

Original Article

Institutional experience with tumor budding in invasive breast carcinoma: A histopathological study of 25 cases.

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ABSTRACT

Objectives: Tumor budding, defined as single cells or small clusters (≤ 4 cells) at the invasive front of tumors, has emerged as a histopathological marker associated with epithelial-mesenchymal transition and poor prognosis in various cancers. While widely studied in colorectal cancer, its significance in breast carcinoma remains underexplored. This study aimed to evaluate the clinicopathological relevance of tumor budding in invasive breast carcinoma of no special type operated at our institute.

Material and Methods: A retrospective observational study was conducted on 25 cases of modified radical mastectomy specimens diagnosed as invasive breast carcinoma, no special type. Tumor budding was assessed on H and E-stained sections by two pathologists. Cases were categorized into low ($< 4/10$ high power field (HPF)) and high ($\geq 4/10$ HPF) budding groups. Correlations with clinicopathological parameters and immunohistochemical profiles estrogen receptor (ER), progesterone receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER-2), Ki-67 were evaluated using the chi-square test.

Results: High tumor budding was observed in 68% of cases and was significantly associated with lymphovascular invasion ($p = 0.008$), tumor necrosis ($p = 0.001$), advanced nodal stage ($p = 0.029$), and high Ki-67 index ($p = 0.024$). No significant correlation was found with age, tumor size, grade, hormone receptor status, or HER2 expression. High tumor budding was prevalent in ER-positive, HER2-negative, and Ki-67-high subtypes.

Conclusion: Tumor budding correlated with several adverse histopathological features in this exploratory study. These findings suggest that tumor budding may serve as a potential prognostic histopathological marker in invasive carcinoma, particularly in setups with limited access to molecular testing. However, larger prospective studies are warranted before considering routine incorporation into histopathological reporting.

Keywords: Breast cancer, Histopathology, Prognostic marker, Tumor budding

INTRODUCTION

Tumor budding is a histopathological feature defined by the presence of detached individual or small clusters of tumor cells at the invasive front or edge of the tumor with surrounding normal tissue. It is commonly linked to aggressive tumor behavior and poor prognosis. Tumor cells detach, lose their epithelial characteristics of cell adhesion, and gain mesenchymal properties (Epithelial-Mesenchymal transition), which in turn help the tumor cells migrate through the extracellular matrix, invade the lymphatic and/or vascular

channels, leading to metastasis, thus resulting in poor overall survival.^[1]

In 1949, Japanese researcher Imai first described tumor budding in relation to gastric cancer, initially referring to it as "sprouting" at the invasive edge of carcinomas.^[1,2] Subsequently, other researchers also discovered an association between tumor budding and prognosis in several cancers, including tongue, larynx, esophagus, and colon. Tumor budding is now regarded as an important histopathological feature for assessing the aggressiveness

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of cancers, especially colorectal cancer, where it serves as an independent adverse prognostic factor.^[3] The 2016 International Tumor Budding Consensus Conference (ITBCC) sought to standardize the pathological classification of tumor budding, defining it as isolated cancer cells or small clusters of up to four tumor cells at the invasive front.^[4] This is validated and now included as a recommended element in the College of American Pathologists (CAP) protocol reporting of colorectal cancers.

Globally, breast cancer is the most common cancer in women. In 2020, there were over 2.3 million new cases of breast cancer and 685,000 related deaths.^[5] Prognosis and treatment of breast cancer vary based on tumor subtype and grade, tumor size, lymph node status, and expression of hormone receptors. Patients with similar prognostic characteristics may still experience different clinical outcomes. Therefore, significant research efforts are needed to investigate new prognostic factors like tumor budding.

Interest in tumor budding and its clinical implications has increased significantly in recent years, with several recent studies demonstrating that high tumor budding in breast carcinoma is linked to unfavorable clinicopathological features, including tumor size, tumor differentiation, lymph node metastasis, and lymphatic or vascular invasion.^[6,7] However, the absence of a validated histological tumor budding scoring system and the lack of clinical data supporting its practical application limit the broader incorporation of tumor budding into routine histopathology reporting of breast cancers.

The objective of the study was to assess the clinicopathologic significance of tumor budding in breast carcinoma and explore its correlation with various histopathological parameters.

MATERIAL AND METHODS

This observational retrospective study was conducted in the department of histopathology over a period of 1 year, from January 2024 to December 2024.

Inclusion criteria

It includes 25 newly diagnosed female patients who underwent modified radical mastectomy (MRM) with axillary dissection and were diagnosed on histopathology as invasive breast carcinoma, no special type.

Exclusion criteria

Male patients, patients with other breast cancer subtypes, core biopsy, lumpectomy specimens, MRM done post lumpectomy, and those who received neoadjuvant chemoradiation were

excluded from our study. Clinical data such as age, laterality, tumor site, and tumor size were recorded.

Hematoxylin and Eosin (H and E) stained slides of the cases and the pathological data were retrieved from the pathology department archives. Slides were reviewed and analyzed for various histopathological parameters. A record of tumor grade using Nottingham histologic score, lymphovascular invasion, presence of tumor necrosis, axillary lymph node involvement, and pathological staging was done.

Pathological staging was done as per the eighth edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system. Immunohistochemical data of hormone status, including ER, PR, HER2/neu, and Ki67 index, were recorded. Molecular subtyping of the cases was done based on the immunohistochemistry findings.

Tumor budding

Tumor buds were defined as either a single tumor cell or a cluster of up to four cells located at the invasive front of the tumor.^[8] Microscopic visualization and tumor bud assessment were done by two pathologists independently using a standard bright field microscope (Olympus BX43, Olympus corporation, Tokyo, Japan) equipped with 4x, 10x, and 40x objectives. To assess tumor budding on H&E-stained slides, the invasive front of the tumor (hotspot) was located under a 4x objective of the microscope [Figure 1]. Within this region, tumor buds were then counted in 10 consecutive high-power fields (HPF, 40x objective, area 0.950 mm²) and the mean count per 10 high power field (HPF) was calculated in each case.

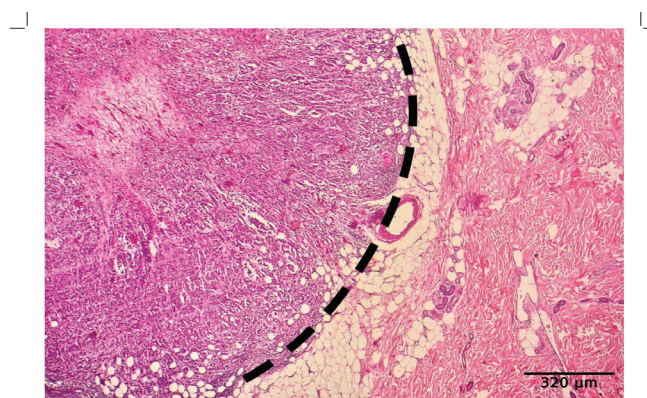


Figure 1: Hematoxylin and eosin (H and E) stain, 10x magnification. Low-power image showing the invasive tumor front with tumor cells infiltrating the surrounding stroma. Tumor buds are identified and counted at the invasive front.

Cells displaying a similar morphology to the tumor were selected for counting. Structures that resembled tumor buds,

such as peri-tumoral inflammatory cells, endothelial cells, and fibroblasts, were excluded after careful examination under high power [Figure 2]. Tumor buds bordering the ductal carcinoma in situ or confined within the retraction spaces were not counted as they did not represent true stromal invasion [Figure 3]. Tumor buds adjacent to areas showing crushing or cautery artefact and overlapped/folded tissue were excluded. Only the clearest available fields were considered. International Tumor Budding Consensus Conference (ITBCC) recommends counting tumor buds in a single hotspot using a 20x objective (field area 0.785mm²). Since our microscope lacked a 20x objective, tumor bud count was performed using the 40x objective (Field area 0.950mm²). To ensure comparability with the ITBCC reference field size, tumor bud counts obtained at 40x magnification were normalised using the ITBCC normalization table, mentioned in the CAP protocol of colorectal carcinoma.

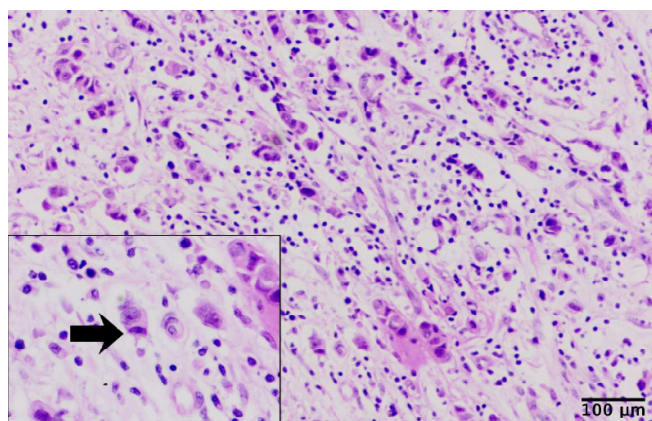


Figure 2: Hematoxylin and eosin (H and E) stain, 40× magnification. High-power image of the invasive tumor front showing tumor buds (arrow; defined as clusters of fewer than four tumor cells). Also visible are inflammatory cells, endothelial cells, and fibroblasts, which can mimic the morphology of tumor buds.

Cases were subsequently categorized into low-grade tumor buds (mean tumor buds < 4/10 HPF) and high-grade tumor buds (mean tumor buds \geq 4 /10 HPF).^[9,10] For interobserver consistency, two pathologists independently assessed the tumor budding score. Discrepant cases were jointly reviewed to reach consensus. In cases where there was a discrepancy in the tumor bud grades between the two pathologists, the slides were reviewed, and a consensus grading was given (Cohen's Kappa 0.655).

Statistical analysis

The chi-square test was utilized for statistical analysis to evaluate the associations between tumor budding, clinical characteristics, histopathological parameters, and

immunohistochemical marker expression. Fisher's exact test was applied when expected cell counts were <5. A p-value of less than 0.05 was deemed statistically significant.

Ethical approval: Ethical approval was obtained from the Institutional Ethics Committee.

RESULTS

In this study, a total of 25 cases of diagnosed invasive breast carcinoma, of no special type, were studied for tumour budding.

Female patients had a wide age distribution ranging from 33 to 73 years, with the median age being 53 years. The majority of the patients were in the age range of 41-60 years. 40% of the patients were <50 years, while 60% were > 50 years of age.

In 60% (15/25) of cases, the tumor was present on the left side of the breast, and in 40% (10/25) of cases, the tumor was on the right side of the breast.

The majority of the cases 72% (18/25), had the greatest tumour dimension of 2–5 cm (T2 stage). 28% (7/25) cases had tumor size > 5cm. There were no cases with a tumor size < 2cm.

Most tumors were grade 2 and grade 3, i.e., 44% each, while 12% were grade 1 tumors. 68% (17/25) of the tumors showed necrosis. The majority of cases showed lymphovascular invasion (72%) and had positive axillary lymph nodes (68%). Amongst the patients with axillary lymph node involvement, most were in the N2 stage (28%), followed by the N1 (24%) and the N3 (16%).

The majority were ER positive (68%), PR positive (64%), HER2 negative (92%), with a Ki67 index >15% (68%), characteristic of luminal B molecular subtype (56%). 16% of the cases were Luminal A subtype, followed by triple negative (20%) and HER-2 enriched (8%). Table 1 shows the distribution of clinicopathological parameters.

Table 1: Summarizes the clinic-pathological parameters of the cases

Parameter	Frequency (n=25)	Percentage (%)
Median age (years)	53	
Range (years)	33 - 73	
Laterality		
Right breast	10	40
Left breast	15	60
Tumor size (cms)		
<2 cm	00	00
2- 5cm	18	72
>5 cm	07	28
Mean tumor size (Mean \pm SD)	4.2 \pm 1.6	

Table 1: Contd:		
Parameter	Frequency (n=25)	Percentage (%)
Nottingham grade		
Grade 1	03	12
Grade 2	11	44
Grade 3	11	44
Lymphovascular invasion		
Present	18	72
Absent	07	28
Pathological T stage		
pT1	00	00
pT2	16	64
pT3	08	32
pT4	01	04
Axillary lymph node involvement		
Present	17	68
Absent	08	32
Axillary lymph node involvement (N stage)		
N0	08	32
N1	06	24
N2	07	28
N3	04	16
Molecular subtype		
Luminal A	04	16
Luminal B	14	56
HER-2 enriched	02	08
Triple negative	05	20
ER receptor		
Positive	17	68
Negative	08	32
PR receptor		
Positive	16	64
Negative	09	36
HER-2 receptor		
Positive	02	08
Negative	23	92
KI67 index		
<15%	08	32
>15%	17	68
Tumor necrosis		
Present	17	68
Absent	08	32
The highlighted bold value is less than 0.05, making the p value significant. ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor -2,		

Correlation of tumor budding with different parameters

The mean tumor budding was 6.43 (± 3.49), with 8 patients (32%) categorized as having low tumor budding and 17 patients (68%) as having high tumor budding [Table 2].

Table 2: Tumor budding assessment	
Tumor budding	n=25 (%)
Low	8 (32%)
High	17 (68%)

Tumor budding and its association with clinical and histopathological parameters are illustrated in Table 3.

Table 3: Association of tumor budding with clinical and histopathological parameters.			
Parameter	High tumor budding n=17	Low tumor budding n=8	p value
Age			
≤50 years	06	04	0.483
>50 years	11	04	
Laterality			
Right breast	07	03	0.86
Left breast	10	05	
Tumor size			
≤5 cm	09	07	0.09
>5 cm	08	01	
Nottingham grade			
Grade 1	01	02	0.25
Grade 2	07	04	
Grade 3	09	02	
Lymphovascular invasion			
Present	15	03	0.008
Absent	02	05	
Tumor necrosis			
Present	17	04	0.001
Absent	00	04	
Pathological T stage			
T1 and T2	09	07	0.07
T3 and T4	08	01	
Axillary lymph node involvement			
Present	13	04	0.185
Absent	04	04	
Pathological N stage			
N0 and N1	07	07	0.029
N2 and N3	10	01	

Table 3: Contd.			
Parameter	High tumor budding n=17	Low tumor budding n=8	p value
ER receptor			
Positive	12	05	0.685
Negative	05	03	
PR receptor			
Positive	10	06	0.431
Negative	07	02	
HER-2 receptor			
Positive	02	00	0.311
Negative	15	08	
KI67 index			
<15%	03	05	0.024
>15%	14	03	
Molecular subtype			
Luminal A	02	02	0.623
Luminal B	10	04	
HER2-enriched	02	00	
Triple negative	03	02	
Significance level: $p < 0.05$			

An increased number of tumor buds was found to be associated with the presence of lymphovascular invasion ($p = 0.008$), tumor necrosis ($p = 0.001$), pathological N stage ($p = 0.029$), and Ki-67 index ($p = 0.024$). High tumor budding showed a strong association with tumor necrosis (Odds ratio (OR) = 35.0; 95% Confidence interval (CI): 1.74–706.9; $p = 0.001$). A significant association was also observed between high tumor budding and lymphovascular invasion (OR = 12.5; 95% CI: 1.60–97.65; $p = 0.008$). High tumor budding additionally demonstrated a significant association with advanced pathological nodal stage (OR = 10.0; 95% CI: 1.00–100.47; $p = 0.029$). Furthermore, high tumor budding was associated with a high Ki-67 index (OR = 7.78; 95% CI: 1.17–51.92; $p = 0.024$).

No statistically significant difference was found in age, tumor size, histological grade, pathological T stage, estrogen receptor, or progesterone receptor expression between the tumor budding groups.

65% of the patients with high tumor budding were more than 50 years old. 52% of the patients with high tumor budding had tumors that were at least 5 cm in maximum dimension and were histologic grade 3. Lymphovascular invasion and axillary lymph node metastasis were closely linked in patients with high tumor budding (88% and 76% respectively). All cases (100%) with high tumor budding showed tumor necrosis.

Interestingly, qualitative assessment of the cases shows that fewer tumor-infiltrating lymphocytes and dense fibrosis were

seen in the cases with high tumor budding foci, as compared to low tumor budding cases.

High tumor budding (58%) was observed in cases with pN2 and pN3 nodal staging, while in tumor size T staging, high tumor budding (53%) was linked to pT1 and pT2. Cases that showed high tumor budding demonstrated positive expression of Estrogen receptor (71%), progesterone receptor (59%), negative expression of HER-2 receptor (88%), and KI-67 index more than 15% (82%).

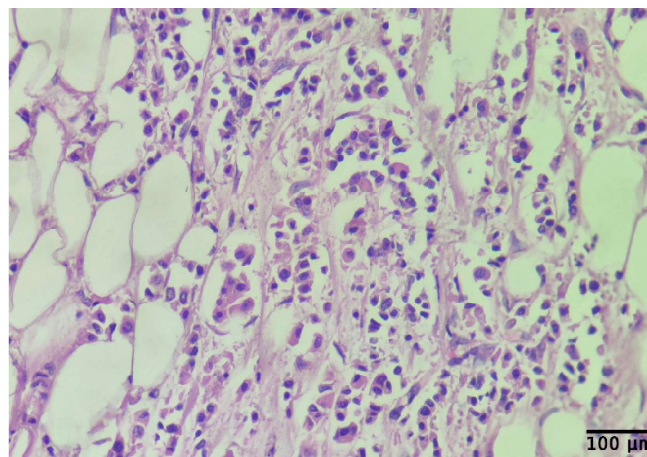


Figure 3: H and E (40x), High power image of invasive tumor front displaying tumor cells within retraction spaces. Such foci were not considered for counting tumor buds. H and E: Hematoxyline and eosin

DISCUSSION

In this retrospective observational study, we investigated the clinicopathological significance of tumor budding in invasive breast carcinoma of no special type. Our findings indicate that high tumor budding is significantly associated with adverse prognostic factors such as lymphovascular invasion, tumor necrosis, advanced nodal stage, and a high Ki-67 proliferation index. These results reinforce the growing body of evidence supporting tumor budding as a potential histopathological marker of tumor aggressiveness in breast cancer.

Tumor budding, initially described in gastric cancer by Imai in 1949^[2] was later formalized as a prognostic tool in colorectal carcinoma by the ITBCC in 2016.^[4] It has since gained recognition as a morphological correlate of epithelial-mesenchymal transition (EMT), with budding cells showing reduced adhesion and enhanced motility, favoring invasion and metastasis.^[1] While routinely assessed in colorectal cancer, its application in breast cancer is still emerging due to limited standardization and validation studies.

In our study, 68% of cases exhibited high tumor budding, which was significantly correlated with lymphovascular invasion ($p = 0.008$). This finding is consistent with previous reports by Liang *et al.* and Salhia *et al.*, who showed that tumor

budding at the invasive margin was associated with vascular and lymphatic spread in breast cancer.^[6,7] EMT, characterized by loss of E-cadherin and gain of vimentin expression, underpins this biological behavior and may explain the aggressive phenotype associated with budding cells.^[1]

We also observed a strong association between high tumor budding and tumor necrosis ($p = 0.001$). Necrosis is commonly associated with high-grade, rapidly proliferating tumors and hypoxic microenvironments. Hypoxia-inducible factors such as HIF-1 α have been implicated in driving EMT under such conditions, which could further promote tumor budding.^[11] Therefore, necrosis and budding may represent converging morphological indicators of tumor hypoxia and aggressiveness.

Another critical association was observed between tumor budding and advanced pathological nodal stage (N2 and N3) ($p = 0.029$). Lymph node metastasis remains a pivotal factor in breast cancer prognosis and treatment decisions. Previous studies have demonstrated that tumor budding is an early event in the metastatic cascade and may predict nodal involvement even before overt metastasis is histologically evident.^[9] This suggests that tumor budding could be a valuable adjunct in risk stratification, particularly in clinically node-negative patients.

Moreover, a high Ki-67 index ($>15\%$) was significantly associated with high tumor budding ($p = 0.024$). Ki-67 is a well-established marker of cellular proliferation and poor prognosis, especially in hormone receptor-positive breast cancers.^[12] The combined presence of high budding and a high Ki-67 index may signify a particularly aggressive tumor subset that warrants closer surveillance and possibly more intensive therapy.

Interestingly, while over half of the patients with high tumor budding had grade 3 tumors and larger tumor sizes (>5 cm), these associations were not statistically significant. Tumor grade, as per the Nottingham system, evaluates tubular formation, nuclear pleomorphism, and mitotic count. However, tumor budding may represent a distinct biological phenomenon not fully captured by conventional grading.^[13] This supports the view that budding should be evaluated as a separate parameter with independent prognostic significance.

No significant associations were found between tumor budding and hormone receptor status (ER/PR) or HER2 expression. A 2023 meta-analysis of 1,763 breast cancer patients showed that low-grade budding correlated significantly with the triple-negative subtype. Our findings did not mirror this subtype association, possibly due to the limited sample size or population-specific differences.^[14]

Salhia *et al.* found that high peripheral tumor budding in breast cancer, assessed using pan-cytokeratin staining,

significantly correlated with lymph node metastasis and lymphatic invasion, even in ER-positive, low proliferative tumors.^[7] Their findings support our results and suggest tumor budding's utility as an early marker of metastatic potential and as a useful addition to preoperative risk assessment.

Gabal *et al.* demonstrated that tumor budding significantly correlated with MMP-2 expression in invasive breast carcinoma, particularly in tumors with ill-defined borders and lymph node metastasis.^[15] The co-expression of tumor budding and MMP-2 highlights a possible interplay between cellular detachment, proteolysis, and ER signaling in promoting tumor invasion.

A recent study by Manimaran *et al.* further validated tumor budding's prognostic value, showing its association with advanced tumor and nodal stages, as well as systemic metastasis.^[16] Notably, grade 3 tumors with high tumor budding exhibited poorer event-free survival, reinforcing budding as a simple but potent morphological predictor of aggressive behavior in breast cancer.

From a technical perspective, our method of assessing tumor budding on H and E-stained sections was straightforward and reproducible. Nonetheless, budding can be underestimated in areas with dense stroma or inflammatory infiltrates. Studies suggest that immunohistochemical staining using pan-cytokeratin can enhance accuracy and interobserver agreement, especially in low-grade cases or those with subtle budding.^[17]

Several limitations must be acknowledged. Our study was monocentric, retrospective, and involved a modest sample size, all of which may limit the generalizability of our results. A sample size of 25 cases was determined pragmatically based on the number of eligible mastectomies during the study period. This is because the primary aim was hypothesis-generating rather than confirmatory.

Additionally, the absence of survival endpoints, disease-free survival/overall survival, precludes direct assessment of the prognostic value of tumor budding. Thus, its relevance remains inferential via associations with adverse pathological features. Some patients were lost to follow-up, precluding meaningful survival analysis. Larger, outcomes-based studies are needed to confirm its clinical utility.

The inclusion of mastectomy-only specimens introduces a potential sampling bias as smaller tumors managed by lumpectomy were excluded. The absence of a standardised consensus-based scoring system for tumor budding in breast cancer, unlike the well-established ITBCC criteria in colorectal cancer, poses a methodological limitation. Furthermore, possible preanalytical variability related to tissue fixation and processing could have influenced the microscopic assessment of tumor budding.

Nevertheless, the study adds valuable data to the limited literature on tumor budding in breast cancer, particularly from South Asian cohorts.

A key strength of this study lies in its use of a uniform histological subtype (invasive breast carcinoma, no special type), which reduced variability and allowed for focused analysis. Comprehensive assessment of histopathological and immunohistochemical parameters further enhanced the robustness of our correlations.

CONCLUSION

In summary, this retrospective, single-centre study adds to the emerging evidence supporting the role of tumor budding as a potential histopathological marker of tumor aggressiveness in breast cancer. Its significant associations with lymphovascular invasion, tumor necrosis, high Ki-67 index, and advanced nodal stage underscore its prognostic potential. However, given the limited cohort size and lack of correlation with survival outcomes, these findings should be interpreted as hypothesis-generating. Larger multicentric prospective studies are needed to validate the prognostic value before routine implementation in histopathological reporting.

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Author contributions: KS: Conceived and designed the study, analyzed and interpreted the data, and drafted the manuscript, DS: Supervised the study and critically revised the manuscript, AS: Contributed to data collection, literature review, and manuscript preparation. All authors reviewed and approved the final manuscript.

Ethical approval: Ethical approval was waived by the Institutional Ethics Committee as this was a retrospective, observational study based on archived histopathology material and did not involve any patient interaction or intervention. IEC Ref. No: DYP/IECBH/2025/145. Dated: 27/05/2025

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