: Association of PDC with various clinicopathological and immunohistochemical features.
Chi-square test is used as a Statistical test and *p-value <0.05 considered as significant

Multivariable binary logistic regression was conducted to determine the independent predictors of high PDC grade, including tumour grade and TBC grade in the model. After adjustment, there was no statistically significant independent correlation between high PDC grade and either tumour grade or TBC grade. There was no discernible impact of tumour grade; the odds for Grade 1 (OR = 0.395, 95% CI: 0.014-11.369, p-value=0.588) and Grade 2 (OR = 0.272, 95% CI: 0.043–1.730, p-value=0.168) tumours were both non-significantly lower than those for Grade 3 tumours. Among TBC categories, only grade 1 TBC showed a statistically significant inverse relationship with high PDC grade (OR=0.052, 95% CI: 0.003-0.864, p-value=0.039), indicating that tumours with low TBC were less likely to exhibit high PDC. Whereas, the significance of grade 2 TBC was lost (OR=0.484,95% CI: 0.096-2.427, p-value=0.378) [Table/Fig-5].

With respect to molecular subtyping, Luminal A tumour had frequent low grade PDC (9 cases; 52.9%) whereas triple negative cases had a greater number of higher PDC grade (4 cases; 80%). Whereas HER enriched tumours had more cases of intermediate grade PDC (4 cases; 44.4%) [Table/Fig-6].

DISCUSSION

Breast carcinomas have significant morphological, hormonal, and molecular variability, resulting in varying tumour behaviour and prognosis [18]. Outcome of breast cancer is determined by various well known traditional prognostic markers like tumour grade, size, tumour type, lymph node metastasis, lymphovascular invasion [2]. However, patients with similar clinicopathological profile may behave differently. Hence additional prognostic marker may act as a supplement to the conventional markers in determining the outcome.

Tumour budding and PDCs represent the key morphological manifestation of tumour dedifferentiation and invasive potential [10,11]. Both are believed to arise from Epithelial Mesenchymal Transition (EMT), a fundamental biological process that enables the tumour cells to lose the epithelial polarity and adhesion, downregulates the molecules like E-cadherin, and acquire mesenchymal characteristics that are associated with motility and invasiveness [10,11,19,20]. Through these EMT-driven alterations, tumour cells interact with the surrounding microenvironment, promoting cellular dissociation and formation of both TBC and PDC. Together, these morphological changes reflect a more aggressive phenotype and may provide a valuable prognostic information in breast carcinoma [3,4,10-12,20].

Tumour budding is well-established prognostic marker in several carcinomas, including breast cancer [4,8,21,22]. However, it is difficult to identify the small cluster of cells, sometimes cytokeratin immunohistochemical staining is required. In this context, PDC have emerged as promising alternative [4,6,8]. Both PDC and TBC are thought to represent tumour de-differentiation and invasiveness making them valuable histological indicators in routine diagnostics. Furthermore, PDC have gained more attention as it is easy to identify the large cluster compared to tumour budding and it also considered less subjective [8].

The present study's strong association between PDC and tumour budding aligns studies by Shaik S et al., and Sun Y et al., with a p-value of 0.007 and <0.001, respectively [3,12]. Because both PDC and TBC may reflect the EMT, an important step in cancer invasion and metastasis, the relationship seems biologically possible [4,6,23]. Further on multivariate analysis, TBC showed an independent association. Grade 1 TBC showed a marked reduction in odds ratio of high PDC compared to grade 3 (OR; 0.052, p-value=0.039). Although grade 2 TBC also showed a downward trend in odds, the association did not reach statistical significance. These findings strengths the evidence that tumour budding reflect the key biological behaviour linked to cellular detachment, invasiveness and tumour progression [3,4,12,24,25].

Variable	B	SE	Wald	Df	p-value	OR (Exp(B))	95% CI for OR
Tumour grade			1.934	2	0.380	—	—
Grade 1 vs Grade 3	–0.928	1.714	0.293	1	0.588	0.395	0.014 – 11.369
Grade 2 vs Grade 3	–1.302	0.944	1.903	1	0.168	0.272	0.043 – 1.730
TBC grade			4.276	2	0.118	—	—
Grade 1 vs Grade 3	–2.966	1.439	4.249	1	0.039*	0.052	0.003 – 0.864
Grade 2 vs Grade 3	–0.726	0.823	0.779	1	0.378	0.484	0.096 – 2.427
Constant	1.439	0.844	2.908	1	0.088	4.216	—

[Table/Fig-5]: Multivariate binary logistic regression analysis of factors associated with high PDC.

Molecular subtype	PDC grade 1	PDC grade 2	PDC grade 3
Luminal A (n=17)	9 (52.9%)	3 (17.6%)	5 (29.4%)
Luminal B (n=13)	5 (38.5%)	3 (23.1%)	5 (38.4%)
HER enriched (n=9)	2 (22.2%)	4 (44.4%)	3 (33.3%)
Triple negative (n=5)	1 (20%)	0	4 (80%)

[Table/Fig-6]: Distribution of PDC among different Molecular subtype of tumours.

Tumour grade also showed a statistically significant association with PDC with a p value of 0.02 underscoring the role of PDC in determining the tumour aggressiveness.This finding was in contrast with studies by Sun Y et al., and Shaik et al, where they did not show any association with a p-value of 0.09 and 0.13, respectively [3,12]. However, on multivariate analysis, the association with the PDC grade, did not remain statistically significant. Neither grade 1 nor grade 2 demonstrated a significant difference when compared with grade 3. Although a trend toward lower odds was observed, the wide confidence intervals indicate unstable estimates, likely reflecting the limited sample size.

Although there was slight predominance of higher PDC grade in cases with positive lymphovascular invasion, the results were not statistically significant similar to study by Shaik et al., [3]. In contrast study by Sun Y et al., showed a positive association with a p value of 0.007 [12]. Similarly, lymph node metastasis also did not show any statistically significant association. However, studies by Shaik S et al,, and Sun Y et al., showed a positive association with a p-value of <0.001 [3,12]. This lack of association could be attributed to limited sample size and biological heterogeneity of breast carcinoma. Also, tumour microenvironment and stromal response might influence the cluster behaviour. Hence, larger cohort studies are required to further clarify this relationship.

Hormone receptor positivity was more frequently noted in lower PDC grade (14 cases; 46.7%) compared to higher grade (10 cases; 33.3%). However, this trend did not reach statistical significance with a p value of 0.28 similar to study by Sun Y et al., [12]. This trend suggests that PDC grading might serve as independent morphological criteria that are unrelated to hormone receptors and it might provide an additional prognostic information irrespective of hormone receptor status. However, to validate these findings larger studies with follow-up are required. HER2 expressions also did not show a statistically significant association. In contrast study by Sun et al., showed an association with a p-value of 0.003 [12].

There was an increase in trend of higher PDC grade towards the high Ki-67 expression. However, the trend did not reach the statistical significance. This indicates that PDC grade may reflect the tumour aggressiveness independent of proliferation index. Luminal A tumour which has got better prognosis had nine cases out of 17 cases (52.9%) in low PDC grade compared to five cases out of 13 cases (38.5%) in Luminal B, two cases out of nine cases (22.2%) in HER 2 enriched and only one case out of five cases (20%) in triple negative cases.

Incorporating PDC evaluation in routine histopathology reporting might improve the prognostic stratification of patients, especially in resource limited setting where there is lack of advanced molecular testing. As, it does not add extra cost to the patients and with the development of standardised criteria, it could be integrated in a synoptic reporting protocol in future.

The findings of the present study underscore the potential utility of incorporating the PDC evaluation in routine histopathology reporting of breast carcinoma. PDC grading is a simple, cost effective, and does not require any special stains or advanced molecular techniques making it more useful in limited resource setting. When it is incorporated along with conventional prognostic markers, PDC evaluation may enhance the risk stratification and helps in more robust therapeutic decision making. With further validation and development of standardised criteria, PDC has the potential to be integrated in future synoptic reporting guidelines of breast cancer.

Limitation(s)

Despite these advantages, the present study had few limitations. The sample size was less and it was single centered; did not do survival analysis.

CONCLUSION(S)

The PDC grading is a simple and cost-effective tool for assessing the tumour aggressiveness in invasive ductal carcinoma of breast on routine H&E stain. Incorporation of PDC assessment along with other parameters may enhance the risk stratification. Further, multicentric studies with long term follow-up are needed for generalisation of results. If it is proved it can be incorporated in routine synoptic reporting protocol in future.

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