

Vascular Endothelial Growth Factor (VEGF-C) as a Perioperative Serum Biomarker for Gastric Cancer Prognostication

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ABSTRACT

Background: Vascular Endothelial Growth Factor (VEGF) plays a critical role in tumor angiogenesis, progression, and metastasis. Despite advances in gastric cancer treatment, the prognosis remains poor, necessitating better biomarkers for risk stratification and assessing tumor biology to provide individualised care. This study evaluates VEGF-C as a prognostic biomarker in patients with gastric carcinoma.

Methods: A prospective cohort of 46 histologically confirmed gastric carcinoma patients was studied. Serum VEGF-C levels were measured preoperatively and post-operatively using ELISA. Clinicopathological features and survival data were collected and analyzed using SPSS. Perioperative VEGF-C levels were correlated with patient-tumor characteristics and survival outcomes using t-tests, correlation analysis, and Kaplan-Meier survival curves.

Results: Most patients were male (78.3%) and over 60 years old (54.3%). A majority had distal gastric tumors (69.6%) and stage IV disease (43.5%). Elevated preoperative VEGF-C was significantly associated with lymphatic involvement ($p < 0.001$), systemic metastasis ($p = 0.012$), and poorer survival. VEGF-C levels significantly decreased post-surgery (mean difference: 437.67 pg/mL, $p < 0.001$). Kaplan-Meier analysis revealed patients with greater fall in VEGF-C levels ($> 50\%$) post-surgery had a better median survival (17 months) compared to those with no/poor fall in VEGF-C levels (17 months) (Log-rank $p = 0.013$).

Conclusion: Increased serum VEGF-C levels is significantly associated with aggressive tumor biology and adverse prognosis in gastric carcinoma patient. Monitoring VEGF-C levels in the perioperative period may guide therapeutic decisions and predict clinical outcomes.

Keywords: VEGF-C, gastric carcinoma, prognosis, biomarker, tumor biology, perioperative levels

INTRODUCTION

Gastric cancer remains one of the leading causes of cancer-related mortality globally, particularly in East and South Asia (1). In India, it accounts for the fifth most common malignancy in adult males and seventh most common cancer in adult females (2) Despite advancements in surgical techniques and adjuvant therapies, survival rates remain dismal largely due to its high metastatic

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potential, delayed presentation with advanced stage and delayed diagnosis (3). Tumor angiogenesis is essential for cancer growth and metastasis. Vascular Endothelial Growth Factor (VEGF) is a key angiogenic factor secreted by tumor cells promoting endothelial proliferation, vascular permeability, and neovascularization (4). Elevated VEGF expression has been reported in various malignancies, especially gastric cancer, and is associated with tumor aggressiveness and poor prognosis (5). Several studies have explored tissue-based VEGF expression using immunohistochemistry (IHC), yet serum-based VEGF measurements offer a minimally invasive alternative with potential for dynamic monitoring (6). VEGF-C has been overexpressed in 30-60% of gastric cancer patients and increased serum levels has been associated with poor prognosis (7). In this study, we evaluated the pre-operative and post-operative levels of serum VEGF-C in gastric cancer patients to determine their association with clinicopathological features, and prognostic implications for survival.

MATERIALS AND METHODS

Study Design and Participants

This prospective observational study was conducted on 46 patients with histopathologically confirmed gastric carcinoma at the Institute of Surgical Gastroenterology,

Madras Medical College, Rajiv Gandhi Government General Hospital, Chennai – 600003 between July 2022 to June 2025 (including a two year follow up for survival analysis). Indian Patients aged >18 years, who underwent elective surgery were included. Patients with previous / concurrent history of other malignancies, emergency procedures, severe comorbidities, autoimmune and inflammatory conditions are excluded.

Ethical Approval

The study was approved by the Institutional Ethics Committee (IEC no. 16072022) and a written informed consent was obtained from all participants.

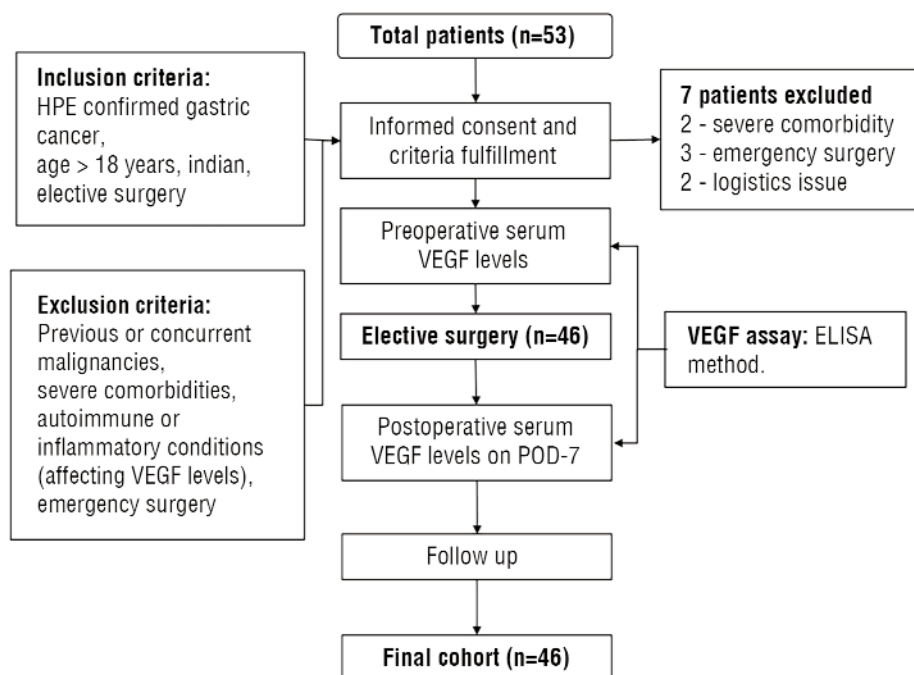
Data Collection

Demographic and clinical details including age, sex, BMI, blood group, comorbidities, past treatment history, alcohol/smoking history, ECOG performance status, tumor location, staging, intraoperative findings, procedure details and postoperative recovery were documented and patients were followed up as shown by the study flow diagram (fig. 1).

VEGF Assay

Blood samples were collected from the patients pre-operatively on the day before surgery and post-operatively on postoperative day 7. Serum VEGF-C levels

Figure 1 - Study Flow diagram



were measured using a commercially available ELISA kit (Elbasience Human VEGF-C ELISA) according to manufacturer instructions. All samples were run in duplicate.

Statistical Analysis

Data were analyzed using SPSS v26. Continuous variables were expressed as mean $\pm$ SD, and categorical variables as frequency (%). Paired t-tests were used to compare pre- and post-op VEGF levels. Correlations were assessed using Pearson's correlation coefficient. Group comparisons were performed using independent t-tests and ANOVA. Survival analysis was conducted using Kaplan-Meier curves, with comparisons via Log-rank, Breslow, and Tarone-Ware tests. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Profile

Out of 46 patients, 78.3% were male, and 54.3% were over 60 years of age. Most had a normal BMI (58.7%), while 30.4% were underweight. Blood group O+ve was the most common (47.8%). Substance use history included alcohol (15.2%), smoking (13%) or both (26.1%). Comorbidities were present in 39.1% and 13% had a family history of cancer (*table 1*).

Tumor Characteristics

Distal gastric cancer accounted for more than two-third of the cases (69.6%) with a mean pre-operative VEGF-C level of 1287 ($\pm$ 605) pg/ml. Proximal gastric cancers and stump carcinoma accounted for 23.9 % and 6.5% respectively with mean VEGF-C levels of 1292 ($\pm$ 559) pg/ml and 1259 ($\pm$ 531) pg/ml respectively. All patients were taken up for elective surgery and among them 52.2% and 6.5% underwent D2 and D1 gastrectomies respectively. As features of advanced (Stage IV) disease were noted intraoperatively in 41.3% of cases, they underwent palliative options of Gastro-jejunostomy or feeding jejunostomy. Postoperative histo-pathological examination revealed that 34.8% had moderately differentiated adenocarcinoma with lymphatic involvement in 89.1%, and systemic metastasis in 19.6% cases as represented in *table 1*.

VEGF Levels and Surgical Outcome

Preoperative VEGF levels averaged 1285.67 $\pm$ 578.53 pg/mL. Patients with metastatic disease had

Table 1 - Demographics and clinicopathological features of patients

Variables	Patients (n = 46)
Gender	
Male	36 (78.3)
Female	10 (21.7)
Age < 60	21 (45.7)
Age > 60	25 (54.3)
Blood Group	
(O+ve)	22 (47.8)
A+ve	7 (15.2)
B+ve	15 (32.6)
AB+ve	2 (4.3)
BMI <18.5	14 (30.4)
BMI 18.5-24.9	27 (58.7)
BMI 25-29.9	5 (10.9)
Alcohol	7 (15.2)
Smoking	6 (13.0)
Alcohol and Smoking	12 (26.1)
Family history of malignancy	6 (13.0)
Co-Morbidity	18 (39.1)
ECOG 0, 1	16 (34.8)
ECOG 2	30 (65.2)
Distal gastric cancer	32 (69.6)
Proximal gastric cancer	11 (23.9)
Stump carcinoma	3 (6.5)
D1 Gastrectomy	3 (6.5)
D2 Gastrectomy	24 (52.2)
Palliative Surgery	19 (41.3)
Clinical stage - I	4 (8.7)
Clinical Stage II	8 (17.4)
Clinical Stage III	14 (30.4)
Clinical Stage IV	20 (43.5)
Lymphatic involvement	41 (89.1)
Systemic metastasis	9 (19.6)
Alive	19 (41.3)
Deceased	27 (58.7)

significantly higher preoperative VEGF (1713.62 $\pm$ 255.62 pg/mL) than those without metastasis (1181.54 $\pm$ 588.90 pg/mL, $p = 0.012$). VEGF was also markedly elevated in cases with lymphatic involvement (1409.72 $\pm$ 480.37 pg/mL vs. 288.44 $\pm$ 80.71 pg/mL, $p < 0.001$) (*table 2*).

There was significant decline in the postoperative VEGF-C levels for the patients who underwent curative resections (D2 gastrectomy) had a mean fall of 798 pg/ml (more than 50% of their preop values) (*table 3*).

Survival Analysis

Kaplan-Meier survival analysis (*table 4* and *fig. 2*) revealed significantly poorer survival among patients with high VEGF expression. The patients who presented with advanced stages and underwent palliative options

Table 2 - Comparison of metastatic and lymphatic involvements with VEGF levels

Variables	Groups	Mean $\pm$ SD (Pre-op VEGF)	p-value
Metastatic disease	Yes	1713.62 $\pm$ 255.62	0.012
	No	1181.54 $\pm$ 588.90	
Lymphatic involvement	Yes	1409.72 $\pm$ 480.37	<0.001
	No	288.44 $\pm$ 80.71	

Table 3 - Comparison table for VEGF fall and other variable

Variable	VEGF 50% fall	No change	p value
Alive	14 (56.0%)	5 (23.8%)	0.02
Death	11 (44.0%)	16 (76.2%)	
Stage 1	4 (16.0%)	0	< 0.001
Stage 2	7 (28.0%)	1 (4.8%)	
Stage 3	13 (52.0%)	1 (4.8%)	
Stage 4	1 (4.0%)	19 (90.5%)	
D1 gastrectomy	1 (4.0%)	2 (9.5%)	< 0.001
D2 gastrectomy	23 (92.0%)	1 (4.8%)	
Palliative surgery	1 (4.0%)	18 (85.7%)	

Table 4 - Kaplan-Meier survival analysis

Group	Mean Survival (months) $\pm$ SE	95% CI	Median Survival (months) $\pm$ SE	95% CI
Fall in postop VEGF-C levels	16.56 $\pm$ 1.812	13.01 – 20.11	17.0 $\pm$ 1.717	10.36 – 19.64
No fall in postop VEGF-C levels	10.43 $\pm$ 1.592	6.96 – 13.90	7.0 $\pm$ 1.471	3.64 – 10.36
Overall	13.78 $\pm$ 1.112	11.61 – 16.41	12.0 $\pm$ 2.896	6.32 – 17.68

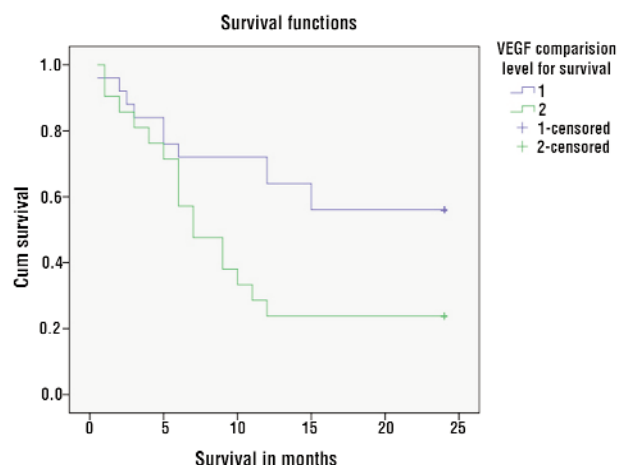
Test	Chi-Square	df	Sig. (p-value)
Log Rank (Mantel-Cox)	6.166	1	0.013
Breslow (Generalized Wilcoxon)	4.084	1	0.043
Tarone-Ware	4.676	1	0.031

had less than 50% fall in serum VEGF and a median survival of 7 months whereas the patients who underwent a complete curative resection had more than 50% fall in serum VEGF levels and a median survival of 17 months. Event rates were 76.2% and 44%, respectively. Mean survival times were 10.43 $\pm$ 1.59 months and 16.56 $\pm$ 1.81 months respectively. These findings are summarised in *tables 3 and 4*. Log-rank ($p = 0.013$),

Breslow ($p = 0.043$), and Tarone-Ware ($p = 0.031$) tests confirmed these differences.

DISCUSSION

Previous studies have established VEGF as a central mediator of angiogenesis and a poor prognostic factor in gastric cancer (8,9). Yildirim et al. observed that elevated VEGF levels were predictive of metastasis and recurrence (10). Similarly, Seo et al. reported serum VEGF as an independent predictor of overall survival in gastric carcinoma (11). VEGF family of glycoproteins consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, PlGF (Placenta Growth factor), VEGF-E, VEGF-F, interacting with specific tyrosine kinase receptors VEGFR - 1,2,3. VEGF-C interacts with VEGFR-3/FLT-4 and play an important role lymphangiogenesis (12). Increased VEGF-C and VEGFR3 expression in histopathological examination of gastric cancer patients was associated with increased lymphatic spread (13). Our findings demonstrate that elevated serum VEGF-C levels are significantly associated with aggressive tumor behavior like lymphatic and systemic spread and reduced survival in gastric carcinoma. The post-operative decline in VEGF-C levels (more than 50% of their preop values) reflects the reduction in tumor

**Figure 2 - Kaplan-Meier Survival Analysis**

burden in patients undergoing D1/D2 gastrectomies. The strong correlation between VEGF-C and advanced disease in our cohort underscores its potential utility in preoperative risk stratification. Unlike static histological parameters, serum VEGF-C levels can be dynamically monitored, providing insights into disease progression or therapeutic response. Our survival analysis highlights that high VEGF-C expression correlates with worse outcomes. This supports its potential as a negative prognostic biomarker and highlights the therapeutic promise of targeted therapies (Anti-VEGF) in selected patients (14,15). Significant fall in serum VEGF-C levels (more than 50 % of its pre-operative values) in the immediate postoperative period may be useful in assessing adequate tumor clearance and predicting survival as indicated by a better survival compared to those with no fall/increase in postoperative VEGF-C levels ($p = 0.02$). Thus perioperative monitoring of VEGF-C levels may serve as a real-time indicator of surgical clearance and treatment response.

CONCLUSION

Increased serum VEGF-C levels are associated with aggressive tumor biology like lymph node involvement, metastasis, and reduced survival in gastric cancer patients establishing the role of VEGF-C as a potential negative biomarker for gastric cancer prognostication. Thus, monitoring the perioperative levels of VEGF-C can aid in the assessment of disease progression, treatment response and surgical clearance and guide therapeutic decision-making, enhancing the personalized care for gastric cancer patients.

Limitations

Our study is limited by its single-center design and relatively small sample size with a short follow up. There was no serial assessment of VEGF-C levels during follow up and the study was not powered to assess other prognostic factors or targeted therapy. Thus future multicentric RCTs with improved sample size and longer follow up is required to validate these findings and establish serial VEGF-C levels monitoring protocols and explore its integration into clinical algorithms.

Author's Contributions

All authors contributed equally to the study.

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Conflict of Interest: None declared.

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