DOI: 10.7860/JCDR/2025/81466.21989

Original Article

Pathology Section

Expression of p53, VEGF and E-cadherin in Gastric Carcinoma and its Association with Pathological Prognostic Factors: A Cohort Study from a Tertiary Care Hospital in Eastern India

CHAYASMITA MALI[1], PRANATI MISRA[2], URMILA SENAPATI[3], SABYASACHI PARIDA[4]

ABSTRACT

Introduction: Gastric Carcinoma (GC) has a poor prognosis with most of the cases being detected at an advanced stage. Several potential biomarkers like p53, Vascular Endothelial Growth Factor (VEGF) and E-cadherin, have been identified for early detection and guiding the management of GC.

Aim: To analyse the expression of p53, VEGF and E-cadherin in GC and to find the association of these markers with various prognostic parameters.

Materials and Methods: The present cohort study was conducted over a period of 26 months. Follow-up was done for a minimum period of six months in Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India. Gastrectomy specimens, with histopathological confirmation, were included in the study, p53, VEGF and E-cadherin expression was studied along with their association with pathological prognostic parameters like histological type as per Lauren classification, histological grade and pathological stage and clinical prognostic parameters like age and gender. Statistical analysis was carried out using Microsoft Spreadsheet Excel 2010 Mini Tab/Statistical Package for Social Sciences (SPSS) version 23. Chi-square test was used and a p-value of <=0.05 was taken as statistically significant. Patient survival was calculated by Kaplan-Meier survival plot analysis.

Results: In the 40 cases studied, majority were males (75%), sixth decade being the most common age group affected (Mean=56.9±11.84years). Of the three biomarkers considered, E-cadherin showed a significant association with Lauren classification (p=0.002), histologic grade (p=0.026) and nodal stage (p=0.021) of the tumour. No significant association of p53 and VEGF expression was found with various prognostic markers in the study. The median survival time for the 19 cases followed up was 40.74 months. No significant results were obtained in cumulative survival rates.

Conclusion: E-cadherin can be a valuable prognostic marker in GC. Studies on larger scale and longer duration are warranted for more information on prognosis, recurrence and survival.

Keywords: Biomarkers, Gastric cancer, Invasiveness, Lauren classification, Tumour grade

INTRODUCTION

The GC is the 4th most common cause of mortality due to cancer [1]. There is an increase in incidence in persons under the age of 50 [2,3], especially for non-cardia tumours in the affluent populations [4,5]. The incidence of stomach cancer is declining in India. It is the second leading cause of cancer in males and third leading cause in females in India [6]. There is ongoing research to identify potential biomarkers for early detection and guiding management in gastric cancers. A number of molecular events have been implicated in gastric carcinogenesis. TP53 is the most commonly mutated gene in human cancer [7]. It has been suggested that the frequency of p53 mutations increases with the progression to GC from normal gastric mucosa [8]. Angiogenesis plays an essential role in tumourigenesis and metastasis. VEGF is known to modulate angiogenesis. Numerous studies reveal that VEGF expression is associated with poorer survival in gastric cancer and may represent a potential target for therapy [9]. E-cadherin, an adhesion molecule and a prototype of superfamily of calcium mediated membrane glycoproteins, has been recently viewed as a growth suppressor gene. E-cadherin plays an important role in maintaining functions of gastric mucosa and its dysregulation contributes to gastric cancer initiation and progression [10].

Studies have been done mostly in countries like China, Korea and UK to assess the prognostic association between biomarkers and gastric cancer and to evaluate their role in disease free and Overall Survival (OS) [11]. But such studies on role of various biomarkers in prognosis of gastric cancers are limited in Eastern India [12].

This study was done to assess the expression of p53, VEGF and E-cadherin in GCs by Immunohistochemistry (IHC) and, also to find the association of these markers with various prognostic parameters and with the prognosis of gastric cancer. The histologically proven gastric adenocarcinomas as well as Siewert type III Gatroesophageal Junction (GEJ) cancers, which are cancers located between 2 and 5 cm below the GEJ with invasion of the oesophagus and considered to be gastric cancers, were included in the study [13].

MATERIALS AND METHODS

The present cohort study was done over a period of 26 months (March 2022- May 2024) with a minimum period of six months follow-up in Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India. This study was approved by the Institutional Ethics Committee (ref. no: KIIT/KIMS/IEC/480/2022). All the consecutive gastrectomy specimens received in the histopathology section during the study period, which satisfied the inclusion/exclusion criteria along with retrospective archival blocks were part of the study. Retrospective archived blocks were collected from 2019 January to July 2023.

A total of 40 cases, both retrospective and prospective, were included in the study as these were the number of gastrectomy specimens that was received by the department. No other sample size calculator was feasible for the study.

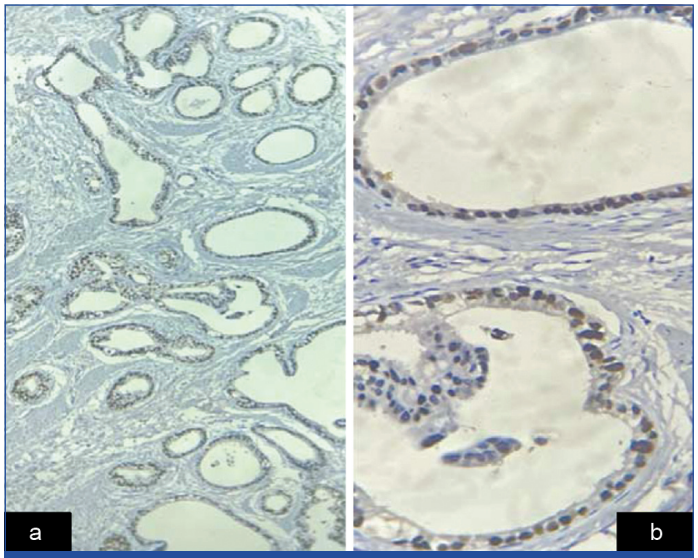
Inclusion criteria: Radical excision specimen of histologically confirmed specimen of GC and Siewert type III carcinoma of Gastroesophageal (GE) junction were included in the study.

Exclusion criteria: Small biopsies, cases where nodal status or tumour stage were not known, patients with neoadjuvant therapy, recurrent cases and Siewert type I and II Carcinoma of GE junction were excluded from the study.

Study Procedure

Formalin Fixed Paraffin Embedded (FFPE) blocks from the selected cases was retrieved. Routine H&E sections were studied and evaluated for histologic type (according to the Laurens classification of GC), grade and TNM staging. Immunohistochemistry (IHC) evaluation of p53, VEGF and E-cadherin was done using anti p53 (QR025) clone, VEGF clone VG1 and E-cadherin clone (EP6), respectively on 3µ thick FFPE tissue sections coated with poly-L-lysine. The antibodies were pre-diluted and ready to use which were acquired from Quartett. The IHC was done as per the Standard Operating Procedures (SOP) in the laboratory.

For p53, VEGF and E-cadherin IHC staining colonic adenocarcinoma, angiosarcoma of breast and chronic active gastritis, respectively were taken as positive control. Negative control was taken from the same tumour block under study by omitting the primary antibody. A positive reaction for p53 was taken only in the presence of immunostained nuclei in brown shades in more than 10% of tumour cells [Table/Fig-1] [14].



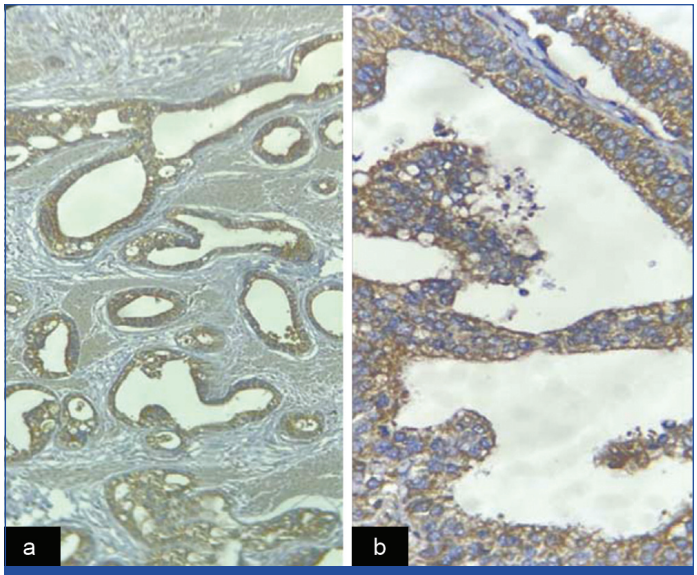
[Table/Fig-1]: a) (200x) IHC staining showing positive nuclear staining for p53 in GC; b) (400x) IHC staining showing nuclear staining for p53 in GC.

Cytoplasmic staining for VEGF was taken as positive. The staining intensity and percentage of positively stained cells were observed and graded as follows [Table/Fig-2] [14].

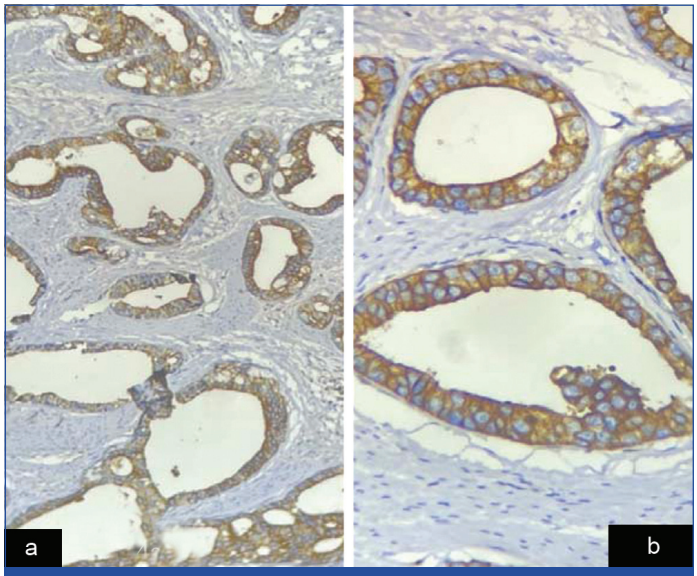
Stain intensity	Percentage of positively stained cells
0-no colouration	1: 0-20
1-light brown	2: 21-40
2-brown	3: 41-60
3-dark brown	4: 61-80
3-dark brown	5: 81-100

[Table/Fig-2]: Grading of staining intensity and proportion of cells [14].

The results of these parameters were multiplied to obtain the final score. VEGF negative and positive were defined, respectively, as total scores of 0-5 and >=6 [Table/Fig-3] [15]. Strong membranous staining in more than 90% of tumour cells (high staining) was considered positive for E-cadherin.Weak to moderate membranous staining in less than 10% and 0-90% of tumour cells was considered negative (low staining) [Table/Fig-4] [16].



[Table/Fig-3]: a) (200x) IHC staining showing complete cytoplasmic staining for VEGF in GC; b) (400x) IHC staining showing complete cytoplasmic staining for VEGF in GC.



[Table/Fig-4]: a) (200x) IHC staining showing complete membranous staining for E-cadherin in GC; b) (400x) IHC staining showing complete membranous staining for E-cadherin in GC.

Expression of these biomarkers were studied and their association with various clinical and pathological parameters such as age, gender, histological type, histological grade and pathological stage were studied [8]. Follow-up of the patients was done via telephonic conversation and radiological and clinical investigations were obtained from the hospital database.

STATISTICAL ANALYSIS

Statistical analysis was carried using Microsoft Excel Spreadsheet 2010 Mini Tab/SPSS version 23. Chi-square test was used. A p-value of <=0.05 was taken as statistically significant. The duration from the day of surgery until the patient's death or the last date follow-up was calculated as OS. Patient survival was estimated by Kaplan-Meier analysis.

RESULTS

A total of 40 cases were found to satisfy the inclusion and exclusion criteria which included 30 males (75%),10 females (25%). The age range was 22 to 75 years (Mean=56.9±11.84years). Frequency of

gastric cancers was seen to be more in higher age groups [Table/Fig-5]. A total of 38 cases (95%) were in the non-cardia region and two cases (5%) were in the cardia region. The most frequent site of involvement was found to be in the distal end of stomach (pylorus=50%, n=20). As per Laurens classification 45% (n=18), 37.5% (n=15) and 17.5% (n=7) cases were of intestinal, diffuse and mixed type, respectively. Of the 40 cases, most of the cases (47.5%) were Grade 3 tumours as per the World Health Organisation (WHO) grading, 11(27.5%) were in Grade 2 and 10 (25%) were in Grade 1 at the time of surgical resection. Maximum cases presented with higher depth of infiltration with 24 (60%) cases being in pT3 and 9 (22.5%) cases being in pT4. Most of the cases were in pN3 at the time of surgery comprising of 23(57.5%) cases of the 40 GC cases. None of the patients were observed to have distant metastasis at the time of initial diagnosis [Table/Fig-5].

Variables	n (%)
Age (years)	
Above 60	16 (40)
Under 60	24 (60)
Gender	
Male	30 (75)
Female	10 (25)
Histologic type (%)	
Intestinal	18 (45)
Diffuse	15 (37.5)
Mixed	7 (17.5)
Histologic grade (%)	
Well differentiated, Grade 1	10 (25)
Moderately differentiated, Grade 2	11 (27.5)
Poorly differentiated, Grade 3	19 (47.5)
Primary tumour (%)	
pT1	2 (5)
pT2	5 (12.5)
pT3	24 (60)
pT4	9 (22.5)
Regional lymph nodes (%)	
pN0	5 (12.5)
pN1	6 (15)
pN2	6 (15)
pN3	23 (57.5)

[Table/Fig-5]: Clinicopathologic findings in patients with GC.

pN1 (66.67%). Thus, it was found that p53 expression was more common in well-differentiated and lower stage tumours. But no statistical association was found between the p53 expression and Lauren's classification (p=0.676), histologic grade (p=0.123), tumour stage (p=0.924) or nodal status(p=0.283) [Table/Fig-6,7].

Positive expression of VEGF in GC was seen in 85% of cases (n=34). No relevant association of VEGF expression was found with either age or sex. Lauren's classification (p=0.392), histologic grade (p=0.307), tumour stage (p=0.894), or nodal stage (p=0.309) did not show any statistically significant association with VEGF expression [Table/Fig-6,7].

In the present study, 17 cases (42.5%) showed strong membranous E-cadherin positivity. Age and sex had no significant association with E-cadherin expression .Most of the intestinal type tumours (72.22%) showed a high E-cadherin expression. However, in diffuse and mixed type, majority of tumours showed a low expression of E-cadherin accounting for 87.5% and 66.67% respectively. In higher histologic grade, higher pT stage and higher pN stage, low E-cadherin expression was more frequent. Statistically significant association was found E-cadherin expression with respect to Lauren's classification (p=0.002), histologic grade (p=0.026), and nodal stage (p=0.021) [Table/Fig-6,7].

Of the 40 cases, 19 could be followed up for a minimum period of six months. The remaining was lost to follow-up. The follow-up was primarily focused on evidence of clinical and radiological recurrence as well as mortality of remaining patients. Three out the 19 patients showed locoregional recurrence in the form of ascites and lung and vertebral metastasis. VEGF was positive but p53 was negative in all three cases. High expression of E-cadherin was seen in two of the three cases [Table/Fig-8].

A total of 7 (17.5%) patients, out of the 40 patients, had died over the course of the study, the cause of death of these patients were not known. The median survival time for the followed up patients was 40.74 months. The cumulative survival rates in this study did not significantly correlate with the expression of p53, VEGF, or E-cadherin, according to the Kaplan-Meier survival analysis (p=0.533, p=0.069 and p=0.674, respectively) [Table/Fig-9-11].

DISCUSSION

Gastric cancer is the result of the accumulation of various genetic abnormalities and a mix of environmental factors.This study was done to look at the association of alteration in expression of biomarkers and disease progression in our local population.

The association between diminished E-cadherin expression and increased invasiveness in GC has been reported in literatures [16].

Parameters		p53 expression		p-value	VEGF		p-value	E-cadherin		p-value
		Positive (17)	Negative (23)		Positive (34)	Negative (6)		High (17)	Low (23)	
Age	<60 (n=23)	9 (39.14%)	14 (60.86%)	0.616	19 (82.6%)	4 (17.4%)	0.622	10 (43.47%)	13 (56.52%)	0.884
	≥60 (n=17)	8 (47.06%)	9 (52.94%)		15 (88.24%)	2 (11.76%)		7 (41.17%)	10 (58.82%)	
Sex	F (n=10)	5 (50%)	5 (50%)	0.58	10 (100%)	0 (0.00%)	0.125	4 (40%)	6 (60%)	0.853
	M (n=30)	12 (40%)	18 (60%)		24 (80%)	6 (20%)		13 (43.33%)	17 (56.66%)	

[Table/Fig-6]: Association of various clinicalparameters with p53, E cadherin and VEGF.

Of the 40 cases, 17 (42.5%) showed p53 nuclear positivity. There was no association between p53 expression and either age (p=0.616) or sex (p=0.58). Most of the cases of diffuse (62.5%) and mixed (66.67%) type were negative for p53 whereas there was an equal distribution of p53 negative and positive cases in intestinal type. Majority of well differentiated tumours (70%) showed a positive p53 expression whereas most of the moderately (63.34%) and poorly differentiated tumours (68.42%) had a negative p53 expression. Negative p53 expression was seen to be more frequently in higher pT stages with pT2 (60%), pT3 (54.17%) and pT4 (66.67%). p53 overexpression was seen in majority of cases in pN0 (60%) and

The present study was undertaken to look at the association in our local population.

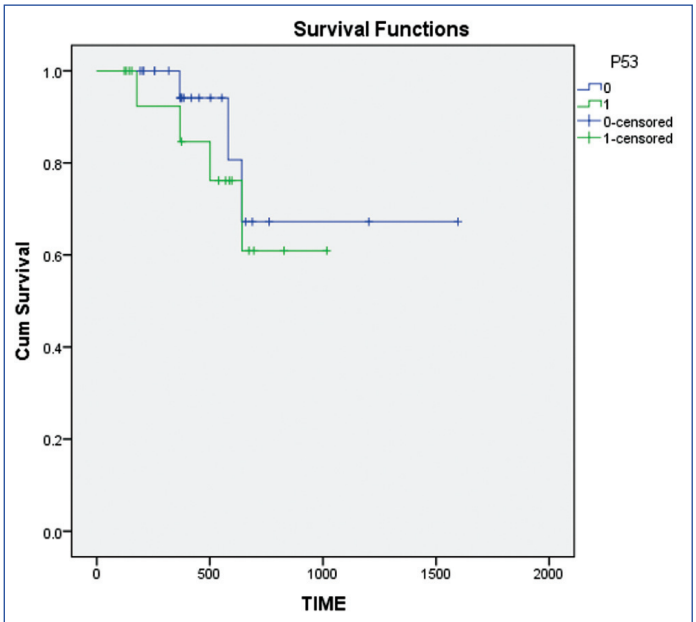
E-cadherin, a calcium-mediated membrane molecule, has a protective mechanism against tumour formation as it plays an important role in adhesion and differentiation of gastric epithelial cells [16]. In this study, 17 cases (42.5%) showed strong membranous E-cadherin positivity and 72.22% cases of intestinal type, 12.5% cases of diffuse type and 33.33% cases of mixed type cancers showed high E-cadherin staining. There was a significant association between Lauren's classification, histologic grade and nodal stage. Reduced E-cadherin expression is found in tumours

Parameters		p53		p-value	VEGF		p-value	E-cadherin		p-value
		Positive (17)	Negative (23)		Positive (34)	Negative (6)		High (n=17)	Low (n=23)	
Laurens classification	Diffuse (n=16)	6 (37.5%)	10 (62.5%)	0.676	14 (87.5%)	2 (12.5%)	0.392	2 (12.5%)	14 (87.5%)	0.002*
	Intestinal (n=18)	9 (50%)	9 (50%)		14 (77.78%)	4 (22.22%)		13 (72.22%)	5 (27.78%)	
	Mixed (n=6)	2 (33.33%)	4 (66.67%)		6 (100%)	0 (0.00%)		2 (33.33%)	4 (66.67%)	
Histological grade	Well differentiated (n=10)	7 (70%)	3 (30%)	0.123	7 (70%)	3 (30%)	0.307	7 (70%)	3 (30%)	0.026*
	Mod differentiated (n=11)	4 (36.36%)	7 (63.64%)		10 (90.91%)	1 (9.09%)		6 (54.55%)	5 (45.45%)	
	Poorly differentiated (n=19)	6 (31.58%)	13 (68.42%)		17 (89.47%)	2 (10.53%)		4 (21.05%)	15 (78.95%)	
pT	T1 (n=2)	1 (50%)	1 (50%)	0.924	2 (100%)	0 (0.00%)	0.894	2 (100%)	0 (0%)	0.395
	T2 (n=5)	2 (40%)	3 (60%)		4 (80%)	1 (20%)		2 (40%)	3 (60%)	
	T3 (n=24)	11 (45.83%)	13 (54.17%)		20 (83.33%)	4 (16.67%)		9 (37.5%)	15 (62.5%)	
	T4 (n=9)	3 (3.33%)	6 (66.67%)		8 (88.89%)	1 (11.11%)		4 (44.44%)	5 (55.56%)	
pN	N0 (n=5)	3 (60%)	2 (40%)	0.283	3 (60%)	2 (40%)	0.309	4 (80%)	1 (20%)	0.021*
	N1 (n=6)	4 (66.67%)	2 (33.33%)		6 (100%)	0 (0.00%)		5 (83.33%)	1 (16.67%)	
	N2 (n=6)	1 (16.67%)	5 (83.33%)		5 (83.33%)	1 (16.67%)		2 (33.33%)	4 (66.67%)	
	N3 (n=23)	9 (39.13%)	14 (60.87%)		20 (86.96%)	3 (13.04%)		6 (26.08%)	17 (73.91%)	

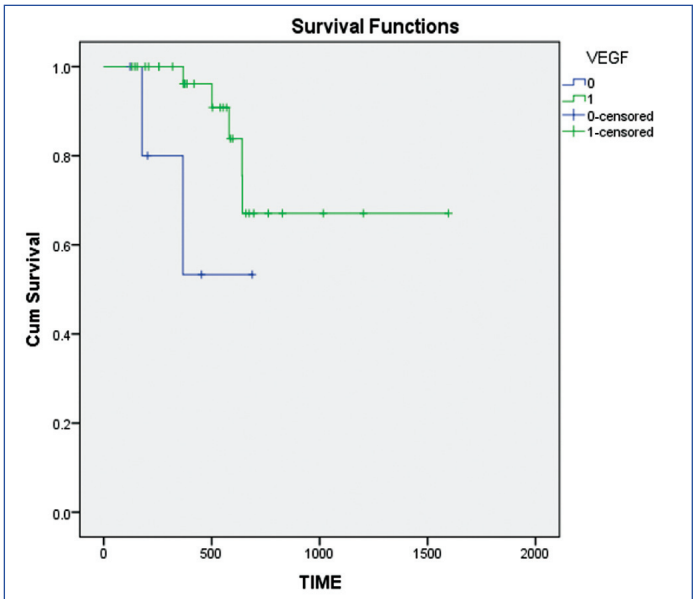
[Table/Fig-7]: Association of various pathological parameters with p53, E cadherin and VEGF.

S. No.	Recurrence Data (n=3)	p53	VEGF	E-cadherin
1.	Patient presenting with ascites (n=1)	Negative	Positive	Negative
2.	Patient presenting with lung and vertebral metastasis(n=1)	Negative	Positive	Positive
3.	Patient presenting with ascites(n=1)	Negative	Positive	Positive

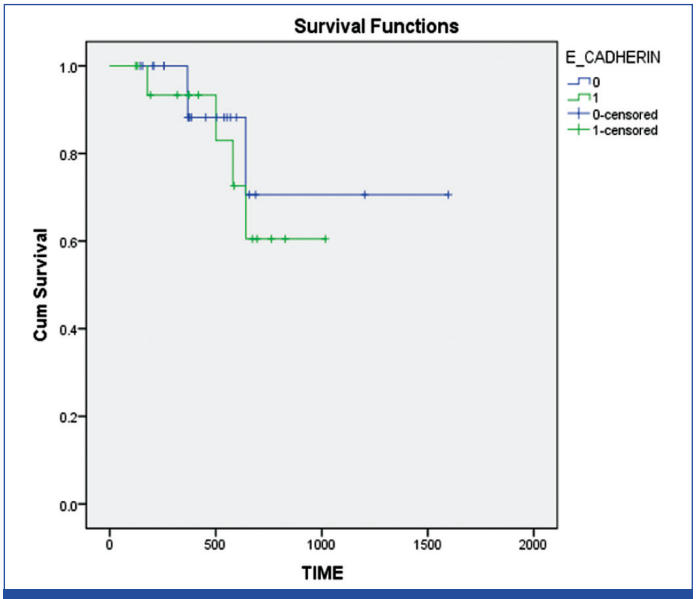
[Table/Fig-8]: Expression of the biomarkers in patients with recurrence.



[Table/Fig-9]: Kaplan-Meier analysis of p53 expression and patient survival.



[Table/Fig-10]: Kaplan-Meier analysis of VEGF expression and patient survival.



[Table/Fig-11]: Kaplan-Meier analysis of E-cadherin expression and patient survival.

with higher grade. Thus, E-cadherin mutation can be used as a significant prognostic factor, and the rate of invasive cancers can be decreased by detecting the causes of mutation and preventing them [16]. This may help in assessing the patient survival which is one of the major goals of our study. A similar study done by Sridevi C et al., in 2018 in Andhra Pradesh showed significant association between Lauren's classification and E-cadherin expression [12]. They observed significant association with tumour grade and lymph node metastasis which is found in our study as well. Another study done by Wu ZY et al., in 30 GC cases showed significant association between poor differentiation of tumours and loss of E-cadherin molecules [17]. In their study, also high staining of E-cadherin was seen intestinal type and low staining was seen in mixed and diffuse type. Lazar D et al., and Zhao H et al., in their study also reported that E-cadherin expression was related to cellular differentiation [18,19]. Thus, we conclude that the loss of E-cadherin from the membranes promote tumour dissemination [12].

Author	Year/place of study	IHC	Sample size	Association with age and gender	Association with histologic type	Association with grade	Association with tumour status	Association with nodal status
Lee SJ et al., [22]	2009, Korea	VEGF	355	0.001 0.394	-	-	0.566	0.707
Lazar D et al., [14]	2010, Timisoara	p53	265	0.6444 0.8295	0.0212	0.0390	0.0229	0.0382
Sridevi C et al., [12]	2018, India	E-cadherin	60	-	<0.05	<0.05	<0.05	<0.05
Present study	2022, Bhubaneswar, India	p53	40	0.616 0.58	0.676	0.123	0.924	0.283
		VEGF	40	0.622 0.853	0.392	0.307	0.894	0.309
		E-cadherin	40	0.884 0.853	0.002	0.026	0.395	0.021

[Table/Fig-12]: Comparison study with different authors [12,14,22].

p53 mutations have been observed in different human cancers such as colorectal cancer, gall bladder cancer, oesophageal cancer, breast cancer and gastric cancer. The relation between tumour differentiation, vascular invasion and lymph node metastasis with the expression of p53 helps in understanding its expression with the aggressiveness of the tumour [20]. In the present study, 17/40 (42.5%) cases showed p53 overexpression and greater frequency of p53 positivity was seen in intestinal type carcinomas 9/18 (50%) cases and 6/16 (37.5%) cases of diffuse type GC, although no significant expression was seen between different clinicopathological parameters and p53 expression. In a study by Lazar D et al., in 2010, an increased positive expression of p53 was noted in intestinal type carcinomas (47.4%) similar to our study where p53 positivity in intestinal type is 52.9% [14]. However, contrary to our study, they had found a significant association between the tumour type, grade and nodal stage of tumour. Negative p53 expression was seen in higher nodal status (pN2= 83.33% and pN3= 60.87%) in our study. These results were in contrast to the study done by Lazar D et al., who found p53 overexpression in majority of cases in pN3 (75%).

VEGF is the most potent angiogenic factor identified till date and VEGF based anti-angiogenesis therapy maybe of therapeutic benefit against tumours including gastric cancer [21]. Also, its expression has been identified as a marker for tumour recurrence and reduced survival independent of conventional clinicopathological parameters in GC [20]. In the current study positive VEGF expression was found in 87.5% diffuse, 77.78% intestinal type GC and in 100% mixed type carcinomas. But there was no significant association of its expression with the considered parameters. In a study done by Lee SJ et al., no significant association was observed between VEGF expression and clinicopathological parameters in their study [22]. But the pathologic stage and older age were independent prognostic factors of survival for the patients [Table/Fig-12] [12,14,22].

By using Kaplan-Meier analysis, the authors observed that p53 overexpression, reduced expression of VEGF and increased expression of E-cadherin were all associated with worse patient survival. But these results did not meet statistical significance (p=0.533, p=0.069, and p=0.674). Lee SJ et al., identified p53 overexpression as an independent risk factor for poor prognosis in gastric cancer (p=0.005) [22]. Zhou Y et al., in their study discovered a strong association of normal expression E-cadherin and lower VEGF expression and longer patient survival (p=0.001 for each) [23]. VEGF overexpression was significantly associated (p<0.005) with poor survival in Chinese patients with stomach cancer, according to a research by Chen J et al., [24].

Limitation(s)

Various limitations have been observed during the course of the study. The sample size of our study was limited to 40 cases more significant associations could have been achieved with a bigger sample size. Also, the scoring system of E-cadherin and VEGF do not have a standardised protocol for interpretation and gradingwhich could affect the comparison between various studies. Another limitation is inadequate patient follow up to allow comparison of prognosis and survival rate. Also most of the tumours were of higher stage when diagnosed initially indicating the uneven distribution of the cases.

CONCLUSION(S)

E-cadherin expression is a reliable prognostic indicator since it significantly correlates with the aggressiveness of tumour. p53 expression was more commonly observed in well differentiated node negative tumours but the results were not statistically significant. No significant association was found between VEGF expression and the various clinicopathological parameters. VEGF was found to be positive in most of the tumours. Hence, a potential role of antiangiogenic therapy may be evaluated in gastric cancers. Further studies are required with a larger sample size, longer study period, follow-up and survival analysis, to assess the true associations between the prognostic biomarkers and GC survival and translate these associations into clinical practice.

REFERENCES

[1] Ilic M, Ilic I. Epidemiology of stomach cancer. World J Gastroenterol. 2022;28(12):1187-203. Doi: 10.3748/wjg.v28.i12.1187.
[2] Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjoma- taram I. Is gastric cancer becoming a rare disease? A global assess- ment of predicted incidence trends to 2035. Gut. 2020;69:823-29.
[3] Heer EV, Harper AS, Sung H, Jemal A, Fidler-Benaoudia MM. Emerging cancer incidence trends in Canada: The growing burden of young adult cancers. Cancer. 2020;126:4553-62.
[4] Anderson WF, Rabkin CS, Turner N, Fraumeni JF, Rosenberg PS, Camargo MC. The changing face of non-cardia gastric cancer incidence among US non-Hispanic whites. J Natl Cancer Inst. 2018;110:608-15.
[5] Gupta S, Tao L, Murphy JD, Camargo MC, Oren E, Valasek MA, et al. Race/ethnicity-, socioeconomic status-, and anatomic subsite-specific risks for gastric cancer. Gastroenterology. 2019;156(1):59-62.
[6] Shakuntala TS, Krishnan SK, Das P, Sudarshan KL, Kotian CM, Santhappan S, et al. Descriptive Epidemiology of Gastrointestinal Cancers: Results from National Cancer Registry Programme, India. Asian Pac J Cancer Prev. 2022;23(2):409-18. Published 2022 Feb 1. doi:10.31557/APJCP.2022.23.2.409.
[7] Fenoglio-Preiser CM, Wang J, Stemmermann GN and Noffsinger A. TP53 and gastric carcinoma: A review. Hum Mutat. 2003;21(3):258-70.
[8] Kim KW, Kim N, Choi Y, Kim WS, Yoon H, Shin CM, et al. Different effects of p53 protein overexpression on the survival of gastric cancer patients according to Lauren histologic classification: A retrospective study. Gastric Cancer. 2021;24:844-57.
[9] Lin C, Zhang Z, Xu Y, Wang R, Chen S, Gao J, et al. High tumour vascular endothelial growth factor expression is associated with poorer clinical outcomes in resected T3 gastric adenocarcinoma. Am J Clin Pathol. 2016;146:278-88.
[10] Torabizadeh Z, Nosrati A, SajadiSaravi SN, Yazdani Charati J, Janbabai G. Evaluation of E-cadherin expression in gastric cancer and its correlation with clinicopathologic parameters. Int J Hematol Oncol Stem Cell Res. 2017;11:158-64.
[11] Zhou C, Zhong X, Song Y, Shi J, Wu Z, Guo Z, et al. Prognostic biomarkers for gastric cancer: An umbrella review of the evidence. Front Oncol. 2019;9:1321. Published 2019 Nov 29. Doi: 10.3389/fonc.2019.01321.
[12] Sridevi C, Pavitra K, Jijiyabai, Evaluation of e-cadherin expression in gastric cancer as a prognostic marker. Indian J Pathol Oncol. 2019;6(1):90-97.
[13] Hashimoto T, Kurokawa Y, Mori M, Doki Y. Surgical treatment of gastroesophageal junction cancer. Journal of Gastric Cancer. 2018;18(3):209-17.

[14] Lazăr D, Tăban S, Sporea I, Dema A, Cornianu M, Lazăr E, et al. The immunohistochemical expression of the p53-protein in gastric carcinomas. Correlation with clinicopathological factors and survival of patients. Rom J Morphol Embryol. 2010;51(2):249-57.
[15] Li X, Zhu X, Wang Y, Wang R, Wang L, Zhu M-L, et al. Prognostic value and association of Lauren classification with VEGF and VEGFR-2 expression in gastric cancer. Oncol Lett. 2019;18(5):4891-99. Doi: 10.3892/ol.2019.10820.
[16] Torabizadeh Z, Nosrati A, SajadiSaravi SN, Yazdani Charati J, Janbabai G. Evaluation of E-cadherin expression in gastric cancer and its correlation with clinicopathologic parameters. Int J Hematol Oncol Stem Cell Res. 2017;11(2):158-64.
[17] Wu ZY, Zhan WH, Li JH, He Y-L, Wang J-P, Lan P, et al. Expression of E-cadherin in gastric carcinoma and its correlation with lymph node micrometastasis. World J Gastroenterol. 2005;11(20):3139-43. Doi: 10.3748/wjg.v11.i20.3139.
[18] Lazar D, Taban S, Ardeleanu C. The immunohistochemical expression of E-cadherin in gastric cancer; correlations with clinicopathological factors and patients' survival. Rom J Morphol Embryol. 2008;49(4):459-67.
[19] Zhao H, Hu H, Chen B, Xu W, Zhao J, Huang C, et al. Overview on the role of E-cadherin in gastric cancer: Dysregulation and clinical implications. Frontiers in Molecular Biosciences. 2021;8:689139.
[20] Al-Maghrabi J, Emam E, Gomaa W, Saggaf M, Buhmeida A, Al-Qahtani M, et al. c-MET immunostaining in colorectal carcinoma is associated with local disease recurrence. BMC Cancer. 2015;15(1):01-06.
[21] Dey N, De P, Brian LJ. Evading anti-angiogenic therapy: Resistance to anti-angiogenic therapy in solid tumours. American Journal of Translational Research. 2015;7(10):1675.
[22] Lee SJ, Kim JG, Sohn SK, Chae YS, Moon JH, Kim SN, et al. No association of vascular endothelial growth factor-A (VEGF-A) and VEGF-C expression with survival in patients with gastric cancer. Cancer Res Treat. 2009;41(4):218-23. Doi: 10.4143/crt.2009.41.4.218.
[23] Zhou Y, Li G, Wu J, Zhang Z, Wu Z, Fan P, et al. Clinicopathological significance of E-cadherin, VEGF, and MMPs in gastric cancer. Tumour Biology. 2010;31(6):549-58.
[24] Chen J, Zhou SJ, Zhang Y, Zhang G-Q, Zha T-Z, Feng Y-Z, et al. Clinicopathological and prognostic significance of galectin-1 and vascular endothelial growth factor expression in gastric cancer. World J Gastroenterol. 2013;19(13):2073-79. Doi: 10.3748/wjg.v19.i13.2073.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Pathology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya, India.
2. Professor, Department of Pathology, Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, Odisha, India.
3. Senior Professor, Department of Pathology, Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, Odisha, India.
4. Senior Consultant, Department of Pathology, Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Chayasmita Mali,
North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences,
Shillong, Meghalaya, India.
E-mail: drchayasmita@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 22, 2025
- Manual Googling: Aug 16, 2025
- iThenticate Software: Aug 18, 2025 (8%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 21, 2025**
Date of Peer Review: **Jul 02, 2025**
Date of Acceptance: **Aug 20, 2025**
Date of Publishing: **Nov 01, 2025**