RESEARCH PAPER

Vascular Endothelial Growth Factor Expression In Colorectal Carcinoma And Its Clinicopathological Correlation: A Cross-Sectional Hospital Based Study

Dr. Kawde Sanket Ashok[1], Dr. Ashwini Ratnakar[2]
[1] Post graduate, [2]Associate Professor
Department of Pathology, KAHERs Jawaharlal Nehru Medical College, Belagavi
kingmakuga@gmail.com, ashwininov5@gmail.com

ABSTRACT

Background: Colorectal carcinoma (CRC) is one of the leading causes of cancer-related morbidity and mortality worldwide. Tumor angiogenesis plays a crucial role in its progression, with vascular endothelial growth factor (VEGF) being a key mediator. Evaluation of VEGF expression and its correlation with clinicopathological parameters may provide insights into tumor behavior and prognosis.

Objectives: To evaluate VEGF expression in colorectal carcinoma and to correlate its expression with clinicopathological parameters.

Materials and Methods: This hospital-based cross-sectional study was conducted in the Department of Pathology at KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, from April 2024 to March 2025. A total of 44 resected specimens of colorectal carcinoma were included. Histopathological evaluation was performed using hematoxylin and eosin staining, and immunohistochemical analysis for VEGF expression was carried out using a semi-quantitative scoring system. Statistical analysis was performed using SPSS version 22, with $p<0.05$ considered significant.

Results: High VEGF expression was observed in 61.36% of cases. Increased VEGF expression was more frequently associated with advanced tumor stages and higher pTNM categories, though these associations were not statistically significant. A significant association was found between VEGF expression and perineural invasion ($p<0.001$), while no significant correlation was noted with lymphovascular invasion, tumor size, histological type, grade, or tumor site.

Conclusion: VEGF is commonly overexpressed in colorectal carcinoma and is significantly associated with perineural invasion, indicating its role in tumor aggressiveness. VEGF may serve as a useful prognostic biomarker and potential therapeutic target in colorectal carcinoma.

How to cite this article: Ashok KS, Ratnakar A. Vascular endothelial growth factor expression in colorectal carcinoma and its clinicopathological correlation: A cross-sectional hospital-based study. *Asian Journal of Drug Delivery Technology.* 2026;16(6s): 388-396; DOI: 10.25258/ijddt.16.6s.41.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Colorectal carcinoma (CRC) is one of the most prevalent malignancies worldwide and constitutes a major public health concern due to its high incidence, morbidity, and mortality. It ranks among the top three most commonly diagnosed cancers and is a leading cause of cancer-related deaths globally (1). In recent years, there has been a noticeable increase in the incidence of colorectal cancer in developing countries, including India, attributed to rapid urbanization, adoption of westernized dietary patterns, sedentary lifestyle, obesity, and increased life expectancy (2). "Although advancements in diagnostic modalities, surgical management, and adjuvant therapies have improved survival rates, the prognosis of colorectal carcinoma still largely depends on tumor stage at diagnosis and its underlying biological behavior. Hence, there is a growing need to identify molecular markers that can provide insight into tumor progression, prognosis, and therapeutic response (3).

Colorectal carcinogenesis is a multistep process involving a series of genetic and epigenetic alterations that transform normal colonic epithelium into adenomatous polyps and eventually invasive carcinoma. Alongside these molecular events, tumor progression is critically dependent on the tumor microenvironment, particularly the process of angiogenesis (4). Angiogenesis refers to the formation of new blood vessels from pre-existing vasculature and is essential for tumor growth beyond a minimal size, typically 1–2 mm (5). Without an adequate blood supply, tumors cannot sustain their metabolic demands or facilitate metastatic spread. Thus, angiogenesis is considered a

**Author for Correspondence: Dr. Kawde Sanket Ashok*

hallmark of cancer and a key factor in tumor aggressiveness and dissemination (6).

Among the various angiogenic factors identified, vascular endothelial growth factor (VEGF) is the most potent and widely studied mediator (7). VEGF is a glycoprotein that specifically acts on endothelial cells, stimulating their proliferation, migration, and survival. It also increases vascular permeability, contributing to the formation of a tumor-friendly microenvironment (8). VEGF expression is upregulated in response to hypoxia through hypoxia-inducible factors (HIFs), as well as by oncogenic signaling pathways commonly activated in colorectal carcinoma (9,10). Tumor cells, stromal cells, and inflammatory cells within the tumor microenvironment can all contribute to VEGF production, thereby promoting neovascularization (8).

In colorectal carcinoma, increased expression of VEGF has been consistently associated with tumor growth, invasion, and metastasis. Studies have demonstrated that higher levels of VEGF expression correlate with advanced tumor stage, deeper invasion of the bowel wall, lymph node involvement, and distant metastasis, particularly to the liver (11,12). Additionally, VEGF expression has been linked with poor differentiation, lymphovascular invasion, and reduced overall survival, making it a potential prognostic biomarker. The degree of angiogenesis within a tumor, often assessed by microvessel density, is also influenced by VEGF levels and reflects tumor aggressiveness (13).

The clinical significance of VEGF extends beyond its role as a biomarker. It has become an important therapeutic target in colorectal carcinoma. Anti-angiogenic agents, such as bevacizumab, a monoclonal antibody against VEGF, have shown significant benefit in the treatment of advanced and metastatic colorectal cancer when used in combination with chemotherapy (8). These therapies work by inhibiting tumor angiogenesis, thereby restricting tumor growth and spread. Consequently, evaluation of VEGF expression in tumor tissues may help identify patients who are more likely to benefit from targeted anti-angiogenic therapy (14).

Immunohistochemistry (IHC) is a commonly employed technique for detecting VEGF expression in formalin-fixed, paraffin-embedded tissue sections. It allows for localization of VEGF within tumor cells and surrounding stromal elements, providing both qualitative and semi-quantitative assessment (15). Correlating VEGF expression with clinicopathological parameters such as age, gender, tumor location, histological type, grade, stage, and lymph node status can provide valuable insights into its role in tumor biology and disease progression (16).

The present study aims to evaluate the expression of vascular endothelial growth factor in colorectal carcinoma and to correlate its expression with various clinicopathological parameters". Understanding these associations may enhance our knowledge of tumor behavior, assist in prognostication, and potentially contribute to the development of targeted therapeutic strategies in colorectal cancer management.

AIMS AND OBJECTIVES

Objectives:

- To evaluate the expression of VEGF in colorectal carcinoma.
- To correlate the VEGF expression in colorectal carcinoma with clinicopathological parameters.

MATERIAL AND METHODS

The present study was conducted in the Department of Pathology at KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, a tertiary care teaching hospital affiliated to KLE Academy of Higher Education and Research (KAHER). This hospital-based cross-sectional study was carried out over a period of one year from 1st April 2024 to 31st March 2025. A total of 40 cases of colorectal carcinoma constituted the sample size. All resected specimens obtained through colectomy, sigmoidectomy, anterior resection, and abdominoperineal resection for colorectal growths were included in the study. "In cases where the number of specimens exceeded the required sample size, selection was done in ascending numerical order, whereas retrospective samples were included if the number of cases during the study period was insufficient.

Only epithelial malignancies of the colorectum were included, while biopsy specimens, non-epithelial malignancies, cases with prior history of chemotherapy, and inadequately fixed or poorly preserved specimens were excluded. All specimens were received in the histopathology laboratory and immediately fixed in 10% neutral buffered formalin. Routine tissue processing was carried out, and paraffin-embedded blocks were prepared. Sections of 3–4 μm thickness were cut and stained with hematoxylin and eosin for histopathological evaluation, grading, and reporting. Representative sections were further subjected to immunohistochemical analysis for VEGF expression. The IHC interpretation was performed using a semi-quantitative scoring system based on the percentage of positive tumor cells and staining intensity, followed by combined scoring.

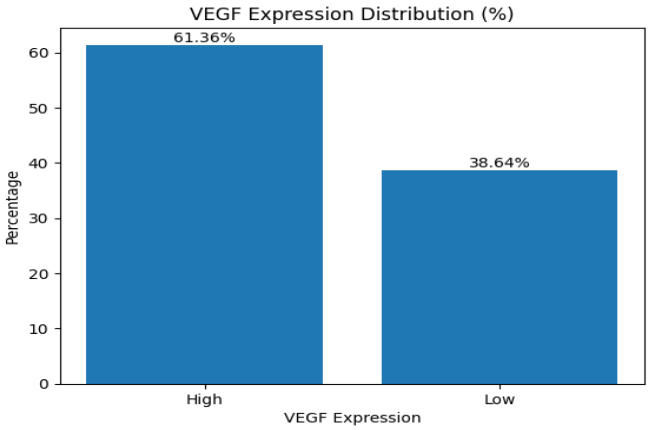
The collected data were systematically recorded and analyzed using appropriate statistical methods". Descriptive statistics were applied, wherein qualitative variables were expressed as percentages and quantitative variables as mean ± standard deviation. The association between VEGF expression and clinicopathological parameters was assessed to determine its potential role as a prognostic marker in colorectal carcinoma.

RESULTS

Table 1: Distribution of VEGF Expression in Colorectal Carcinoma (N=44)

VEGF Expression	n	%
High	27	61.36%
Low	17	38.64%

Graph 1: Distribution of VEGF Expression in Colorectal Carcinoma (N=44)

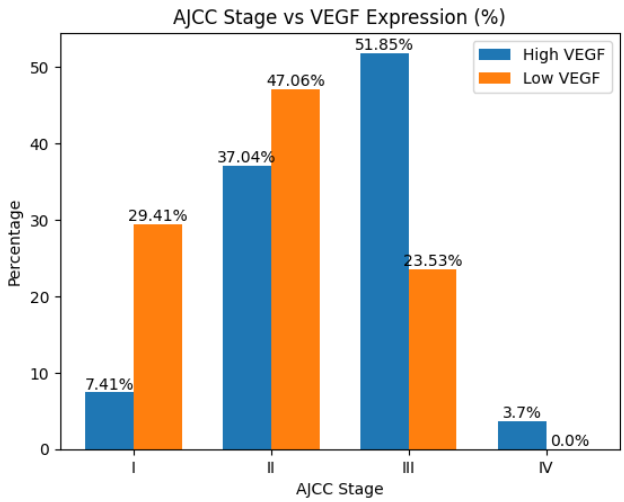


In the present study, high VEGF expression was observed in the majority of cases (61.36%), while low expression was seen in 38.64% of cases. This indicates that VEGF overexpression is common in colorectal carcinoma, supporting its role in tumor angiogenesis and progression.

Table 2: Association of VEGF Expression with AJCC Staging (N=44)

AJCC Stage	High VEGF (N=27)	Low VEGF (N=17)	Total	Chi-square	P value
I	2 (7.41%)	5 (29.41%)	7	5.46	0.141
II	10 (37.04%)	8 (47.06%)	18		
III	14 (51.85%)	4 (23.53%)	18		
IV	1 (3.70%)	0 (0%)	1		

Graph 2: Association of VEGF Expression with AJCC Staging (N=44)



High VEGF expression was predominantly observed in advanced stages, particularly Stage III (51.85%), whereas low VEGF expression was more common in early stages (Stage I and II). Although this trend suggests a relationship between VEGF expression and tumor progression, the association was not statistically significant (p=0.141).

Table 3: Association of VEGF Expression with pTNM Staging (N=44)

pTNM Stage	High VEGF	Low VEGF	Total	Chi-square	P value
T2N0M0	2	5	7	10.74	0.150
T2N1M0	2	0	2		
T3N0M0	9	8	17		
T3N1M0	5	1	6		
T3N2M0	5	1	6		
T4N0M0	1	0	1		
T4N1M0	3	1	4		
T4N2M0	0	1	1		

Higher VEGF expression was more frequently associated with advanced tumor invasion and nodal involvement (T3/T4 stages). However, the association between VEGF expression and pTNM staging was not statistically significant (p=0.150).

Table 4: Association of VEGF Expression with Histological Type (N=44)

Histological Type	High VEGF	Low VEGF	Total	Chi-square	P value
Adenocarcinoma NOS	14	15	29	3.40	0.334
Mucinous carcinoma	9	2	11		
Signet ring carcinoma	3	0	3		
Squamous cell carcinoma	1	0	1		

Adenocarcinoma NOS was the most common histological type. High VEGF expression was relatively more frequent in mucinous and signet ring carcinomas. However, no statistically significant association was found between histological type and VEGF expression (p=0.334).

Table 5: Association of VEGF Expression with Histological Grade (N=29)

Grade	High VEGF	Low VEGF	Total	Chi-square	P value
Grade 1	1	1	2	1.12	0.571
Grade 2	12	14	26		
Grade 3	1	0	1		

Most cases were Grade 2 tumors. High VEGF expression did not show a significant association with tumor grade (p=0.571), indicating limited correlation with histological differentiation.

Table 6: Association of VEGF Expression with Tumor Size (N=44)

Tumor Size	High VEGF	Low VEGF	Total	Chi-square	P value
≤5 cm	8	7	15	0.619	0.431
>5 cm	19	10	29		

Higher VEGF expression was observed more frequently in tumors larger than 5 cm. However, this association was not statistically significant (p=0.431).

Table 7: Association of VEGF Expression with Tumor Site (N=44)

Specific Site of Tumour	VEGF Expression		Total	Chi square	P value
	High (N=27)	Low (N=17)			
Caecum	2 (7.41)	0 (0%)	2 (4.55%)	7.73	0.259
Ascending Colon	6 (22.22)	4 (23.53%)	10 (22.73%)		
Hepatic Flexure	2 (7.41%)	0 (0%)	2 (4.55%)		
Splenic Flexure	1 (3.7%)	0 (0%)	1 (2.27)		
Descending Colon	2 (7.41%)	2 (11.76%)	4(9.09%)		
Sigmoid Colon	6 (22.22%)	9 (52.94%)	15 (34.09%)		
Rectum	8 (29.63%)	2 (11.76%)	10 (22.73%)		

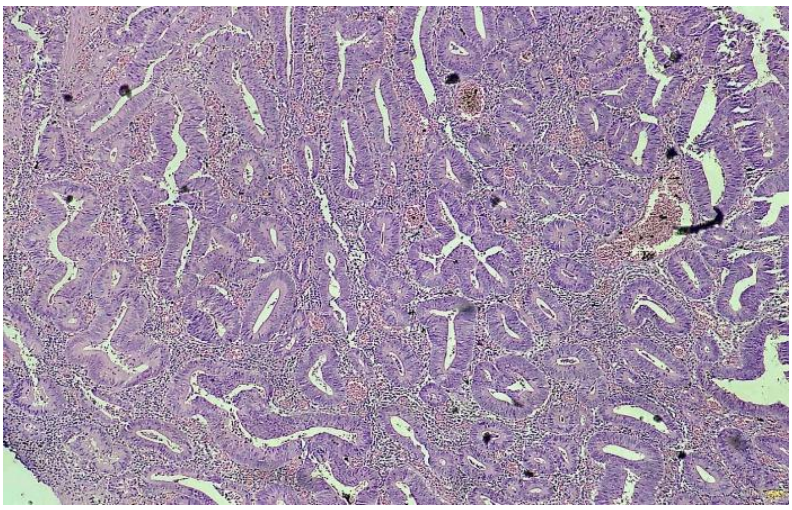
Rectum and sigmoid colon were the most common tumor sites. High VEGF expression was more frequent in rectal tumors, while low expression was more common in sigmoid colon. However, the association was not statistically significant (p=0.259).

Table 8: Association of VEGF Expression with LVI and PNI (N=44)

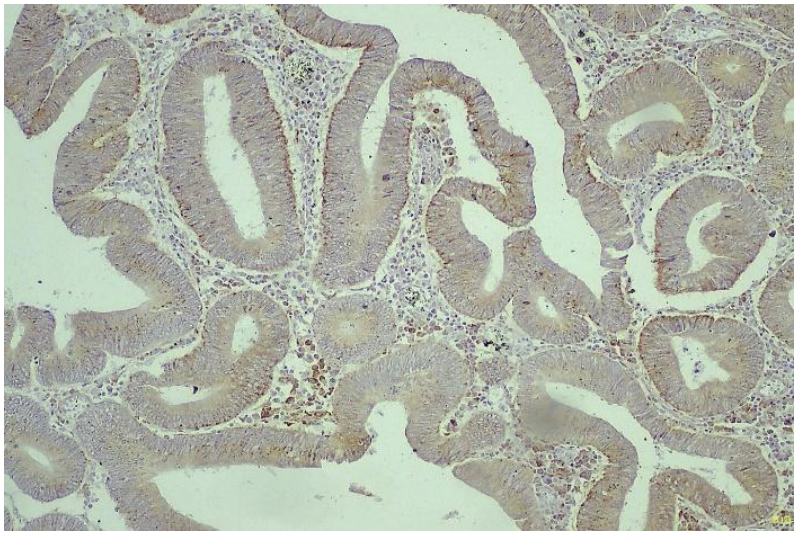
Parameter	Status	High VEGF	Low VEGF	Total	Chi-square	P value
LVI	Present	23	14	37	0.063	1.00
	Absent	4	3	7		
PNI	Present	26	6	32	19.57	<0.001
	Absent	1	11	12		

No significant association was observed between VEGF expression and lymphovascular invasion (p=1.00). However, a strong statistically significant association was found between VEGF expression and perineural invasion (p<0.001), with high VEGF expression markedly associated with presence of PNI. This suggests that VEGF may play a role in aggressive tumor behavior and neural invasion.

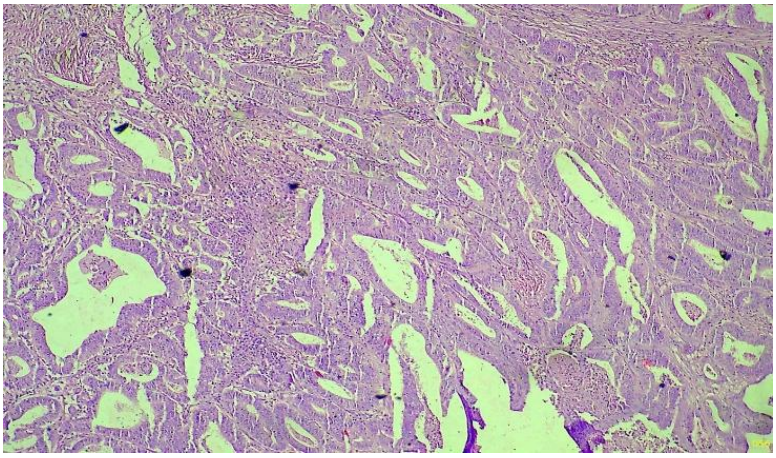
PHOTOMICROGRAPH



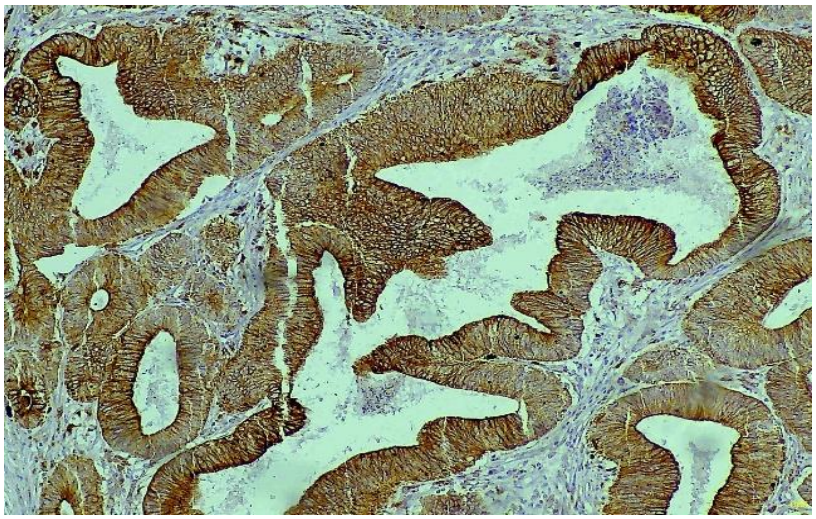
Photomicrograph 1a. Well differentiated Adenocarcinoma, H&E, 40X



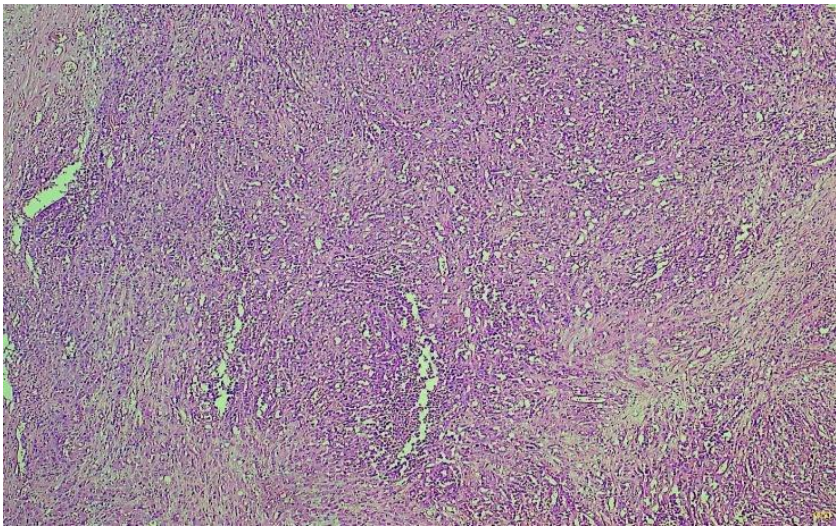
Photomicrograph 1b. Well differentiated Adenocarcinoma with low VEGF expression IHC 100x



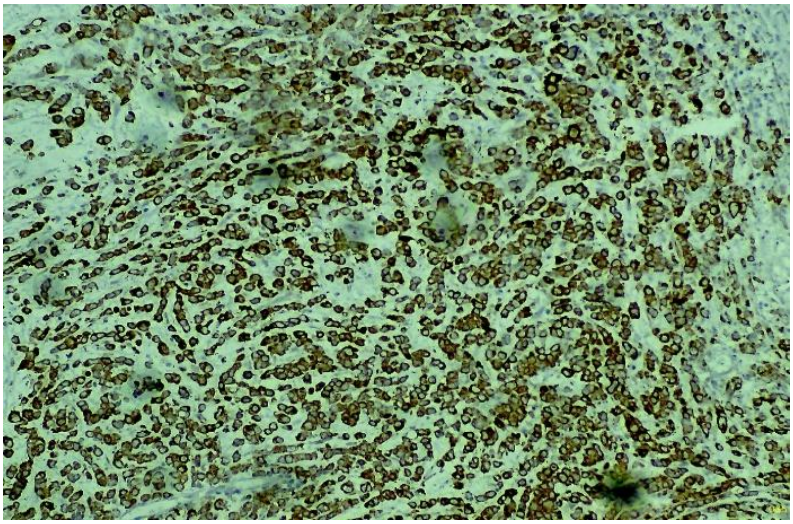
Photomicrograph 2a. Moderately differentiated Adenocarcinoma, H&E, 40X



Photomicrograph 2b. Moderately differentiated Adenocarcinoma with high VEGF expression IHC 100X



Photomicrograph 3a. Poorly differentiated Adenocarcinoma, H&E, 40X



Photomicrograph 3b. Poorly differentiated Adenocarcinoma with high VEGF expression IHC 100X

DISCUSSION

In the present study, high VEGF expression was observed in 61.36% of colorectal carcinoma cases, indicating that VEGF overexpression is a frequent event in colorectal tumor biology. This finding is in agreement with the established role of VEGF in promoting tumor angiogenesis, progression, and metastatic potential. Ferrara (2004) emphasized that VEGF is a central mediator of angiogenesis and plays a critical role in sustaining tumor vascularization (7). Similarly, Hicklin and Ellis (2005) described the VEGF pathway as a major driver of tumor growth and angiogenesis, supporting the biological basis for increased VEGF expression in colorectal carcinoma (12).

The predominance of high VEGF expression in the present study is comparable to the observations of Balasubramanian et al. (2022), who demonstrated significant VEGF expression in colorectal adenoma and carcinoma, suggesting that angiogenic activity increases along the adenoma-carcinoma sequence (11). This concept is also supported by Staton et al. (2007), who reported that the angiogenic switch begins at the adenoma stage, and by Hanrahan et al. (2003), who documented progressive alteration in VEGF family expression during colorectal cancer progression (17,18). “These findings collectively indicate that VEGF overexpression is involved not only in established carcinoma but also in early tumor evolution.

In the present study, high VEGF expression was more frequently seen in advanced AJCC stages, particularly Stage III, and in tumors with higher pTNM categories, although these associations were not statistically significant. A similar trend was reported by Zheng et al. (2003), who found that VEGF expression and neovascularization were closely related to tumor progression in colorectal carcinoma (19). Hashim et al. (2010) also observed that VEGF receptor expression correlated with tumor stage and histologic grade,

suggesting that angiogenic markers become more prominent with advancing disease (20). Although statistical significance was not achieved in the present study, the higher proportion of VEGF positivity in advanced stages may still reflect its contribution to aggressive tumor behavior.

Regarding histological type, the present study showed relatively higher VEGF expression in mucinous and signet ring carcinomas compared with conventional adenocarcinoma, though without statistical significance. This may suggest that tumors with more aggressive histomorphological patterns tend to show increased angiogenic activity. Ahmed and Ilias (2024) also evaluated VEGF in relation to clinicopathological variables in colorectal cancer and highlighted its association with markers of tumor aggressiveness (10). Martins et al. (2011) similarly supported the prognostic relevance of VEGF family expression in colorectal carcinoma (21).

An important finding of the present study was the strong association between high VEGF expression and perineural invasion, which was statistically significant. This observation indicates a possible link between angiogenic signaling and locally aggressive tumor spread. Wang et al. (2023) discussed the clinical relevance of perineural invasion in colorectal cancer and emphasized its association with adverse prognosis (22). Chen et al. (2019) further explained that perineural invasion results from complex molecular crosstalk within the perineural niche, and VEGF may contribute to such a microenvironment (23). In contrast, lymphovascular invasion did not show a significant association with VEGF expression in the present study". This differs from Liana et al. (2022), who reported an association between VEGF expression and lymphovascular invasion in colorectal adenocarcinoma. Such differences may be attributable to variations in sample size, tumor distribution, and scoring methods (24).

Overall, the present study supports the role of VEGF as an important angiogenic marker in colorectal carcinoma. Its frequent overexpression and significant association with perineural invasion suggest that VEGF may reflect aggressive tumor biology. Although some clinicopathological correlations were not statistically significant, the observed trends are consistent with previous studies by Zheng et al. (2003), Balasubramanian et al. (2022), Hashim et al. (2010), and Ahmed and Ilias (2024), thereby reinforcing the potential prognostic and therapeutic relevance of VEGF in colorectal carcinoma (10,11,19,20).

CONCLUSION

The present study demonstrates that vascular endothelial growth factor (VEGF) is frequently overexpressed in colorectal carcinoma, highlighting its significant role in tumor angiogenesis and progression. "A higher proportion of cases showed increased VEGF expression, suggesting its involvement in tumor growth and aggressive biological behavior. Although most clinicopathological parameters such as stage, tumor size, histological type, and grade did not show statistically significant association, a clear trend of higher VEGF expression in advanced stages was observed. Notably, a strong and statistically significant association was found between VEGF expression and perineural invasion, indicating its potential role in local tumor aggressiveness and spread. These findings suggest that VEGF can serve as a useful biomarker for assessing tumor behavior in colorectal carcinoma". Furthermore, evaluation of VEGF expression may aid in identifying patients who could benefit from targeted anti-angiogenic therapies, thereby contributing to improved prognostication and personalized treatment strategies.

REFERENCES

1. Klimeck L, Heisser T, Hoffmeister M, Brenner H. Colorectal cancer: A health and economic problem. Best Pract Res Clin Gastroenterol. 2023;66:101839. doi:10.1016/j.bpg.2023.101839.

2. Jin X, Dong D, Xu Z, Sun M. The global burden of colorectal cancer attributable to high body-mass index in 204 countries and territories: findings from 1990 to 2021 and predictions to 2035. Front Nutr. 2024;11:1473851. doi:10.3389/fnut.2024.1473851.

3. Kwan ASH, Uwishema O, Mshaymesh S, Choudhary K, Salem FK, Sengar AS, et al. Advances in the diagnosis of colorectal cancer: the application of molecular biomarkers and imaging techniques: a literature review. Ann Med Surg (Lond). 2025;87(1):192. doi:10.1097/MS9.0000000000002830.

4. Bardhan K, Liu K. Epigenetics and colorectal cancer pathogenesis. Cancers (Basel). 2013;5(2):676–684. doi:10.3390/cancers5020676.

5. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. Cell Mol Life Sci. 2020;77(9):1745–1770. doi:10.1007/s00018-019-03351-7.

6. Liu ZL, Chen HH, Zheng LL, Sun LP, Shi L. Angiogenic signaling pathways and anti-angiogenic therapy for cancer. Signal Transduct Target Ther. 2023;8(1):198. doi:10.1038/s41392-023-01460-1.

7. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev. 2004;25(4):581–611. doi:10.1210/er.2003-0027.

8. Ghalehbandi S, Yuzugulen J, Pranjol MZI, Pourgholami MH. The role of VEGF in cancer-induced angiogenesis and research progress of drugs targeting VEGF. Eur J Pharmacol. 2023;949:175586. doi:10.1016/j.ejphar.2023.175586.

9. Cao D, Hou M, Guan YS, Jiang M, Yang Y, Gou HF. Expression of HIF-1alpha and VEGF in colorectal cancer: association with clinical outcomes and

prognostic implications. BMC Cancer. 2009;9:432. doi:10.1186/1471-2407-9-432.

10. Ahmed H, Ilias M. Colorectal cancer in correlation with clinicopathological variables: the effects of hypoxia-inducible factor-1 alpha or interleukin-33 and vascular endothelial growth factor. Cureus. 2024;16(1):e51658. doi:10.7759/cureus.51658.

11. Balasubramanian S, Priyathersini N, Johnson T. Expression of vascular endothelial growth factor (VEGF) in colorectal adenoma and carcinoma in a tertiary care center. Cureus. 2022;14(11):e31393. doi:10.7759/cureus.31393.

12. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol. 2005;23(5):1011–1027. doi:10.1200/JCO.2005.06.081.

13. Wang Y, Yao X, Ge J, Hu F, Zhao Y. Can vascular endothelial growth factor and microvessel density be used as prognostic biomarkers for colorectal cancer? A systematic review and meta-analysis. ScientificWorldJournal. 2014;2014:102736. doi:10.1155/2014/102736.

14. Ciombor KK, Goldberg RM. Update on anti-angiogenesis therapy in colorectal cancer. Curr Colorectal Cancer Rep. 2015;11(6):378–387. doi:10.1007/s11888-015-0292-3.

15. Chung JY, Braunschweig T, Hong SM, Kwon DS, Eo SH, Cho HJ, et al. Assessment of vascular endothelial growth factor in formalin-fixed, paraffin-embedded colon cancer specimens by means of a well-based reverse phase protein array. Proteome Sci. 2014;12(1):27. doi:10.1186/1477-5956-12-27.

16. Hutajulu SH, Paramita DK, Santoso J, Sani MIA, Amalia A, Wulandari G, et al. Correlation between vascular endothelial growth factor-A expression and tumor location and invasion in patients with colorectal cancer. J Gastrointest Oncol. 2018;9(6):1099–1106. doi:10.21037/jgo.2018.07.01.

17. Staton CA, Chetwood ASA, Cameron LC, Cross SS, Brown NJ, Reed MWR. The angiogenic switch occurs at the adenoma stage of the adenoma-carcinoma sequence in colorectal cancer. Gut. 2007;56(10):1426–1432. doi:10.1136/gut.2007.125286.

18. Hanrahan V, Currie MJ, Gunningham SP, Morrin HR, Scott PAE, Robinson BA, et al. The angiogenic switch for vascular endothelial growth factor (VEGF)-A, VEGF-B, VEGF-C and VEGF-D in the adenoma-carcinoma sequence during colorectal cancer progression. J Pathol. 2003;200(2):183–194. doi:10.1002/path.1339.

19. Zheng S, Han MY, Xiao ZX, Peng JP, Dong Q. Clinical significance of vascular endothelial growth factor expression and neovascularization in colorectal carcinoma. World J Gastroenterol. 2003;9(6):1227–1230. doi:10.3748/wjg.v9.i6.1227.

20. Hashim AF, Al-Janabi AA, Mahdi LH, Al-Toriahi KM, Yasseen AA. Vascular endothelial growth factor receptor expression correlates with histologic grade and stage of colorectal cancer. Libyan J Med. 2010;5:5059. doi:10.3402/ljm.v5i0.5059.

21. Martins SF, Reis RM, Rodrigues AM, Baltazar F, Filho AL. Role of endoglin and VEGF family expression in colorectal cancer prognosis and anti-angiogenic therapies. World J Clin Oncol. 2011;2(6):272–280. doi:10.5306/wjco.v2.i6.272.

22. Wang H, Huo R, He K, Cheng L, Zhang S, Yu M, et al. Perineural invasion in colorectal cancer: mechanisms of action and clinical relevance. Cell Oncol (Dordr). 2023;47(1):1–13. doi:10.1007/s13402-023-00857-y.

23. Chen SH, Zhang BY, Zhou B, Zhu CZ, Sun LQ, Feng YJ. Perineural invasion of cancer: a complex crosstalk between cells and molecules in the perineural niche. Am J Cancer Res. 2019;9(1):1–21.

24. Liana N, Hilbertina N, Devianti L, Yetti H. The association of VEGF expression with degree of differentiation and lymphovascular invasion in colorectal adenocarcinoma. Maj Patol Indones. 2022;31(1):368–375. doi:10.55816/mpi.v31i1.490.