ISSN: 3067-8528
Research Article
American Journal of Clinical Pathology Research

Association of Vascular Endothelial Growth Factor (VEGF) Expression with Histological Stage in Gastric Carcinoma

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Submitted: 21 July 2025 **Accepted:** 29 July 2025 **Published:** 05 August 2025

https://doi.org/10.63620/MKAJCPR.2025.1011

Citation: *Saha, N., Adhikary, L., Tabassom, T., Chowdhury, G., Podder, O. R., Podder, A. R., Saba, S., & Haque, S. M. A. (2025). Association of Vascular Endothelial Growth Factor (VEGF) Expression with Histological Stage in Gastric Carcinoma. Ame Jo Clin Path Res, 2(3), 01-07.*

Abstract

Background: *Gastric carcinoma (GC) is one of the most prevalent forms of human cancer worldwide and a significant public health concern. Histopathologic grade and stage are well-established prognostic indicators; however, additional biomarkers are needed to better predict patient outcomes and enhance targeted treatment strategies. Vascular endothelial growth factor (VEGF) plays a crucial role in the growth and progression of GC and can be used as a complementary tool to GC histopathological characteristics.*

Objective: *To determine the immunohistochemical expression of vascular endothelial growth factor (VEGF) in gastric cancer (GC) in relation to tumor stage.*

Materials and Methods: *It was a cross-sectional descriptive study conducted in the Department of Pathology, Mymensingh Medical College, Mymensingh and BSMMU, Dhaka over the period of March 2021 to February 2023. Total 50 samples (29 resected specimen that underwent partial or total gastrectomy in the Department of Surgery, MMCH & 21 paraffin embedded gastric tissue collected from BSMMU) were studied. TNM staging was done as per AJCC and immunohistochemical staining for VEGF was performed.*

Results: *In this study, 11(22%) cases were in stage I, 14(28%) cases stage II and 25 (50%) cases were in stage III. Most of the stage II (71.4%) and III (80%) tumors revealed a positive Vegf expression. On the other hand, most of the cases of stage I (36.4%) showed negative/weak VEGF expression. Statistically significant ($p<0.05$) differences were observed between VEGF expression and tumor stages.*

Conclusion: *The study was carried out to evaluate the expression of VEGF in gastric carcinoma. It was observed that Vegf expression was significantly associated with histological stage*

Keywords: Gastric Carcinoma (GC), Angiogenesis, VEGF, Immunohistochemistry.

Introduction

Gastric cancer (GC) is a global health problem, with more than one million people newly diagnosed worldwide each year, almost two-thirds occurring in developing countries. Although improvements in systemic therapy have been made, the mortality rate is still high, with five-years survival rate only around 30% worldwide [1]. Gastric cancer (GC) is also a leading cancer in Bangladesh with a prevalence rate of 6.21 per 100000 population according to Globocan 2020 [2]. The development of gastric cancer is a complex and multifactorial process involving a number of etiological factors [3, 4].

It is known that malignant tumors depend on neovascularization for their growth and metastasis and it is so important that a malignant tumor cannot grow more than 3 mm in the absence of blood vessels [5]. It has also been suggested that the degree of tumor angiogenesis is related to clinical outcome, suggesting that angiogenic properties may be associated with tumor aggressiveness [6]. One of the tumor-secreted angiogenesis factors, such as Vegf, appears to play an important role in tumor angiogenesis [7]. Vegf promotes endothelial cell proliferation and angiogenesis, and increases vascular permeability to serum proteins. This provides a basis for migration of endothelial cells and metastasis of tumor cells.

The rate of expression of Vegf in gastric carcinoma are higher than those in the normal gastric tissue [8]. it is significantly correlated with vascular invasion. Patients with positive staining for Vegf showed a significantly lower survival rate than VEGF negative patients [9].

In case of gastric carcinoma, angiogenesis is a promising therapeutic target to inhibit tumor growth. Recently, numerous clinical studies on anti-angiogenic drugs have been performed in patients with GC. Among them monoclonal antibodies like Bevacizumab (Avastin®, Roche-Genentech) And Ramucirumab has been shown to have a significant antitumor activity against GC in preclinical and clinical studies which act by inhibiting the function of Vegf receptor [10, 11].

However, almost two-thirds of patients with gastric cancer diagnosed when the disease is already at an advanced stage and is not manageable by radical surgical treatment. Despite advances in diagnostic techniques, targeted therapy and surgery, the treatment outcome of gastric cancer remains poor. So that, the inhibition of angiogenesis has received considerable attention in oncological research of gastric cancer [12].

Materials and Methods

This was a cross-sectional descriptive study. The study was carried out at the Department of Pathology, Mymensingh Medical College, Mymensingh and the Department of Pathology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. The study was carried out from March 2021 to February 2023. The samples were taken from 50 patients during the period of March, 2021 to February, 2023.Among them 29 resected gastrectomy samples who underwent total or partial gastrectomy for gastric carcinoma in Surgery Department of MMCH. Other 21 paraffin blocks of diagnosed gastric carcinoma were taken from BSMMU.

All the 29 specimens were fixed with 10% neutral buffered formalin for 24 hours.

The specimens were subsequently processed and examined at the Department of Pathology, MMCH, for histopathological examination. The 21 paraffin blocks collected from BSMMU were sectioned at 3-4 micrometer thickness and slides were prepared. All slides were stained with Haematoxylin and eosin-stain and microscopic evaluation of tumor stage was done. Tumor staging was done according to AJCC (2018). Immunohistochemistry was done for all cases in the Department of Pathology at Bangabandhu Sheikh Mujib Medical University (BSMMU). Placental tissues were used as positive control. VEGF were considered positive only if cytoplasmic staining were observed.

Scoring System for Assessment of Vegf Expression

VEGF expression was evaluated using a scoring system based on two parameters: the proportion of stained tumor cells and the intensity of staining among all malignant cell.

Percentage score of VEGF expression was counted as follows: <1% = 0,1-25% = 1, 26-50% = 2, >50% = 3
Intensity of VEGF staining was counted as follows: negative = 0, weak = 1, intermediate = 2, strong = 3.

Final score of VEGF was calculated by adding two previous score as negative = 0, weak positive = 1-2, moderate positive = 3-4, strong positive = 5-6 [5, 13].

For statistical purposes, the negative and weak positive immunoreaction were considered as negative/weak group, on the other hand moderate and strong positive immunoreaction final scores were considered as positive group [5, 13].

Results and Observations

Statistical analysis was done using the SPSS software version 26. A total number of 50 diagnosed cases of gastric adenocarcinoma were taken for this study. Age distribution of the patient was ranged from 22-76 years. 17 (34.0%) were in 41-50 years age group and 15 (30.0%) patients were in 51-60 years age group. The mean age of the patients was 52.3 (±11.5) years.

Table 1: Distribution of Patients by Age (n=50)

Age group (in years)	Frequency (n)	Percentage (%)
Up to 40	9	18.0
41-50	17	34.0
51-60	15	30.0
>60	9	18.0
Mean (±SD) (range)	52.3 (±11.5) (22-76)	

32 (64.0%) patients were male while 18 (36.0%) patients were female with male female ratio of 1.7:1.

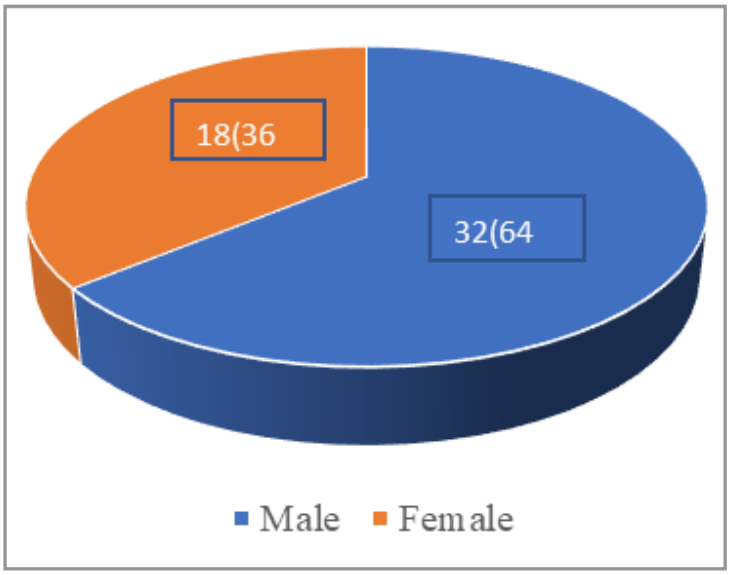


Figure 1: Sex Distribution of Patients: The Maximum Numbers of Lesion 23 (46.0%) were Found in Antrum Followed by Lesser Curvature 16 (32.0%), Greater Curvature 5 (10.0%), Body 4 (8.0%) and Gastric Cardia 2 (4.0%).

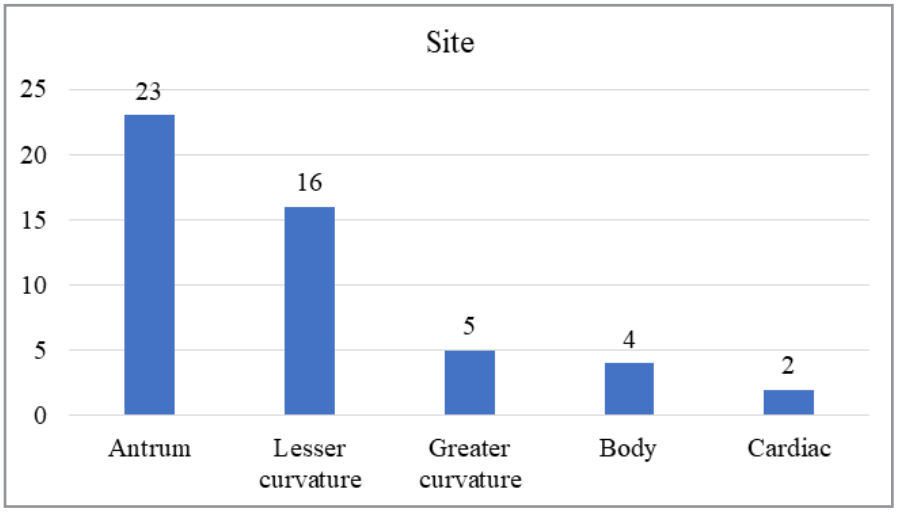


Figure 2: Bar Diagram of The Patients According to Site of Tumor (n=50)

According to TNM Staging, 13 (26.0%) Patients were in T2 Stage and 17 (34.0%) were in T3 Stage. In 21 (42.0%) Patients, Nearby Lymph Nodes Could not be Measured While 14 (18%) Patients were in N2 Stage. Metastasis Could Not be Measured in any Patient.

Table 2: Patient Distribution According to Staging (TNM) (n=50)

Staging	Frequency (n)	Percentage (%)
T staging		
T1	1	2.0
T2	13	26.0
T3	17	34.0
T4	7	14.0
T4a	9	18.0
T4b	3	6.0
N staging		
NX	21	42.0
N1	9	18.0
N2	14	28.0

N3	4	8.0
N3a	2	4.0
M staging		
MX	50	100.0

According to Pathological Staging, 1(2%) Patient was in Stage IA and 10(20%) Patients were in Stage IB. 11(22%) Patients were in Stage IIA and 2(4%) patients were in Stage IIB. Whereas, 15(30%) Patients were in Stage IIIA and 11(22%) Patients were in Stage IIIB.

Table 3: Patients Distribution by Pathological Staging (n=50)

Stage		Frequency	Percentage (%)
Stage I	IA	1	2.0
	IB	10	20.0
Stage II	IIA	11	22.0
	IIB	2	4.0
Stage III	IIIA	15	30.0
	IIIB	11	22.0

3 (6.0%) Patients had Negative Expression of Vegf. on the Other Hand, 13 (26.0%) Patients Had Weak Staining (1+) Intensity and 22 (44.0%) Patients had Moderate Staining (2+) Intensity. Remaining 12 (24.0%) Patients had Strong Staining (3+) Intensity.

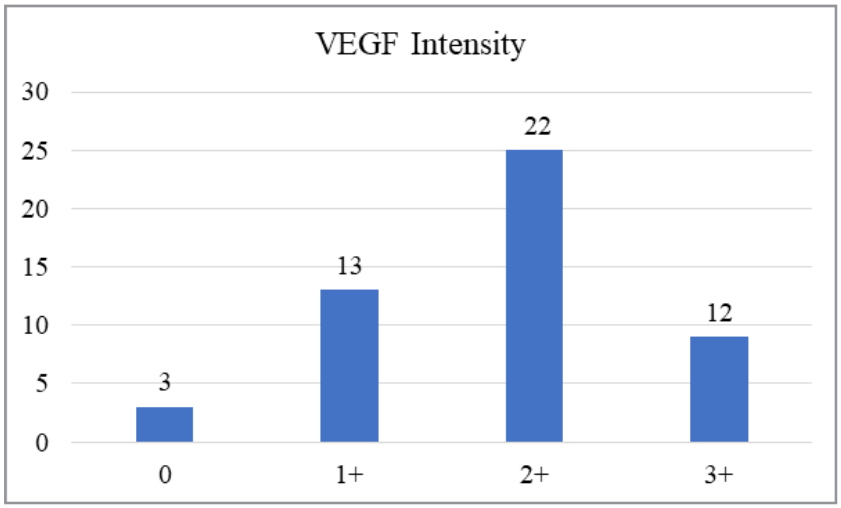
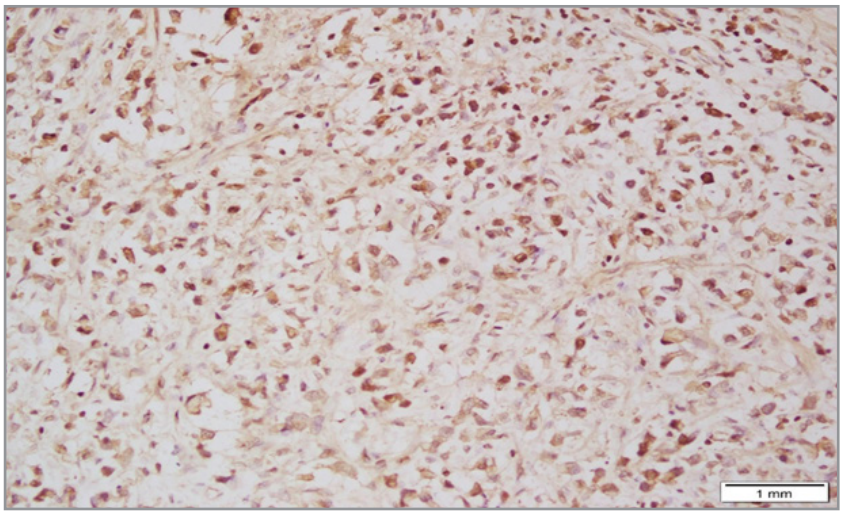


Figure 3: Bar Diagram of the Patients by Vegf Intensity (n=50)

Fisher's Exact Test was used for Comparison Between Vegf Expression and Age of Patient. No Significant Association was Found Between Age Group and Vegf Expression as p=0.124.

Figure 4: Patterns of Vascular Endothelial Growth Factor (VEGF) Immunostaining in Gastric Carcinomas.



- **Figure 4(a):** VEGF expression: Strong positive (+++),

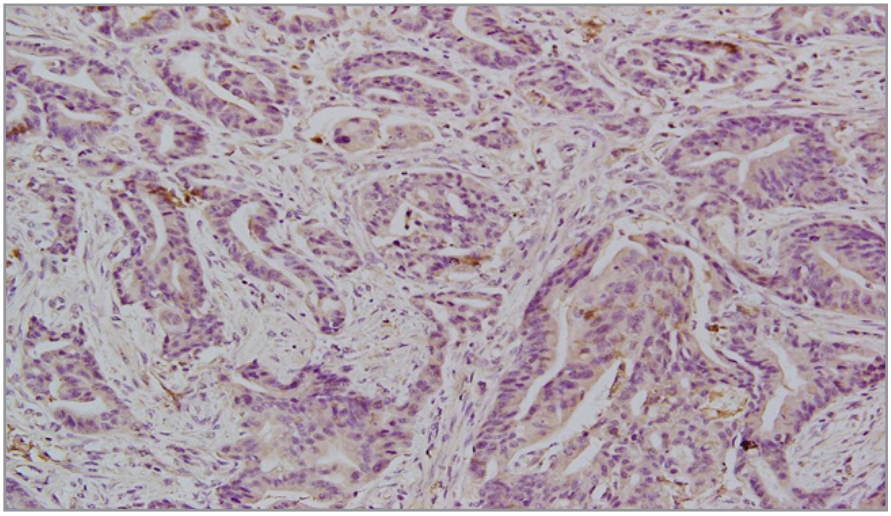


Figure 4(b): VEGF expression: Moderate positive (++),

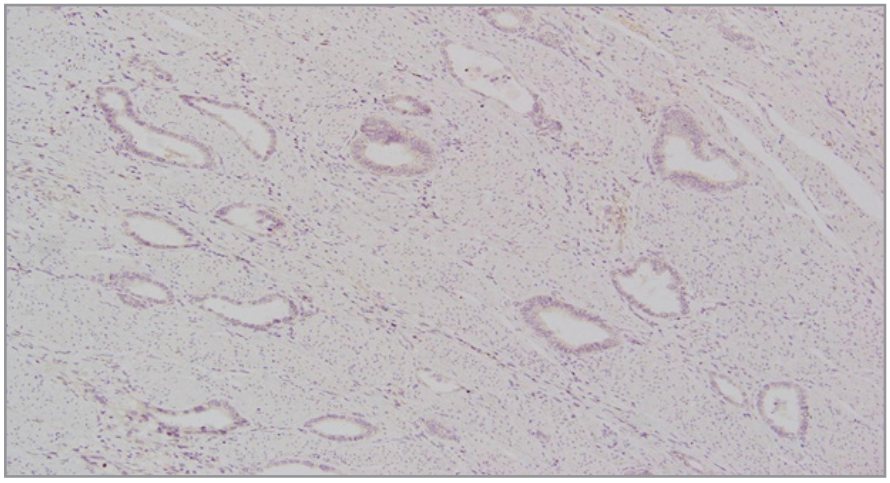


Figure 4(c): VEGF expression: Weak positive (+),

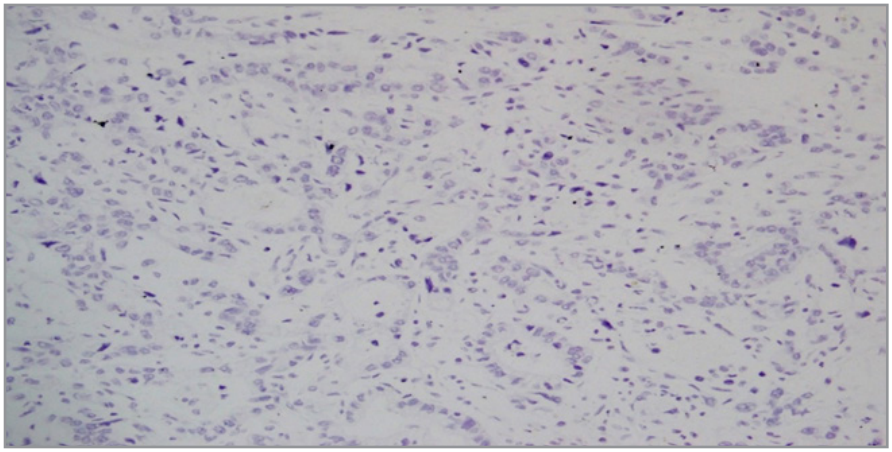


Figure 4(d): VEGF expression: Negative (-) (40X)

Table 4: Association Between Age Group and Vegf Expression (N=50)

Age group (years)	VEGF Expression		P value
	Negative/ weak	Positive	
Up to 40	1 (11.1%)	8 (88.9%)	0.124ns
41-50	9 (52.9%)	8 (47.1%)	
51-60	3 (20.0%)	12 (80.0%)	
>60	3 (33.3%)	6 (66.7%)	

Association of Vegf Expression with Stage of Gastric Carcinoma were Analyzed by Fisher's Exact Test. P Value Less Than 0.05 ($p< 0.05$) Was Considered Statistically Significant. For Statistical Purposes, the Stage IA and IB were Considered as Stage I, on the Other Hand Stage IIA and IIB Were Considered as Stage Group II, and Stage IIIA and IIIB Were Considered as Stage Group III. Fisher Exact Test Showed That There was Significant Association Between Staging and Vegf Expression as p=0.04.

Table 5: Association Between Staging and Vegf Expression (n=50)

Staging	Expression		P value
	Negative/ weak	Positive	
I	7 (63.6%)	4 (36.4%)	
II	4 (28.6%)	10 (71.4%)	0.043s
III	5 (20.0%)	20 (80.0%)	

Discussion

In the present study, age distribution of the patients was ranged from 22-76 years. The mean age of the patients was 52.3 (±11.5) years ranged from 22-76 years. The study showed no significant association was found between age group and VEGF expression as p=0.124. However, peak incidence of patient's age group in other study was higher than that of our current study [14]. Maeda and his team observed that, among 129 patients, 95 were men, and 34 were women. The patients ranged in age from 33 to 78 years (average age, 59.3 years), which is similar to this study.6 In the current study, according to TNM staging, 13 (26.0%) patients were in T2 stage and 17 (34.0%) were in T3 stage. In 21 (42.0%) patients, nearby lymph nodes could not be measured while 14 (18%) patients were in N2 stage. Iordache and his colleague showed 77.5% patients in 3rd and 4th TNM stages. Among 40 patients, only 3 were in the first TNM stage and 6 in second TNM stage [4].

Most of the stage II (71.4%) and III (80%) tumors showed a positive VEGF expression. On the other hand, most of the cases of stage I (36.4%) showed negative/weak VEGF expression. Statistically significant ($p<0.05$) differences were observed between VEGF expression and tumor stages. Several other studies got the significant association between Vegf expression and staging of tumor
[3, 6].

Conclusion

The study was carried out to evaluate the expression of Vegf in gastric carcinoma. It was observed that Vegf expression was significantly associated with histological stage but not associated with lymph vascular invasion & perineural invasion. It revealed Vegf expression was associated with higher stage of gastric carcinoma. Thus, assessing Vegf expression in Gc provides valuable prognostic information and helps to identify high risk patients.

Acknowledgements

We thank Prof. Dr. Shaikh Alamgir Hossain, ex-Head of Department, Department of Pathology, Mymensingh Medical College, for his careful and expert guidance, constructive criticism, useful suggestions, and loving advice.

Author Contributions

Saha N prepared the research protocol and was responsible for data collection, arranging the data analysis and preparing the manuscript, grossing and microscopy. The rest were responsible for conceptualizing the study and assisted in protocol development, manuscript preparation, proofreading, grossing and microscopy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

None.

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