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Original article

E-Cadherin Immunohistochemical Expression as a Prognostic Biomarker in Colorectal Adenocarcinoma: Correlations with Clinicopathological Variables and Tumor Progression in AL-Beyda Medical Center

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Abstract
Colorectal carcinoma (CRC) continues to be a significant global health concern, underscoring the need for reliable prognostic markers to enhance risk assessment and therapeutic planning. This study assessed the potential of E-cadherin expression, determined via immunohistochemistry, as a prognostic marker in 30 CRC cases diagnosed at AL-Beyda Medical Center between 2014 and 2022. Using paraffin-embedded tissue samples, hematoxylin-eosin staining was performed for histopathological grading, complemented by E-cadherin immunohistochemistry with monoclonal antibodies. The expression levels were semiquantitatively scored from 0 to 3 based on the intensity and extent of membranous staining, with Scores 0-1 were classified as low expression; 2-3 as high expression. High E-cadherin expression was detected in 24 out of 30 cases (80%). Statistical analysis showed significant correlations between high E-cadherin expression and several clinicopathological factors: younger age (<49 years, 93.8% vs. ≥ 49 64.3% in older patients; $p = 0.044$), male gender (90.9% vs. 50% in females; $p = 0.013$), absence of a family history of CRC (94.7% vs. 54.5% in individuals with positive family history; $p < 0.001$), non-metastatic disease status (95.2% vs. 44.4% in cases with metastasis; $p = 0.001$), well to moderately differentiated tumors (83.3--90.0% while poorly differentiated tumors showed predominantly low expression (75.0%) with only 25.0% high expression; $p = 0.012$), and earlier tumor stages (85.7--93.8% in stages I--II vs. 33.3--50.0% in stages III--IV; $p = 0.039$). The findings highlight the critical role of E-cadherin in preserving epithelial integrity, with its loss being associated with aggressive characteristics such as advanced disease stages, poor differentiation, and heightened metastatic potential. These results support incorporating E-cadherin immunohistochemistry into standard pathological evaluations to improve prognostic accuracy and identify high-risk patients who may benefit from closer monitoring or tailored therapeutic strategies. Further multicenter studies are needed to confirm these findings and investigate potential treatments targeting E-cadherin-related pathways.

Keywords. *Colorectal Carcinoma, E-Cadherin, Immunohistochemistry, Prognostic Marker, Tumor Differentiation, Metastasis.*

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide, with approximately 2 million new cases and 880,000 deaths annually [1]. While the molecular pathogenesis of CRC is well-characterized—involving chromosomal instability, microsatellite instability, and epigenetic alterations in key genes such as *APC*, *KRAS*, and *TP53* [2]. The mechanisms driving tumor invasion and metastasis remain incompletely understood. A critical event in this process is the epithelial-mesenchymal transition (EMT), during which tumor cells lose cell-cell adhesion and acquire migratory and invasive properties [3]. E-cadherin, a core component of adherens junctions, plays a pivotal role in maintaining epithelial integrity. Downregulation of E-cadherin has been consistently associated with increased tumor aggressiveness and poor prognosis across multiple malignancies [4].

In CRC specifically, disruption of E-cadherin-mediated adhesion facilitates tumor cell dissociation from the primary lesion and invasion into surrounding tissues. This downregulation occurs through diverse mechanisms, including germline and somatic mutations in *CDH1*, loss of heterozygosity, and promoter hypermethylation [5–9]. Furthermore, E-cadherin loss intersects with canonical Wnt/β-catenin signaling—a pathway fundamentally altered in the majority of CRC cases [10,11]. Normally, E-cadherin sequesters β-catenin at the membrane, thereby restraining its transcriptional activity; when E-cadherin is lost, β-catenin accumulates in the cytoplasm and translocates to the

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nucleus, driving expression of genes that promote proliferation, stemness, and metastasis [12]. Despite extensive characterization of E-cadherin in other cancers, its specific mechanistic contribution to CRC progression particularly the interplay between E-cadherin loss, Wnt/β-catenin hyperactivation, and EMT induction in the colorectal microenvironment remains insufficiently elucidated. Therefore, the purpose of this study is to evaluate E-cadherin immunohistochemical expression as a prognostic biomarker in colorectal adenocarcinoma and its association with clinicopathological variables. We hypothesize that reduced E-cadherin expression correlates with advanced tumor stage, poor differentiation, and metastatic disease. Understanding this association is clinically significant, as it may identify high-risk patients who may benefit from closer monitoring or tailored therapeutic strategies.

Material and Methods

This retrospective study was conducted at Al-Beyda Medical Center, a teaching hospital serving >350,000 inhabitants, to evaluate E-cadherin expression as a prognostic biomarker in colorectal adenocarcinoma. This study received ethical approval from the Jabal Al-Akhdar Branch Committee for Bioethics (JCB), Libyan National Committee for Biosafety and Bioethics, at its meeting No. (7) held on 11 February 2025 (Reference number**:** NBC: 004.H.25.6).

Thirty consecutive CRC cases diagnosed between 2014 and 2022 were retrieved, comprising 6 well-differentiated (Grade I), 20 moderately differentiated (Grade II), and 4 poorly differentiated (Grade III) tumors. Specimens were obtained via either colonoscopy or hemicolectomy. Clinicopathological data, including age, sex, family history, tumor grade, and stage, were extracted from medical records and reevaluated independently. Tissue sections (4 μm) were cut from formalin-fixed paraffin-embedded blocks, mounted on positively charged slides, baked at 60°C, deparaffinized in xylene, and rehydrated through a graded ethanol series (100%, 95%, 70%). H&E staining was performed for histopathological grading according to the WHO Classification of Tumours of the Digestive System [13]. For immunohistochemistry, antigen retrieval was performed in citrate buffer (pH 6.0) by microwave heating (100°C, 3 × 5 min cycles).

Endogenous peroxidase was blocked with 3% H_2O_2 (5 min), followed by protein block (5 min, room temperature). Sections were incubated with mouse monoclonal anti-E-cadherin antibody (Novocastra) for 1 h at room temperature in a humidified chamber, followed by sequential application of biotinylated secondary antibody (RE7103, 30 min) and streptavidin-HRP conjugate (30 min), with PBS washes between steps. Chromogenic detection used DAB substrate (5–15 min), counterstained with Mayer's hematoxylin, dehydrated, cleared in xylene, and mounted in DPX. Positive (normal colonic mucosa) and negative (omission of primary antibody) controls were run concurrently. E-cadherin membranous staining was semiquantitatively scored using a modified scoring system adapted from Allred [14]: 0 (negative), 1 (weak), 2 (intermediate), 3 (strong). Scores 0-1 were classified as low expression; 2-3 as high expression. This simplified 4-point scale was used instead of the complete Allred score (0-8) to facilitate practical implementation in routine diagnostic practice. Two independent observers evaluated all slides blinded to clinicopathological data. Associations between E-cadherin expression and clinicopathological variables were analyzed by Chi-square test using SPSS v23.0 (SPSS Inc., Chicago, IL). Statistical significance was set at $P < 0.05$.

Results

Patient Demographics and Tumor Characteristics

Thirty cases of colorectal adenocarcinoma diagnosed between 2014 and 2022 were analyzed. All selected cases were diagnosed with colorectal adenocarcinoma during this period. Specimens were obtained following either colonoscopy or hemicolectomy, with the final diagnosis based on the evaluation of clinico-pathological findings. The median age was 49 years, with 53.3% (n=16) aged <49 years and 46.7% (n=14) ≥49 years. Males predominated (73.3%, n=22). Family history of CRC was positive in 36.7% (n=11). Metastatic disease was present in 30.0% (n=9). Histologically, 20.0% (n=6) were Grade I, 66.7% (n=20) were Grade II, and 13.3% (n=4) were Grade III.. TNM staging distribution was: Stage I 53.3% (n=16), Stage II 23.3% (n=7), Stage III 13.3% (n=4), and Stage IV 10.0% (n=3).

E-cadherin Expression

High E-cadherin expression (scores 2–3) was observed in 80.0% (n=24) of cases, while 20.0% (n=6) showed low expression (scores 0–1) (Table 1).

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Association with Clinicopathological Parameters

Statistical analysis revealed significant associations between E-cadherin expression and all evaluated parameters (Table 2). High expression was more frequent in patients <49 years (93.8% vs. 64.3%, p=0.044), males (90.9% vs. 50.0%, p=0.013), and those without family history (94.7% vs. 54.5%, p<0.001). Non-metastatic tumors demonstrated significantly higher E-cadherin retention (95.2% vs. 44.4%, p=0.001). Histological grade showed an inverse relationship, with Grade III tumors exhibiting markedly reduced high expression (25.0%) compared to Grade I (83.3%) and Grade II (90.0%) (p=0.012). Similarly, advanced TNM stage correlated with E-cadherin loss: Stage IV showed 33.3% high expression versus 93.8% in Stage I (p=0.039).

Table 1. Association of Social and Clinical Characteristics with E-cadherin Immunohistochemical Findings in Colorectal Adenocarcinoma.

Characteristics	**N.**	**E-cadherin**		**Chi-square test**
		High Expression	**Low Expression**	
		24 cases (80 %)	**6 cases (20 %)**	
Age group				
< 49	16	15 (93.8%)	1 (6.2%)	P=0.04414*
≥ 49	14	9 (64.3%)	5 (35.7%)	
Sex group				
Male	22	20 (90.9%)	2 (9.1%)	P=0.01324*
Female	8	4 (50%)	4 (50%)	
Family history of cancer				
Yes	11	6 (54.5%)	5 (45.5%)	P=0.00008*
No	19	18 (94.7%)	1 (5.3%)	
Tumor metastases to other body parts				
Yes	9	4 (44.4%)	5 (55.6%)	P=0.00144*
No	21	20 (95.2%)	1 (4.8%)	
Tumor grade				
Grade I	6	5 (83.3%)	1 (16.7%)	P=0.01195*
Grade II	20	18 (90%)	2 (10%)	
Grade III	4	1 (25%)	3 (75%)	
Tumor stage				
Stage I	16	15 (93.8%)	1 (6.2%)	P=0.03901*
Stage II	7	6 (85.7%)	1 (14.3%)	
Stage III	4	2 (50%)	2 (50%)	
Stage IV	3	1 (33.3%)	2 (66.7%)	

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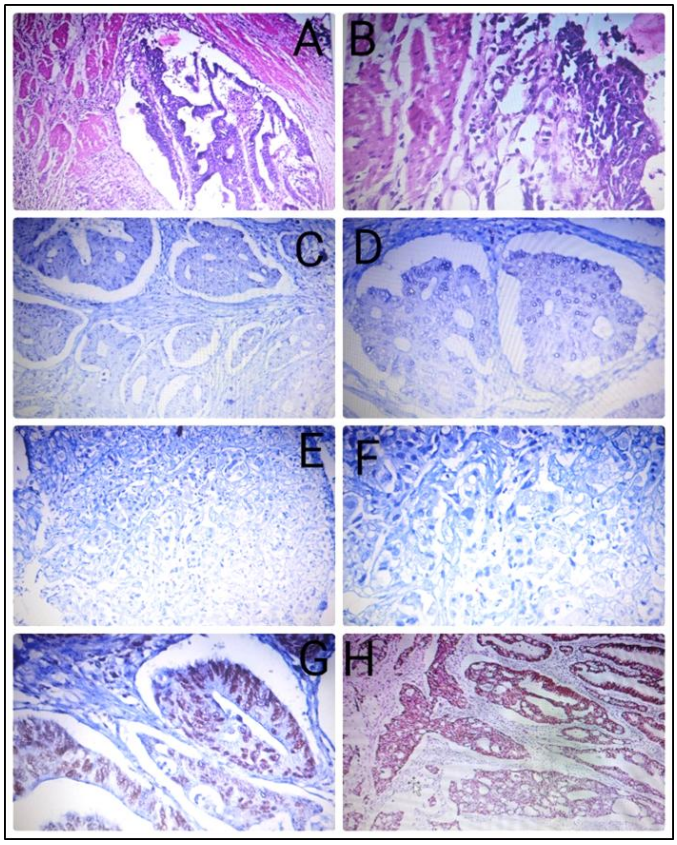

Figure 1. A-Histological section showing low-grade glandular structures with mild atypia, consistent with low-grade adenocarcinoma. The slide is stained with Hematoxylin and Eosin (H&E), and the image is captured at 200× magnification, B- and the image is captured at 400× magnification, C- Negative E-cadherin immunohistochemistry (IHC) staining at 200× magnification for low grade adenocarcinoma, D- and the image is captured at 400× magnification, E- Negative E-cadherin immunohistochemistry (IHC) staining at 200× magnification for high grade adenocarcinoma, F- and the image is captured at 400× magnification, G- Positive E-cadherin immunohistochemistry (IHC) staining at 400× magnification for low grade adenocarcinoma, H- Positive E-cadherin immunohistochemistry (IHC) staining at 100× magnification for Moderately differentiated (Grade 2) colorectal adenocarcinoma.

Discussion

Colorectal adenocarcinoma remains a leading cause of cancer mortality worldwide, with tumor progression driven by cumulative genetic/epigenetic alterations and epithelial--mesenchymal transition (EMT) [3,4]. Central to this process is E-cadherin, a transmembrane glycoprotein that maintains epithelial integrity by anchoring β-catenin at the cell membrane. Theoretically, its loss may release β-catenin into the cytoplasm, potentially enabling aberrant Wnt/β-catenin signaling; however, this study did not evaluate β-catenin localization or Wnt pathway activation, and these proposed mechanisms require direct experimental validation [4,10,11]. This study evaluated E-cadherin immunohistochemical expression in 30 CRC cases and identified significant associations with age, sex, family history, metastatic status, tumor grade, and TNM stage, reinforcing its role as a multifaceted prognostic biomarker. Age significantly influenced E-cadherin expression ($p = 0.044$), with 93.8% of patients <49 years demonstrating high expression compared to 64.3% of older patients. This finding aligns with Markowski et al. [15], who observed lower E-cadherin expression in tumor centers among younger patients ($p = 0.041$), and Djikic Rom et al. [16], who reported higher cytoplasmic E-cadherin in early-onset CRC, though membrane expression did not differ significantly. These data support the emerging concept that early-onset CRC exhibits distinct molecular profiles [15,16], though conflicting evidence exists Rajkumar et al. [17] found no significant age correlation ($p = 0.202$), likely due to broader age ranges that obscure early-onset-specific biology.

The elevated E-cadherin in our younger cohort suggests less aggressive tumor biology or unique microenvironmental interactions, underscoring the necessity of age-stratified analyses in biomarker studies. Sex emerged as a significant variable ($p = 0.013$), with males showing higher E-cadherin retention (90.9%) than females (50%). This contrasts with

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Markowski et al. [15], who observed higher expression in tumor budding sites among women, though their focus on intratumoral heterogeneity differs from our assessment of overall immunoreactivity. The sex disparity may reflect hormonal influences on epithelial integrity; however, the mechanisms remain speculative. Iseki et al. [19] reported that men with intact E-cadherin demonstrated superior chemotherapy response and longer survival in metastatic colorectal cancer, though sex lost independent prognostic significance in multivariate analysis. These findings suggest that sex hormones may modulate cadherin--catenin axis function, warranting dedicated molecular investigation. Estrogen receptor signaling may influence epithelial integrity in breast cancer [18], though direct evidence in colorectal cancer remains limited.

Family history was the strongest predictor of E-cadherin loss ($p < 0.001$), with only 54.5% of familial cases maintaining high expression versus 94.7% of sporadic tumors. This supports the paradigm that hereditary CRC develops invasive properties through early cadherin–catenin axis suppression [20–22]. Richards et al. [20] established that germline CDH1 mutations drive syndromic susceptibility to gastrointestinal malignancies via constitutional loss of cellular adhesion, while Wheeler et al. [21] demonstrated that CDH1 promoter hypermethylation increases from 57% in sporadic cancers to 85% in chronic inflammatory states. Jungck et al. [22] extended these observations to FAP adenomas, showing consistent E-cadherin reduction with concurrent nuclear β-catenin translocation, a pattern rarely seen in non-polyposis adenomas. Our data bridge this concept from adenomatous polyps to invasive adenocarcinoma, suggesting that once E-cadherin suppression is epigenetically established in familial mucosa, it remains inactive throughout malignant progression.

Clinically, integrating family history with E-cadherin immunohistochemistry may enhance risk stratification beyond Amsterdam or Bethesda criteria, though germline confirmation is essential for definitive hereditary syndrome diagnosis. Metastatic disease showed robust association with E-cadherin loss ($p = 0.001$), corroborating established literature [23–27]. Low expression was observed in 55.6% of metastatic cases versus 4.8% of non-metastatic tumors, supporting E-cadherin as an independent predictor of dissemination [23]. Stanczak et al. [23] identified low E-cadherin as an independent prognostic factor for distant metastasis and poorer disease-free survival in stage III/IV CRC, while He et al. [24] demonstrated that reduced E-cadherin significantly increased combined odds of lymph node and liver metastasis, particularly in Asian populations. Palaghia et al. [25] quantified this gradient, reporting a 38% reduction in mean H-score as tumor cells penetrated lymph node subcapsular sinuses, even before histological extranodal extension. Qu et al. [26] further integrated E-cadherin into a prognostic nomogram for stage II–III CRC, demonstrating its ability to predict metachronous metastases.

Our synchronous metastasis data complement these findings, suggesting E-cadherin serves dual predictive roles for both immediate and delayed dissemination. Histological grade ($p = 0.012$) and TNM stage ($p = 0.039$) correlated inversely with E-cadherin, with Grade III and Stage IV tumors showing 25% and 33.3% high expression, respectively [23,27--32]. Mitrović Ajtić et al. [27] demonstrated that poorly differentiated adenocarcinomas exhibit decreased E-cadherin alongside altered proliferation markers, while Niknami et al. [28] showed concomitant E-cadherin downregulation and vimentin upregulation in advanced stages, confirming EMT-facilitated invasiveness. Busuioc et al. [29] expanded this framework by linking decreased E-cadherin with EMT and stemness markers (OCT3/4, vimentin), indicating that dedifferentiation and stem cell-like properties collectively drive aggressive behavior. Rajkumar et al. [17] validated that strong E-cadherin expression predominates in well-differentiated tumors, whereas its loss associates with higher grades and nodal metastasis. Wang et al. [30] reported reduced E-cadherin as a critical driver of progression in signet ring cell carcinoma, while Kim et al. [31] identified E-cadherin loss in pT3 tumors as predictive of extranodal extension and poorer survival beyond TNM staging. Yun et al. [32] similarly observed diminished E-cadherin in Stage III CRC correlated with unfavorable prognosis. These consistent observations across diverse populations and methodologies underscore that E-cadherin depletion is integral to dedifferentiation and EMT, rather than merely a consequence of aggressive behavior [27–29].

Study Limitation

This study is limited by its small sample size, retrospective design, and reliance on file data for family history without germline confirmation. The use of a simplified semiquantitative scoring system (0–3) rather than the complete Allred score (0–8), and the evaluation of total E-cadherin without subcellular localization assessment, may affect comparability with other studies. Future multicenter investigations with larger cohorts, standardized immunohistochemical protocols, and molecular correlation (CDH1 sequencing, methylation analysis) are warranted

to validate these findings and establish E-cadherin as a routine prognostic tool in CRC management.

Conclusion

E-cadherin immunohistochemical expression is a significant prognostic marker in colorectal adenocarcinoma. Its downregulation is strongly associated with advanced tumor grade, stage, metastasis, and familial predisposition. Incorporating E-cadherin assessment into standard histopathological evaluation may improve prognostication and guide personalized management strategies. Larger multicenter studies with molecular validation are warranted to confirm these findings and explore therapeutic targeting of E-cadherin-related pathways.

Conflict of interest. Nil

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