Tumor Budding Grade Based on the ITBCC 2016 Criteria is Associated with Lymphovascular Invasion and Lymph Node Involvement in Invasive Breast Carcinoma

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ABSTRACT
Invasive breast carcinoma is a malignant neoplasm with metastatic potential influenced by various histopathological parameters, including tumor budding (TB). TB has emerged as a potential indicator of tumor aggressiveness; however, differences in assessment criteria may affect its clinical relevance. This study aimed to evaluate the association between TB grade and lymphovascular invasion (LVI) as well as lymph node involvement in invasive breast carcinoma using three different assessment criteria. A cross-sectional study was conducted on 44 cases of invasive breast carcinoma that met the inclusion criteria. TB was assessed at the invasive front using the International Tumor Budding Consensus Conference (ITBCC) 2016 criteria, as well as the criteria proposed by Usta et al. and Manimaran et al. LVI and lymph node status were determined through histopathological examination. The associations between variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Tumor budding grade based on one standardized assessment system demonstrated a significant association with both LVI and lymph node involvement. In contrast, the other two grading approaches did not show statistically significant associations. As conclusion, within the context of this study, the ITBCC 2016 criteria appear to be more representative in reflecting tumor invasive activity in invasive breast carcinoma. These findings support the potential role of tumor budding as an additional indicator of tumor aggressiveness and highlight the importance of standardizing its assessment method in invasive breast carcinoma.
Keywords: invasive breast carcinoma; tumor budding; lymphovascular invasion; lymph node involvement

INTRODUCTION
Invasive breast carcinoma is a malignant epithelial neoplasm characterized by the ability of tumor cells to breach the basement membrane, infiltrate surrounding stromal tissue, and disseminate through lymphatic and hematogenous pathways [1]. Globally, breast cancer represents the most frequently diagnosed malignancy among women, accounting for approximately 2.26 million new cases and more than 684,000 deaths according to GLOBOCAN 2020 [2]. In Indonesia, breast cancer likewise constitutes the most common malignancy in women and contributes substantially to cancer-related mortality, largely because many patients present at advanced stages and at a younger age compared with those in developed countries [3,4].

Comprehensive histopathological evaluation—including histologic grade, molecular subtype, lymphovascular invasion (LVI), and lymph node status—plays a central role in prognostic stratification and therapeutic decision-making [1,5]. LVI reflects an early step in the metastatic cascade and has been established as an independent predictor of recurrence and distant metastasis [6]. Similarly, lymph node involvement remains a key determinant of pathological staging and guides the selection of adjuvant therapy [5].

One microscopic parameter that has gained increasing attention as a marker of biological aggressiveness is tumor budding (TB), defined as the presence of single tumor cells or small clusters composed of up to four cells identified at the invasive front of the tumor [7–9]. TB is considered a morphological manifestation of epithelial–mesenchymal transition (EMT), a process that enhances tumor cell motility, invasiveness, and metastatic potential [10–12]. Unlike colorectal carcinoma, in which TB assessment has been standardized through the International Tumor Budding Consensus Conference (ITBCC) 2016 criteria, TB has not yet been incorporated into routine histopathological reporting for breast carcinoma. To date, no specific consensus guidelines exist for breast cancer, resulting in heterogeneity across studies with respect to magnification, counting area, scoring approach (hotspot versus cumulative), and cut-off values, thereby yielding variable findings [13,14].

In Indonesia, investigations on TB in breast carcinoma remain limited. Sriwidyani et al. (2016) reported that high-grade TB was associated with metastasis, whereas Saragih et al. (2021) observed correlations between TB, histologic grade, and LVI, but inconsistent findings regarding lymph node involvement [15,16]. These discrepancies underscore the need for further research examining the relationship between TB and established prognostic parameters in invasive breast carcinoma using multiple representative assessment criteria.

Accordingly, the present study applied three representative TB grading systems: the ITBCC 2016 criteria, Usta et al. (2025), and Manimaran et al. (2024), which reflect differences in hotspot versus cumulative assessment approaches as well as the use of 20× and 40× objectives [7,17,18]. The application of these three methods is expected to provide a more comprehensive understanding of the association between TB, LVI, and lymph node involvement, while contributing to ongoing efforts toward standardizing TB evaluation in invasive breast carcinoma.

The objective of this study was to evaluate the association between tumor budding grade—assessed using the ITBCC 2016, Usta et al., and Manimaran et al. criteria—and lymphovascular invasion as well as lymph node involvement in invasive breast carcinoma, in order to determine the most representative assessment approach for reflecting tumor invasive activity.

METHODS
This observational study was conducted at the Anatomic Pathology Laboratory of RSUP Dr. M. Djamil Padang. The study included cases examined during the period from January 2023 to June 2025. This study employed an observational analytic design with a cross-sectional approach. The objective was to evaluate the association between tumor budding (TB) grade and lymphovascular invasion (LVI), as well as lymph node involvement (LNI), in invasive breast carcinoma.

The study population consisted of all cases of invasive breast carcinoma diagnosed at the Anatomic Pathology Laboratory of RSUP Dr. M. Djamil Padang during the specified period. Sampling was performed using a total sampling method. All cases meeting the inclusion criteria and not meeting the exclusion criteria were included as study samples, resulting in a final total of 44 cases. Inclusion criteria wre all cases of invasive breast carcinoma obtained from excision, lumpectomy, or mastectomy procedures; availability of complete anatomic pathology medical records; and availability of complete hematoxylin–eosin (HE) stained slides. Meanwhile, exclusion criteria was cases meeting inclusion criteria but having received neoadjuvant chemotherapy prior to tissue sampling.

The independent variable was tumor budding (TB) grade. TB was defined as the presence of single tumor cells or small clusters consisting of up to four tumor cells at the invasive front of the tumor. TB assessment was performed using three different criteria representing variations in hotspot versus cumulative approaches and the use of 20× and 40× objective magnifications [7,17,18].
A summary of the three TB grading systems is presented in Table 1.

Table 1. Criteria for tumor budding grading used in this study [7,17,18]

Criteria	Approach	Objective magnification	Counting method	Classification
ITBCC 2016 (Lugli et al., 2017)	Single hotspot	20×	Count TB in 1 hotspot	Low (0–4 buds/0.785 mm²), intermediate (5–9 buds/0.785 mm²), high (≥10 buds/0.785 mm²)
Usta et al. (2025)	Cumulative	40×	Count TB in 10 consecutive high-power fields	Low (<15 buds/10 HPF [2.37 mm²]), high (≥15 buds/10 HPF [2.37 mm²])
Manimaran et al. (2024)	Single hotspot	40×	Count TB in 1 hotspot	Low (≤5 buds/0.196 mm²), high (>5 buds/0.196 mm²)

The dependent variables were lymphovascular invasion (LVI) and lymph node involvement (LNI). LVI was defined as the presence of tumor cells or tumor cell clusters within vascular or lymphatic lumina located in the peritumoral area. Assessment was performed on hematoxylin–eosin stained slides [6]. LNI was determined based on the presence of metastatic tumor deposits in axillary, infraclavicular, supraclavicular, and/or internal mammary lymph nodes. Histopathologic evaluation was conducted on lymph node dissection specimens according to the pN classification of the AJCC TNM 8th edition staging system [5]. LNI was categorized as negative: pN0 (no regional lymph node metastasis or only isolated tumor cells ≤0.2 mm or ≤200 cells) and positive: pN1–pN3. pN1 with metastasis in 1–3 lymph nodes; pN2 with metastasis in 4–9 lymph nodes; pN3 with metastasis in ≥10 lymph nodes; includes micrometastasis (>0.2–2 mm or >200 cells; pN1mi) and macrometastasis (>2 mm).

The research procedure began with medical record tracing to identify eligible cases. Hematoxylin–eosin slides were reviewed to confirm the representativeness of the invasive tumor front. Tumor budding was assessed according to each grading criterion. Subsequently, LVI status and lymph node involvement were evaluated. All collected data were compiled into a structured research worksheet for statistical analysis.

Statistical analysis was performed to assess the association between TB grade and LVI, as well as TB grade and LNI. The chi-square test or Fisher's exact test was applied according to the distribution and characteristics of the data. The results were presented descriptively in tabular form and analytically as measures of association with corresponding significance values.

RESULTS

Clinicopathologic characteristics of the samples

A total of 44 cases of invasive breast carcinoma met the study eligibility criteria. The distribution of clinicopathologic characteristics, including age, histologic grade, molecular subtype, LVI status, LNI and TB grade based on three different assessment criteria, is presented in Table 2. Overall, the majority of cases were in the ≤50-year age group, and the most frequent histologic grade was grade 3. Molecular subtypes were relatively evenly distributed, with the highest proportions observed in Luminal B HER2-negative, HER2-positive, and triple-negative subtypes.

Most cases demonstrated the presence of lymphovascular invasion. Lymph node involvement data were available in 33 cases, among which positive involvement was more frequent than negative. The distribution of tumor budding grades varied depending on the assessment criteria applied, reflecting methodological differences among the grading systems. Representative microscopic features of tumor budding based on the ITBCC 2016 criteria at the invasive tumor front are illustrated in Figure 1.

Morphologically, low-grade tumor budding is characterized by the presence of only a few isolated single tumor cells or small clusters of cells at the invasive front. At higher grades, there is a marked increase in the number of single tumor cells or small detached clusters dissociating from the main tumor mass within the invasive margin.

Table 2. Clinicopathologic characteristics of invasive breast carcinoma cases

Characteristic	Category	Frequency	Percentage
Age	≤ 50 years	23	52.3
	> 50 years	21	47.7
Histologic grade	Grade 1	1	2.3
	Grade 2	19	43.2
	Grade 3	24	54.5
Molecular subtype	Luminal A	3	6.8
	Luminal B HER2-negative	11	25.0
	Luminal B HER2-positive	6	13.6
	HER2-positive	11	25.0
	Triple-negative	11	25.0
LVI	Negative	14	31.8
	Positive	30	68.2
LNI	Negative	11	22.4 (33.3*)
	Positive	22	44.9 (66.7*)
TB grade (ITBCC 2016 criteria)	Low	12	27.3
	Intermediate	14	31.8
	High	18	40.9
TB grade (Usta et al. criteria)	Low	10	22.7
	High	34	77.3
TB grade (Manimaran et al. criteria)	Low	20	45.5
	High	24	54.5

*Percentages in parentheses are calculated based on the 33 cases with available lymph node data

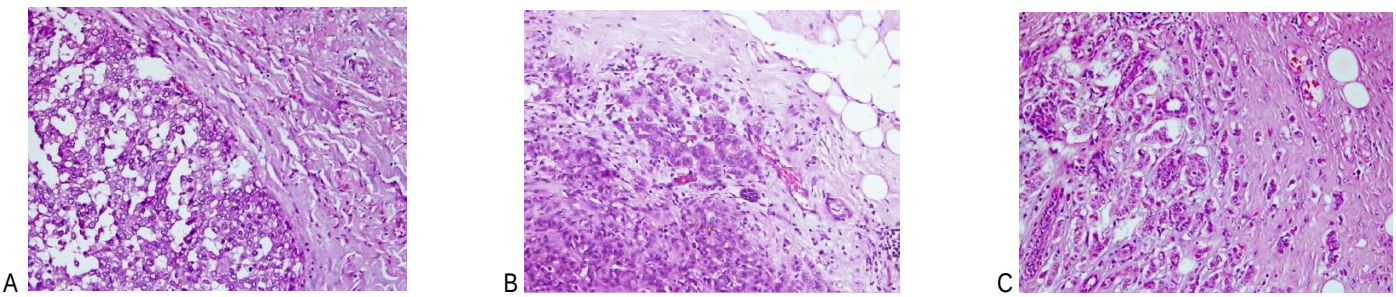

Figure 1. Tumor budding grades in invasive breast carcinoma based on the ITBCC 2016 criteria. A: low grade (0–4 buds per 0.785 mm²); B: intermediate grade (5–9 buds per 0.785 mm²); C: high grade (≥10 buds per 0.785 mm²). Hematoxylin–eosin (H&E) staining, original magnification ×200.

Association between tumor budding grade and lymphovascular invasion

The relationship between tumor budding (TB) grade and lymphovascular invasion (LVI) was analyzed using three different TB assessment criteria. The results based on the ITBCC 2016, Usta et al., and Manimaran et al. criteria are presented in Table 3, Table 4, and Table 5, respectively. Overall, a consistent pattern was observed in which the proportion of LVI-positive cases increased with higher TB grades. However, the strength and statistical significance of this association varied according to the assessment method, with only the ITBCC 2016 criteria demonstrating a statistically significant relationship.

Table 3. Association between TB grade (ITBCC 2016 criteria) and LVI

TB Grade (ITBCC 2016 criteria)	LVI negative	LVI positive	p-value
Low (0–4 buds/0.785 mm²)	7 (58.3%)	5 (41.7%)	0.024
Intermediate (5–9 buds/0.785 mm²)	5 (35.7%)	9 (64.3%)	
High (≥10 buds/0.785 mm²)	2 (11.1%)	16 (88.9%)	

Table 4. Association between TB grade (Usta et al. criteria) and LVI

TB Grade (Usta et al. criteria)	LVI negative	LVI positive	p-value
Low (<15 buds/2.37 mm²)	5 (50.0%)	5 (50.0%)	0.247
High (≥15 buds/2.37 mm²)	9 (26.5%)	25 (73.5%)	

Table 5. Association between TB grade (Manimaran et al. criteria) and LVI

TB Grade (Manimaran et al. criteria)	LVI negative	LVI positive	p-value
Low (≤5 buds/0.196 mm²)	9 (45.0%)	11 (55.0%)	0.087
High (>5 buds/0.196 mm²)	5 (20.8%)	19 (79.2%)	

Association between tumor budding grade and lymph node involvement

The association between tumor budding (TB) grade and lymph node involvement (LNI) was analyzed in cases with complete lymph node data. The results according to the ITBCC 2016, Usta et al., and Manimaran et al. criteria are presented in Table 6, Table 7, and Table 8, respectively. Overall, the proportion of lymph node involvement tended to be higher in cases with high tumor budding grades. However, the strength and statistical significance of the association varied across assessment methods, with only the ITBCC 2016 criteria demonstrating a statistically significant relationship.

Table 6. Association between TB grade (ITBCC 2016 criteria) and LNI

TB Grade (ITBCC 2016 criteria)	LNI negative	LNI positive	p-value
Low (0–4 buds/0.785 mm²)	4 (50.0%)	4 (50.0%)	0.049
Intermediate (5–9 buds/0.785 mm²)	5 (55.6%)	4 (44.4%)	
High (≥10 buds/0.785 mm²)	2 (12.5%)	14 (87.5%)	

Table 7. Association between TB grade (Usta et al. criteria) and LNI

TB Grade (Usta et al. criteria)	LNI negative	LNI positive	p-value
Low (<15 buds/2.37 mm²)	1 (25.0%)	3 (75.0%)	1.000
High (≥15 buds/2.37 mm²)	10 (34.5%)	19 (65.5%)	

Table 8. Association between TB grade (Manimaran et al. criteria) and LNI

TB Grade (Manimaran et al. criteria)	LNI negative	LNI positive	p-value
Low (≤5 buds/0.196 mm²)	6 (42.9%)	8 (57.1%)	0.459
High (>5 buds/0.196 mm²)	5 (26.3%)	14 (73.7%)	

DISCUSSION

The findings of this study demonstrate a statistically significant association between TB grade and both LVI and LNI when assessed using the ITBCC 2016 criteria, whereas the two alternative criteria did not yield statistically significant relationships. These results suggest that, within the context of this study, the single-hotspot approach recommended by ITBCC may be more representative in capturing invasive tumor activity at the advancing tumor front. The invasive margin is widely recognized as a biologically dynamic area in which tumor–stromal interactions and cellular dissociation actively occur, thereby rendering hotspot-based evaluation particularly relevant for identifying the most aggressive foci of tumor behavior.

From a biological perspective, the observed association between high TB grade and both LVI and LNI can be explained through the mechanism of epithelial–mesenchymal transition (EMT). EMT involves phenotypic reprogramming of epithelial tumor cells into a more mesenchymal state, enhancing their migratory capacity, reducing intercellular adhesion, and facilitating invasion through the basement membrane into surrounding stroma and vascular structures. This process is characterized by the loss of epithelial markers such as E-cadherin, increased expression of mesenchymal proteins including vimentin and N-cadherin, and activation of transcription factors such as SNAIL, SLUG, and TWIST [9–11]. These molecular alterations promote tumor cell detachment from the primary mass, stromal infiltration, and entry into lymphatic or blood vessels, thereby providing a mechanistic explanation for the consistent trend toward higher LVI positivity in tumors with high TB grades as reported in multiple studies [9–11].

The differences in results across TB assessment criteria in this study highlight the critical importance of methodological considerations in TB evaluation. Manimaran et al. reported that the use of a smaller field area with a two-tier categorization system demonstrated a tendency toward association between TB and primary tumor stage and lymph node metastasis, yet no statistically significant relationship with LVI was observed [17]. Together with reports by Koelzer and Buch et al., these findings reinforce the notion that variations in observational area, hotspot versus cumulative approaches, and grading thresholds may substantially influence the sensitivity of tumor bud detection and contribute to discrepancies among studies [13,19]. Differences in magnification, field size, and bud-counting strategy may alter the number of buds identified, thus affecting statistical associations with established prognostic parameters.

The present results are consistent with several previous investigations examining TB in relation to regional spread in invasive breast carcinoma. Sriwidyani et al. reported a strong association between high-grade TB and lymph node metastasis, whereas Saragih et al. identified a relationship between TB, LVI, and high histologic grade but did not observe a significant association with lymph node involvement [15,16]. Such variability further emphasizes that interpretation of TB in relation to tumor aggressiveness and metastatic potential is highly dependent on the assessment methodology employed [13].

The observed differences among criteria in this study underscore the urgent need for standardization of TB assessment in breast carcinoma [13,19]. The ITBCC method, which utilizes a single hotspot at the invasive front with standardized area calibration, may offer greater stability and reproducibility. In contrast, cumulative multi-field approaches such as those proposed by Usta et al. may introduce greater variability due to morphological heterogeneity within the tumor [7,13, 20]. Although Martínez-Ciarpaglini et al. demonstrated in colorectal carcinoma that evaluation across multiple high-power fields can improve risk stratification accuracy, anatomical and invasion pattern differences between colorectal and breast carcinomas limit the direct extrapolation of these findings to breast cancer. Invasive breast carcinoma typically exhibits a radial growth pattern originating from the ductolobular unit, with a more irregular and heterogeneous tumor front, which may render a focused hotspot approach more representative of peak invasive activity [1, 20].

Furthermore, the Manimaran et al. method, which employs a smaller hotspot area and a lower threshold for categorization, may present limitations in terms of count stability and interobserver reproducibility. Karamitopoulou et al. reported lower intraclass correlation coefficients in methods using narrower fields of observation, indicating reduced reliability in bud quantification under such conditions [14,17, 21]. Collectively, the findings of the present study support the potential applicability of the ITBCC 2016 criteria as a more representative and methodologically robust approach for TB evaluation in invasive breast carcinoma, although further multicenter validation studies are warranted.

Several limitations should be acknowledged. The sample size was relatively small, and interobserver agreement analysis was not performed, which may affect reproducibility assessment. Immunohistochemical evaluation of EMT-related markers was not conducted, precluding direct molecular correlation with morphological TB findings. Additionally, long-term clinical outcomes such as recurrence-free survival and overall survival were not analyzed, limiting prognostic extrapolation. The study also did not exclude cases with lobular components; given that the infiltrative growth pattern of invasive lobular carcinoma may mimic tumor budding on hematoxylin–eosin sections, potential overestimation of TB cannot be entirely excluded [1]. These limitations should be considered when interpreting the findings and may serve as a foundation for future research aimed at refining and standardizing TB assessment in invasive breast carcinoma.

CONCLUSION

This study demonstrated that the association between tumor budding grade and both lymphovascular invasion and lymph node involvement reached statistical significance when assessed using the ITBCC 2016 criteria, whereas no significant associations were observed with the other two evaluation methods. These findings suggest that, in this context, the single-hotspot approach with a standardized observation area as applied in the ITBCC 2016 criteria may be more representative in capturing invasive activity at the tumor front of invasive breast carcinoma.

Overall, the results support the role of TB as an additional indicator of biological aggressiveness associated with tumor invasion and regional spread. Further studies with larger sample sizes, interobserver agreement analysis, incorporation of immunohistochemical markers of epithelial–mesenchymal transition, and long-term clinical outcome evaluation are warranted to strengthen the prognostic value of TB and to advance the standardization of its assessment in invasive breast carcinoma.

Ethical consideration, competing interest and source of funding

-This study received ethical approval from the Research Ethics Committee of RSUP Dr. M. Djamil Padang. Ethical clearance number was DP.04.03/D.XVI.10.1/410/2025. All research procedures were conducted in accordance with applicable ethical standards, ensuring confidentiality of patient data and compliance with institutional regulations.
-There is no conflict of interest related to this publication.
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