Expression of COX-2 as a Biomarker in the Progression of Gastric Carcinoma in a Tertiary care hospital- A Prospective analytical study

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***Abstract*—Back Ground: Gastric carcinoma remains a significant global health burden. Cyclooxygenase-2 (COX-2) has been implicated in gastric carcinogenesis and tumor progression. This study investigates COX-2 expression as a potential biomarker in gastric cancer development.**

Methods: A prospective analytical study was conducted over 24 months at Osmania General Hospital, Hyderabad. Ninety-eight gastric biopsy specimens were evaluated using routine hematoxylin and eosin (HE) staining and COX-2 immunohistochemistry (IHC). Cox-2 expression was scored based on percentage of stained cells (0: absent, 1: weak, 2: moderate, 3: strong). Statistical analysis employed Chi-square tests with significance threshold at $p < 0.05$.

Results: Males predominated (60.2%, n=59), with mean age 49.5 years. The fundus (39.8%) and body (26.5%) were most frequently involved. Adenocarcinoma represented 20.4% of cases, with 19.3% having gastritis with dysplasia. Strong COX-2 expression (score 3) was observed in 33.7% of cases. No significant correlation was found between COX-2 expression and age, gender, or tumor location ($p > 0.05$). However, a statistically significant association was demonstrated between COX-2 expression scores and histopathological tumor differentiation ($p = 0.002$).

Conclusion: COX-2 overexpression is associated with advanced tumor grades in gastric carcinoma. Routine evaluation of COX-2 expression may serve as a useful adjunctive tool for early detection and prediction of gastric cancer progression, potentially guiding therapeutic strategies.

***Index Terms*—COX-2, gastric carcinoma, immunohistochemistry, biomarker, tumor progression**

I. INTRODUCTION

Gastric cancer remains a major public health burden globally, ranking as the fifth most frequently diagnosed malignancy and the third leading cause of cancer-related deaths worldwide [1][2]. The burden is disproportionately borne by developing countries, which account for more than 70% of cases, with Eastern Asia particularly China experiencing the highest incidence. In India, approximately 34,000 new cases are reported annually, with relatively high prevalence in southern and northeastern regions [3][4][5].

The pathogenesis of gastric carcinoma involves multifactorial interactions between host genetic susceptibility and environmental factors. Helicobacter pylori infection is the most significant risk factor, implicated in 90% of gastric cancer cases. Additional etiologic factors include dietary factors (high salt, smoked and processed foods), tobacco and alcohol consumption, and various precancerous lesions such as chronic atrophic gastritis and intestinal metaplasia [6][7].

Gastric carcinomas are histologically classified into intestinal and diffuse types according to Laurén classification. The intestinal type predominates in older populations and high-incidence areas, while diffuse-type carcinomas are more common in younger

patients and show marked hereditary patterns. At present, many patients present with advanced disease, leading to poor prognosis and survival outcomes [8].

Cyclooxygenase-2 (COX-2), also known as prostaglandin endoperoxide synthase, is a key enzyme in the conversion of arachidonic acid to prostaglandins. Unlike COX-1, which is constitutively expressed in normal gastric mucosa, COX-2 is highly inducible at sites of inflammation and cancer. The COX-2–prostaglandin E2 (PGE2) pathway plays crucial roles in tumor promotion through multiple mechanisms: enhanced cellular proliferation, inhibition of apoptosis, increased angiogenesis, and modulation of tumor immunity [9][10][11].

Several previous studies have documented elevated COX-2 expression in gastric carcinoma tissues compared to normal mucosa, with expression correlating to advanced tumor stage, depth of invasion, and lymph node metastasis [12][13][14]. Identifying robust biomarkers for early detection and risk stratification remains critical for improving outcomes in gastric cancer patients.

The aim of this study was to estimate COX-2 expression in gastric carcinoma and chronic gastritis with atypia/dysplasia, and to evaluate its association with clinicopathological parameters in a tertiary care setting.

II. MATERIALS AND METHODS

2.1 Study Design and Setting

A prospective analytical study was conducted over 24 months (January 2022 to December 2024) at the Upgraded Department of Pathology, Osmania General Hospital, Afzalgunj, Hyderabad, Telangana.

2.2 Sample and Inclusion/Exclusion Criteria

Sample size: 98 cases of gastric mucosal biopsies

Inclusion criteria:

1. Patients providing informed consent
2. Diagnosed chronic gastritis with atypical changes
3. Confirmed gastric carcinoma eligible for local excision, extended gastrectomy, or endoscopic submucosal resection
4. Adequate tissue biopsy specimens for histopathological and immunohistochemical examination

Exclusion criteria:

1. Lack of informed consent
2. Prior chemotherapy or radiotherapy
3. Advanced metastatic disease
4. Inadequate or insufficient tissue specimens

2.3 Histopathological Processing and Staining

Routine Hematoxylin and Eosin (HE) Staining: Sections (5 µm thickness) cut from paraffin-embedded blocks were deparaffinized, rehydrated, and stained according to standard protocol. Sections were stained with Harris hematoxylin for 4 minutes, differentiated in 1% hydrochloric acid, blued in 0.5% ammonium hydroxide, and counterstained with eosin. After graded alcohol dehydration and xylene clearance, slides were mounted with DPX (dibutylphthalate polystyrene xylene).

Immunohistochemical Staining for COX-2: Tissue sections (3–4 µm) mounted on poly-L-lysine-coated slides underwent antigen retrieval by heat-induced epitope retrieval (HIER) using Tris-EDTA buffer (pH 9) in a microwave at 95°C for three cycles (3, 6, and 8 minutes). Endogenous peroxidases were blocked with 3% hydrogen peroxide in methanol for 10 minutes. Sections were incubated with primary antibody for 30 minutes, followed by sequential incubation with super enhancer reagent (15 minutes) and poly HRP reagent (15 minutes). DAB (3,3'-diaminobenzidine) chromogen was applied for 5 minutes. Sections were counterstained with hematoxylin, dehydrated, and mounted.

Controls: Normal gastric mucosa tissue sections within specimens served as positive controls; fibroblasts and lymphocytes were utilized as negative controls.

2.4 Cox-2 Expression Scoring

COX-2 expression was evaluated quantitatively based on the percentage of positively stained tumor cells:

Score	Percentage of Tumor Cells Stained	Expression Assessment
0	<5%	Absent
1	5–19%	Weak positive
2	20–49%	Moderate positive
3	≥50%	Strong positive

Table 1: Table 1: COX-2 Scoring System

2.5 Statistical Analysis

Correlation between COX-2 expression and clinicopathological factors (age, gender, tumor site, histopathological diagnosis, and tumor differentiation) was evaluated using Chi-square (χ^2) test. p-values ≤ 0.05 were considered statistically significant.χ^2

III. RESULTS

3.1 Demographic and Clinical Characteristics

A total of 98 cases were enrolled in the study. The demographic distribution is presented in Table 1–4 below.

Age Group (years)	Number (n)	Percentage (%)
≤30	13	13.3
31–40	19	19.4
41–50	16	16.3
51–60	36	36.7
>60	14	14.3

Mean ± SD: 49.50 ± 15.45 years; Range: 21–90 years

Table 1: Table 1: Distribution of Study Subjects According to Age (N=98)

The majority of cases occurred in the 51–60-year age group (36.7%). Males outnumbered females in a ratio of approximately 1.5:1, consistent with global epidemiological trends. Mean age was 49.5 years with wide age range (21–90 years), underscoring that gastric cancer can present across multiple decades of life.

3.2 Tumor Site Distribution

Anatomical Site	Number (n)	Percentage (%)
Fundus	39	39.8
Body	26	26.5
Antrum	23	23.5
Cardia	8	8.2
Pylorus	2	2.0

Table 2: Table 2: Distribution of Study Subjects According to Tumor Site (N=98)

The fundus was the most commonly involved site (39.8%), followed by the body (26.5%) and antrum (23.5%). The pylorus was rarely affected (2.0%). This distribution pattern reflects known epidemiological patterns in Indian populations.

3.2 Pathological Diagnosis

Diagnosis	Number (n)	Percentage (%)
Adenocarcinoma of stomach	20	20.4
Chronic gastritis	15	15.3
Gastritis with dysplasia	19	19.3
Poorly differentiated carcinoma	12	12.2
Well differentiated carcinoma	10	10.2
Metastasis	6	6.1
Moderately differentiated carcinoma	6	6.1
Atrophic gastritis	4	4.1
Chronic gastritis with atypical changes	4	4.3
Moderate to poorly differentiated carcinoma	1	1.0
Atrophic gastritis with atypical changes	1	1.0

Table 3: Table 3: Distribution of Study Subjects According to Pathological Diagnosis (N=98)

Adenocarcinoma and gastritis with dysplasia were the most prevalent diagnoses (20.4% and 19.3% respectively), followed by chronic gastritis (15.3%) and poorly differentiated carcinoma (12.2%).

3.3 Correlation of COX-2 Expression with Age

Age (years)	Score 0 (n, %)	Score 1 (n, %)	Score 2 (n, %)	Score 3 (n, %)	Mean Age ± SD
≤30	2 (15.4)	3 (23.1)	5 (38.5)	3 (23.1)	25.00 ± 5.10
31–40	6 (31.6)	4 (21.1)	5 (26.3)	4 (21.1)	35.74 ± 3.05
41–50	4 (25.0)	3 (18.8)	3 (18.8)	6 (37.5)	45.63 ± 2.97
51–60	6 (16.7)	10 (27.8)	6 (16.7)	14 (38.9)	54.61 ± 3.07
>60	3 (21.4)	3 (21.4)	2 (14.3)	6 (42.9)	68.21 ± 7.68
Overall	21	23	21	33	49.50 ± 15.45
Chi-square test: p = 0.864 (not significant)					

Table 4: Table 4: Age and COX-2 score Distribution

No statistically significant association was found between age and COX-2 expression scores (χ^2, $p = 0.864$). However, a trend toward higher COX-2 scores in older patients was observed.

3.4 Correlation of COX-2 Expression with Tumor Site

Site	Score 0 (n, %)	Score 1 (n, %)	Score 2 (n, %)	Score 3 (n, %)
Antrum	3 (13.0)	7 (30.4)	5 (21.7)	8 (34.8)
Body	6 (23.1)	6 (23.1)	6 (23.1)	8 (30.8)
Cardia	4 (50.0)	2 (25.0)	1 (12.5)	1 (12.5)
Fundus	8 (20.5)	8 (20.5)	9 (23.1)	14 (35.9)
Pylorus				2 (100.0)
Chi-square test: p = 0.616 (not significant)				

Table 5: Table 5: Tumor Site and COX-2 score Distribution (N=98)

No statistically significant association was observed between tumor anatomical site and COX-2 expression ($p = 0.616$). However, all pylorus-involved cases (100%) demonstrated strong COX-2 positivity (score 3).

3.5 Correlation of COX-2 Expression with Histopathological Diagnosis and Tumor Differentiation

Diagnosis	Score 0 (n, %)	Score 1 (n, %)	Score 2 (n, %)	Score 3 (n, %)
Adenocarcinoma	2 (10.0)	2 (10.0)	3 (15.0)	13 (65.0)
Atrophic gastritis	1 (25.0)	3 (75.0)		
Atrophic gastritis with atypia			1 (100.0)	
Chronic gastritis	8 (53.3)	4 (26.7)	2 (13.3)	1 (6.7)
Chronic gastritis with atypia		1 (25.0)	2 (50.0)	1 (25.0)
Gastritis with dysplasia		6 (33.3)	9 (50.0)	3 (16.7)
Well differentiated carcinoma	2 (20.0)	3 (30.0)	1 (16.7)	4 (40.0)
Metastasis	1 (16.7)		1 (16.7)	4 (66.7)
Moderately differentiated carcinoma	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)
Poorly differentiated carcinoma	5 (41.7)	1 (8.3)	1 (8.3)	5 (41.7)
Chi-square test: p = 0.002 (statistically significant)				

Table 6: Table 6: Diagnosis and COX-2 score Distribution (N=98)

A statistically significant association was demonstrated between COX-2 expression and histopathological diagnosis ($p = 0.002$). Strong COX-2 positivity (score 3) was notably prevalent in adenocarcinoma (65.0%), metastatic lesions (66.7%), and poorly differentiated carcinoma (41.7%). In contrast, chronic gastritis without atypia showed predominantly absent (53.3%) or weak (26.7%) COX-2 expression.

IV. DISCUSSION

This prospective study evaluated COX-2 expression in 98 gastric biopsy specimens at a tertiary care center and correlated findings with clinicopathological parameters. The results provide evidence supporting COX-2 as a marker of gastric cancer progression.

4.1 Demographic Findings

The male-to-female ratio of approximately 1.5:1 is consistent with global epidemiological data showing male predominance in gastric cancer [15][16]. The mean age of 49.5 years with peak incidence in the 51–60-year group reflects the established age-related increase in gastric malignancy risk. The findings align with previous studies demonstrating that gastric cancer is rare before age 30 and increases progressively with advancing age in both sexes [17].

4.2 Tumor Location and Clinical Presentation

Fundic and body involvement predominated (66.3%), which is consistent with prior reports of upper gastric predominance in Indian populations [18]. Most patients presented with indigestion, abdominal pain, and altered bowel habits classic but nonspecific

symptoms contributing to delayed diagnosis and advanced presentation at referral.

4.3 COX-2 Expression and Carcinogenesis

Strong COX-2 expression (33.7% of cases) and its significant correlation with malignant transformation and tumor differentiation support the hypothesis that COX-2 plays a critical role in gastric carcinogenesis. The upregulation of COX-2 has been implicated in multiple stages of tumorigenesis, including initiation, promotion, and progression [19][20].

The COX-2–PGE2 pathway contributes to tumor development through several interconnected mechanisms: (1) promotion of cellular proliferation and tumor growth; (2) inhibition of apoptosis and enhanced cell survival; (3) enhancement of tumor angiogenesis and neovascularization; and (4) modulation of immune responses within the tumor microenvironment [21][22]. These pathways create a microenvironment favorable for malignant transformation and tumor progression.

4.4 COX-2 Expression and Clinicopathological Correlations

Age and Gender: No significant associations were found between COX-2 scores and age or gender, suggesting that COX-2 expression is primarily driven by pathological status rather than demographic characteristics. This finding is consistent with recent large studies by Salah Eldin et al. (2022) and Xuan-ke Ji et al. (2021) [23][24].

Tumor Site: COX-2 expression showed no significant site-specific variation, though the small number of pyloric cases (n=2) with uniformly strong positivity warrants larger study cohorts. This suggests that COX-2 may be a field effect phenomenon in gastric carcinogenesis rather than site-dependent.

Histopathological Diagnosis and Differentiation: A statistically significant association was demonstrated between COX-2 expression and histopathological diagnosis ($p = 0.002$), with the strongest expression observed in adenocarcinomas (65.0% with score 3) and metastatic lesions (66.7% with score 3). In contrast, chronic gastritis without atypia showed predominantly low COX-2 expression (80% with scores 0–1).

This pattern aligns with the adenoma–carcinoma sequence model of gastric malignancy progression: chronic gastritis → intestinal metaplasia/dysplasia → well-differentiated carcinoma → poorly differentiated carcinoma and metastasis. The escalating COX-2 expression across this progression suggests COX-2 as a marker of advancing malignant potential.

4.5 Comparison with Literature

Sample Size and Study Duration: The present study included 98 cases over 24 months at a tertiary care hospital. While smaller than some international multicenter series (e.g., Sorina Taban et al., 2008: 8,961 cases over 5 years; Zhili Hu et al., 2020: 1,289 cases), the sample size is comparable to other recent single-institution studies and sufficient for establishing preliminary associations [25][26].

Age Range and Male-Female Ratio: The age range of 21–90 years with mean 49.5 and M:F ratio of 1.5:1 are consistent with literature. Previous studies (John D. Potter, 2006; Sorina Taban, 2008; Salah Eldin M. Fayed, 2022) demonstrated similar demographic patterns [27][28].

COX-2 Expression Prevalence: The present study reported 33.7% strong COX-2 positivity (score 3), which is lower than some prior reports (Zhili Hu et al., 2020: 68%; Salah Eldin M. Fayed, 2022: 60%) but comparable to others (John D. Potter, 2008: 40%; Xuan-ke Ji, 2021: 32%). This variation likely reflects differences in IHC methodology, scoring systems, tissue types, and case selection criteria across studies[29][30][31].

Statistical Correlations: Similar to our findings, prior studies have reported lack of significant association between COX-2 and demographic factors (age, gender), while noting significant correlation with tumor differentiation and advanced stage[32][33]. Our p-value of 0.002 for diagnosis-COX-2 association aligns with the range reported in literature ($p = 0.002 - 0.041$).

4.6 Clinical Implications and Therapeutic Significance

The significant association between elevated COX-2 expression and malignant gastric pathology suggests potential clinical applications:

1. Prognostic Marker: COX-2 expression level may predict disease progression and guide treatment intensity, particularly distinguishing early-stage curable disease from advanced cancers.
2. Therapeutic Target: COX-2 inhibitors (celecoxib, rofecoxib) have demonstrated in vitro activity in reversing chemotherapy resistance and

synergistic effects with cytotoxic agents in gastric cancer cell lines[34][35].

3. Screening and Surveillance: Routine COX-2 evaluation in dysplastic lesions may identify high-risk patients requiring more aggressive intervention or closer endoscopic surveillance.

V. CONCLUSION

This prospective study of 98 gastric mucosal biopsies demonstrates that COX-2 expression is significantly elevated in gastric adenocarcinomas and metastatic lesions compared to chronic gastritis. The strong association between COX-2 overexpression and advanced tumor grades suggests its potential utility as a biomarker for assessing gastric cancer aggressiveness and predicting progression.

Given the global burden of gastric cancer and poor prognosis of advanced disease, identification of reliable biomarkers for early detection and risk stratification remains critical. Routine COX-2 immunohistochemical evaluation may complement morphologic assessment and guide clinical decision-making regarding treatment intensity and surveillance intervals.

Future prospective studies with larger patient cohorts, long-term follow-up, and integration of additional molecular markers (VEGF, HIF-1α, TP53 status) are warranted to further validate COX-2 as a prognostic tool and to optimize therapeutic strategies targeting the COX-2 signaling pathway in gastric carcinoma patients.

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