

# Association of E-Cadherin Expression with Histological Type and Grade of Gastric Adenocarcinoma

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## Author's Contribution

<sup>1,3,4</sup>Substantial contributions to the conception or design of the work; or the acquisition, <sup>5</sup>Drafting the work or revising it critically for important intellectual content Critical review <sup>2</sup>analysis, or interpretation of data for the work, <sup>6</sup>Active participation in active methodology

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## ABSTRACT

**Objectives:** To determine the immune expression of E-Cadherin in gastric adenocarcinomas and its association with tumor histological type and grade, thereby evaluating its prognostic significance.

**Methodology:** This descriptive cross-sectional study was conducted at the Pakistan Institute of Medical Sciences, Islamabad, from December 2017 to January 2021. A total of 81 patients of both genders, aged 21 to 83 years, undergoing gastric biopsies and Gastrectomy specimens for diagnosing gastric adenocarcinoma were included. Immunohistochemical processing was performed, and the results were interpreted by a consultant pathologist for E-cadherin expression on gastric adenocarcinoma. Data were analyzed using SPSS version 21.

**Results:** A statistically significant association was found between loss of E-Cadherin and the histological type of adenocarcinoma ( $p = 0.000$ ). Among the 81 cases, 53 (65%) were classified as intestinal type adenocarcinoma and 28 (35%) as diffuse type adenocarcinoma. Among the 28 cases of diffuse type gastric adenocarcinoma, 10 showed complete loss of E-Cadherin expression. Complete loss of Cadherin was also observed in four out of 53 cases of intestinal adenocarcinoma, all of which were poorly differentiated. All nine cases of well-differentiated adenocarcinoma demonstrated high expression of E-Cadherin.

**Conclusion:** This study highlights a strong association between E-Cadherin expression and the histological type and grade of gastric adenocarcinoma. Increased loss of E-Cadherin expression with higher grades of adenocarcinoma underscores its prognostic significance. Additionally, our findings suggest a higher incidence of gastric adenocarcinoma in elderly males.

**Keywords:** Gastric Adenocarcinoma, Histological Subtypes, Immunohistochemistry, E-cadherin.

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## Introduction

Gastric cancer ranks as the fifth most prevalent cancer globally and stands as the third leading cause of cancer-related fatalities.<sup>1</sup> Gastric cancer is diagnosed late because earliest symptoms are usually vague and nonspecific such as dyspepsia, nausea, vomiting and weight loss. When diagnosed, the tumour is usually in its late stages when there is no curative therapy. Surgical resection in earliest stages can be curative. So, it is very important to search for novel diagnostic and prognostic agents which can help in

early detection and timely treatment of this lethal disease.<sup>2</sup> With development in the field of molecular biology, targeted therapies have emerged. Some classical examples of these genes include Human epidermal growth factor receptor 2 (Her2) and Vascular endothelial growth factor receptor (VEGFR) for which targeted therapies are currently in clinical practice with promising results in advanced stages of gastric cancer.<sup>3,4</sup>

E-cadherin is one of the members of family of cadherins which are membrane glycoproteins responsible for cell to

cell adhesion. When E cadherin protein producing gene is mutated there is reduced or absent expression of it in many cancers including gastric cancer.<sup>5, 6</sup> These mutations can be either genetic or epigenetic. In tumour cell cultures the restoration of E cadherin resulted in normal epithelial type from mesenchymal phenotype.<sup>3</sup> E cadherin can be detected by immunohistochemistry. It is present in normal gastric glands. Its abnormal expression has been found in a variety of cancers including gastric adenocarcinoma. It is also found to have correlation with prognosis of the gastric cancer. Studies showed that its expression was lost more in diffuse type of gastric adenocarcinoma and also the loss was more with the increasing grade of intestinal carcinoma.<sup>3</sup> Epigenetic mutations are found in 82% of diffuse gastric carcinoma and 56% of intestinal type of gastric adenocarcinoma.<sup>7</sup>

Targeted therapies for epigenetic mutations are developed with promising results.<sup>8</sup> Oxamflatin is a histone deacetylase inhibitor which induces E-Cadherin expression. So Oxamflatin can be considered for the prevention of both the development and progression through metastasis of gastric cancer. Further research with experiments in vivo and vitro needs to be done regarding the effective dose of the drug.<sup>9</sup> There is no published study regarding E cadherin evaluation in gastric adenocarcinoma in Pakistani population. Evaluation of E cadherin immunoexpression has prognostic value, its downregulation is associated with poor differentiation of the tumor. Presence of positive E cadherin immunoexpression will help to predict the patients which will have better prognosis than the patients with negative E cadherin immunoexpression which show poor prognosis.<sup>10, 11</sup>

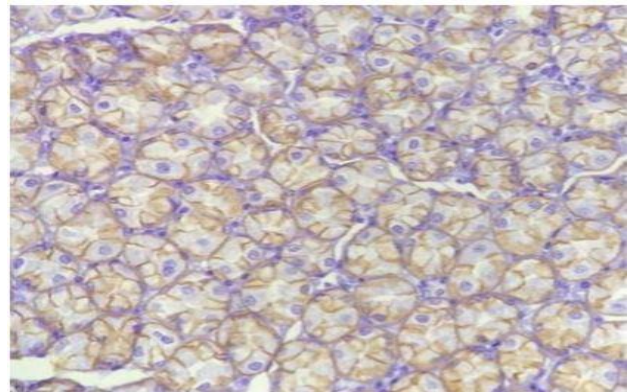
This study is done to evaluate the association of E-cadherin with histological types and grades of gastric adenocarcinoma. The data obtained from such studies can help in evaluating the prognostic and therapeutic significance of gastric adenocarcinoma.

## Methodology

After Hospital Ethical Committee approval and informed verbal consent from the patients, all gastric biopsies and surgical resection specimens with clinical diagnosis of gastric adenocarcinoma received in the Department of Pathology, Pakistan Institute of Medical Sciences (PIMS) Islamabad were collected during three years of duration, from December 2017 to January 2021. Eighty-one cases were chosen for the study using the WHO calculator based on a 95% confidence level, and the anticipated population

proportion was 26% with a 10% absolute precision level. Non epithelial and metastatic malignancies were not included in the study. Patient's all relevant data was collected. After gross examination all the biopsy and resection specimens were fixed in 10% formalin. After fixation, the tissue sections underwent processing in an automatic tissue processor and were subsequently embedded in paraffin. This was followed by cutting, slide preparation, and staining with hematoxylin and eosin (H&E) stain. Immunohistochemical staining was performed using the E-cadherin Antibody NCH-38 by Dako (Ref: ISO59, Lot 10109514, Flex monoclonal mouse). The diagnosis and Immunohistochemical scoring were recorded. Gastric carcinomas were classified by Lauren's classification as intestinal type and diffuse type.

The intestinal type was further divided into well differentiated adenocarcinoma (Grade I), moderately differentiated adenocarcinoma (Grade II) and poorly differentiated adenocarcinoma (Grade III). Immunohistochemical Scoring: Complete membranous staining was considered to be normal (Figure 1).



**Figure 1. Complete Membranous staining of E-cadherin.**

It was considered abnormal when it was either absent or aberrant which included heterogeneous staining (both cytoplasmic and membranous) or only cytoplasmic.<sup>12, 13</sup> Evaluation of E-Cadherin immunostaining was done both by applying qualitative and quantitative score. In the qualitative scoring the intensity of reaction was used as the intensity score: +1 = weak (light brown), +2 = moderate (brown), 3 = strong (intense brown). In quantitative scoring the percentage of tumor cells positive for E cadherin staining was used as: (% positive cells): 0 – negative, 1 =  $\leq 25\%$ , 2 = 25–50%, 3 = 50–75%, 4 =  $\geq 75\%$ . The index of positivity (IP) was calculated by multiplying the two scores, giving the range of: 0–12 as follows: Index of positivity = 0 = negative immunoreactivity (-), 1–4 = low immunoreactivity (+), 5–8 = moderate

immunoreactivity (++) , 9–12 = high immunoreactivity (+++).<sup>14</sup>

The data was assessed by applying the statistical package for social sciences (SPSS) software version 21. Mean and standard deviation (SD) was calculated for quantitative data like age. Qualitative variables like H&E and IHC diagnosis were calculated as proportions and percentages. Chi-square test was applied to determine E-Cadherin expression between histological types and grades of intestinal type adenocarcinomas. P value of  $\leq 0.05$  was taken as significant.

## Results

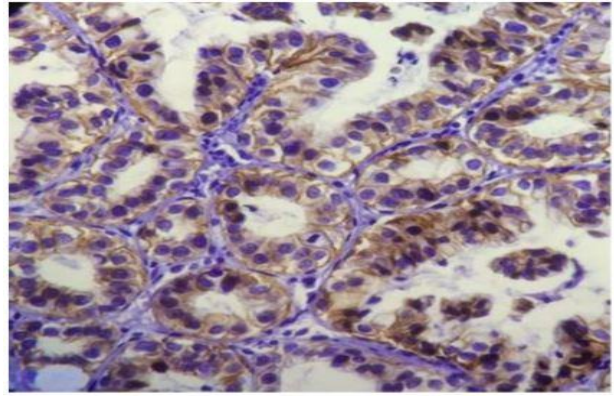
Total 81 cases were studied with a mean age of 51 years ranging from 21 - 83 years. Male patients were 59(73%) and female were 22(27%) with male to female ratio of 2.6:1. The study group consisted of 81 cases of gastric adenocarcinoma. The most frequent type of tumor was intestinal type of gastric adenocarcinoma, 53 cases (65%) with majority of cases 23(28%) showing the poorly differentiated grade of Laurens classification. It was followed by 28 (35%) cases of diffuse type of adenocarcinoma.

Regarding Grade-wise E-cadherin Immunohistochemical expression of these 81 cases, Nine out of nine (100%) cases of well differentiated adenocarcinoma had high index of positivity (Figure 2) while 13/21 (62%) cases of moderately differentiated adenocarcinoma showed high index of positivity, 5/21 (24%) cases showed low index of positivity and 3/21 (14%) cases showed moderate index of positivity. (Figure 3).

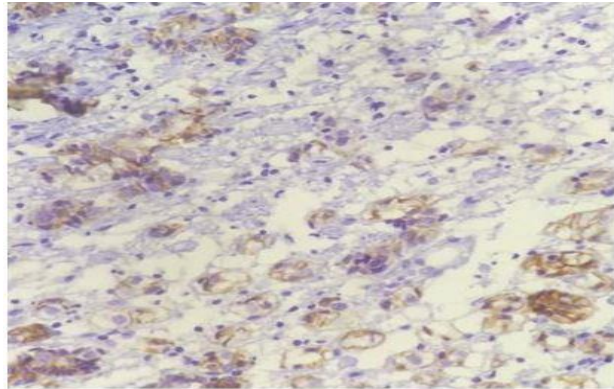
In total 23 cases of poorly differentiated adenocarcinomas majority of cases had low index of positivity (Figure 4) which was 15 cases followed by four cases with moderate and four with negative index of positivity.

As far as E-Cadherin Immunoexpression in Diffuse Type Adenocarcinoma is concerned, 15/28(53%) cases showed low index of positivity, ten cases of Diffuse Type Adenocarcinoma showed negative index of positivity (Figure 5) and only three cases showed moderate index of positivity while none of the case showed high positivity.

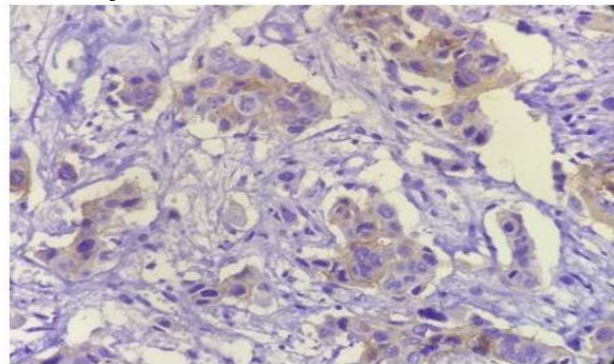
The E-cadherin immunohistochemical results with respect to histological types and grades are summarized in the Table I.



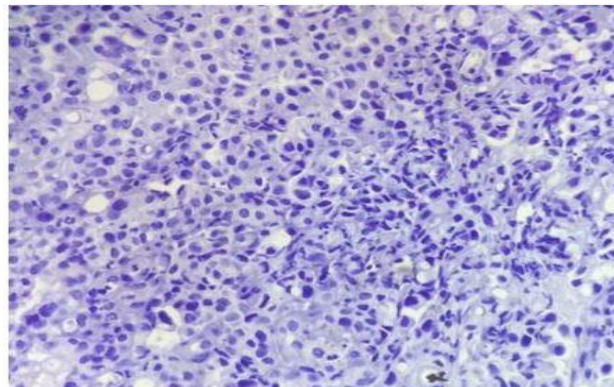
**Figure 2. High index of E-cadherin positivity in well-differentiated Gastric Adenocarcinoma.**



**Figure 3. Moderate index of E-cadherin positivity in Moderately differentiated Gastric Adenocarcinoma.**



**Figure 4. Low index of E-cadherin positivity in Poorly differentiated Gastric Adenocarcinoma.**



**Figure 5. Negative index of E-cadherin positivity in Diffuse type Gastric Adenocarcinoma.**

Intestinal Type Adenocarcinoma	Index of positivity				Total	P value
	High	Moderate	Low	Negative		
Well differentiated	09 (100%)	0(0%)	0(0%)	0(0%)	09	<b>0.001</b>
Moderately differentiated	13 (62%)	3(14%)	5(24%)	0(0%)	21	
Poorly differentiated	0(0%)	4(17%)	15(65%)	4(18%)	3	
Diffuse	0(0%)	3(11%)	15(53%)	10(36%)	28	
<b>Total</b>	22	10	35	14	81	

#### Association of Immunohistochemical Expression of E-Cadherin in Histological Type of Adenocarcinoma

There was a significant statistical correspondence between E-Cadherin loss with histological type of adenocarcinoma ( $p = 0.000$ ). The complete E-Cadherin loss was seen in total 14 cases out of 81 cases. There was a complete loss in 10 cases out of 28 cases in diffuse type gastric adenocarcinoma. While this complete loss was seen in four cases out of 53 cases of intestinal adenocarcinoma. E-Cadherin expression was low in 15 out of 28 cases in diffuse type gastric adenocarcinoma while in intestinal type gastric adenocarcinoma 20 out of 53 cases showed low index of positivity. Conversely, high positivity of index was not seen in any case of diffuse type of adenocarcinoma while moderate index of positivity was seen in only three cases out of 28 cases in diffuse type. High index of positivity was observed in 22 cases out of 53 cases in intestinal type adenocarcinoma and moderate staining in seven cases.

#### Association of Immunohistochemical Expression of E-Cadherin in Histological Grade of Adenocarcinoma

The complete E-Cadherin loss was observed in four patients of intestinal type adenocarcinoma all of which were poorly differentiated. In the remaining, 20 cases showed low and 7 cases showed moderate index of positivity. Total cases of well differentiated type of adenocarcinoma were nine in which all showed the high expression of E-Cadherin. Similarly, moderately differentiated adenocarcinomas (Total of 21 cases) showed high expression (13 cases) and low expression in five cases. Three cases showed moderately index of positivity. None of the cases showed complete loss of expression of E-Cadherin. Low grade tumor (well differentiated and moderately differentiated intestinal type gastric adenocarcinoma) showed high index of positivity when compared with high grade tumor (poorly differentiated intestinal type adenocarcinoma and diffuse type gastric adenocarcinoma) ( $p=0.001$ ).

## Discussion

Out of the 81 cases, 59 (73%) were males and 22 (28%) were females. The male to female ratio obtained was 2.6:1. According to a local study conducted in Karachi, Pakistan by Daniyal M et al. the prevalence of stomach cancer was more in males with male to female ratio of 2:1.2.<sup>15</sup> According to a population-based cohort study conducted by Lindblad M it was observed that treatment with estrogen is related with less risk of gastric cancer. It was supported by the hypothesis that estrogen has a protective role in the gastric carcinoma etiology. The finding that males are affected more than females lead to the studies which try to find out the reasons behind it. One of the most probable reasons can be the protective effect of estrogens in females. Further studies need to be done in this regard.

This finding will greatly help in preventing gastric carcinomas by using estrogen related targeted therapies for the preventive measurements of gastric cancer in high-risk persons or patients belonging to high-risk families.<sup>16</sup> In 81 cases of gastric adenocarcinomas analysis of E-Cadherin expression showed various index of positivity in different types and different grades of the cancer according to Laurens classification. This study shows that reduced E cadherin immune expression is associated with higher grade and poor outcome and so can be considered as a possible prognostic factor in gastric adenocarcinoma. It was completely absent in 14/81 cases (17%) which includes 4/23 (17%) poorly differentiated intestinal type adenocarcinoma and 10/28 (36%) cases in diffuse type gastric adenocarcinoma. The expression was variable in the remaining 67 cases (83%), 18/28 cases of intestinal type (64%) and 49/53 cases (92%) of diffuse type carcinomas. These findings are comparable with the findings obtained by Stanculesce D et al. who studied 60 cases of gastric carcinomas which showed that E-Cadherin immunoreactivity was completely absent in 21/60 cases (35%), 15/27 (55.55%) intestinal-type carcinomas (poorly differentiated tumors) and 6/11(54.54%) diffuse type carcinomas and with variable index of positivity in 39 cases (65%) of cases which included 34/49 cases of intestinal type (69.38%) and 5/11 cases (45%) of diffuse

type carcinomas (14). According to Lazar et al Reduced expression was seen in 12/38 (31.6%) of cases of intestinal type adenocarcinoma and 14/17 (82.4%) of Diffuse type adenocarcinoma while 4/6 (66.7%) of mixed type of adenocarcinoma.<sup>17</sup>

The E-Cadherin immunoexpression loss was more frequently seen in diffuse type of adenocarcinoma (65%) than in intestinal type of adenocarcinoma (20%) according to the Lauren and Ming. There were remarkable E Cadherin aberrations related to invasiveness of the neoplasm ( $P < 0.05$ ). There was also significant correlation of E-Cadherin loss and less survival rate ( $P = 0.109$ ). So, these statistics showed a major connection between E-Cadherin immune expression and different grades of intestinal adenocarcinoma. E-Cadherin immunoexpression loss can have a role in contribution to gastric cancer invasiveness to the nearby viscera.<sup>18</sup>

In a study done by Dewan et al the absent E cadherin expression was found in 11/100 cases, 4/70 (6%) cases of intestinal type adenocarcinoma and 7/27 (26%) cases of diffuse type adenocarcinoma while Berx et al. found 13/26 cases (50%) diffuse GAC to have reduced E-Cadherin expression. He also correlated E-Cadherin expression with a stage of the disease and different studies. His study demonstrated the reappearance of E-Cadherin immune expression in tumor cells in invasive carcinoma of breast. He stated that this re appearance could possibly be for preventing the process of apoptosis. However, due to the less number of the patients in the study, no conclusions can be made.<sup>19</sup>

Mashayd et al in his study has illustrated a remarkable relation among expression of E Cadherin and histology of tumor type. According to his study results E-Cadherin had relation with depth of tumor invasion but it was not related to regional lymph node metastasis significantly. Abnormal immunoreactions of E-Cadherin aberrant immunoreactions are seen more frequently in the diffuse adenocarcinomas contrary to the 76 intestinal adenocarcinomas. So, the data obtained from his study emphasize the convincing association between the Lauren's histological classification of the stomach carcinomas and E-Cadherin immuno expression. The E-Cadherin abnormal immuno expression was observed more frequently in poorly differentiated carcinomas as compared to the moderately differentiated and well differentiated carcinomas. In Intestinal type it was normal in 12/16 (75%) cases and 05/14 (36%) cases showed aberrant expression while in diffuse type 03/16 (19%) cases had normal expression while 07/14 (50%) cases

showed abnormal expression and the remaining mixed type gastric adenocarcinoma showed 01/16 (06%) normal and 02/14 (14%) abnormal expression.<sup>20</sup>

An abnormal E-Cadherin immunoexpression was noted by Lee WA et al. in 55/150 cases (36.7%). Significantly higher aberrant immunoexpression was observed in diffuse type adenocarcinoma than in the other histologic types according to Lauren's classification ( $p = 0.002$ ).<sup>21</sup> According to Joo YE et al. in total 62 cases of gastric adenocarcinoma, 34 cases (52%) showed abnormal immunoexpression of E-Cadherin in which 23 (35%) showed abnormal positivity while it was completely absent in 11 cases (17%). In intestinal type this abnormal expression was observed in 9/28 cases (32%) while 11/25 cases (44%) in diffuse type.<sup>22</sup>

In a study conducted by Torabizade Z et al, 48.6% of cases of gastric carcinoma showed aberrant immuno-expression of E-Cadherin on Immunohistochemistry.<sup>13</sup> This abnormal expression of E-Cadherin in stomach cancer was reported 38% in Dr. Anbiaee et al.'s study in Iran.<sup>23</sup>

## Conclusion

In conclusion, current study suggests a variable loss of E-Cadherin in different histological types and grades according to Laurens classification of gastric adenocarcinoma. Our data highlighted loss of E-Cadherin expression among the various histological types and grades of gastric adenocarcinoma. It shows the association of gastric adenocarcinoma with male gender and increased incidence with age of more than 40 years. Maximum E-Cadherin loss was seen in gastric adenocarcinoma of diffuse type and in intestinal type of adenocarcinoma the maximum loss was observed in poorly differentiated type followed by moderately differentiated adenocarcinoma.

There was a high immune expression of E-Cadherin in well differentiated gastric adenocarcinoma of intestinal type which is consistent with the hypothesis that E-Cadherin is expressed in initial grades which is gradually lost as the grade of the tumor gets higher.

**LIMITATIONS:** The study lacked inclusion of unclassifiable gastric adenocarcinoma types and omitted significant pathological parameters such as tumor site, size, and metastasis. Moreover, follow-up data was unavailable, hindering prognostic analysis. Additionally, various risk factors like family history and dietary habits were not considered due to insufficient clinical data.

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