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Original Research Article

Expression of ERK1/2 and Bcl-2 in gastric carcinoma and their clinicopathological significance: an observational study in a tertiary care cancer hospital

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ABSTRACT

Background: Stomach cancer was ranked fifth in incidence and also fifth rank in mortality globally in 2022. It was seventh most common cancer in India. Studies have shown that ERK/MAPK pathways regulate cellular motility in both neoplastic and normal gastric epithelial cells and are involved in cell migration and invasiveness. Aberrant Bcl-2 is expressed in a sequential manner in gastric carcinogenesis. This study aims to evaluate the association between the clinicopathological features of gastric carcinoma and ERK1/2 and Bcl-2 expression in Eastern Indian Population.

Materials and Methods: The study included 63 surgically resected tumour samples of patients with gastric carcinoma between 2021 and 2023. Processing of tissues was done for histopathological examination and immunohistochemistry with ERK1/2 and Bcl-2. Data was analysed and P values less than 0.05 were considered to be statistically significant.

Results: Sixty-one out of sixty-three cases of gastric carcinoma showed ERK1/2 expression on immunohistochemistry (96.8%) in the carcinoma cells. ERK1/2 expression was significantly associated with patient gender, ≥5cm tumour size, Borrmann type II tumours, Diffuse type, histological type, Grade III tumours, Lymphovascular invasion, advanced T stage, advanced N stage and a higher AJCC prognostic stage. Forty-six out of sixty-three cases of gastric carcinoma showed Bcl-2 expression (73%) in the carcinoma cells. There was a significant association of Bcl-2 expression with patient gender, ≥5cm tumour size, Borrmann type II tumours, Intestinal type, histological type of tumours, Grade II tumours, Lymphovascular invasion, advanced T stage, advanced N stage and a higher AJCC prognostic stage.

Conclusion: Higher expressions of ERK1/2 and Bcl-2 were seen in higher tumour grade and higher AJCC prognostic stage pointing towards a prognostic significance of these markers in gastric carcinoma.

1. Introduction

Stomach cancer was an important cancer worldwide with 968,350 newly diagnosed cases in 2022 and an approximate 659,853 deaths, giving it a fifth rank in incidence and a fifth rank in mortality globally. In India, stomach cancer was the seventh most common cancer with 64,611 new diagnoses.[1] The incidence of gastric cancer is seen to increase with age peaking around 60-80 years while being rare in patients below 30 years.[2,3] The disease shows a male predominance with cases being two to four times more frequent in males than in females.[4,5] Dietary factors and infection with *Helicobacter pylori* have been identified as major risk factors for distal tumours. The major risk factors for proximal tumour development have been found to be

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gastroesophageal reflux disease and obesity.[6] Incidence has been observed to be higher in the southern and north-eastern parts of India.[7,8]

World Health Organisation and Lauren's Classification system have classified gastric cancer into two histological types- intestinal and diffuse. The intestinal type is common in male gender and advanced age group, in African-Americans and has a favourable prognosis. Gastric atrophy and intestinal metaplasia are the commonly encountered preceding lesions in the intestinal type. *H. pylori* infection, obesity and dietary factors are also significant environmental risk factors. The diffuse type, on the other hand, is commoner in endemic areas, in women and younger patients and shows an association with blood group A.[9,10]

H. pylori, a gram-negative bacterium, has been implicated as a significant risk factor for gastric carcinoma.[11–13] The organism induces a series of events resulting in sequential progression of normal epithelium to cancer through atrophic gastritis, intestinal metaplasia and dysplasia.[14–18] There is evasion of host immune response, activation of NF-κB and Wnt-β-catenin pathways, alteration of ionic homeostasis and carcinogenesis.[19]

Mitogen-activated protein kinases (MAPKs) are a large family of serine/threonine kinases which, on receiving a specific stimulus, induce a cascade of phosphorylation and lead to cellular response. ERK1/2 is the most commonly studied member of MAPKs family while other members identified are ERK3, ERK4, ERK5 and ERK7/8.[20,21] Extracellular signal-regulated kinases (ERK) are activated following phosphorylation by MAPKs or ERK-activated protein kinase (MEK). Following activation of the MAPK cascade, ERK is phosphorylated and translocates to the nucleus from the cytoplasm. Following nuclear translocation, several nuclear targets including transcription factors are phosphorylated by ERK.[22] ERK is involved in cellular proliferation, differentiation, apoptosis and transformation. ERK1/2 are the first mammalian MAPK genes that were identified.[23] Studies have shown that ERK/MAPK pathways play a significant role in the regulation of cellular motility both in neoplastic and non-neoplastic gastric epithelial cells. ERK regulates Matrix Metalloproteinase (MMPs) activity in gastric cancer involved in cell migration and invasiveness.[24] EGFR/Ras/MAPK signalling pathways are involved in the activation of NF-κB, which in turn leads to induction of Cyclooxygenase-2 and gastric carcinoma cell proliferation. Upregulation of COX-2 inhibits apoptosis and hence promotes carcinogenesis. Elevated COX-2 and mRNA levels have been detected in gastric cancer cells.[25]

The Bcl-2 protooncogene is involved in impairing programmed cell death (apoptosis).[26,27] Initially Bcl-2 was recognised in follicular and diffuse B-cell lymphomas where overexpression of Bcl-2 resulted from juxtaposition of the Bcl-2 gene with IgH chain gene.[28,29] In the gastrointestinal tract, immunohistochemistry has detected Bcl-2 protein in the proliferative zone indicating its function in protecting the mucosal renewal potential.[30,31] Bcl-2 is aberrantly expressed in a sequential manner in gastric carcinogenesis. Expression has been found in more than half of the cases of chronic atrophic gastritis with intestinal metaplasia and in a majority of cases with epithelial dysplasia but rarely observed in normal mucosa.[32] Abnormal Bcl-2 expression has been shown to be an important factor in biological behaviour of gastric carcinoma. Its increased expression in gastric cancer results in the development of cancer cell resistance to the apoptotic effect of drugs or radiation.[33]

A study carried out to show the correlation between MAPK/c-Jun pathway and expression levels of Bcl-2 and Bcl-xL antiapoptotic proteins hypothesized that JNK1/2/3-, p38 and ERK1/2-MAPK/c-Jun cascade signalling pathways may play a role in the upregulation of the expression levels of Bcl-2 and Bcl-xL in gastric carcinoma cells.[34] Zelivianski et al in a study showed that activated ERK pathway mediates an antiapoptotic response during treatment with certain chemotherapeutic drugs.[35]

2. Material and Methods

2.1. Clinical samples

A hospital based prospective observational study was conducted on surgically resected tumor samples of gastric carcinoma patients received by Department of Pathology at Chittaranjan National Cancer Institute, Kolkata, between the years 2021 and 2023. Patients who had received neoadjuvant therapy prior to surgery were excluded from the study population. All samples were collected with patient consent and approval of the Committee on Medical Ethics of Chittaranjan National Cancer Institute.

2.2. Immunohistochemistry

On receiving the specimen, a systemic gross examination was performed and tumour tissues were routinely processed and 3-5micron sections were cut from paraffin embedded blocks. Following H&E staining, the sections were examined and a detailed histopathological reporting was done. Four μ-meter sections were then cut from the tumour blocks and mounted on slides followed by overnight drying at 45ºC. Sections were dewaxed in xylene and rehydrated with graded concentrations of alcohol. Antigen was retrieved by heating for 30 minutes at 98ºC in 10mmol/L citrate buffer. The sections were incubated in 10% hydrogen peroxide for 3 minutes to block endogenous peroxidase activity. Slides were allowed to cool for 20 minutes and then washed with distilled water. After rinsing, slides were placed for five minutes in phosphate-buffered saline (PBS) followed by overnight incubation with the primary antibody cocktail of ERK1 and ERK2 for ERK1/2

expression study and separate Bcl-2 antibody for Bcl-2 expression study, both at a dilution of 1:1000 for one hour. Antibodies specific for phosphorylated- ERK1/2 were purchased from Abclonal and against Bcl-2 was purchased from Sigma. The chromogenic reaction was carried out with diaminobenzidine for 5 minutes at 37^0C, counterstained with Mayer's hematoxylin, dehydrated and mounted. Positive reaction for proteins was observed in cytoplasm of cancer cells for Bcl-2 and in the nucleus and cytoplasm of cancer cells for ERK1/2. ERK1/2 staining intensity was assessed using the following scoring system: 0 for absent chromogenic signal; 1+ for focal weak staining; 2+ for partial intermediate or focal strong cells staining; 3+ for >50% strong or intermediate staining; 4+ for diffuse strong staining[36]. Bcl-2 expression was visually classified into four groups: No expression in any of the tumour cells (-), slight staining in most of the tumour cells or less than 25% tumour cells with strong staining (+), 26-50% tumour cells with strong staining (++), strong staining in more than 51% tumour cells (+++).[36] ERK1/2 protein expression level was also analyzed in normal gastric mucosa and tumour tissue by Western Blot technique. Normal gastric tissue demonstrated baseline protein expression while tumour tissue showed overexpression of the protein.

2.3. Statistical analysis

Analysis of data was accomplished using Chi Square Test. P values less than 0.05 were considered to be statistically significant.

3. Results

3.1. ERK1/2 expression in gastric carcinoma

Sixty-one out of sixty-three cases of gastric carcinoma showed ERK1/2 expression on immunohistochemistry (96.8%) in the carcinoma cells. Out of these, 3 (4.8%) cases showed 1+ expression, 15 (23.8%) cases showed 2+ expression, 25 (39.7%) cases showed 3+ expression and 18 (28.6%) cases showed 4+ expression (Figures 1, 2 and 3).

3.2. Expression of Bcl-2 in gastric carcinoma

Forty-six out of sixty-three cases of gastric carcinoma showed Bcl-2 expression on immunohistochemistry (73%) in the carcinoma cells. 17 (27%) cases lacked expression, 11 (17.5%) cases showed + expression, 14 (22.2%) cases showed ++ expression and 21 (33.3%) cases showed +++ expression (Figures 4, 5, 6 and 7).

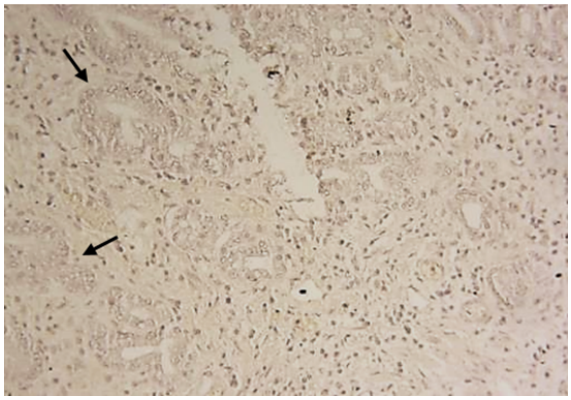

Figure 1: 2+ ERK1/2 expression in the neoplastic glands in Grade 2 Adenocarcinoma (Arrow, 200X magnification)

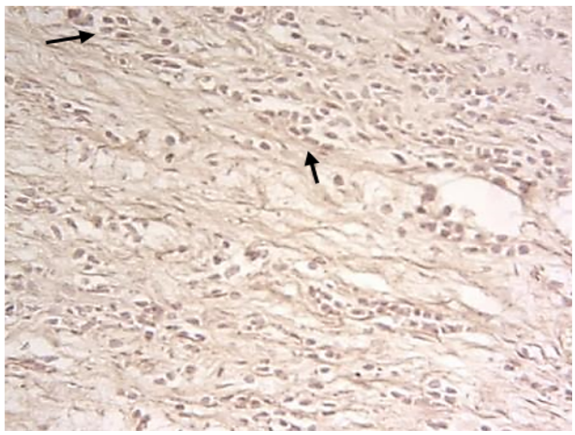

Figure 2: 4+ ERK1/2 expression in the tumour cells Grade 3 Adenocarcinoma (Arrow, 200X magnification)

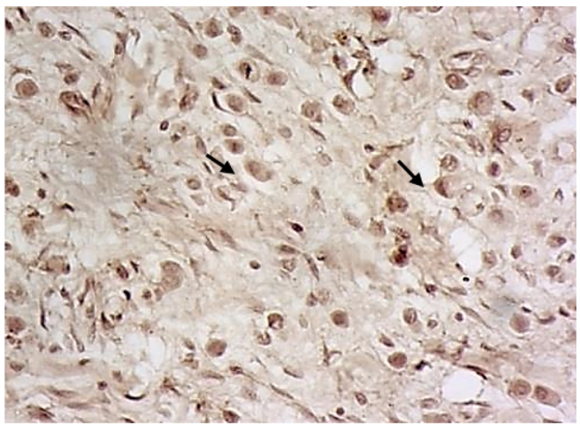

Figure 3: 4+ ERK1/2 expression Grade 3 Adenocarcinoma (Arrow, 400X magnification)

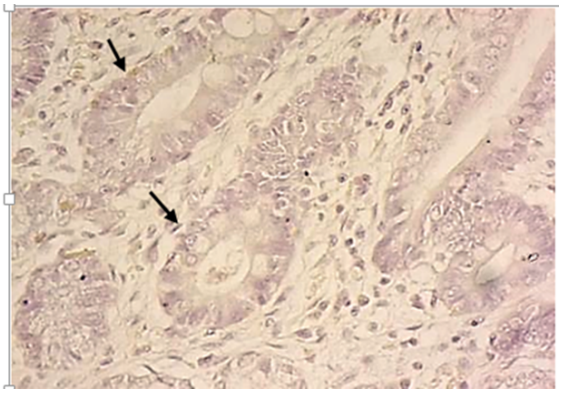

Figure 4: ++ Bcl-2 expression in Grade 1 Intestinal Type Adenocarcinoma (Arrow, 200X magnification)

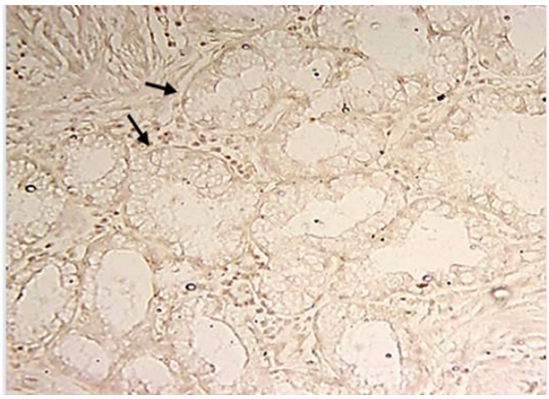

Figure 5: +++ Bcl-2 expression in Grade 2 Intestinal Type Adenocarcinoma (Arrow, 200X magnification)

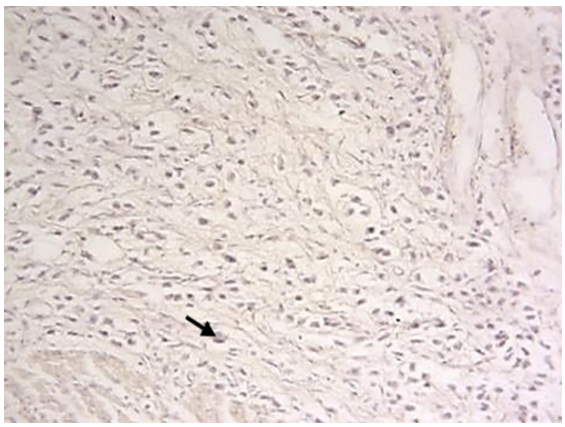

Figure 6: Diffuse Type Adenocarcinoma with weak Bcl-2 staining (Arrow, 200X magnification)

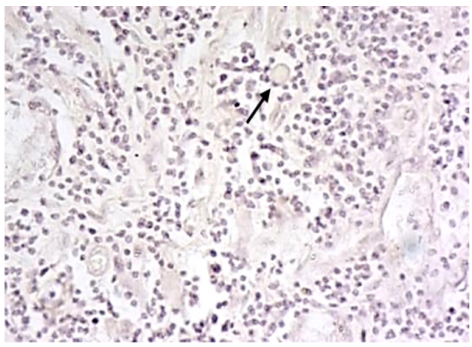

Figure 7: Diffuse Type Adenocarcinoma with weak Bcl-2 staining (Arrow). Strong expression in lymphoid cells acts as internal control. (200X magnification)

3.3. Association between ERK1/2 expression and clinicopathological characteristics of gastric carcinomas

Correlation between ERK1/2 expression and the clinicopathological features of gastric carcinomas have been illustrated in Table 1. ERK1/2 expression was significantly associated with sex of patients (p value 0.002). The expression was more frequently seen in tumours measuring ≥5cm in size (p value <0.0001). There were significant association of ERK1/2 expression with Borrmann type II tumours (p value <0.0001), Diffuse type (p value <0.0001), histological type of tumours (p value <0.0001), Grade III tumours (p value <0.0001), presence of Lymphovascular invasion (p value <0.0001), higher T stage (p value <0.0001), higher N stage (p value <0.0001) and a higher AJCC prognostic stage (p value <0.0001). No significant association of ERK1/2 expression was found with patient age and tumour site.

3.4. Association between Bcl-2 expression and clinicopathological characteristics of gastric carcinomas

Correlation between Bcl-2 expression and the clinicopathological features of gastric carcinomas have been illustrated in Table 2. Bcl-2 expression was significantly associated with sex of patients (p value 0.001). The expression was more frequently seen in tumours measuring ≥5cm in size (p value <0.0001). There were significant association of Bcl-2 expression with Borrmann type II tumours (p value <0.0001), Intestinal type (p value <0.0001), histological type of tumours (p value <0.0001), Grade II tumours (p value <0.0001), presence of Lymphovascular invasion (p value <0.0001), higher T stage (p value <0.0001), higher N stage (p value <0.0001) and a higher AJCC prognostic stage (p value <0.0001). There were no significant association of Bcl-2 expression with patient age and tumour site.

Table 1: Association between ERK1/2 expression and clinicopathological characteristics of gastric carcinomas

	0	1+	2+	3+	4+	N	P Value
Gender							0.002
Male	1	3	13	21	6	44	
Female	1	0	2	4	12	19	
Age							0.909
<31 years	0	0	0	0	2	2	
31-40 years	0	0	1	2	2	5	
41-50 years	1	0	5	8	6	20	
51-60 years	1	2	4	9	3	19	
61-70 years	0	1	5	5	4	15	
>70 years	0	0	0	1	1	2	
Site							0.806
Proximal	1	0	1	4	0	6	
Middle	0	0	0	7	3	10	
Distal	1	3	14	14	15	47	
Size							<0.0001
≥5cm	0	1	0	18	17	36	
<5cm	2	2	15	7	1	27	
Borrmann Classification							<0.0001
I	1	0	0	0	0	1	
Ii	1	3	15	17	2	38	
Iii	0	0	0	7	10	17	
Iv	0	0	0	1	6	7	
Lauren Classification							<0.0001
Intestinal	2	3	14	21	0	40	
Diffuse	0	0	1	4	18	23	
Histological type							<0.0001
Signet ring cell	0	0	1	4	16	21	
Mucinous	0	0	1	4	0	5	
Poorly cohesive	0	0	0	0	2	2	
Tubular	2	3	13	17	0	35	
Grade							<0.0001
Grade 1	1	1	2	0	0	4	
Grade 2	1	2	10	13	0	26	
Grade 3	0	0	3	12	18	33	
Lymphovascular invasion							<0.0001
Absent	2	3	9	2	0	16	
Present	0	0	6	23	18	47	
T stage							<0.0001
T1	2	0	0	0	0	2	
T2	0	3	3	0	0	6	
T3	0	0	12	19	12	43	
T4	0	0	0	6	6	12	
N stage							<0.0001
No	2	3	12	1	0	18	
N1	0	0	3	3	1	7	
N2	0	0	0	11	8	19	
N3	0	0	0	10	9	19	
Ajcc prognostic stage							<0.0001
I	2	3	1	0	0	6	
Ii	0	0	14	4	0	18	
Iii	0	0	0	21	18	39	

Table 2: Association between Bcl-2 expression and clinicopathological characteristics of gastric carcinomas

	-	+	++	+++	N	**P Value**
Gender						0.001
Male	6	7	12	19	44	
Female	11	4	2	2	19	
Age						0.554
<31 Years	2	0	0	0	2	
31-40 Years	3	1	0	1	5	
41-50 Years	4	4	5	7	20	
51-60 Years	4	3	4	8	19	
61-70 Years	4	2	5	4	15	
>70 Years	0	1	0	1	2	
Site						0.659
Proximal	0	1	1	4	6	
Middle	4	1	0	5	10	
Distal	13	9	13	12	47	
Size						<0.0001
≥5cm	15	6	0	15	36	
<5cm	2	5	14	6	27	
Borrmann Classification						<0.0001
I	0	1	0	0	1	
II	2	6	14	16	38	
III	11	2	0	4	17	
IV	4	2	0	1	7	
Lauren Classification						<0.0001
Intestinal	0	5	14	21	40	
Diffuse	17	6	0	0	23	
Histological Type						<0.0001
Signet Ring Cell	17	4	0	0	21	
Mucinous	0	0	1	4	5	
Poorly Cohesive	0	2	0	0	2	
Tubular	0	5	13	17	35	
Grade						<0.0001
Grade 1	0	2	2	0	4	
Grade 2	0	3	10	13	26	
Grade 3	17	6	2	8	33	
Lymphovascular Invasion						<0.0001
Absent	2	5	8	1	16	
Present	15	6	6	20	47	
T stage						<0.0001
T1	0	2	0	0	2	
T2	1	3	2	0	6	
T3	16	0	12	15	43	
T4	0	6	0	6	12	
N stage						<0.0001
NO	2	5	11	0	18	
N1	3	1	3	0	7	
N2	6	2	0	11	19	
N3	6	3	0	10	19	
Ajcc prognostic stage						<0.0001
I	1	5	0	0	6	
II	4	0	14	0	18	
III	12	6	0	19	37	

4. Discussion

Luo et al.,[37] in his study found a significant association of ERK1/2 expression with female patients, tumour size, Lauren classification, histological type of tumour, tumour grade, lymphovascular invasion, pathological tumour and nodal stage, AJCC prognostic stage.

Han et al.,[38] found that ERK1/2 expression had a significant association with patient age, tumour size, histological type and a higher pathological stage.

Our results showed a significant association of ERK1/2 expression with gender, tumour size, Borrmann type, Lauren type, histological tumour type, tumour grade, lymphovascular invasion, pathological tumour stage and AJCC prognostic tumour stage.

Gryko et al.,[39] in his study showed a significant association of Bcl-2 expression with patient age, Lauren and Borrmann types, tumour grade and pathological tumour stage.

Liu et al.[36] found Bcl-2 expression to be significantly associated with tumour size, Lauren classification and AJCC prognostic stage.

In our study, we found Bcl-2 expression in gastric carcinoma to be significantly associated with gender, tumour size, Borrmann type, Lauren type, histological tumour type, tumour grade, lymphovascular invasion, pathological tumour stage and AJCC prognostic tumour stage.

5. Conclusion

Higher expression of ERK1/2 and Bcl-2 were seen in higher tumour grade and higher AJCC prognostic stage which might point towards the prognostic significance of these markers in gastric carcinoma.

Hence it could be concluded that the objectives of the study were achieved in regards to the association of ERK1/2 and Bcl-2 expressions with the clinicopathological features of gastric carcinoma.

6. Source of Funding

None.

7. Conflict of Interest

None.

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