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Seeds of invasion in a field of immunity inside the tumor microenvironment: an H&E-based evaluation of stromal TIL density and tumor budding in colorectal carcinoma

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Abstract

Background Colorectal carcinoma (CRC) is a major cause of cancer-related morbidity and mortality worldwide. Stromal tumor-infiltrating lymphocytes (TILs), an important component of the tumor microenvironment, have emerged as potential modulators of tumor behavior. Their relationship with tumor budding and other histopathological indicators of aggressiveness remains incompletely understood. The objectives of the study were to evaluate the association between stromal TIL density and clinicopathological parameters, including tumor budding and metastatic indicators, in colorectal carcinoma.

Materials and methods This retrospective study included 35 histologically confirmed cases of colorectal carcinoma. Resection specimens were examined on routine H&E-stained sections. Stromal TILs were assessed according to the International Immuno-Oncology Biomarker Working Group guidelines and categorized as low (< 50%) or high (≥ 50%) density, a threshold applied for descriptive dichotomization in this exploratory cohort in the absence of a cut-off specifically validated for colorectal carcinoma. Tumor budding was assessed at the invasive front according to International Tumor Budding Consensus Conference (ITBCC) 2016 criteria. Associations between TIL density and clinicopathological variables, including tumor grade, stage, nodal status, lymphovascular invasion (LVI), perineural invasion (PNI), depth of invasion, tumor side, and tumor budding, were analyzed using Fisher's exact test. A p-value < 0.05 was considered statistically significant.

Results The mean patient age was 50.2 years. Most tumors were moderately differentiated adenocarcinomas and predominantly right-sided. Stromal TIL density was low (< 50%) in 22 cases (62.9%) and high (≥ 50%) in 13 cases (37.1%). High stromal TIL density showed significant associations with lower tumor grade, absence of lymphovascular invasion, absence of perineural invasion, and lower tumor budding **on univariate analysis.**

Conclusion In this small, single-institution cohort, high stromal TIL density was associated with less aggressive histopathological features, including lower tumor grade and reduced tumor budding, lymphovascular invasion and perineural invasion. H&E-based assessment of stromal TILs may represent a simple, reproducible morphological

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parameter warranting further validation as an adjunct marker of tumor aggressiveness in CRC, pending confirmation in larger, prospective, multi-institutional cohorts with outcome data.

Keywords Tumor-infiltrating lymphocytes, Colorectal carcinoma, Tumor budding, Lymphovascular invasion, Tumor microenvironment

Introduction

Colorectal carcinoma (CRC) remains one of the most prevalent malignancies and continues to be a leading cause of cancer-related morbidity and mortality globally. According to GLOBOCAN 2022, CRC is the third most frequently diagnosed cancer accounting for 9.6% of all new cancer cases, and the second leading cause of cancer-related deaths globally. The global burden is projected to rise with an estimated 3 million new cases and 1.5 million deaths annually by 2040 (Bray et al. 2024). Despite advances in screening strategies, surgical techniques and systemic therapies, clinical outcomes vary considerably even among patients with tumors of similar stage (Wang et al. 2025). Traditional prognostic parameters such as tumor stage, grade, lymphovascular invasion and nodal status remain fundamental, however they do not fully explain the biological heterogeneity observed in colorectal carcinoma. This has prompted increasing interest in tumor-associated biological factors that reflect host-tumor interactions (Cotan et al. 2024).

The tumor microenvironment has emerged as a critical determinant of tumor progression. Tumor-infiltrating lymphocytes (TILs) represent the host immune response against cancer cells and serve as morphological markers for anti-tumor immunity (Cotan et al. 2024). In CRC, global evidence indicates that high density lymphocytic infiltrate is associated with reduced metastatic risk and more favorable clinical behavior, highlighting the importance of immune surveillance in colorectal carcinogenesis (Markowski et al. 2022).

CRC demonstrates immunological heterogeneity. Tumors with mismatch repair deficiency and microsatellite instability exhibit a high mutational burden leading to increased neoantigen formation and lymphocytic infiltration. These tumors have been associated with improved clinical outcomes compared to microsatellite-stable counterparts. However, variability in immune infiltration may also be seen in microsatellite-stable CRCs, suggesting that TIL density is biologically and clinicopathologically relevant beyond molecular subtypes alone (Li et al. 2024).

Although both intraepithelial and stromal TILs carry prognostic significance in colorectal carcinoma, and intraepithelial TILs have specifically been reported to show an inverse association with tumor budding, the present study focused on stromal TILs because they can be more readily and reproducibly quantified at low-to-medium magnification on routine H&E sections, without the need to individually score lymphocytes within tumor-cell nests. This makes stromal TIL assessment particularly well suited to settings, such as ours, where immunohistochemical or molecular characterization of the immune infiltrate is not always available. Data specifically addressing the relationship between stromal TIL density and tumor budding remain limited in Indian colorectal carcinoma cohorts, which the present study sought to address.

Tumor budding is defined as the presence of singly scattered or small clusters of tumor cells at the invasive front and is increasingly recognized as a marker of epithelial-mesenchymal transition and aggressive tumor behavior. High tumor budding is associated with increased invasiveness, lymphovascular spread and nodal metastasis. Tumor budding reflects early steps of metastatic dissemination (Shah et al. 2022). Therefore evaluating its relationship with stromal immune infiltration may provide insight into the interplay between tumor aggressiveness and host immune response.

The assessment of stromal TILs offers several advantages. It can be performed on routine H&E stained sections, requires no additional cost and is easily applicable in resource-limited settings (Hendry et al. 2017). International efforts have sought to standardize TIL evaluation and immune-based scoring systems have been proposed but the incorporation of H&E-based stromal TIL assessment into routine reporting of CRC remains inconsistent, particularly in real-world practice and in Indian cohorts where data remains limited.

The present study was undertaken to evaluate stromal TIL density in colorectal carcinoma using an H&E-based approach to analyze their association with clinicopathological parameters like tumor budding and other metastatic indicators. This study aims to explore the potential of stromal TIL density as an accessible and reproducible marker of tumor aggressiveness in colorectal carcinoma.

The present study aimed to evaluate the association between stromal tumor-infiltrating lymphocyte (TIL) density and clinicopathological parameters in colorectal carcinoma with particular emphasis on tumor budding and metastatic indicators such as nodal status, lymphovascular invasion and perineural invasion. The study also sought to assess the applicability of H&E-based stromal TIL evaluation as a practical morphological marker of tumor aggressiveness.

Materials and methods

This retrospective observational study was conducted in the Department of Pathology at Vardhman Mahavir Medical College and Safdarjung Hospital between February 2025 and January 2026. It included histologically confirmed cases of colorectal carcinoma diagnosed during the study period. A total of 35 resection specimens of colorectal adenocarcinoma were included. Cases were selected based on availability of adequate tumor tissue for histopathological evaluation. Patients who had received neoadjuvant chemotherapy or radiotherapy prior to surgery, as well as cases with inadequate tissue or recurrent tumors, were excluded from the study.

All specimens were fixed in 10% neutral buffered formalin, routinely processed, and stained with H&E. Tumors were classified according to the World Health Organization (WHO) classification of tumors of the digestive system. Clinicopathological parameters including age, gender, tumor location, histological subtype, tumor grade, depth of invasion, lymphovascular invasion (LVI), perineural invasion (PNI), nodal status and tumor stage were recorded. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) TNM classification.

Tumor budding was defined and assessed according to the International Tumor Budding Consensus Conference (ITBCC) 2016 criteria, as the presence of isolated single tumor cells or small clusters of up to four tumor cells at the invasive front (Shah et al. 2022, Lugli et al. 2022). Assessment was performed on H&E-stained sections by identifying the area of highest budding density (hotspot) at ×10 magnification, normalized to a standard field area of 0.785 mm^2, followed by bud counting at higher magnification within this hotspot. Tumors were classified as Bd1 (0–4 buds, low), Bd2 (5–9 buds, intermediate) and Bd3 (≥10 buds, high) per ITBCC criteria. For statistical analysis, Bd2 and Bd3 (intermediate and high budding) were combined into a single intermediate/high group and compared with Bd1 (low budding), given the limited sample size in individual tiers; the original three-tier distribution is provided in the Results.

Stromal tumor-infiltrating lymphocytes (TILs) were evaluated on H&E-stained sections in accordance with the recommendations of the International Immuno-Oncology Biomarker Working Group. Each slide was initially scanned at low magnification (×4 or ×10) to identify representative tumor areas. Stromal TILs were then assessed at higher magnification (×40) and quantified as the percentage of stromal area occupied by mononuclear inflammatory cells. Areas of necrosis, crush artifact, abscess formation and non-tumor-associated inflammation were excluded from evaluation. TIL density was categorized into low (<50%) and high (≥50%) groups for statistical analysis. This 50% threshold was applied for descriptive dichotomization in the present exploratory cohort; it was not derived from a cut-off independently validated for colorectal carcinoma. Notably, prior studies applying the International TILs Working Group system in CRC have used three-tier stratification (e.g., low 0–10%, intermediate 15–50%, high 55–100%) rather than a single 50% dichotomy (Lugli et al. 2022). In the absence of an established biological or clinical threshold for stromal TIL density specific to CRC, the cut-off used here should be regarded as empirically selected for this cohort, and the associated findings should be interpreted as hypothesis-generating rather than as validation of a specific clinical threshold.

Mismatch repair (MMR) protein expression (MLH1, PMS2, MSH2 and MSH6) was assessed by immunohistochemistry in a subset of cases in which additional tumor tissue was available. MMR status was classified as proficient (pMMR) or deficient (dMMR) based on complete loss of nuclear expression of one or more MMR proteins in tumor cells, with appropriate internal controls. Cases with non-contributory or technically inadequate staining were excluded from MMR-based analysis. Because of the limited number of evaluable cases, MMR immunohistochemistry status could not be reliably incorporated as a covariate in the statistical analysis of stromal TIL density and is reported descriptively only.

Statistical analysis was performed using latest SPSS software. Associations between stromal TIL density and clinicopathological parameters were analyzed using Fisher's exact test. A P-value of less than 0.05 was considered statistically significant. Given the number of clinicopathological variables tested against TIL density in a cohort of 35 cases, p-values were not adjusted for multiple comparisons; results should therefore be interpreted as exploratory.

Results

A total of 35 cases of colorectal carcinoma were included in the study. The mean age of the patients was 50.2 years.

The distribution of stromal TIL density showed a clear predominance of low TIL infiltration, defined as <50% stromal area occupied by lymphocytes, observed in 22 cases (62.9%) of cases. In contrast, high TIL density, defined as ≥50% stromal lymphocytic infiltration, was present in 13 cases (37.1%) of tumors. Figure 1 represents the distribution of TILs amongst the cases.

Most patients were aged ≤60 years, with no significant age-based clustering observed between TIL groups.

With respect to tumor location, the majority of cases involved the right colon ($n = 19$, 54.3%), followed by the left colon ($n = 14$, 40.0%) and transverse colon ($n = 2$, 5.7%). No statistically significant association was observed between tumor side and stromal TIL density ($p = 0.381$).

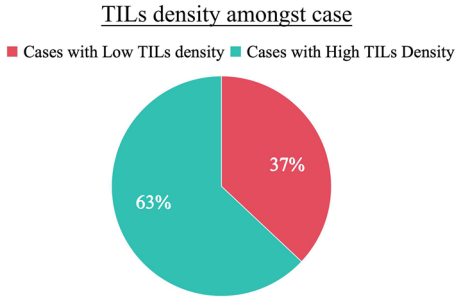


Fig. 1 The distribution of TILs amongst the cases

Histologically, most tumors were conventional adenocarcinomas ($n = 27$, 77.1%) while three cases (8.6%) demonstrated mucinous differentiation. Tumor grading revealed that 26 cases (74.3%) were moderately differentiated, four cases (11.4%) were well differentiated and five cases (14.3%) were poorly differentiated. A statistically significant association was observed between tumor grade and stromal TIL density ($p = 0.007$), with higher TIL density more frequently observed in lower-grade tumors. Figure 2A and B illustrate low and high stromal TIL density.

On pathological staging, six cases (17.1%) were classified as T1–T2, whereas the majority ($n = 29$, 82.9%) were categorized as T3–T4. No statistically significant association was found between tumor stage and stromal TIL density ($p = 0.648$). Similarly, depth of invasion did not show a significant correlation with TIL density.

Lymph node metastasis was identified in 15 cases (42.9%) while 20 cases (57.1%) were node negative. No statistically significant association was observed between nodal status and stromal TIL density ($p = 0.560$). Although high TIL density was observed in a subset of node-negative tumors, this distribution did not reach statistical significance.

Lymphovascular invasion (LVI) was present in 19 cases (54.3%), whereas 16 cases (45.7%) showed no evidence of

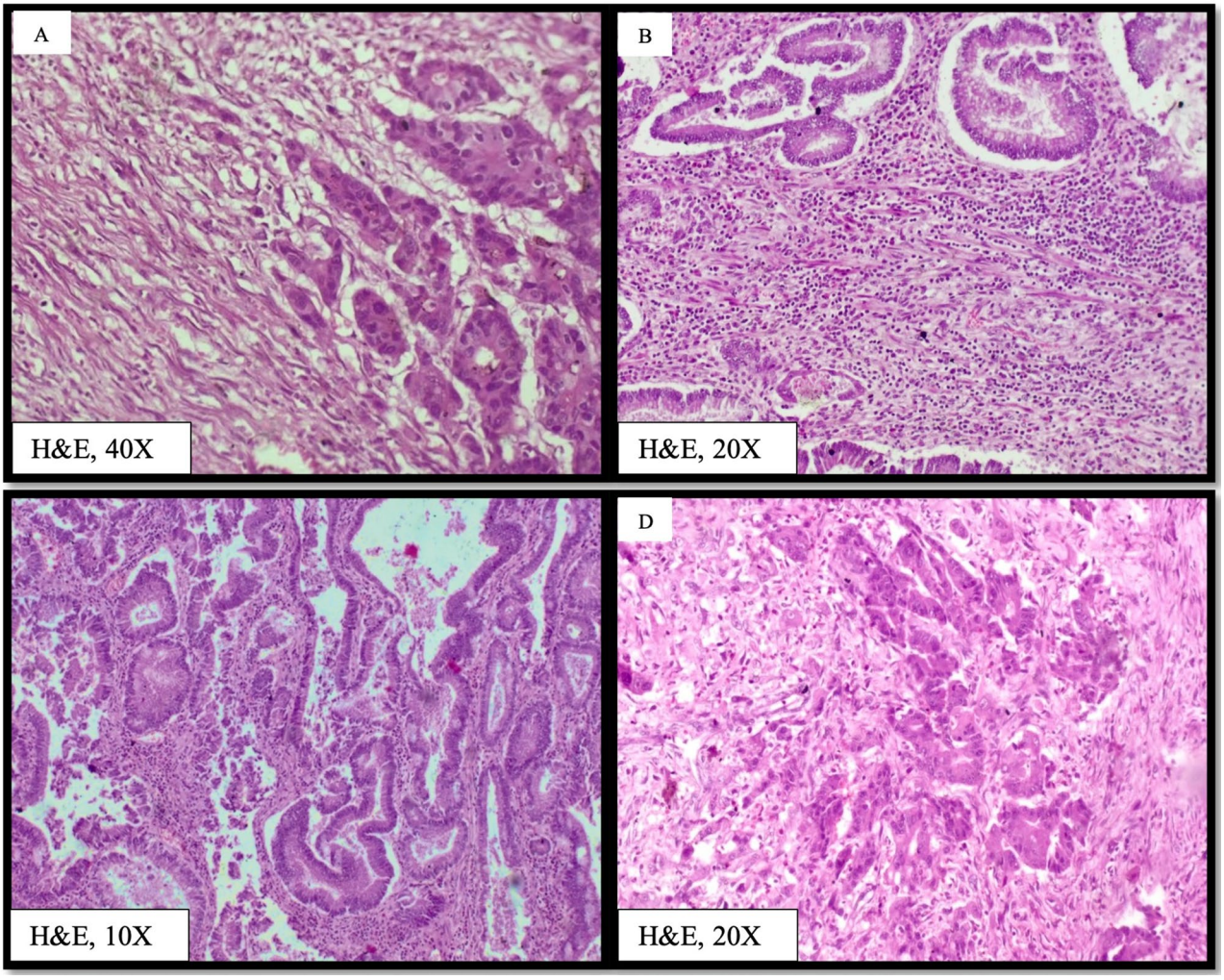


Fig. 2 Histopathological evaluation from tumor sections. A: Low stromal TIL density (< 50%). **B**: High stromal TIL density (≥ 50%). **C**: Well differentiated tumor with high stromal TIL density. **D**: Poorly differentiated tumor with low stromal TIL density

LVI. A statistically significant association was observed between stromal TIL density and lymphovascular invasion ($p = 0.006$), with high TIL density more frequently associated with absence of LVI. Similarly, perineural invasion (PNI) was identified in eight cases (22.9%), while 27 cases (77.1%) showed no evidence of PNI. High stromal TIL density demonstrated a statistically significant association with absence of perineural invasion ($p = 0.047$).

Using the ITBCC three-tier system prior to dichotomization, tumor budding was categorized as Bd1 (low) in 13 cases (37.1%), Bd2 (intermediate) in 13 cases (37.1%), and Bd3 (high) in 9 cases (25.7%). Bd2 and Bd3 were combined ($n = 22$, 62.9%) for statistical comparison with Bd1, given the limited sample size within individual tiers. A statistically significant inverse association was demonstrated between stromal TIL density and tumor budding ($p = 0.041$). Tumors exhibiting high stromal TIL density showed reduced tumor budding, whereas intermediate/high budding was more frequently observed in tumors with low TIL density, an association that is reported here as descriptive rather than causal (see Discussion). Figure 3A and B illustrate a tumor exhibiting tumor budding.

Mismatch repair (MMR) protein expression (MLH1, PMS2, MSH2 and MSH6) was assessed by immunohistochemistry in a subset of cases in which additional tumor tissue was available. MMR IHC was performed in 15 of the 35 cases (42.9%). Expression of all four MMR proteins was retained (proficient, pMMR) in 10 of these 15 cases (66.7%), while loss of nuclear expression of one or more MMR proteins (deficient, dMMR) was identified in the remaining 5 cases (33.3%), with appropriate internal controls. Because MMR IHC was not performed in the remaining 20 cases and the evaluable subset was limited, MMR/MSI status could not be reliably incorporated as a covariate in the statistical analysis of stromal TIL density and is reported descriptively only.

No statistically significant association was observed between stromal TIL density and patient age ($p = 0.689$) or gender ($p = 0.737$), and none was observed with tumor stage, nodal status or tumor side (see Table 1). These findings suggest that, within this cohort, the associations between stromal TIL density and tumor grade, LVI, PNI and tumor budding are not simply attributable to demographic factors, although residual confounding cannot be excluded given the sample size. Table 1 represents univariate analysis and p-values of various parameters with TIL density.

Discussion

The present study evaluated the association between stromal tumor-infiltrating lymphocyte (TIL) density and clinicopathological parameters in colorectal carcinoma with particular emphasis on tumor budding and metastatic indicators. Our findings demonstrate an inverse association between high stromal TIL density and lymphovascular invasion, perineural invasion and tumor budding. These findings suggest a dynamic interplay within the tumor microenvironment, in which invasive tumor budding is more frequently observed in the relative absence of dense stromal immune infiltration; however, given the retrospective, cross-sectional design of this study, a causal or directional relationship cannot be established from these data.

The tumor microenvironment plays a critical role in colorectal carcinogenesis and immune infiltration represents a key component of host-tumor interaction. Stromal TILs reflect the host immune response against neoplastic cells and have been proposed as a barrier to tumor dissemination (Li et al. 2022). In the present study, high TIL density was significantly associated with absence of perineural invasion and lower tumor grade. This association is consistent with, but does not prove, the hypothesis that tumors with a stronger immune microenvironment have

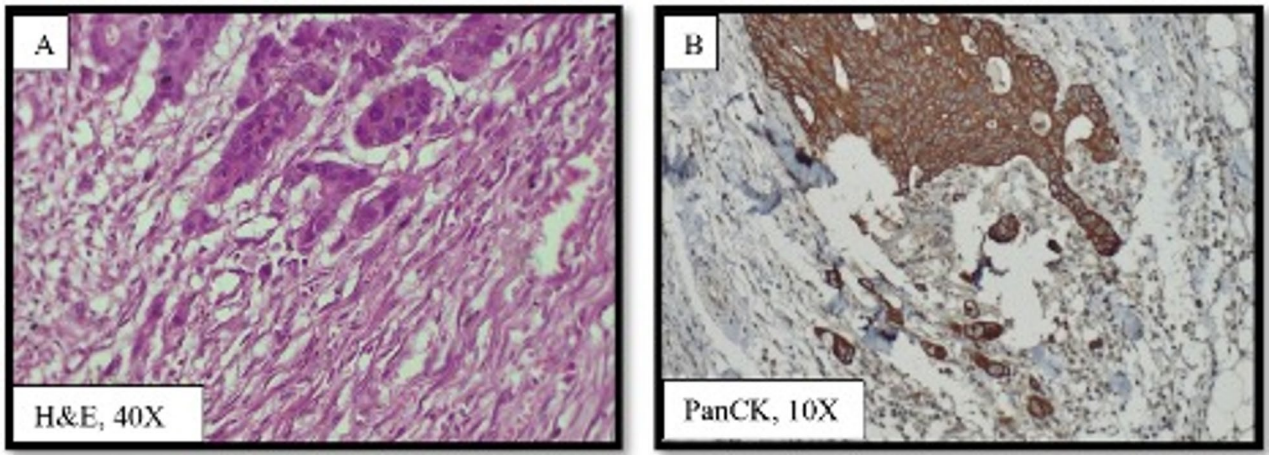


Fig. 3 Histopathological examination. **A**: Tumor budding. **B**: Tumor budding on immunohistochemistry

Table 1 Univariate analysis and p-values of various parameters with TIL density. Row and column labels updated for the tumor-budding tier terminology (Bd1/Bd2/Bd3, ITBCC 2016) are shown in bold as changes from the original table

Parameter	TIL Low (< 50%) (*n* = 22)	TIL High (≥ 50%) (*n* = 13)	*p*-value
Age			0.689
≤ 60 years (*n* = 28)	17	11	
> 60 years (*n* = 7)	5	2	
Gender			**0.737**
Male (*n* = 20)	12	8	
Female (*n* = 15)	10	5	
Tumor Side			**0.381**
Right (*n* = 19)	11	8	
Left + Transverse (*n* = 16)	11	5	
Tumor Stage			**0.648**
T1–T2 (*n* = 6)	3	3	
T3–T4 (*n* = 29)	19	10	
Grade			**0.007**
Grade 1 (*n* = 4)	0	4	
Grade 2 (*n* = 26)	17	9	
Grade 3 (*n* = 5)	5	0	
Nodal Status			**0.560**
N0 (*n* = 20)	12	8	
N+ (*n* = 15)	10	5	
Lymphovascular Invasion			**0.006**
Present (*n* = 19)	16	3	
Absent (*n* = 16)	6	10	
Perineural Invasion			**0.047**
Present (*n* = 8)	8	0	
Absent (*n* = 27)	14	13	
Tumor Budding (Bd1 vs. Bd2/Bd3)			**0.041**
Bd1 – Low (*n* = 13)	5	8	
Bd2/Bd3 – Intermediate/High (*n* = 22)	17	5	

Note: Before dichotomization, tumor budding was distributed across the three ITBCC tiers as Bd1 = 13 (37.1%), Bd2 = 13 (37.1%) and Bd3 = 9 (25.7%); Bd2 and Bd3 were combined into the intermediate/high group (*n* = 22) shown above for statistical analysis

reduced metastatic potential through immune-mediated containment of tumor spread; an equally plausible explanation is that less biologically aggressive tumors independently elicit both lower-grade morphology and greater immune infiltration.

A particularly important finding of our study is the significant inverse association between stromal TIL density and tumor budding. Tumor budding, characterized by isolated single cells or small clusters at the invasive front, is considered an early event in metastatic dissemination. High tumor budding has been associated with increased invasiveness, lymphovascular invasion and nodal metastasis (Shah et al. 2022). The predominance of intermediate/high tumor budding in tumors with low stromal TIL density suggests that the earliest morphological steps of invasion may occur when the local immune response is diminished. Conversely, increased stromal immune infiltration may suppress tumor budding, which could limit local invasion (Li et al. 2024). As above, the present associative, single-timepoint data cannot distinguish this from the alternative possibility that a common underlying tumor biology independently drives both lower budding and higher TIL density.

In addition to tumor budding, significant associations were observed between high TIL density and absence of lymphovascular and perineural invasion. Both LVI and PNI are established markers of aggressive tumor behavior and are strongly linked to metastasis. The inverse relationship observed in this study is in keeping with prior reports and adds to the hypothesis that stromal immune infiltration may be associated with a less invasive tumor phenotype in colorectal carcinoma; however, this study was not designed or powered to test a protective or causal effect, and prospective validation is required (Jakubowska et al. 2019).

Tumor grade demonstrated a statistically significant association with stromal TIL density. All poorly differentiated (Grade 3) tumors in the present study exhibited low TIL density, whereas well-differentiated tumors were predominantly associated with high immune infiltration. This observation is consistent with prior reports linking tumor dedifferentiation and reduced immune infiltration,

although the small number of Grade 1 ($n = 4$) and Grade 3 ($n = 5$) cases in this cohort limits the precision of this estimate (Fuchs et al. 2020).

No statistically significant association was identified between stromal TIL density and tumor stage, age, gender or tumor side. The absence of correlation with tumor stage may be due to the predominance of advanced T3–T4 tumors in our cohort, which reduced discriminatory power. Nodal metastasis represents a complex, multistep biological process involving tumor survival, immune escape and successful colonization at distant sites, and stromal TIL density may primarily reflect local immune dynamics within the primary tumor microenvironment (Ji et al. 2023). The relatively small sample size may also have limited the ability to detect more subtle associations.

MMR/MSI status was assessed by immunohistochemistry in a subset of cases; the number of cases tested, the method used, and the proportion classified as dMMR/MSI-H are described in the Methods. Although mismatch repair-deficient tumors are generally known to show increased lymphocytic infiltration, the limited number of evaluable cases in our study did not allow a reliable assessment of this association, and MMR/MSI status could not be adjusted for as a potential confounder of the TIL–clinicopathological associations reported here. Larger studies with comprehensive molecular profiling would help better understand the relationship between stromal TIL density and microsatellite instability.

One of the strengths of this study lies in the use of H&E-based evaluation of stromal TILs according to established international guidelines for morphological assessment. A significant aspect of the present study was that clinically relevant associations were identified using routine H&E-based assessment alone. In settings where advanced molecular profiling and immunohistochemistry may not be routinely accessible, morphological evaluation of stromal TIL density offers a practical tool for assessing tumor aggressiveness, although the specific 50% cut-off applied here requires independent validation before it can be recommended for routine use.

However, the present study has several important limitations. The relatively small sample size ($n = 35$) relative to the number of clinicopathological variables examined increases the likelihood of chance findings; p-values were not corrected for multiple comparisons, and the statistically significant associations reported here should be regarded as preliminary and hypothesis-generating rather than confirmatory. The single-institution setting may also introduce selection bias. The 50% threshold used to dichotomize stromal TIL density was not independently validated for colorectal carcinoma and was selected empirically for descriptive purposes in this cohort; the direction and strength of the reported associations may differ if TIL density is instead analyzed as a continuous or ordinal variable, or using alternative, previously reported cut-offs. The study focused on assessment of stromal TIL density without IHC characterization of the infiltrate or correlation with survival outcomes, which could provide additional insight into the functional status of the immune response. MMR/MSI status could not be incorporated as a covariate because of the limited number of evaluable cases, so residual confounding by molecular subtype cannot be excluded. Finally, because this is a retrospective, cross-sectional study without outcome or survival data, no causal or prognostic conclusions can be drawn; the associations reported here require confirmation in larger, prospective, multi-institutional cohorts with clinical follow-up before stromal TIL density can be considered for clinical or prognostic use.

Despite these limitations, the findings provide preliminary evidence for an inverse association between "seeds of invasion" in the form of tumor budding and the surrounding "field of immunity" represented by stromal TILs within the tumor microenvironment, an association that warrants confirmation in larger, appropriately powered studies.

Conclusion

This study suggests an inverse association between stromal TIL density and key histopathological markers of tumor aggressiveness in colorectal carcinoma. Tumors with higher stromal TIL density showed numerically lower rates of lymphovascular invasion, perineural invasion, and tumor budding, features that reflect invasive and metastatic potential. Given the exploratory nature of this analysis, these findings raise the possibility that a robust immune presence within the tumor microenvironment may act as a biological restraint, limiting the early steps of tumor spread; however, this cannot be confirmed by the present associative, single-institution data.

Although no significant association was observed with tumor stage or demographic variables, the consistent inverse correlation with established aggressive features is of potential clinical interest and reflects a hypothesis worth testing regarding the host immune response. These insights were derived using routine H&E assessment alone, highlighting that meaningful information about tumor morphology can be recognized through careful morphological evaluation. These findings should be considered hypothesis-generating: they are based on a small, single-institution cohort, a non-validated TIL cut-off, and therefore require validation in larger, prospective, multi-institutional studies before stromal TIL density can be recommended as a prognostic marker in colorectal carcinoma. In the interplay between tumor and host, stromal TILs emerge as sentinels of the immune response,

and further work incorporating molecular and outcome data is needed to define their clinical utility in colorectal cancer.

Author contributions
A.A. and S.A. wrote the main manuscript text and A.A. prepared figures. All authors reviewed the manuscript.

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None.

Data availability
All data supporting the findings of this study are available within the paper.

Declarations

Ethical approval
The study was exempt from Ethics approval due to use of retrospective anonymised data.

Competing interests
The authors declare no competing interests.

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