Relationship between Clinicopathological Features and Expression of COX-2 among Colorectal Cancer Patients: A Prospective Observational Study

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Track Record Article

Revised: 20 November 2025
Accepted: 25 December 2025
Published: 31 December 2025

How to cite :
Romdhoni, M., Lukman, K., Rudiman, R., Purnama, A., Degrees, B. A. S. S., Ruchimat, T., Wijaya, A., Sribudiani, Y., & Nugraha, P. (2025). Relationship between Clinicopathological Features and Expression of COX-2 among Colorectal Cancer Patients: A Prospective Observational Study. *Contagion : Scientific Periodical of Public Health and Coastal Health*, 7(3), 218–230.

Abstract

Colorectal cancer (CRC) is the third most common cancer globally and a leading cause of cancer-related mortality. Cyclooxygenase-2 (COX-2) plays a critical role in CRC pathogenesis by promoting inflammation, tumor proliferation, and metastasis. COX-2 inhibitors, such as NSAIDs, have shown potential in reducing CRC progression. However, the relationship between COX-2 expression and clinicopathological features remains controversial. This study aims to assess the correlation between COX-2 expression and clinicopathological characteristics in CRC patients in Indonesia. A prospective observational study was conducted on 81 CRC patients at a tertiary hospital in West Java, Indonesia, from January to June 2024. COX-2 expression was quantified using qPCR from tumor tissue samples. Clinicopathological data, including age, sex, tumor grade, stage, and complications, were collected and analyzed. Among the 81 participants, 81.5% were over 50 years old. Low-grade adenocarcinoma was the most prevalent histopathological type (73%), followed by high-grade adenocarcinoma (11%) and mucinous adenocarcinoma (11%). The majority of cases were in regional or early stages (74%), while 26% were in late stages. Higher COX-2 expression was more frequent in males, rectal tumors, high- grade adenocarcinomas, advanced stages, and metastatic cases. Although no statistically significant association was found, a trend toward increased COX-2 expression in advanced CRC was observed. No significant association was found between COX-2 expression and clinicopathologic characteristics of CRC. However, higher COX-2 expression may be associated with advanced disease.

Keyword: Clinicopathological features, Colorectal cancer, Cyclooxygenase-2, Inflammation, Metastasis

INTRODUCTION

Colorectal Cancer (CRC) refers to a type of cancer that originates in the colon or rectum (parts of the large intestine). Depending on its location, CRC can be called colon cancer or rectal cancer. CRC develops from polyps or the abnormal growths on the inner lining of the colon or rectum. CRC is related to environmental and genetic factors, and 70% of CRC cases are sporadic and are diagnosed mostly at the age of over 50 years; 20% are familial clustering, such as familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary non-polyposis colorectal cancer) and the rest are related to both genetic syndromes (Rebuzzi et al., 2023). Colorectal cancer ranks third after lung and female breast cancer, with new cases reaching two million and ranking second in the death ranking, with the number of death-related diseases

reaching nine hundred thousand cases (Sung et al., 2021). In Indonesia, new cases of colorectal cancer reached 34,189 cases, or around 8.9% of the total cancer cases in Indonesia (Indratama et al., 2024).

The pathogenesis of CRC is multi-phase, starting from dysplastic lesions and adenomatous polyps to invasive cancer (Kasi et al., 2021). At the molecular level, the development of carcinogenesis depends on the accumulation of progressive changes that are beneficial for tumour growth over time, which eventually leads to invasive malignancy (Parmar & Easwaran, 2022). There are several hallmarks in the development of CRC, namely chromosome instability, microsatellite instability (MSI), telomere dysfunction and telomerase reactivation, dysregulation of cell cycle checkpoints, chronic activation of Wnt components, and so on (Li et al., 2021). The APC gene is usually the main trigger, followed by KRAS and TP53 mutations (Yan et al., 2025). However, there are three main molecular pathways in the development of CRC: chromosome instability pathway (CIN), mismatch repair pathway (MMR), and hypermethylation pathway (Yang et al., 2024).

Over the decades, significant progress has been made in the discovery of effective drugs for CRC (Yu et al., 2025). One of them is nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase-2 (COX-2) (R. K. V. and D. S. Negi, 2020). Different NSAIDs can work through different signalling pathways, such as ibuprofen, indomethacin, and naproxen, which can bind to the COX-2 activity site, reversibly inhibiting its activity, while aspirin acetylates the COX-2 activity site, thereby permanently weakening its activity (Kolawole & Kashfi, 2022). Some NSAIDs, such as aspirin, can facilitate the effects of COX-2 inhibitors for the treatment of stage III colorectal cancer. Aspirin can reduce CRC mortality in women by 50%. Recently, the hybrid drug KSS19, a combination of the NSAIDs refecoxib and cis-stilbene, has been found to be a potent COX-2 inhibitor, effectively inhibiting the growth of colon cancer cells (Punganuru et al., 2018; Rashid et al., 2023).

Inflammation is one of the hallmarks of cancer due to its ability to produce bioactive molecules that promote cancer proliferation, invasion, and metastasis; limit cell apoptosis; and induce angiogenic processes (Gupta et al., 2011; Nigam et al., 2023). Stromal cells, such as fibroblasts, actively participate in cancergenesis (Zhou et al., 2025). Several studies have reported that fibroblasts from the stromal compartment play an important role in COX-2 signalling and carcinogenesis (Goradel, 2018). These cells express many receptors for cytokines and hormones and modulate the intestinal response to inflammatory mediators by releasing PGE2 (Mizuno et al., 2019). Therefore, increased COX-2 expression is a marker for

tumour diagnosis, which is associated with patient survival (Yoo et al., 2020). COX-2 is also important for promoting metastasis by participating in metastasis to the bones, brain, liver, and lymph nodes (He et al., 2023).

Cyclooxygenase-2 mediates the biosynthesis and release of prostaglandins using arachidonic acid (AA) as a substrate (Hu et al., 2024). The major form of prostaglandin involved in colorectal cancer is PGE2. Prolonged elevation of PGE2 is usually a sign of inflammation, cancer genesis, and metastasis. PGE2 can act on receptors, such as EP1, EP2, EP3, and EP4, to induce the PGE2 signalling cascade, which causes changes in intracellular calcium, cAMP, and several inflammatory factors (Norel et al., 2025). As a result, physiological or pathological processes occur. PGE2 derived from COX-2 can also contribute to tumour development through several mechanisms, including inhibition of apoptosis (Kulesza et al., 2023). In addition, overexpression of COX-2 also promotes overexpression of VEGF, which can induce tumour angiogenesis in colorectal cancer (Zhang et al., 2020). In a study conducted in a mouse model, deletion of the COX-2 gene can result in reduced tumour xenograft growth and blood vessel density, which can occur through activation of Rac1 and Cdc42 (Durand-onaylı et al., 2018). Overall, the evidence suggests that COX-2 may cause uncontrolled angiogenesis in colorectal cancer.

Recent systematic reviews suggest that the expression of COX-2 in colorectal cancer is related to lymphatic and distant metastasis (Purnama et al., 2023). There is still controversy about whether the clinician needs to measure the expression of COX-2 in colorectal cancer related to personal targeted therapy, especially in the late stage. This study aims to assess the relationship between the expression of COX-2 and clinicopathological features in colorectal cancer patients.

METHODS

The research design is a prospective observational study in the West Java, Indonesian population, and follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (Cuschieri, 2019; Elm et al., 2022). The subjects in this study were colorectal cancer patients who came to the policlinic and emergency room of the digestive surgery in the tertiary hospital in West Java, Indonesia, during January–June 2024. There are 81 participants in this study, using a purposive sampling technique to determine participants who met the criteria, which included patients with colorectal cancer criteria diagnosed clinically, radiologically, and histopathologically and undergoing tumor removal

surgery. The exclusion criteria in this study were patients who had surgery in another hospital and who had an unresectable tumour.

The COX-2 expression was examined from the tumour; a small part of the patient's tumour after surgery was sent to the genetic molecular laboratory. Gene expression analysis was carried out using fresh tumor tissues, which were processed in the Biomolecular Laboratory. For COX-2 analysis, DNA was extracted either from stored biological specimens or from fresh tissues preserved in RNAlater® solution (Qiagen). Extraction followed the Quick-DNA kit protocol (Zymo Research), and the resulting DNA samples were stored at -20°C in the AIRA® tissue bank. DNA concentration and purity were assessed using a Nanodrop 2000™ spectrophotometer (Thermo Fisher Scientific), based on 230/260 and 280/260 OD ratios. The COX-2 expression was analyzed using the qt-PCR-HRM Kit method. A total of 1000 ng of DNA, diluted to 20 ng/μL with nuclease-free water, was used for target locus amplification via quantitative PCR. PCR amplification was carried out until the Cycle Threshold (CT) value reached ≤37.

Before testing, all reagents were thawed, centrifuged, and vortexed; controls were also thawed and centrifuged. Reaction mixtures were prepared under light-protected conditions, consisting of 8 μL of master mix and 2 μL of DNA template per reaction, with each sample tested in duplicate. The high-resolution melting (HRM) protocol consisted of three main stages: heat activation (40 cycles), final extension, and a pre-melt followed by HRM analysis. The thermal cycling steps included 10 seconds of denaturation at 95°C, 30 seconds of annealing at 55°C, and 20 seconds of elongation at 72°C. This was followed by a 2-minute final extension at 72°C, pre-melt steps at 95°C for 15 seconds and 60°C for 5 seconds, and HRM from 60°C to 90°C in 0.3°C/1% increments. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the housekeeping gene to normalize gene expression data. The expression of COX-2 was calculated by subtracting the average CT value of GAPDH from the average CT value of COX-2, expressed as delta CT (ΔCT). A lower ΔCT value indicates higher COX-2 expression, whereas a higher ΔCT value reflects lower expression levels. The clinicopathological feature from colorectal cancer patients was extracted from the hospital cancer registry.

Histopathological evaluation determined both tumor grade and histologic subtype according to the WHO classification. For the purposes of this study, patients were categorized into four distinct groups: (1) Low-grade adenocarcinoma (well-to-moderately differentiated adenocarcinoma NOS); (2) High-grade adenocarcinoma (poorly differentiated to undifferentiated adenocarcinoma NOS); (3) Mucinous adenocarcinoma (characterized by >50% extracellular mucin); and (4) Signet ring cell carcinoma (characterized by >50% signet

ring cells). This stratification was used to assess the specific correlation between COX-2 expression and various aggressive histologic subtypes. The data were analysed using SPSS version 26. Characteristic data were presented as percentages. As the data were normally distributed, an independent t-test and one-way Anova were calculated for the differences in mean expression of COX-2 and clinicopathological features. A P value less than 0.05 was considered significant.

RESULT

Eighty-one participants have met the inclusion criteria. Research data obtained includes age, sex, grade of histopathological features, stage, and complication as presented in Table 1. The participants' ages ranged from 23 to 78 years, with an average of 54.7±11.0 ΔCT. Based on gender, there was no significant difference between the number of male subjects and female subjects (49% versus 51%). More tumours are located in the rectum than the colon (65% versus 35%), with the majority showing low-grade adenocarcinoma (73%). The most common cancer stage in the subjects was stage 3 (37%). The relationship between the expression of COX-2 and clinicopathological features is presented in Table 2.

Based on the results of statistical analysis, the probability value of each characteristic was obtained above 0.05. This indicates that there is no significant difference in COX-2 expression against the characteristics studied. Based on gender, it was found that females had a lower average COX2 expression (6.45 ± 5.07 ΔCT) when compared to male subjects (5.94 ± 4.90 ΔCT). Based on tumor location, the average COX2 expression was lower in the colon (7.56 ± 4.56 ΔCT) when compared to the rectum (5.48 ± 5.06 ΔCT). Based on grade and stage, the average COX2 expression was found to be higher in grade 2 (2.37±4.06 ΔCT).

Table 1. Characteristics of Research Subjects

Variable	N	Percentage (%)
Age		
Mean ± SD	54.7±11.0	
Min - Max	23 - 78	
< 50 years	15	18.5
> 50 years	66	81.5
Sex		
Male	40	49
Female	41	51
Tumor Location		
Colon	28	35
Rectum	53	65
Grade		
Low grade adenocarcinoma	59	73
High grade adenocarcinoma	9	11
Mucinous adenocarcinoma	9	11

Variable	N	Percentage (%)
Signed ring cell	4	5
T stage		
1	0	0
2	4	5
3	43	53
4	34	42
N stage		
0	34	42
1	31	26
2	26	32
M stage (metastasis)		
Absent	60	74
Present	21	26
Stage		
1	3	4
2	27	33
3	30	37
4	21	26
Complication		
Fistula	6	7.4
Obstruction	21	26
Peritonitis	3	3.7
Other (abscess, jaundice)	2	2.5
Absent	49	60.4

The relationship between the expression of COX-2 and clinicopathological features is presented in Table 2.

Table 2. The expression of COX-2 and Clinicopathological Characteristic of Colorectal Cancer Patients

Variable	COX-2 expression Mean	(ΔCT) SD	p-*value*
Sex			
Male	5.94	4.90	0.646[a]
Female	6.45	5.07	
Tumor Location			
Colon	7.56	4.56	0.072[a]
Rectum	5.48	5.06	
Grade			
Low grade adenocarcinoma	6.72	4.98	
High grade adenocarcinoma	2.37	4.06	0.067[b]
Mucinous adenocarcinoma	7.43	5.08	
Signed ring cell	4.39	2.63	
Stage T			
1	0.000	0.000	
2	6.84	3.43	0.518[b]
3	6.73	5.35	
4	5.45	4.62	
Stage			
0	7.59	4.80	0.092[b]
1	5.52	4.59	
2	4.93	5.20	

Variable	COX-2 expression Mean	(ΔCT) SD	p-*value*
Stage M (metastasis)			
Absent	6.47	4.09	0.407[a]
Present	5.42	6.95	
Stage			
1	5.49	2.59	
2	7.31	4.92	0.559[b]
3	5.82	3.28	
4	5.42	6.95	
Complication			
Fistula	7.23	6.18	
Obstruction	6.41	5.52	0.942[b]
Peritonitis	4.52	3.61	
Other (abscess, jaundice)	4.83	13.92	
Absent	6.14	4.4.1	

Note: [a]= *independent t-test,* [b]= *oneway anova*

DISCUSSION

The incidence of colorectal cancer in Indonesia is increasing with age. This suggests a higher incidence of colorectal cancer in the elderly, consistent with this study, which found that elderly patients (81.5%) and those over 50 years of age had a higher incidence than younger patients (18.5%). The risk of colorectal cancer rises significantly beyond the age of fifty. According to data from China (Han et al., 2024), Hong Kong (Oi et al., 2021), about 90% of cancer patients receive their diagnosis beyond the age of 50. The prevalence of colorectal cancer in the US rises with age, according to data from the National Cancer Institute (Miller et al., 2020). While a prior study found that the average age for early age onset colorectal cancer is 44 years, and that the majority (75%) of colorectal cancer cases develop between the ages of 40 and 49 as opposed to less than 40 years, the incidence of colorectal cancer at early age onset showed an increase at this time (Cercek et al., 2021; Low et al., 2021).

Based on grade of colorectal cancer, histological features is grouped into four groups; low grade adenocarcinoma, high grade adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma. In research by, adenocarcinoma accounted for 82.6% of the groups with signet ring cell carcinoma and mucinous adenocarcinoma types, following closely behind. Since the glandular mucosa is where the majority of colorectal malignancies begin, our findings are in line with those of other researchers who have discovered that adenocarcinoma is the most prevalent type (Wu et al., 2019). According to data from the North America Association Central Cancer Registry, adenocarcinomas accounted for 87.5% of cases, followed by mucinous adenocarcinomas (7.8%), signet ring cell carcinomas (1%), and other histopathologies (3.7%). A study by Georgiou et al., (2019). performed in the United Kingdom also revealed that

adenocarcinomas accounted for 87% of all histological types, with mucinous adenocarcinomas (10%), signet ring cell carcinomas (2%), and other types (1%). In this study, the most prevalent histopathological feature was low-grade adenocarcinoma (73%), followed by high-grade adenocarcinoma and mucinous adenocarcinoma (11% each).

In this study, the prevalence of late stage was 26%, while regional stage 3 was 37%, and early stage (stages 1 and 2) was 37%, the data from this study in line with another research. Data from a cancer epidemiology survey from the United States from 1975–2015 described the changes in the proportion of colorectal cancer stage at the time of diagnosis. There was an increase in distant stage colorectal cancer, which ranged from 21% to 27%, while regional stage was decreasing from 39% to 36%, and early stage did not change in around 33% (Meester et al., 2019). Previous study by Rudiman et al., (2023). in Indonesia showed late stage around 48%, regional around 29%, and early around 23%. A study by Lukman et al., (2023). in Indonesia found late stages reaching 46%, regional 29%, and the rest around 25%. In this study, 26% of patients came with signs of obstruction, 7.4% with fistulas, and 3.7% with peritonitis. This percentage is higher than data from literature that stated patients with colorectal cancer showed an incidence rate of bowel obstruction between 15% and 29%, fistula between 0.3% and 0.7%, and peritonitis between 1.2% and 9% (Gök et al., 2021; Perez & Eisenstein, 2024).

Analysis to calculate the differences between the mean of COX-2 expression and clinicopathological features of colorectal cancer patients using an independent t- test and an ANOVA test showed there was no significant association. However, from Table 2, there was a trend of higher expression of COX-2 (lower mean ofΔCT) in male patients, tumours located at the rectum, high-grade adenocarcinomas, higher stages of T and N, and patients with metastasis. The result of this study expressed a different result from much previous research that stated the role of COX-2 in tumorigenesis and metastasis. The study of Stamatakis et al., (2020) showed that PG/COX signaling pathways could be critical mediators of some of the tumor growth and metastasis advantage induced by COX-2. Furthermore, Nasry et al. demonstrated that inhibition of inflammation-related mechanisms in cancer, such as the COX-2/PGE2 and CD147 pathways, can help reduce tumor formation and progression, potentially improving the quality of life and survival of cancer patients, including those with OSCC (Nasry et al., 2018). The study of Ibrahim et al., (2023) showed a significant relationship between high expression of COX-2 and high-grade adenocarcinoma, deeper invasion, lymphatic metastasis, lymphovascular invasion, and advanced age ($P<0.005$). The study of Negi et al., (2019). showed that higher expression of COX-2 significantly corelate with female colorectal cancer patients. Systematic review by Purnama et al., (2023) showed higher expression of COX-2 associated

with lymph node metastasis and liver metastasis (P<0.05).

Although statistically there was no significant relationship between COX-2 expression and clinicopathological features of colorectal cancer patients, the presentation data of this study show that patients with higher expression of COX-2 show more advanced disease and poorer characteristics. The understanding of COX-2 mechanism and role in colorectal cancer pathogenesis could give advantages in the implementation of targeted therapy in selected groups for anti- COX-2 medication. Since there is a small number of research samples and the sample's overly homogeneous condition due to the saturation of patients from one subgroup in multiple groups who came from one general tertiary hospital, some subgroups cannot be analysed and must be combined with other subgroups due to a lack of data, further studies on this issue are required.

In addition to that, there is an absence of a control sample, which prevents the calculation and analysis of a cut-off point for COX-2 expression. Also, there is an inconsistency in sample collection, as samples were obtained either from intestinal resection surgeries or colonoscopic pinch biopsies. To avoid contamination with normal tissue, which could affect cancer analysis samples should ideally be collected exclusively from intestinal resection procedures. This is important, as high-quality samples are essential for ensuring the validity of findings related to genetic expression or cancer cell morphology.

We suggest that future research on COX-2 expression in colorectal cancer should include control samples to facilitate the determination of a precise cut-off point for COX-2 expression levels. Standardizing sample collection, ideally using fresh tissue obtained from tumor resection procedureswould minimize contamination from normal tissue and enhance the accuracy of molecular and morphological analyses. Additionally, incorporating tumor size measurements may allow for the exploration of potential correlations between tumor size and COX-2 expression. Further investigations could also examine the relationship between COX-2 expression and clinical outcomes, such as patient prognosis, treatment response, and recurrence rates. Evaluating COX-2 as a predictive or prognostic biomarker could provide meaningful insights into its role in colorectal cancer progression and therapeutic targeting. Moreover, analyzing COX-2 expression across various molecular subtypes of colorectal cancer may help identify specific patient subgroups that could benefit from COX-2-targeted therapies.

CONCLUSION

There was no relationship between the expression of COX-2 and clinicopathological features of colorectal cancer patients. However, higher expression of COX-2 is more commonly presented in patients with a poorer prognosis.

ACKNOWLEDGEMENTS

We thank all the patients who agreed to participate in this study, the digestive surgeon trainees, surgical residents, and molecular genetic laboraticians who helped carry out this study.

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