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p53 Expression and its Association with Histological Grade of Gastric Adenocarcinoma

Mst. Mahmuda Khatun[1]*, S.M. Asafudullah[1], Khadiza Khanam[1], Sadia Refat[3], Swapna Majumder[1]

[1] Department of Pathology, Rajshahi Medical College
[2] Department of Pathology, Barind Medical College
[4] Department of Pathology, Dhaka Medical College

Abstract: ***Background& Objective:*** Gastric cancer is known as one of the most common cancers and cause of death. Early and accurate diagnosis is an important tool for proper treatment response. Mutation of the p53 tumor suppressor gene is the most frequent genetic alteration observed in human cancers. The aim of this study was to evaluate the expression of p53 in gastric adenocarcinoma and its association with histological grade. ***Methods & Materials:*** This cross-sectional study was conducted in the Department of Pathology, Rajshahi Medical College, from September 2019 to August 2021. A total of 50 gastrectomy samples with a histologically confirmed diagnosis of gastric adenocarcinoma were included in this study. Expression of p53 was evaluated in formalin-fixed and paraffin embedded specimens by immunohistochemistry. ***Result:*** p53 expression was observed in all cases among which 31 (62%) patients showed low and 19 (38%) patients showed high p53 expression. Level of p53 expression was found significantly associated with histological grade. But, the p53 expression levels was not associated with the age of the patients with gastric adenocarcinoma (p>0.05). ***Conclusion:*** The expression of p53 involved in the progression and differentiation of gastric adenocarcinoma. These expression levels can be utilized as indicators of biological behavior and prognosis of gastric adenocarcinoma.

Keywords: Gastric adenocarcinoma, p53 expression, Histological grade.

Original Research Article

***Correspondence:**
Dr. Mst. Mahmuda Khatun
Lecturer, Department of Pathology, Rajshahi Medical College
E-mail: miturmc47@gmail.com

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Article at a glance:

Study Purpose: *To evaluate the immunoexpression of p53 in gastric adenocarcinoma and its association with histological grade.*
Key findings: *There was significant association between p53 expression with tumor grade and lymph node involvement.*
Newer findings: *High p53 expression in gastric adenocarcinoma suggesting aggressive behavior.*
Abbreviations: *IHC – Immunohistochemistry, p53 – Tumor Protein 53, H&E – Hematoxylin and Eosin, TNM – Tumor, Node, Metastasis (staging system), IRS – Immunoreactive Score.*

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide, being the 5th most commonly diagnosed cancer. More than 90% of gastric cancers are adenocarcinomas.[1,] The survival is generally poor for stomach cancers. Absence of screening program and less awareness regarding gastric cancer might have lead to delayed medical consultation for gastric carcinoma in Bangladesh. However, in India, the 5 years survival is dismal and is less than 10%.[2] Tumor cell kinetics currently attract attention because it is thought that these reflect tumor aggressiveness. A correlation between proliferative activity and poor prognosis has been indicated in numerous human malignancies.[3] Accumulation of genetic alterations plays a role in cancer progression and development of human cancers is a multistep process. Cellular proliferation follows an organized and timely regulated progression through the cell cycle, which is regulated by cell-cycle regulators, such as p53. [4] p53 was first classified as an oncogene, encoded by

the *TP53* gene, suppresses growth and oncogenic transformation in cell culture, that inactivating *TP53* mutations are common in human tumors, and in many cancers linked to poor patient prognosis. [5]

The evidence accumulated to date suggests that the most frequent genetic abnormality in human cancer may be a mutation of p53, and it is known that such a mutation plays a significant role in the carcinogenesis of colonic carcinoma and gastric carcinoma.[6] Level of p53 expression was found significantly associated with age, tumor site, tumor size, histological grade, T stage, M stage and Clinical stage. They concluded expression of p53 correlates with the survival and is a simple, effective and reproducible modality to determine the prognosis and survival in various grades & stages of gastric cancer.[7] The key role of mutation of some tumor suppressor genes such as p53 in the incidence of gastric cancers is considered and the relationship between its immunoexpression with pathological indicators of tumors can be determined. So, this study evaluate expression of p53 in gastric adenocarcinoma and its relationship with different histological grades regarding the utility of p53 immunoexpression in determining the prognosis of gastric adenocarcinoma.

METHODS

This descriptive cross-sectional study was conducted in the department of pathology, Rajshahi medical college over a period of two years from September 2019 to August 2021. A total of 50 gastrectomy samples with a histologically confirmed diagnosis of gastric adenocarcinoma were included in this study. Expression of p53 was evaluated in formalin-fixed and paraffin embedded specimens by immunohistochemistry. p53 expression was categorized as low and high expression. Specimen of tissue was fixed with 10% formalin and stained with haematoxyline and eosin stain was examined. For immunohistochemistry, 3-4 micrometer thick sections of formalin fixed, paraffin-embedded tissues with a MIB-1 monoclonal antibody in appropriate dilutions was used. Standard immunohistochemical method was applied for subsequent staining. Data were analyzed by using windows software SPSS version 23.

The result of p53 protein immunohistochemistry was quantified as scores, according to the following method. First, percentages of the total number of p53 positive cells was assigned to one of four categories. Second, the intensity of p53 protein immunostaining was scored. [7]

IMMUNOREACTION SCORE (IRS)

Percentage of p53 positive cells	Score	Staining intensity	Score
≤ 10%	1	Negative	0
11-49%	2	Weak	1
50-79%	3	Moderate	2
≥ 80%	4	Strong	3

IRS score = Percentage of p53 positive cells × Staining intensity

Total score= 0 to 12{≤6= low and >6= high}

RESULTS

A total of 50 cases diagnosed with gastric adenocarcinoma were subjected to immunohistochemical examination of p53. Out of 50 patients, p53 was highly expressed in 19 (38%) patients. On the other hand 31 (62%) patients had low expression of p53 (Table-I). Table II depicts that, the p53 expression levels was not associated with the age of the patients with gastric adenocarcinoma (p>0.05). Though the proportion with high level of p53 expression was higher among male (40.6%) compared to female patients (33.3%), the difference failed to reach statistical significance (p=0.610) (Table – III). Table IV depicts that, high p53 expression was the highest in poorly differentiated tumor and in the entire well differentiated tumor had low expression for p53. The association between tumor differentiation and level of p53 expression was highly significant statistically (p=0.003). Table V depicts that, proportion of high p53 expression was significantly higher in high grade tumor than the low-grade tumor (56.7% versus 10%, p=0.001). Table VI depicts that, though the proportion of high p53

expression was gradually increased as the tumor invasion level increased (0%, 33.3%, and 41.0% respectively in T1, T2, and T3) but the differences were not statistically significant (p=0.482). Table VI depicts that, though the proportion of high p53

expression was gradually increased as the tumor invasion level increased (0%, 33.3%, and 41.0% respectively in T1, T2, and T3) but the differences were not statistically significant (p=0.482).

Table 1: Distribution of the patients according to p53 expression (n=50)

p53 expression	Frequency	Percent
Low	31	62
High	19	38

Table 2: Association between age and p53 expression level (n=50)

	p53 expression		
Age (years)	Low	High	p value
30-39	4 (100.0)	0 (0)	
40-49	4 (57.1)	3 (42.9)	
50-59	13 (48.1)	14 (51.9)	
60-39	10 (83.3)	2 (16.7)	0.078*
Mean ± SD	53.81±9.66	53.79±5.72	0.994[t]

*Chi-square test; independent sample t test.

Table 3: Association between sex of the patient and p53 expression level (n=50)

	p53 expression		
Sex	Low	High	p value
Male	19 (59.4)	13 (40.6)	0.610*
Female	12 (66.7)	6 (33.3)	

*Chi-square test.

Table 4: Association between type of tumor differentiation status and p53 expression level (n=50)

Tumor type	p53 expression		
	Low	High	p value
Poorly differentiated	13 (43.3)	17 (56.7)	
Moderately differentiated	9 (81.8)	2 (18.2)	
Well differentiated	9 (100.0)	0 (0)	**0.003***

*Chi-square test; independent sample t test.

Table 5: Association between type of tumor grade and p53 expression level (n=50)

Tumor grade	p53 expression		p value
	Low	High	
Low grade	18 (90.0)	2 (10.0)	0.001*
High grade	13 (43.3)	17 (56.7)	

*Chi-square test.

Table 6: Association between type of tumor size and p53 expression level (n=50).

	p53 expression		
Tumor size	Low	High	p value
T1	2 (100.0)	0 (0)	
T2	6 (66.7)	3 (33.3)	
T3	23 (59.0)	16 (41.0)	0.482*

. *Chi-square test.

Table 7: Association between nodal status and p53 expression level (n=50)

	p53 expression		
Nodal status	Low	High	p value
NX	16 (76.2)	5 (23.8)	
N1	8 (80.0)	2 (20.0)	
N2	0 (0)	12 (100.0)	
N3	7 (100.0)	0 (0)	<0.001*

*Chi-square test.

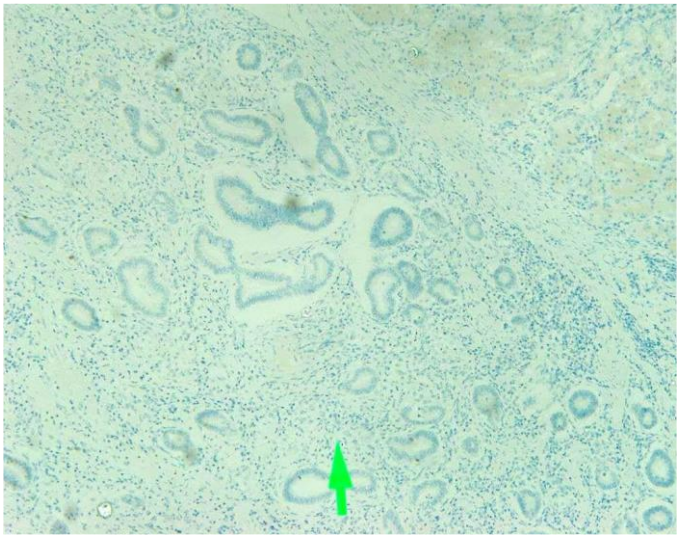

Figure 1: Photomicrograph showing low expression of p53 in well differentiated (low grade) intestinal type gastric adenocarcinoma. (immunostain of p53×100)

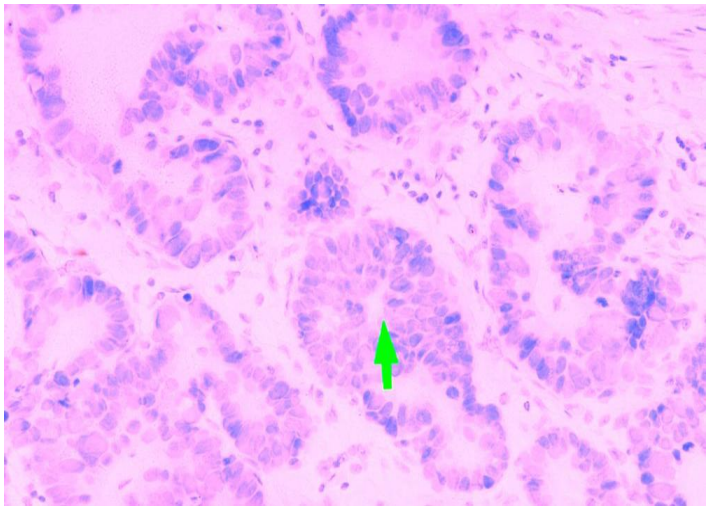

Figure 2: Photomicrograph showing low expression of p53 in moderately differentiated intestinal type gastric adenocarcinoma. (immunostain of p53×400)

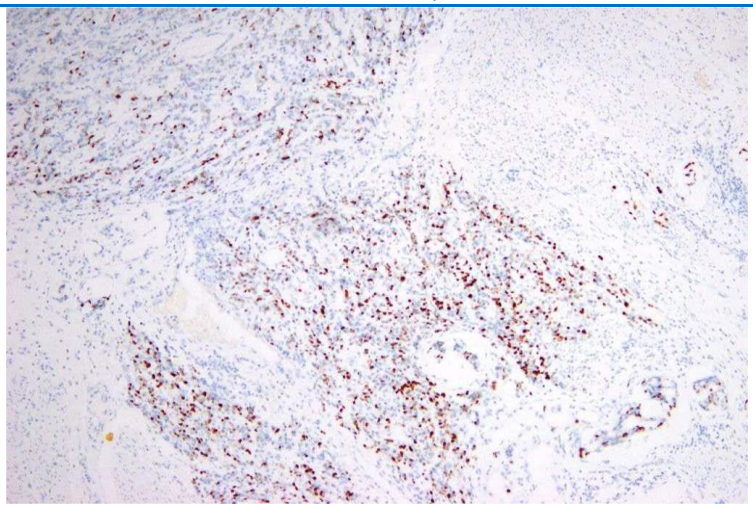

Figure 3: Photomicrograph showing high expression of p53 in poorly differentiated gastric adenocarcinoma (immunostain of p53×100)

DISCUSSION

Gastric cancer is a leading cancer in Bangladesh like that of the global incidences. Approximately 84% of gastric cancer patients present with advanced disease and their median survival time is only 3-4 months if they are not treated with chemotherapy.[8] Therefore, it is necessary to diagnose at an early stage in order to improve the survival rate. According to the study from India conducted by Sankalecha et al,[7] p53 expression was in 90% of gastric cancer patients among which 37 (63.8%) patients showed high and 21 (36.2%) patients showed low p53 expression. In the present study, p53 expression was observed in 100% of the gastric adenocarcinoma among which high expression was observed in only 38% of the cases. The result of the current study was lower than most of the earlier studies. However, similar low rate of high expression of p53 in gastric adenocarcinoma was reported by few other studies.[9-11] The discrepancy in p53 expression in different studies might be due to the type and concentration of antibody that had been used, differences in the detection system, and differences in the method of p53 scoring, or it may be due to genetic or environmental factors. A study by Jung et al., [12] reported an exceptionally high proportion of p53 in 90.3% of their patients with gastric cancer as only its expression was considered positive in the study.

In the present study the p53 expression levels was not associated with the age of the patients with gastric adenocarcinoma (p>0.05). Another study by Al –Moundhri et al.,[13] p53 over expression was 63.8% in patients with age less than 60 years but in the patients with age more than 60 years it was 44.4%, and the difference was statistically significant (p=0.03). In the current study no significant association was found between sex and high p53 expression. It was in accordance with other study findings where no significant association was found between p53 expression and sex. [9,14] In previous studies, the incidence of p53 abnormalities varied on the basis of the histological type of cancer. In the current study, a higher percentage of p53 expression for diffuse-type, rather than intestinal type lesions, but the difference was not significant (47.3 versus 32.3%, p=0.285). Similar non-significant higher positivity of p53 in gastric carcinoma was observed by Calik et al.,[10] Al-Moundhri et al.,[13] and Ahadi et al.,[11] who did not observe a significant association between p53 expression and Lauren's classification, grade of tumor, or location of the tumor.[15]

One of the important parameter to assess prognosis in gastric cancer is histopathologic grade of tumor. As grade increases prognosis become poorer. In the present study, p53 over expression was the highest in poorly differentiated tumor and low in well differentiation and level of p53 expression was statistically highly significant (p=0.003). Regarding tumor grade proportion of high p53 expression was significantly higher in high grade tumor than the low grade tumor (56.7%versus10%, p=0.001). Similar results were seen in the study by Sankalecha et al.,[7] while in

study done by Akshatha et al.,[16] showed no correlation with histological grade. However, the proportion of high p53 expression was gradually increased as the tumor size increased (0%, 33.3%, and 41.0% respectively in T1, T2, and T3) but the differences were not statistically significant (p=0.482). Disagreement with the present study, Al-Moundhri et al.,[13] did not observed any significant association between p53 expression with tumor grade and stage. However, the present study findings were more or less in agreement with the findings of the studies conducted on Indian populations.[7,17] In these studies, expression of p53 was associated with the histologic grade of the tumor. In the study by Sankalecha et al.,[7] p53 expression was found significantly associated with age, tumor site, tumor size, histological grade and stage, where as it was not associated with gender, nodal involvement, Lauren classification and histopathological type of tumor.[15]

In the present study, p53 over expression was also higher in patients with positive lymph node than the patients with negative lymph node (48.3% and 13.8%) but the difference was not significant statistically (p=0.079). Kakeji et al.,[18] reported that gastric cancer with p53 over expression has a high potential for metastasizing to lymph nodes. Similarly, Calik et al.,[10] found a significant association between overexpression of p53 and lymph node metastases and a significant relationship between over expression of p53 and depth of tumor invasion. Thus, it is not surprising to find that p53 over expression suggesting aggressive behavior.

CONCLUSION

There was no significant association between p53 expression and demographic parameters while the expression of p53 is significantly associated with grade and differentiation of gastric adenocarcinoma. So, immunohistochemical expression of p53 can be utilized as indicator of biological behavior and prognosis of gastric adenocarcinoma.

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Authors' contribution

Dr. Sadia Refat Wahid & Dr. Swapna Majumder carried out the data aquisition. The concept, study design, write-up, and statistical analysis were done by Dr. Mst. Mahmuda Khatun. Dr. S.M. Asafudullah and Dr. Khadiza Khanam provided constant supervision, critical feedback and helped to shape the manuscript.

Declaration

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

Ethical approval of this study was obtained from Ethical Review Committee, Rajshahi Medical College, Rajshahi. All the study methodology was carried out following the relevant ethical guidelines and regulations.

Consent for publication: Taken.

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