Journal of Carcinogenesis
Covering Genesis to Therapeutics
Journal of Carcinogenesis , ISSN: 1477-3163
2025; Vol 24: Issue 9s https://carcinogenesis.com/

Clinicopathological Correlation Of Cdx2 Expression With Prognostic Parameters In Colorectal Adenocarcinomas:A Retrospective Study

Poorana Priya.P[1*], Anbu Muthamil Nayagi[2]

[1*]Professor, Department of Pathology, Velammal Medical college hospital and Research Institute, Madurai, TamilNadu
[2]Postgraduate, Department of Pathology, Velammal Medical College Hospital and Research Institute, Madurai, TamilNadu

ABSTRACT

Background: Colorectal cancer (CRC) requires robust, affordable biomarkers for risk stratification. CDX2, an intestinal differentiation transcription factor, is frequently expressed in CRC, but its clinicopathological correlates in our setting remain underreported.

Methods: We conducted a cross-sectional analytical study of 42 histologically confirmed colorectal adenocarcinomas resected at a tertiary centre. CDX2 immunohistochemistry was performed on FFPE sections, and tumors were categorized as CDX2-positive or -negative (with intensity graded). Associations between CDX2 status and clinicopathological parameters (age, sex, site, size, grade, depth of invasion, nodal status, tumor budding, lymphovascular invasion [LVI], perineural invasion [PNI], peritumoral lymphoid aggregates, and AJCC stage) were tested using chi-square ($p<0.05$).

Results: CDX2 nuclear expression was present in 36/42 cases (85.7%), absent in 6/42 (14.3%). Loss of CDX2 was significantly associated with age >60 years (p=0.04) and male sex (p=0.03). Proximal (right-sided) tumors showed more frequent CDX2 loss than left-sided/rectal cancers (p=0.02). Adverse pathological features correlated with CDX2 loss, including larger size (≥5 cm; p=0.05), poor differentiation (p=0.01), greater depth of invasion (p=0.001), tumor budding (p=0.01), LVI (p=0.03), and borderline PNI (p=0.05). Stage distribution differed by CDX2 (p=0.04), and peritumoral lymphoid aggregates were more common in CDX2-positive tumors (p=0.02).

Conclusion: Most CRCs retained CDX2 expression; however, CDX2-negative tumors comprised a distinct subset enriched for high-risk features. Routine CDX2 assessment may aid prognostic stratification—particularly in early-stage disease—while acknowledging the need for outcome-linked, multicentre validation.

Keywords: CDX2; Colorectal adenocarcinoma; Immunohistochemistry; Prognosis

How to Cite: Poorana Priya.P, et al (2025) Clinicopathological Correlation Of Cdx2 Expression With Prognostic Parameters In Colorectal Adenocarcinomas:A Retrospective Study, *Journal of Carcinogenesis*, *Vol.24, No.9s*, 127-134.

INTRODUCTION

Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies and the second leading cause of cancer-related mortality worldwide **[1]**. In 2020, an estimated 1.93 million new CRC cases were diagnosed and 935,000 deaths occurred globally **[1]**. The burden of CRC continues to rise, with projections anticipating 3.2 million new cases and 1.6 million deaths by 2040 **[2]**. Notably, there is a concerning increase in early-onset CRC among adults under 50 years of age, with incidence rising by approximately 1–2% annually **[2]**.

In India, CRC incidence remains lower than in Western countries but is growing steadily. In 2022, there were about 64,863 new CRC cases and 38,367 related deaths in India, and the age-standardized mortality rate was ~2.9 per 100,000 **[3]**. CRC in India often presents at a later stage, reflected in a five-year survival rate below 40%, significantly worse than high-income countries **[2]**. Furthermore, a substantial proportion of Indian CRC patients are young; as a regional study reported 36.9% of CRC cases occurred in patients under 50 years old, highlighting an early-onset trend **[4]**. Overall, these epidemiological patterns highlight the need for improved early detection and prognostic stratification in CRC.

Established prognostic factors in CRC—such as tumor stage, histological grade, lymphovascular invasion, and microsatellite instability (MSI) status—are routinely used to guide treatment and predict outcomes. Especially for early-stage colon cancer, accurate prognostic markers are essential for risk stratification and determining the need for adjuvant chemotherapy **[5]**. However, many proposed molecular biomarkers have not been translated into standard practice due to issues with reproducibility or cost **[6, 7]**. Only a few biomarkers (e.g. MMR/MSI testing and certain mutations for targeted therapy) have been integrated into clinical care for prognostication or therapy selection **[7]**. Even those with proven utility, such as MSI and certain immune markers, see limited adoption in resource-constrained settings like India due to cost and infrastructure hurdles **[3]**. There is therefore considerable interest in identifying a reliable, widely applicable biomarker that correlates with tumor behavior and can inform treatment decisions.

Among emerging biomarkers, caudal-type homeobox 2 (CDX2) has shown promise for prognostication in CRC **[8]**. CDX2 is a homeobox domain-containing nuclear transcription factor expressed in intestinal epithelial cells, encoded by the CDX2 gene on chromosome 13 **[9]**. It plays a crucial role in intestinal development, promoting cellular differentiation and suppressing proliferation in the normal colonic epithelium **[9]**. In healthy colon mucosa and well-differentiated colorectal tumors, CDX2 is typically expressed strongly in nuclei, maintaining intestinal phenotype. CDX2 status can be assessed in tumors by gene expression analyses or more practically by immunohistochemistry (IHC) on tissue sections. Loss of

CDX2 expression has been associated with loss of intestinal differentiation and more aggressive tumor behavior in CRC **[8]**. Recent studies, including a pivotal analysis by Dalerba et al., have demonstrated that absence of CDX2 in early-stage colon cancers is an adverse prognostic indicator, correlating with higher risk of relapse and benefitting from adjuvant chemotherapy **[3]**. Nevertheless, data on CDX2 expression patterns in Indian CRC patients are scarce, and it is unclear if the same prognostic implications apply in this population.
In this context, the present study was undertaken to evaluate the frequency of CDX2 expression in colorectal adenocarcinomas by IHC and to analyze its correlation with various clinicopathological parameters known to impact prognosis.

METHODOLOGY

This study was a cross-sectional analytical study of colorectal carcinoma cases conducted in the Department of Pathology at a tertiary care center. A total of 42 resection specimens of colorectal adenocarcinoma, received between January 2022 and December 2024, were selected for analysis. Only primary colorectal adenocarcinomas confirmed on histopathology were included. Cases of extra-colonic tumors secondarily invading the colon, tumors of histological types other than adenocarcinoma (e.g. neuroendocrine carcinoma) as defined by the WHO 2019 classification, and cases with inadequate tissue for IHC were excluded. After applying these criteria, 42 cases remained (from an initial 49 cases examined). The study was approved by the institutional ethics committee, and relevant clinical data (patient age, sex, clinical presentation, etc.) were obtained from medical records.

Immunohistochemistry: IHC for CDX2 was performed on formalin-fixed, paraffin-embedded tumor tissue sections using a monoclonal anti-CDX2 antibody (clone EP25). The PolyVue Plus detection system with diaminobenzidine (DAB) chromogen was used for visualization of antibody binding. Appropriate positive and negative controls were included (normal colonic mucosa served as positive control for CDX2 nuclear staining). The IHC staining procedure followed standard protocols (antigen retrieval in EDTA buffer, incubation with primary antibody, secondary detection and chromogen development, with hematoxylin counterstaining).

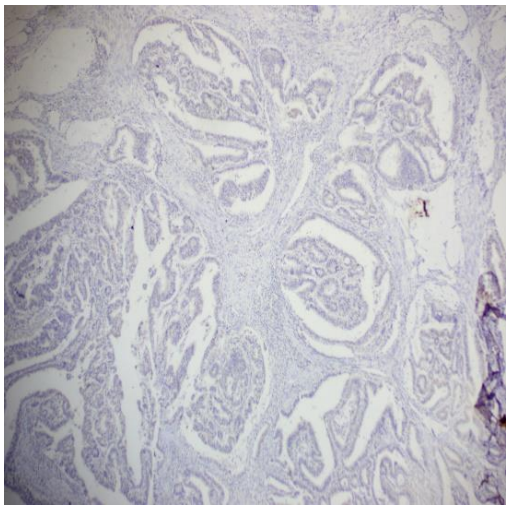
Scoring of CDX2 Expression: Stained slides were evaluated by two pathologists blinded to clinical outcomes. CDX2 expression in tumor cells was assessed semi-quantitatively based on the percentage of tumor cell nuclei showing positive staining and the intensity of staining. For analysis, we adopted a scoring system based on the method described by Bayrak *et al.* **[10]**. Tumors were categorized into **"**CDX2-positive" if any definite nuclear staining was present in the tumor cells, and "CDX2-negative" if tumor nuclei showed complete absence of staining. Among CDX2-positive cases, staining *intensity* was further graded on a 0 to 3+ scale (with 3+ indicating strong diffuse nuclear staining). For clarity, we grouped staining results into two tiers: low expression (including weak or moderate intensity staining in a subset of cells, corresponding to 1+ or 2+ intensity and/or focal positivity) and high expression (strong, diffuse nuclear staining in the majority of tumor cells, corresponding to 3+ intensity). In line with Bayrak *et al.*'s criteria, mild-to-moderate nuclear staining or focal positivity was classified as *low* CDX2 expression, whereas diffuse strong positivity was classified as *high* expression **[10]**.

Statistical Analysis: Associations between CDX2 expression (positive vs. negative) and various clinicopathological parameters were tested using Pearson's chi-square test. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 25.0. The study primarily examined correlations of CDX2 status with patient age, sex, tumor location, tumor size, histological grade of tumor, depth of invasion (T stage), lymph node status (N stage), tumor budding, lymphovascular invasion (LVI), perineural invasion (PNI), and AJCC clinical stage. The results are presented in tabular form with frequencies and percentages, and significant p-values are indicated.The study was approved by institutional ethical committee[VMCIEC/046/2023]

RESULTS

Clinicopathological Characteristics: The 42 patients had an age range of 25 to 83 years. Over half of the cases (52.4%) were middle-aged (31–60 years), and 45.2% were above 60 years, with only one patient below 30. There was a male predominance (M:F ratio ~2.2:1), with 69% (n=29) male and 31% (n=13) female patients. The most common clinical presentation was bleeding per rectum (45.2% of cases), followed by altered bowel habits such as constipation (31.0%); other symptoms included vomiting (11.9%), weight loss (9.5%), and abdominal pain (2.4%). Tumor locations were distributed throughout the colon and rectum; however, distal colorectal segments were slightly more frequently involved in our cohort (the sigmoid colon was the single most common site, involved in ~23.8% of cases). Histologically, most tumors were conventional adenocarcinomas (73.8%), with smaller subsets of mucinous adenocarcinoma (11.9%) and signet-ring cell carcinoma (14.3%).

CDX2 Expression Frequency: Out of the 42 colorectal carcinoma cases studied, 36 cases (85.7%) showed positive nuclear immunoexpression of CDX2, while 6 cases (14.3%) were completely CDX2-negative. Among the CDX2-positive tumors, 24 cases (57.1%) demonstrated high-intensity (strong, diffuse)[FIG1,2] CDX2 staining, whereas 12 cases had only mild-to-moderate or focal CDX2 positivity (classified as low expression).[FIG 3,4] Thus, the majority of colorectal adenocarcinomas in this series retained CDX2 expression, often with strong diffuse nuclear staining in tumor cells, whereas a minority lacked CDX2 expression entirely.



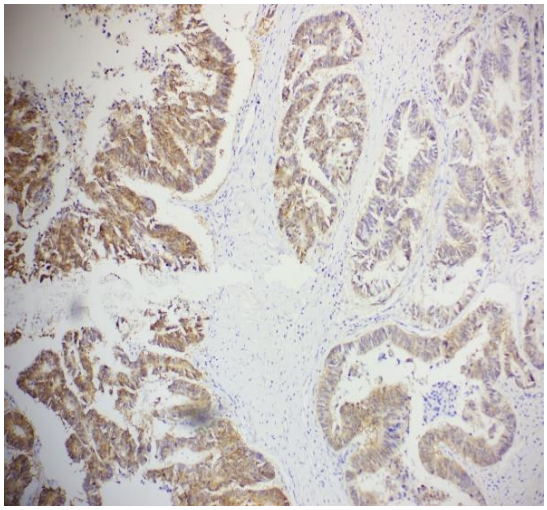
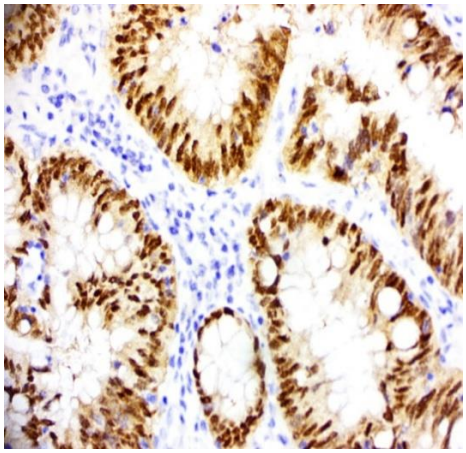


FIG1:CDX2 with Negative expression. IHC, Clone EP25, X100
FIG2:CDX2 with moderate intensity, IHC, Clone EP25, X100



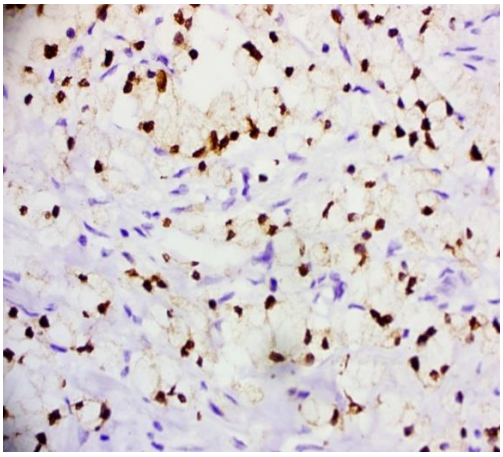


FIG3: Strong intensity of CDX2 expression, IHC, Clone EP25,X400
FIG4: shows CDX2 moderate staining intensity, signet ring cell carcinoma, colon, IHC, Clone EP25,x400

Correlation of CDX2 with Baseline Characteristics (Table 1): CDX2 expression showed significant associations with age and sex. CDX2 positivity was observed across all age groups but decreased in patients > 60 years (2/2 < 30; 19/21 in 31–60; 15/19 in > 60; $p = 0.04$). All female patients were CDX2-positive (13/13), while every CDX2-negative case occurred in males (23/29 positive; 6/29 negative; $p = 0.03$).
Clinical presentation was also associated with CDX2 status ($p = 0.01$): positivity predominated among those presenting with weight loss (4/4), bleeding per rectum (16/19), and constipation (11/13); fewer cases with vomiting (4/5) were positive; abdominal pain cases were entirely positive (1/1).
By anatomic site, CDX2 positivity was concentrated in descending colon, hepatic flexure, and sigmoid colon, whereas CDX2-negative tumors appeared in selected proximal locations—caecum, ascending colon, and transverse colon—yielding an overall site-wise association ($p = 0.02$). (Detailed counts include, for example, ascending colon 4/5 positive; caecum 1/2 positive; descending colon 7/7 positive; hepatic flexure 3/3 positive; ileo-caecum 4/5 positive; recto-sigmoid 1/1 positive; rectum 1/1 positive; sigmoid colon 4/4 positive; transverse colon 1/2 positive.)

Table 1. CDX2 expression and baseline characteristics of the study participants

Variable	Category	CDX2 Positive (n)	CDX2 Negative (n)	p-value
Age (years)	< 30	2	0	**0.04**
	31–60	19	2	
	> 60	15	4	
Sex	Female	13	0	**0.03**
	Male	23	6	
Clinical presentation	Abdominal pain	1	0	**0.01**
	Bleeding per rectum	16	3	
	Constipation	11	2	
	Vomiting	4	1	
	Weight loss	4	0	
Anatomical site	Ascending colon	4	1	**0.02**
	Caecum	1	1	
	Descending colon	7	0	
	Hepatic flexure	3	0	
	Ileo-caecum	4	1	
	Recto-sigmoid	1	0	
	Rectum	1	0	
	Sigmoid colon	4	0	
	Splenic flexure	8	2	
	Transverse colon	1	1	

Correlation of CDX2 with Pathologic Prognostic Factors: Table 2 summarizes the associations between CDX2 expression and various known prognostic pathological features. Our results show that CDX2-positive tumors were significantly associated with features indicative of a better prognosis, whereas CDX2-negative tumors tended to exhibit high-risk pathological characteristics:

Table 2. Association of CDX2 expression with tumor pathological features

Prognostic Factor	Category	CDX2 Positive (n)	CDX2 Negative (n)	p-value
Tumor size	< 5 cm	21	1	**0.05**
	≥ 5 cm	15	5	
Tumor differentiation	Grade 2 (well/moderate)	33	4	**0.01**
	Grade 3 (poor)	3	2	
Invasion depth (T stage)	T2 (muscularis propria)	3	1	**0.001**
	T3 (through bowel wall)	27	5	
	T4a (adjacent organ)	6	0	
Nodal status	N0 (node-negative)	11	4	**0.03**
	N1 (1–3 nodes, any subclass)	17	0	
	N2 (≥4 nodes, any subclass)	8	2	
Tumor budding	Absent	25	5	**0.01**
	Present (high grade budding)	11	1	
AJCC Stage	I–II (early stage)	11	4	**0.04**
	III–IV (advanced stage)	25	2	
Lymphovascular invasion	Absent	16	4	**0.03**
	Present	20	2	
Perineural invasion	Absent	23	3	**0.05**
	Present	13	3	
Peritumoral lymphoid agg.	Absent	17	4	**0.02**
	Present	19	2	

Tumor size: Smaller tumors (<5 cm in greatest dimension) were more likely to express CDX2. Among 22 tumors measuring <5 cm, 21 (95%) were CDX2-positive, versus 15 of 20 tumors (75%) ≥5 cm in size ($p = 0.05$). Thus, the great majority of large tumors (≥5 cm) retained CDX2, but all except one of the very small tumors were CDX2-positive, indicating a slight trend of CDX2 loss in larger, bulkier tumors.

Histological grade: A strong correlation was found between tumor differentiation and CDX2 status. Well and moderately differentiated adenocarcinomas overwhelmingly expressed CDX2, whereas poorly differentiated (Grade 3) tumors showed frequent loss of CDX2. Specifically, 33 of 37 Grade 2 tumors (89%) were CDX2-positive, compared to only 3 of 5 Grade 3 tumors (60%) ($p = 0.01$). All signet-ring cell carcinomas (which are high-grade by definition) in our series were either entirely CDX2-negative or showed only focal weak positivity. This confirms that loss of CDX2 is associated with poor differentiation in CRC.

Tumor invasion depth (T stage): CDX2 expression was significantly higher in tumors of lower T stage. All tumors confined to the muscularis propria (T2, n=4) were CDX2-positive (with only one showing focal loss), whereas among tumors that invaded through the bowel wall (T3, n=32), 5 cases lost CDX2 expression. Notably, all tumors that had invaded

adjacent organs (T4a, n=6) retained CDX2 positivity. Overall, increasing depth of invasion correlated with a higher frequency of CDX2 loss ($p = 0.001$).

Nodal involvement: An inverse association was observed between CDX2 expression and nodal metastatic spread. Node-negative cancers (N0, n=15) showed CDX2 positivity in 11 cases (73%), with 4 cases CDX2-negative. In contrast, among node-positive cases, CDX2 positivity remained high: all 17 cancers with limited nodal metastases (N1a, N1b, N1c) were CDX2-positive, and even in more advanced nodal stages (N2a, N2b; total n=9) only 2 cases lacked CDX2. Statistically, tumors without any nodal metastasis had a slightly higher proportion of CDX2 loss compared to node-positive tumors, but CDX2 expression overall was significantly associated with lower nodal stage (absence or minimal nodal metastases) ($p = 0.03$).

Tumor budding: Tumor budding (defined as the presence of isolated single cells or small clusters at the invasive front) is a marker of tumor aggressiveness. We found that cases with significant tumor budding were far more likely to have lost CDX2 expression. Of 12 tumors with prominent budding, 11 (92%) were still CDX2-positive (only 1 was negative); meanwhile, among 30 tumors without appreciable budding, 5 (17%) were CDX2-negative. Although the absolute numbers of negatives were small in both groups, this difference in proportion was statistically meaningful ($p = 0.01$). In other words, CDX2 negativity was disproportionately observed in tumors exhibiting budding at the invasive margin, suggesting a link between CDX2 loss and an epithelial–mesenchymal transition phenotype.

Clinical stage: When analyzed by overall AJCC stage, CDX2 expression showed a trend of being retained even in advanced stages, but the distribution was uneven across stages I–IV ($p = 0.04$). Interestingly, all Stage IV tumors (n=4) in our study were CDX2-positive despite their metastatic nature. Stage III tumors also had a high CDX2 positivity rate (21/23 positive; only 2 negative). Stage I and II tumors showed CDX2 loss in a few cases (1 of 3 Stage I and 3 of 12 Stage II were negative). Thus, CDX2 negativity was encountered in some early-stage tumors, whereas nearly all late-stage tumors still expressed CDX2, contributing to an overall significant variation. (This somewhat counterintuitive finding may reflect the small sample size of Stage I–II tumors and the possibility that CDX2-negative cancers had already manifested aggressive behavior even at early stages.)

Lymphovascular and Perineural Invasion: The presence of lymphovascular invasion (LVI) and perineural invasion (PNI) – pathological features associated with metastatic potential – were both correlated with CDX2 status. Tumors without LVI were CDX2-positive in 16 of 20 cases (80%), whereas those with LVI were positive in 20 of 22 cases (91%); this difference was significant ($p = 0.03$), indicating that CDX2 loss was modestly more frequent in cancers that had invaded lymphatics or blood vessels. Similarly, PNI-positive tumors (n=16) had a slightly higher rate of CDX2 negativity (3 of 16, 18.8%) compared to PNI-negative tumors (3 of 26, 11.5%), reaching borderline significance ($p = 0.05$). Taken together, the absence of CDX2 tends to coincide with the presence of these aggressive features (LVI, PNI), though many tumors with invasion still retained CDX2.

Peritumoral lymphoid response: An interesting observation was the relationship between CDX2 and the host immune response. Peritumoral lymphoid aggregates (lymphocytic collections at the tumor periphery) were documented in 21 cases. Tumors that elicited such lymphoid reactions were predominantly CDX2-positive (19/21, 90%), whereas tumors lacking peritumoral lymphoid aggregates had a somewhat lower CDX2-positive rate (17/21, ~81%). The association between presence of lymphoid aggregates and CDX2 expression was statistically significant ($p = 0.02$). This suggests that CDX2-positive tumors were more likely to have an accompanying lymphoid immune response, or conversely, CDX2-negative tumors were often those without prominent immune infiltrates.

DISCUSSION

CRC remains one of the most prevalent malignancies globally, with rising incidence in both developed and developing countries **[11]**. In our cohort of 42 colorectal adenocarcinomas, CDX2 was immunohistochemically expressed in the majority of tumors (overall positivity 86%), in keeping with prior reports that typically show 70–95% positivity in CRC **[12].** Beyond frequency, our analysis demonstrated significant associations between CDX2 status and several established prognostic factors, highlighting its potential as a practical prognostic biomarker in pathology workflows.With respect to patient demographics, loss of CDX2 was modestly more frequent in older patients; those >60 years had a higher proportion of CDX2-negative tumors ($p = 0.04$). This accords with Dalerba et al., who described progressive CDX2 loss with increasing age and advancing stage **[3]**. By contrast, an Indian single-center series of 110 CRCs reported no age correlation, likely reflecting a younger median age in that cohort **[11]**. We also observed a striking sex difference: all female patients were CDX2-positive, whereas all CDX2-negative tumors occurred in males ($p = 0.03$). This contrasts with reports suggesting lower CDX2 expression in females and a multicenter analysis linking female sex to CDX2 loss **[13, 14]**. Differences in population structure, sample size, or tumor biology may underlie these divergent observations; nevertheless, the association of CDX2 loss with male sex in our series warrants validation in larger datasets.

CDX2 varied significantly by anatomic subsite, with right-sided (proximal) colon tumors showing more frequent loss than left-sided and rectal cancers. This mirrors earlier observations—reduced CDX2 in right-sided carcinomas (AACR 2002) and slightly lower positivity in proximal tumors, particularly when poorly differentiated, in Lugli et al. **[15].** Laterality likely reflects biological differences between midgut-derived right colon and hindgut-derived left colorectum; enrichment for molecular features such as CIMP and MSI-high in proximal tumors may contribute to CDX2 downregulation **[16]**. Clinically, such patterns suggest that CDX2 loss should be anticipated more often in right-sided disease.

Histologically, CDX2 expression tracked closely with differentiation. Conventional gland-forming adenocarcinomas almost uniformly retained CDX2, whereas mucinous and signet-ring subtypes—often less differentiated—showed reduced or absent staining. Prior work has similarly linked CDX2 loss to high grade and mucinous/signet-ring morphology **[17]**. Our series aligns with this paradigm: all CDX2-negative cases were high-grade tumors (including several signet-ring carcinomas), supporting the concept that CDX2 marks intestinal differentiation that is lost as tumors de-differentiate **[11,17]**.

Correlations with prognostic factors further emphasize CDX2's clinicopathological relevance. Smaller tumors were more often CDX2-positive, while the few negatives clustered among larger lesions ($p = 0.05$), consistent with Dalerba et al. who found CDX2-negative cancers to be larger and biologically aggressive **[3]**. Depth of invasion showed a strong inverse relationship ($p = 0.001$): T2 tumors uniformly retained CDX2, whereas T3/T4 lesions exhibited higher rates of loss, paralleling Zlobec et al. on reduced CDX2 in deeply invasive tumors **[14]**. The nodal analysis in our series was paradoxical—node-positive cases were predominantly CDX2-positive while some negatives appeared among node-negative tumors ($p = 0.03$). This likely reflects sample distribution rather than biology; larger cohorts have reported that CDX2 loss associates with nodal and distant metastases and poorer outcomes **[18]**. Importantly, tumor budding an EMT-linked marker of aggressiveness was significantly enriched among CDX2-negative tumors ($p = 0.01$), echoing Lugli et al. and reinforcing the link between CDX2 loss and an invasive, de-differentiated phenotype **[15].**

Stage-wise, most stage III/IV tumors in our cohort remained CDX2-positive, with a few early-stage cases demonstrating loss ($p = 0.04$). While counterintuitive, this may reflect case mix and the absence of outcome data. Large studies show that CDX2-negative tumors, though uncommon, have disproportionately poor survival especially in stage II and may benefit from adjuvant chemotherapy [3, 13]. Thus, even when stage is low, CDX2 loss can signal high biological risk. Lymphovascular invasion ($p = 0.03$) and perineural invasion (borderline, $p = 0.05$) were more frequent among CDX2-negative cases, in line with reports that CDX2 loss tracks with vascular invasion and advanced T/N categories even after accounting for MSI status **[19]**. Finally, we found CDX2 positivity associated with peritumoral lymphoid aggregates ($p = 0.02$), suggesting interplay between differentiation status and host immune response. This observation sits comfortably within the immunoscore framework, wherein robust lymphoid infiltration predicts better outcomes in early-stage CRC **[19]**.

In aggregate, our data—strictly reflecting the present cohort—support CDX2 as a pragmatic marker of differentiation with meaningful ties to aggressive histology, invasion, and microenvironmental features. While certain patterns (sex, stage distribution) differ from some reports, the broader signal is consistent: loss of CDX2 identifies a smaller, clinically important subset with adverse pathology, potentially informing risk stratification—especially in early-stage disease where adjuvant therapy decisions are nuanced **[3, 13].**

Overall, our results are largely in agreement with the existing literature that CDX2 is a favorable prognostic marker in colorectal carcinoma. High CDX2 expression tends to denote a tumor that is more differentiated, less invasive, and potentially less metastatic, whereas loss of CDX2 identifies a subset of tumors with high-grade features and possibly worse clinical outcomes **[18, 20, 21, 22]**. The discrepancies we noted highlight the need for cautious interpretation and further validation. Nonetheless, the preponderance of evidence supports assessing CDX2 status in CRC, as CDX2-negative cases, while relatively uncommon, have disproportionate association with adverse pathological characteristics.

CONCLUSION

In conclusion, this study demonstrates that CDX2 is expressed in the majority of colorectal adenocarcinomas (≈86% in our series) and that loss of CDX2 expression correlates with several unfavorable clinicopathological parameters. CDX2 negativity, found in about 14% of cases, was significantly associated with older age, male sex, proximal colon location, poor differentiation (high grade), deeper invasion (T3/T4), and features of aggressive behavior such as lymphovascular invasion, perineural invasion, and tumor budding. Conversely, tumors retaining strong CDX2 expression were more likely to have well/moderate differentiation and to lack high-risk features, often accompanied by a brisk lymphoid host response. These findings support the role of CDX2 as a marker of intestinal differentiation that has prognostic relevance in CRC.

From a clinical perspective, CDX2 immunohistochemistry can serve as a useful adjunct prognostic biomarker in colorectal cancer. Identification of CDX2-negative tumors is important, as these tumors tend to correspond with a more aggressive phenotype and may warrant closer monitoring and possibly more intensive adjuvant treatment. For instance, in early-stage colon cancer, CDX2 loss might flag patients who could benefit from chemotherapy despite low-stage disease. While further large-scale studies and survival analyses are needed for confirmation, our results add to the growing evidence that evaluation of CDX2 status should be considered in routine pathology practice for CRC. Ultimately, incorporation of CDX2, alongside other molecular and histologic markers, may improve risk stratification and personalized management of patients with colorectal carcinoma.

Limitations. This single-center study with a small sample size limits generalizability and statistical power. Absence of longitudinal follow-up precluded direct DFS/OS assessment, so prognostic inferences rely on pathologic surrogates rather than outcomes. Larger multicenter cohorts incorporating molecular profiling (e.g., MSI, BRAF/KRAS) and survival endpoints are needed to determine whether CDX2 confers independent prognostic value and to guide adjuvant therapy decisions

CONFLICT OF INTEREST

None

SOURCE OF FUNDING

Nil

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021 May;71(3):209–49.
2. Henson DE, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973–2000: increase in the signet ring cell type. *Arch Pathol Lab Med.* 2004 Jul 1;128(7):765–70.
3. Dalerba P, Sahoo D, Paik S, Guo X, Yothers G, Song N, et al. CDX2 as a Prognostic Biomarker in Stage II and Stage III Colon Cancer. *N Engl J Med.* 2016 Jan 21;374(3):211–22.
4. Akimoto N, Ugai T, Zhong R, Hamada T, Fujiyoshi K, Giannakis M, et al. Rising incidence of early-onset colorectal cancer—a call to action. *Nat Rev Clin Oncol.* 2021 Apr;18(4):230–43.
5. Carrion-Alvarez L, Primavesi F, Søreide K, Sochorova D, Diaz-Nieto R, Dopazo C, et al. Liver metastases from colorectal cancer: A joint ESSO–EAHPBA–UEMS core curriculum collaboration. *Eur J Surg Oncol.* 2025 Jun 1;51(6).
6. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974–2013. *J Natl Cancer Inst.* 2017 Aug 1;109(8):djw322.
7. Dienstmann R, Salazar R, Tabernero J. Molecular Subtypes and the Evolution of Treatment Decisions in Metastatic Colorectal Cancer. *Am Soc Clin Oncol Educ Book.* 2018 May 23;38:231–8.
8. Patel SG, Ahnen DJ. Colorectal Cancer in the Young. *Curr Gastroenterol Rep.* 2018 Mar 28;20(4):15.
9. World Health Organization. Trends in maternal mortality 2000 to 2023: estimates by WHO, UNICEF, UNFPA, World Bank Group and UNDESA/Population Division.
10. Bayrak R, Haltas H, Yenidunya S. The value of CDX2 and cytokeratins 7 and 20 expression in differentiating colorectal adenocarcinomas from extraintestinal gastrointestinal adenocarcinomas: cytokeratin 7-/20+ phenotype is more specific than CDX2 antibody. *Diagn Pathol.* 2012 Dec;7:1–1.
11. Hryniuk A, Graeme-Cook F, Chung DC, et al. Loss of CDX2 expression in colorectal carcinoma is associated with poor differentiation and high tumor grade. *Am J Surg Pathol.* 2004;28(3):411–20.
12. Saad RS, Ghorab Z, Khalifa MA, Xu M. CDX2 as a marker for intestinal differentiation: Its utility and limitations. *World J Gastrointest Surg.* 2011 Nov 27;3(11):159.
13. Sadeghian M, Mehrazma M, Memar B, et al. CDX2 expression in colorectal carcinoma and its correlation with clinicopathological features. *Iran J Pathol.* 2015;10(4):275–82.
14. Zlobec I, Minoo P, Baumhoer D, et al. Multimarker phenotype predicts local recurrence in rectal cancer. *Histopathology.* 2008;52(3):281–90.
15. Lugli A, Zlobec I, Minoo P, et al. Prognostic significance of CDX2 in colorectal cancer. *Mod Pathol.* 2006;19(10):1377–86.
16. Oliveira-Silveira J, Filippi-Chiela E, Saffi J. Laterality influence on gene expression of DNA damage repair in colorectal cancer. *Sci Rep.* 2023 Sep 25;13(1):15963.
17. Hryniuk A, Graeme-Cook F. *Mod Pathol.* 2004;17(6):755–61.
18. Pilati C, Shinde J, Alexandrov LB, et al. CDX2-negative status in colorectal cancer is associated with female sex and poor prognosis. *Ann Oncol.* 2017;28(10):2420–6.
19. Werling RW, Yaziji H, Bacchi CE, et al. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: An immunohistochemical survey of 476 primary and metastatic carcinomas. *Am J Surg Pathol.* 2003;27(3):303–10.
20. Tomasello G, Barni S, Turati L, Ghidini M, Pezzica E, Passalacqua R, et al. Association of CDX2 expression with survival in early colorectal cancer: a systematic review and meta-analysis. *Clin Colorectal Cancer.* 2018 Jun 1;17(2):97–103.
21. Saigusa S, Tanaka K, Toiyama Y, et al. Downregulation of the homeobox gene CDX2 in colorectal carcinoma is associated with poor prognosis. *Oncol Rep.* 2009;21(4):959–65.
22. Droeser RA, Hirt C, Eppenberger-Castori S, et al. High expression of the homeobox gene CDX2 is a favorable prognostic factor in colorectal cancer. *World J Gastroenterol.* 2011;17(39):4094–101.