Section: Pathology

Original Research Article

CLINICOPATHOLOGICAL CORRELATION OF CDH17, CYTOKERATIN 7, AND CYTOKERATIN 20 EXPRESSION IN GASTRIC CARCINOMA

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ABSTRACT

Background: Gastric carcinoma remains a significant global health burden, with prognosis and treatment outcomes influenced by tumor biology and biomarker expression. This retrospective study aimed to evaluate the expression of Cadherin 17 (CDH17), Cytokeratin 7 (CK7), and Cytokeratin 20 (CK20) in gastric cancer and analyze their clinicopathological correlations. **Materials and Methods:** Conducted at Chengalpattu Medical College from 2018 to 2021, the study included 40 histologically confirmed gastric carcinoma cases. Clinical and pathological parameters assessed included age, sex, tumor site, histological grade, lymph node involvement, and depth of infiltration. Immunohistochemistry was performed to detect CDH17, CK7, and CK20 expression, and statistical analysis was done to determine correlations with clinicopathological features. **Result:** CDH17 expression showed a statistically significant association with tumor grade ($p = 0.001$), indicating its potential role in tumor differentiation assessment. CK7 and CK20 expression exhibited limited clinicopathological correlation. **Conclusion:** CDH17 may serve as a valuable prognostic biomarker in gastric carcinoma, whereas CK7 and CK20 have limited predictive value. Further large-scale studies are warranted to validate these findings.

INTRODUCTION

Gastric carcinoma remains a major public health problem worldwide, ranking as the fifth most common malignancy and the third leading cause of cancer-related mortality globally, accounting for approximately 6.8% of all cancers and 8.8% of cancer deaths annually.[1] In India, an estimated 34,000 new cases are recorded each year, with a pronounced male preponderance (male-to-female ratio of around 2:1). Its burden is especially significant in East Asia, Eastern Europe, and portions of South America. The northeastern states of India have the greatest prevalence, which is probably due to a combination of dietary and environmental factors. Due in large part to late-stage presentation, the prognosis for stomach cancer is still dismal despite advancements in diagnostic and treatment approaches; in most countries, the overall five-year survival rate is around 25%.[2]

There are several histological subtypes of gastric cancer, each with unique biological characteristics, making it a diverse illness. Adenocarcinomas, which originate from the stomach mucosa, account for around 90% of cases; the remaining instances are made up of uncommon mesenchymal tumours, gastrointestinal stromal tumours, and lymphomas.[3] The WHO and Japanese classification systems describe early gastric cancer as a lesion that is limited to the mucosa or submucosa, irrespective of the presence of lymph nodes, and that has a good prognosis when surgically removed. On the other hand, advanced phases are usually aggressive and linked to negative results. The Lauren classification further subtypes gastric adenocarcinomas into diffuse and intestinal kinds, each of which has a unique prognosis, aetiology, and epidemiology.[4]

Gastric cancer has a complex aetiology. The most well-established risk factor for non-cardia gastric cancer is Helicobacter pylori infection, which also contributes to known precursor diseases such as intestinal metaplasia, atrophic alterations, and chronic gastritis.[5-9]. Autoimmune gastritis, dietary variables (high salt intake, smoked and preserved foods), alcohol use, tobacco smoking, obesity (especially for cardia tumours), and genetic predispositions such hereditary diffuse gastric cancer (HDGC) due to CDH1 mutations are additional risk factors.[5] There are additional links to conditions including Barrett's oesophagus, chronic gastro-oesophageal reflux disease (GERD), and certain gastric polyps. Geographical and racial differences

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also affect incidence; Japan and Korea have among of the highest rates in the world.[6]

Gastric cancer has a complicated molecular landscape. Gastric tumours have been divided into four molecular subgroups by the Cancer Genome Atlas (TCGA) project: microsatellite instability-high (MSI-H), chromosomal instability (CIN), genomically stable, and Epstein-Barr virus (EBV)-positive. A number of carcinogenic pathways are implicated, such as changes in the Wnt/β-catenin and NF-κB signalling pathways, as well as abnormalities in E-cadherin (CDH1), TP53, KRAS, and C-MET. Because they play a function in tumour cell cohesion, invasion, and metastasis, cell adhesion molecules like cadherins are particularly interesting. The single-pass transmembrane glycoprotein known as cadherin 17 (CDH17), or liver-intestine cadherin (LI-cadherin), is mostly expressed in normal intestinal epithelium and several types of tumours of the digestive system.[7]

In contrast to traditional cadherins, CDH17 is engaged in Ca2+-dependent homophilic cell attachment and has seven extracellular cadherin repeats. It is a possible marker for determining the primary location of metastatic tumours since its expression is mostly limited to the epithelial cells of the colon and small intestine, with little dispersion in other normal organs. Numerous gastrointestinal cancers, such as colorectal adenocarcinoma (96–100%), esophageal adenocarcinoma (67–82%), and gastric adenocarcinoma (23–90%), have been shown to overexpress CDH17.

TNM stage, lymph node metastasis, tumour grade, and depth of invasion have all been connected to CDH17 expression in gastric cancer. By activating the NF-κB and Wnt/β-catenin pathways, CDH17 may mechanistically accelerate the growth of tumours by increasing the transcription of oncogenes such cyclin D1, promoting proliferation, and decreasing apoptosis. A promising prognostic biomarker and possible therapeutic target, CDH17 has limited expression in normal tissues and a strong connection with clinicopathological characteristics.[8]

Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20) in Tumor Diagnosis

Intermediate filament proteins called cytokeratins (CKs) are a component of the cytoskeleton found in epithelial cells. They are useful immunohistochemistry (IHC) markers for identifying the genesis of epithelial malignancies because their expression patterns are tissue-specific and retained in the majority of carcinomas. CK7 is a type II keratin that is normally missing from normal gastrointestinal mucosa but expressed in the epithelia of the lung, breast, ovary, endometrial, and bile ducts. On the other hand, intestinal epithelium, gastric foveolar epithelium, and urothelial umbrella cells all express CK20, a type I keratin.[9]

In diagnostic pathology, the combined CK7/CK20 immunoprofile is commonly utilised to pinpoint the origin of metastatic adenocarcinomas. In contrast to gastric carcinomas, which can exhibit a variety of patterns based on histological subtype and differentiation, colorectal carcinomas generally exhibit a CK7-negative/CK20-positive profile. According to some research, intestinal metaplasia and early carcinogenesis are associated with CK7 positive in gastric cancer, whereas intestinal differentiation may be reflected by CK20 expression. In contrast to CDH17, their prognostic significance in gastric cancer is yet unclear.[10]

MATERIALS AND METHODS

Study Design and Duration

This retrospective observational study was conducted in the Department of Pathology, Chengalpattu Medical College, over a period of four years, from 2018 to 2021.

Sample Size: A total of 40 histopathologically confirmed cases of gastric carcinoma were included in the study.

Inclusion Criteria

- Patients diagnosed with gastric carcinoma.
- Availability of well-preserved formalin-fixed paraffin-embedded (FFPE) tissue blocks.

Exclusion Criteria

- Patients who had received chemotherapy or radiotherapy prior to tissue sampling.
- Poorly fixed or autolyzed tissue specimens.

Clinical and Histopathological Parameters Assessed

For each case, the following data were collected and analyzed:

- Age and sex of the patient
- Tumor site
- Specimen type
- Tumor size
- Histological grade (Grade I, II, III)
- Lymph node status
- Surgical margin status
- Depth of tumor infiltration
- Pathological staging

Immunohistochemistry (IHC)

IHC was performed on FFPE tissue sections using monoclonal antibodies against **Cadherin 17 (CDH17)**, **Cytokeratin 7 (CK7)**, and **Cytokeratin 20 (CK20)**.

- **CDH17 expression** was assessed semi-quantitatively based on both staining intensity and the proportion of tumor cells showing positivity.
- **CK7 and CK20 expression** were evaluated based on cytoplasmic staining patterns.

Scoring Criteria

- **CDH17:** Scored using the Index of Positivity (IP), ranging from 0 to 12:
  - IP = 0: Negative
  - IP = 1–4: Very low expression
  - IP = 5–8: Low expression
  - IP = 9–12: High expression
- **CK7 and CK20:**

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- Score 1 (<5% of tumor cells positive): Low expression
- Score 2–4 (>5% of tumor cells positive): High expression

Statistical Analysis

Data analysis was performed using SPSS software version 21.0. Correlations between immunohistochemical marker expression and clinicopathological parameters were assessed using the Kruskal–Wallis test and the Mann–Whitney U test. A p-value of < 0.05 was considered statistically significant.

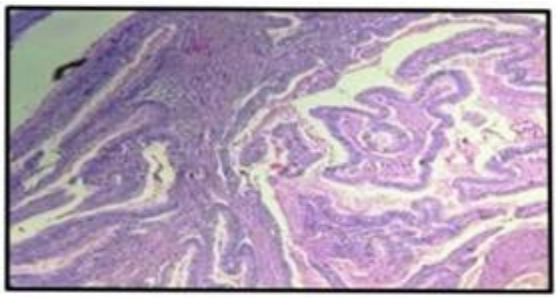

Figure 1: Well differentiated adenocarcinoma II & E (40x)

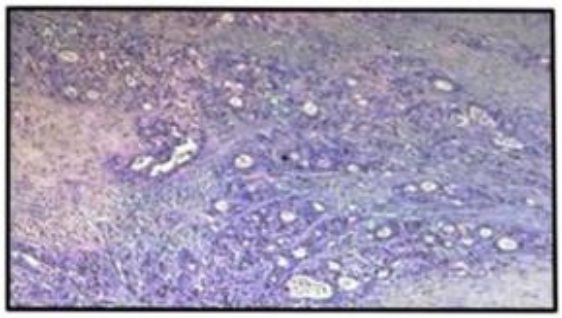

Figure 2: Moderately differentiated adenocarcinoma H & E (40x)

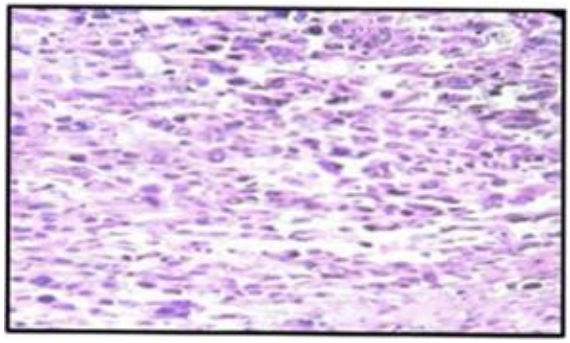

Figure 3: Poorly Differentiated adenocarcinoma H & E (40x)

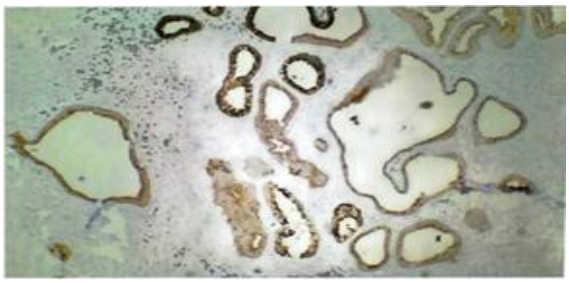

Figure 4: CDH 17 score of 8 (Low immunopositivity) in well differentiated adenocarcinoma

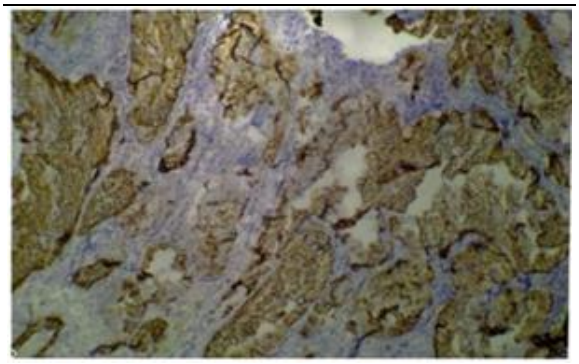

Figure 5: CDH 17 Low immunopositivity in Moderately differentiated adenocarcinoma

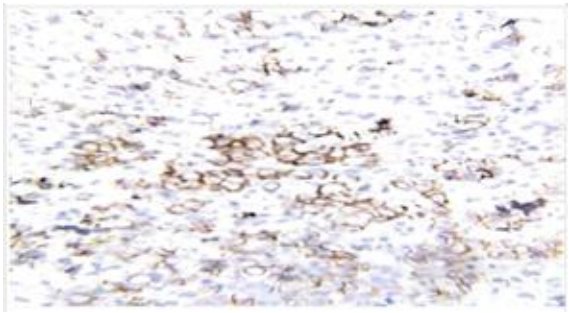

Figure 6: CDH 17 very low immunopositivity in poorly differentiated carcinoma

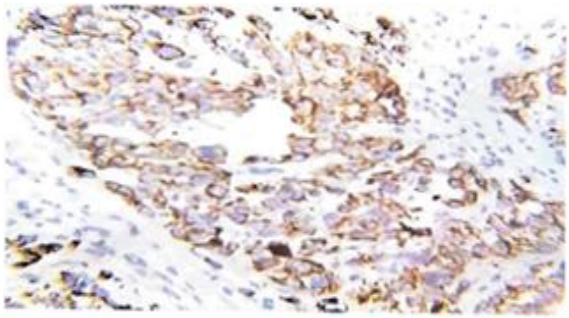

Figure 7: Cytokeratin 7 in poorly differentiated adenocarcinoma- stomach

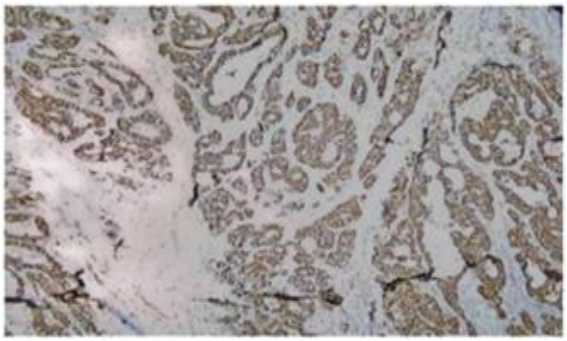

Figure 8: Cytokeratin 20 shows cytoplasmic staining in well differentiated adenocarcinoma- stomach

RESULTS

[Table 1] summarizes the demographic characteristics of the 40 gastric carcinoma cases included in this study. The majority of patients were

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between 51–60 years of age (50%), followed by 61–70 years (25%). A smaller proportion of cases occurred in the 31–40 years (15%) and 41–50 years (10%) age groups. There was a marked male predominance, with 34 males (85%) and 6 females (15%), resulting in a male-to-female ratio of approximately 5.6:1.

Table 1: Demographic characteristics of gastric carcinoma cases (n = 40)

Age Group (years)	No. of Cases	Percentage
31–40	6	15%
41–50	4	10%
51–60	20	50%
61–70	10	25%
Gender		
Male	34	85%
Female	6	15%

Table 2: Tumor location, specimen type, histological grade, and lymph node status

Variable	Category	n (%)
Tumor site	Pylorus	16 (40.0)
	Other sites	24 (60.0)
Specimen type	Endoscopic biopsy	26 (65.0)
	Resection specimen	14 (35.0)
Histological grade	Grade I	10 (25.0)
	Grade II	21 (52.5)
	Grade III	9 (22.5)
Lymph node status	Positive	9 (22.5)
	Negative	31 (77.5)

[Table 2] presents the distribution of tumor location, specimen type, histological grade, and lymph node status. The pylorus was the most frequently involved site (40%), with the remaining 60% located in other gastric regions. The majority of samples were obtained via endoscopic biopsy (65%), while 35% were resection specimens. Histologically, Grade II tumors were most common (52.5%), followed by Grade I (25%) and Grade III (22.5%). Lymph node metastasis was identified in 22.5% of cases, whereas 77.5% had no nodal involvement.

Table 3: Tumor infiltration and pathological stage

Parameter	Category	n (%)
Serosal involvement	Present	10 (25.0)
	Absent	30 (75.0)
Pathological stage	T1	1 (2.5)
	T2	2 (5.0)
	T3	7 (17.5)
	T4	2 (5.0)
	NA	28 (70.0)

[Table 3] outlines tumor infiltration and pathological staging. Serosal involvement was observed in 25% of cases, with the remaining 75% showing no evidence of serosal invasion. Pathological staging revealed T3 tumors in 17.5% of cases, T4 in 5%, T2 in 5%, and T1 in 2.5%. Notably, 70% of cases lacked available pathological stage data, largely due to the predominance of biopsy specimens.

Table 4: Immunohistochemical marker expression and correlation with histological grade

Marker	Expression category	n (%)	p-value	Significance
CDH17	Strong positive (IP 9–12)	13 (32.5)		
	Moderate positive (IP 5–8)	12 (30.0)		
	Weak positive (IP 1–4)	6 (15.0)		
	Negative	9 (22.5)	0.001	Significant
CK7	Positive	26 (65.0)	0.080	Not significant
	Negative	14 (35.0)		
CK20	Positive	20 (50.0)	0.489	Not significant
	Negative	20 (50.0)		

[Table 4] details the immunohistochemical expression of CDH17, CK7, and CK20, along with their correlation with histological grade. CDH17 expression was strong (IP 9–12) in 32.5%, moderate (IP 5–8) in 30%, weak (IP 1–4) in 15%, and negative in 22.5% of cases, showing a statistically significant correlation with histological grade ($p = 0.001$). CK7 was positive in 65% and negative in 35%, with no significant association with grade ($p = 0.080$). CK20 showed an equal distribution of positive (50%) and negative (50%) cases, also without significant correlation ($p = 0.489$).

DISCUSSION

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As one of the primary causes of cancer-related morbidity and mortality globally, gastric carcinoma continues to pose a significant threat to global health. The stage of diagnosis, histological grade, and underlying molecular features all have a significant impact on its clinical fate. In the current retrospective observational investigation, 40 histopathologically confirmed cases of gastric cancer were examined, with special attention paid to the immunohistochemical (IHC) expression of CDH17, CK7, and CK20 and how they were related to other clinicopathological characteristics.

Demographic and Clinicopathological Profile

The majority of patients in our sample (50%) were between the ages of 51 and 60, and there was a noticeable male predominance (male-to-female ratio of 5.6:1). This demographic trend is in line with worldwide epidemiological statistics, which show that gastric cancer is more common in men and peaks in the sixth decade of life, potentially as a result of a confluence of exposure factors from the workplace, lifestyle, and hormones. Zheng et al. 2019[11] and Qiu et al 2021,[12] showed similar age and gender distributions, indicating a shared demographic profile across communities.

The pylorus accounted for 40% of the tumours in our analysis, with the body and fundus following closely after. In contrast to the increasing incidence of proximal gastric and gastro-oesophageal junction tumours reported in Western populations, which is probably caused by different dietary and Helicobacter pylori infection patterns, this finding is consistent with previous Indian series Shukla et al., 2018,[13] that reported distal gastric predominance.

The most prevalent histologically were Grade II tumours (52.5%), Grade I tumours (25%) and Grade III tumours (22.5%). Similar findings in other Asian cohorts are supported by the prevalence of moderately differentiated adenocarcinomas. The high percentage of endoscopic biopsy specimens (65%) where lymph node evaluation is not feasible may be the reason why lymph node metastases was found in 22.5% of patients, a comparatively lower percentage than some literature. A minority of patients had advanced local illness, as seen by the 25% of instances with serosal involvement.

CDH17 Expression and Clinicopathological Correlation

The calcium-dependent adhesion molecule CDH17 (Cadherin-17), often referred to as LI-cadherin, is crucial in the preservation of intestinal epithelium. Tumour growth and gastric carcinogenesis have been connected to its abnormal expression. 77.5% of the patients in the current research had CDH17 positive, and 32.5% had significant positivity (IP 9–12). Crucially, there was a statistically significant connection between CDH17 expression and histological grade ($p = 0.001$), indicating that poorer tumour differentiation is linked to greater expression. Our results are consistent with those of Jacobsen F et al. (2024),[8] and Ordóñez NG et al (2014),[7] who showed that CDH17 overexpression is associated with poor differentiation and tumour aggressiveness. It is possible that CDH17 improves tumour cell invasion and adhesion via altering β-catenin signalling pathways. Curiously, some research also suggests that CDH17 may be useful in predicting survival, especially in cases of advanced stomach cancer.

CK7 and CK20 Expression Profiles

In our study, 50% of patients had positive CK20 and 65% of cases had expressed CK7. The intermediate filament proteins CK7 and CK20 are employed in the immunophenotypic categorisation of epithelial cancers. Depending on the tumour subtype and location, the traditional immunoprofile for gastric carcinoma has been described as CK7+/CK20+, CK7+/CK20–, or CK7–/CK20+.

Histological grade and CK7 or CK20 expression did not significantly correlate ($p = 0.080$ and $p = 0.489$, respectively). This lack of connection implies that CK7 and CK20 may have little predictive utility in original gastric cancer, although they remain useful markers for determining the origin of tumours in metastatic situations. These findings are in line with those of Park et al (2012),[14] and Jacobsen F et al. (2024),[8] who likewise observed that there was no reliable correlation between cytokeratin expression patterns and tumour differentiation.

Comparisons and Implications: The significant association between CDH17 expression and histological grade in our study underscores its potential role as a biomarker for tumor differentiation. This could have implications in both diagnostic pathology and potentially in prognostication, especially in biopsy specimens where architectural assessment is limited. The relatively high rate of CK7 and CK20 positivity without prognostic correlation aligns with their more established role in differential diagnosis rather than outcome prediction.

Our findings support the incorporation of CDH17 immunostaining in the ancillary panel for gastric carcinoma evaluation, particularly in cases with ambiguous morphology. However, further prospective studies with survival analysis are warranted to validate its prognostic utility.

Limitations: It is important to recognise the limitations of the current study. First, the findings may not be as broadly applicable as they may be due to the relatively small sample size ($n = 40$). Second, there is an inherent risk of selection bias and insufficient clinicopathological data with the retrospective methodology. Third, it is difficult to fully evaluate the predictive significance of CDH17, CK7, and CK20 expression in gastric cancer due to the lack of survival study and molecular profiling. To confirm and build on these findings, large-scale, prospective investigations including molecular and follow-up data are crucial.

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CONCLUSION

According to this study, CDH17 is a promising immunohistochemical marker that has a strong correlation with the histological grade of gastric cancer, indicating that it may have a function in prognostication. On the other hand, CK7 and CK20 showed inconsistent expression patterns; nonetheless, when assessed in conjunction with CDH17, they could improve tumour categorisation precision. Histopathological evaluation may be enhanced by including these indicators into diagnostic procedures. To determine the precise therapeutic value of these indicators in gastric cancer, further multicenter trials with bigger cohorts, survival information, and molecular correlations are necessary.

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