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Correlation between Serum Levels of Cyclooxygenase II and Microsomal Prostaglandin E Synthase 1 in Iraqi Colorectal Cancer Patients and Healthy Controls

Zainab I. Abbas[1,*], Ahmed Gh. Sabbar[1], and Wajeeh K. Obaid[2]

[1]Department of Medical Laboratory Techniques, College of Health and Medical Techniques, Middle Technical University, Iraq

[2] Department of Pharmacy Techniques, Medical Technical Institute, Middle Technical University, Iraq

*Corresponding author; E-mail: zzainabismaiil998@gmail.com

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Abstract

Colorectal cancer (CRC) ranks among the most widespread cancers worldwide, exhibiting considerable mortality rates. Chronic inflammation plays a crucial role in driving tumor development. Cyclooxygenase-II is an inducible enzyme that aids in the production of prostaglandins using arachidonic acid, particularly during inflammatory responses. Microsomal prostaglandin E synthase-1, functioning downstream of COX-2, specifically converts PGH2 to PGE2, and correlates with unfavorable outcomes in CRC. While their roles have been well documented in tissue, limited research has assessed their levels in serum. The present study aimed to evaluate the serum levels of COX-2 and mPGES-1 in CRC patients compared to healthy controls, and to investigate the correlation between these biomarkers across all participants, regardless of clinical grouping. A total of 70 patients, 35 newly diagnosed and 35 undergoing treatments were included, along with 30 healthy individuals as controls. Blood samples were collected from healthy individuals and Iraqi CRC patients. Serum concentrations of COX-2 and mPGES-1 were measured using ELISA. Marked variations in the levels of these enzymes were noted among the examined groups, with newly diagnosed patients showing the highest levels compared to treated patients and healthy control. A robust positive correlation was observed between levels of COX-2 and mPGES-1 in all groups. These outcomes suggest that serum levels of Cyclooxygenase II and Microsomal Prostaglandin E synthase 1 could serve as prospective diagnostic indicators for CRC patients.

Keywords: *serum biomarkers; COX-2; mPGES-1; CRC, ELISA.*

1. Introduction

Colorectal cancer (CRC) poses a critical public health issue, noted for its high incidence and mortality rates worldwide. CRC is the third most prevalent cancer and the second leading cause of cancer deaths. Around 1.8 million new diagnoses and 881,000 fatalities were recorded in 2018 (Baidoun et al., 2021). In Iraq, the overall incidence rate rose from 2.28 to 6.18 per 100,000 individuals from 2000 to 2019, with a notable increase among younger patients aged 20 to 50 years (Alwan et al., 2022). Similarly, mortality rates increased, from 1.25 to 1.77 per 100,000 during the same period (Ibrahem et al., 2022). Long-term inflammation is recognized as a major contributor to the onset and advancement of various cancers, involving colorectal carcinoma (Grivennikov et al., 2010; Masae et al., 2025). A primary pathway connecting inflammation to cancer is arachidonic acid (AA). This fatty acid originates from membrane phospholipids and is metabolized by cyclooxygenases (COXs) and other enzymes into various bioactive lipids, such as PGE2 and leukotrienes, which are

associated with CRC progression (Ricciotti & FitzGerald, 2011; Mohammed & Shoemaker, 2022; Gretschel et al., 2024). Therefore, the interaction between chronic inflammation and AA metabolism fosters an environment favorable for CRC progression. Cyclooxygenase (COX) controls necessary steps in the production of prostanoids (Ekhlas et al., 2022). In particular, COX-2 is an inducible enzyme that facilitates the conversion of arachidonic acid into a volatile prostaglandin H_2 (Nanda & Dhawan, 2021). Previous research found that CRC tissues displayed significantly higher levels of COX-2 mRNA compared to adjacent normal tissues (Negi et al., 2019). Moreover, this enzyme was found to influence tumor initiation, progression, metastasis, and prognosis (Albasri et al., 2018). Other isoforms of cyclooxygenase include COX-1, represents the constitutive variant, and COX-3, which is mainly found in the brain and spinal cord (Fitzpatrick, 2004; Davies et al., 2004).

Microsomal prostaglandin E synthase 1 (PGES 1) is an enzyme that can be triggered by inflammatory response, facilitating the transformation of prostaglandin H_2 into PGE_2 into several cancers (Korotkova & Jakobsson, 2014; Kamei et al., 2010). The other isoforms of PGES include microsomal PGES-2 and cytosolic PGES (cPGES) (Gudis et al., 2005). Unlike mPGES-1, mPGES-2 is constitutively expressed across various tissues and shows minimal regulation from inflammatory signals (Murakami & Kudo, 2006). In colorectal cancer, mPGES-1 is frequently co-expressed with COX-2, and is increasingly recognized as a critical driver of CRC development and progression (Sasaki et al., 2015; Stamatakis et al., 2015; Sabah & Hassan, 2024). Furthermore, the heightened expression of PGES, especially the microsomal variant, has been observed in colorectal adenomas and cancers, resulting in increased PGE_2 levels (Kim & Kim, 2021). The high levels of PGE_2 can promote the development and invasion of tumor through many mechanisms, including stimulating cell proliferation, local immunosuppression, preventing apoptosis, regulating angiogenesis, enhancing cell migration , and contributing to drug resistance (Karpisheh et al., 2019; Sheng et al., 2020). COX-2 and mPGES-1 represent promising targets for diagnosis, prognosis, and therapeutic strategies in colorectal cancer. Overexpression of COX-2 in CRC patients has been associated with to lymph node and liver metastasis, along with poor prognosis (Purnama et al., 2023). Moreover, previous studies showed that genetic deletion or suppression of mPGES-1 in mice reduced tumor growth by approximately 80-90% (Yarla et al., 2020). Furthermore, mPGES-1inhibitors may offer a promising target to avoid cardiovascular side effects that are associated with COX-2 inhibitors (Yarla et al., 2020). Previous studies have focused on tissue-based methods such as immunohistochemistry (IHC) or polymerase chain reaction (PCR), while serum-based studies remain limited, particularly in Iraqi populations.

2. Objective

This study intends to measure the serum levels of Cyclooxygenase II (COX-2) and microsomal prostaglandin E synthase 1 (mPGES-1) in CRC patients compared with healthy controls using enzyme-linked immunosorbent assay (ELISA). It also explores the relationship between these two biomarkers.

3. Materials and Methods

3.1 Study Design

This case-control study consisted of 70 CRC patients and 30 apparently healthy individuals, with blood samples and data collected from Al-Amal Hospital for Radiation and Nuclear Medicine and the Digestive and Liver Disease Teaching Hospital in Medical City, Baghdad, Iraq, from January until April 2025. The studied groups were primarily categorized into 3 groups: Group I: included 35 newly diagnosed patients (without treatment, covering all stages). Group II: included 35 CRC patients undergoing medication (chemotherapy and radiotherapy). Group III: consisted of 30 healthy volunteers with no history of cancer or any gastrointestinal problems such as inflammatory bowel disease (IBD), celiac disease, or GI infections. Patients were carefully selected based on specific inclusion and exclusion standards. The inclusion criteria included newly diagnosed CRC patients and patients who had received treatment (chemotherapy and radiotherapy). Exclusion criteria included individuals with conditions that could influence the inflammatory biomarkers, such as diabetes, heart disease, kidney failure, and gastrointestinal disorders.

A comprehensive set of parameters, including age, gender, smoking status, and treatment regimen, was collected from patients' medical records. The necessary permissions were obtained from Al-Amal Hospital for Radiation and Nuclear Medicine and the Digestive and Liver Disease Teaching Hospital in Medical City. All patients in the medication group received at least two cycles of chemotherapy. Treatment regimens included standard chemotherapy

combinations (e.g., FOLFOX, XELOX) and/ or radiotherapy, with some patients receiving biological agents such as AVASTIN. In this study, the sample size was determined utilizing G*Power software version 3.1. An effect size of f = 0.5 was assumed due to the absence of consistent local data. This large effect size assumption was supported by previous literature (Han et al., 2014; Yang et al., 2018). The analysis indicated that a minimum of 18 participants per group was sufficient to provide meaningful results. However, a total sample size of 100 participants was chosen based on practical considerations and potential variation. Ethical approval was obtained by the Institutional Review Board (IRB) of Middle Technical University, Iraq (approval number: 71; date:11/01/2025, P. C. No.10074). The study was conducted with full respect for participants' rights, in line with the ethical authorization of the Declaration of Helsinki. All participants provided written consent before any sample was taken.

3.2 Estimation of Serum COX-2 and mPGES-1 Levels

Blood samples were obtained from Iraqi patients with colorectal cancer and healthy individuals; 10 mL of blood was drawn intravenously, transferred to a vacuum gel tube, and allowed to stand for approximately 15 to 20 minutes to clot. Afterward, serum samples were obtained through centrifugation for 15 minutes at 1000×g. After being divided into smaller portions, all sera were frozen at -80ºC until ready for use. The concentrations of the studied enzymes were measured using commercial ELISA® kits: Human COX-2 ELISA kit (ELK Biotechnology, USA; Cat. No. ELK2096) and human mPGES-1 ELISA kit (Cloud-Clone Corp, USA; Cat. No. SEA167Hu). Absorbance was measured using a human reader HS microplate reader (human GmbH, Germany). Both assays utilized a sandwich enzyme immunoassay method. For COX-2, 100 µL of each serum sample or standard was placed in the wells and incubated at 37°C for 80 minutes, followed by incubating with a biotin-conjugated detection antibody for 50 minutes, washing, and then adding streptavidin-HRP for another 50 minutes. After the final washes, the TMB substrate was added and kept in the dark. The reaction was stopped with sulfuric acid, and optical density (OD) was measured at 450 nm using a microplate reader. For mPGES-1, a similar procedure was followed with minor variations in incubation times. Samples were incubated for 2 hours at 37°C. All measurements were performed in duplicate, and concentrations were determined using a standard curve.

3.3 Statistical Analysis

SPSS (2019) program was used to assess the impact of various sets (patients and control group) on the study variables. An independent t-test and one-way ANOVA with LSD post-hoc analysis were conducted for COX-2 and mPGES-1 levels after confirming the normality and homogeneity of variances. The Chi-square test was used to evaluate significant differences in percentages at probability levels of 0.05 and 0.01. The correlation coefficient was calculated to examine the relationship between COX-2 and mPGES-1.

4. Results and Discussion

4.1 The Demographic Characteristics of the Studied Groups

Seventy patients were divided into two groups according to their treatment status: 35 CRC newly diagnosed patients with colorectal cancer and 35 patients diagnosed with CRC and undergoing treatment. The control group consisted of 30 apparently healthy participants.

In this study males represented a slightly higher proportion (54.29%) compared to females (45.71%). However, the differences in sex distribution were not statistically significant among the studied groups (p = 0.502, NS). These findings are consistent with several Iraqi studies (Al-Saigh et al., 2019; Radhi et al., 2018, Falih et al., 2020), which reported no significant sex differences among CRC patients. A previous literature suggested that although sex may influence CRC risk factors, it may not always be reflected in the distribution across clinical groups (Siegel et al., 2023).

Individuals under 50 years represent the young-onset CRC group, a subgroup that has shown a rising incidence globally (Siegel et al., 2020). The 50-60 years age group represents a transitional group, aligning with the age threshold for initiating CRC screening (Shaukat et al., 2021). Meanwhile, individuals above 60 years represent the population with the highest incidence of CRC. The distribution of study participants across age groups is summarized in Table 1. Most newly diagnosed CRC patients (60%) were above 60 years old. In contrast, patients undergoing treatment were mostly between 50-60 years old (37. 14%). The control group had a large proportion of younger participants (43.33%). Moreover, the younger age group (<50 years) had fewer new diagnoses (8.57%) compared to other age groups. The results revealed

a significant association between age groups and CRC treatment status (p = 0.0267) were significantly associated. The mean age for each group showed that the newly diagnosed patients were significantly older (62.11 ± 2.08) than both patients undergoing treatment and control patients (53.91 ± 2.32, 52.17 ± 2.83) respectively. These findings are consistent with both the annual report of Iraqi Cancer Registry (2023) and a registry-based study conducted over two decades in Iraq, confirming that CRC incidence in Iraq is lowest under 50, intermediate in 50-60 bracket, and highest above 60 (Ibrahem et al., 2022).The control group had the youngest mean age, as it reflects the healthy population. The noted age differences among the studied groups- particularly in newly diagnosed patients' group - may influence the inflammatory pathways, which are central to colorectal cancer development, as aging is associated with a chronic, low-grade inflammation known as "inflammaging" (Serrano-López & Martín-Antonio, 2021). Therefore, age may act as a confounding factor by partially contributing to the elevation of inflammatory biomarkers.

The association between cigarette smoking and colorectal cancer (CRC) was non-significant among the studied groups (p = 0.086, NS). As presented in Table 1, these findings mirror the results of a previous descriptive study conducted in Iraq (Al-Saigh et al., 2019). The association between CRC and smoking may vary based on tumor characteristics, such as immune response, indicating that the relationship is not uniform across all cases (Hamada et al., 2019). Moreover, meta-analysis research indicated that the risk was greater in nations with higher Human Development Index (HDI), suggesting that socioeconomic factors may influence this relationship (Keivanlou et al., 2023).

Table 1 Groups of patients with CRC categorized by age and gender, with the group of healthy persons as the control

Factor		New diagnosis No. (%)	Undergoing treatment No. (%)	Control No. (%)	p-value
Gender	Male	19 (54.29%)	19 (54.29%)	16 (53.33%)	0.502 ^{NS}
	Female	16 (45.71%)	16 (45.71%)	14 (46.67%)	
Age groups (year)	<50 yr.	3 (8.57%)	11 (31.43%)	13 (43.33%)	
	50-60 yr.	11 (31.43%)	13 (37.14%)	9 (30.00%)	
	>60 yr.	21 (60.00%)	11 (31.43%)	8 (26.67%)	0.0267 *
	Mean ± SE	62.11 ± 2.08 ^{a}	53.91 ± 2.32 ^{b}	52.17 ± 2.83 ^{b}	0.0087 **
Smoking	Yes	12 (34.29%)	9 (25.71%)	8 (26.67%)	0.086 ^{NS}
	No	23 (65.71%)	26 (74.29%)	22 (73.33%)	
Total		35	35	30	--

Values are presented as number (%) and Mean ± SE.
Means in the same column followed by different superscript letters differ significantly. *p ≤ 0.05; **p ≤ 0.01; NS = not significant.

Table 2 Mean serum levels of COX-2 and mPGES-1 in different study groups

Group	Mean ± SE	
	COX-2	**mPGES-1**
Newly diagnosed	4.49 ± 0.06 ^{a}	53.74 ± 1.79 ^{a}
Under medication	3.27 ± 0.03 ^{b}	28.90 ± 1.23 ^{b}
Control	2.07 ± 0.04 ^{c}	19.33 ± 0.32 ^{c}
L.S.D.	0.139 **	3.736 **
p-value	0.0001	0.0001
**** (p≤0.01)**		

Values are presented as Mean ± SE.
Means in the same column followed by different superscript letters differ significantly (**p ≤ 0.01).

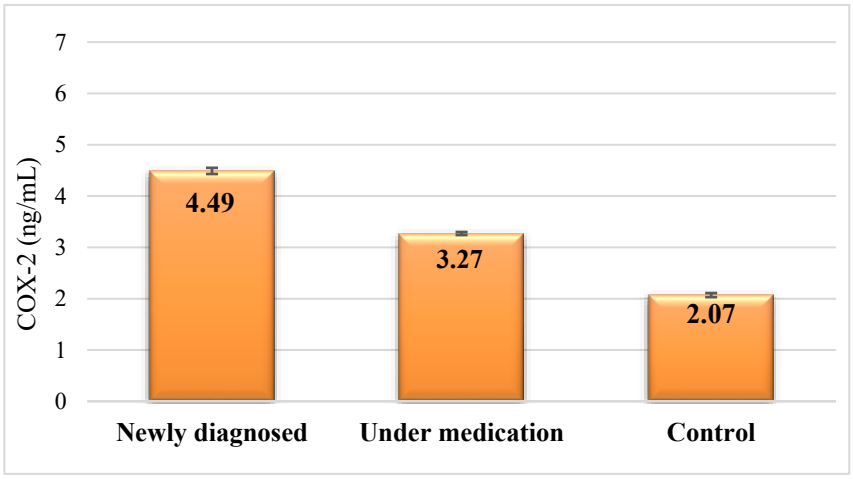

Figure 1 Comparison of serum COX-2 levels (ng/mL) among newly diagnosed CRC patients, patients under medication, and healthy controls

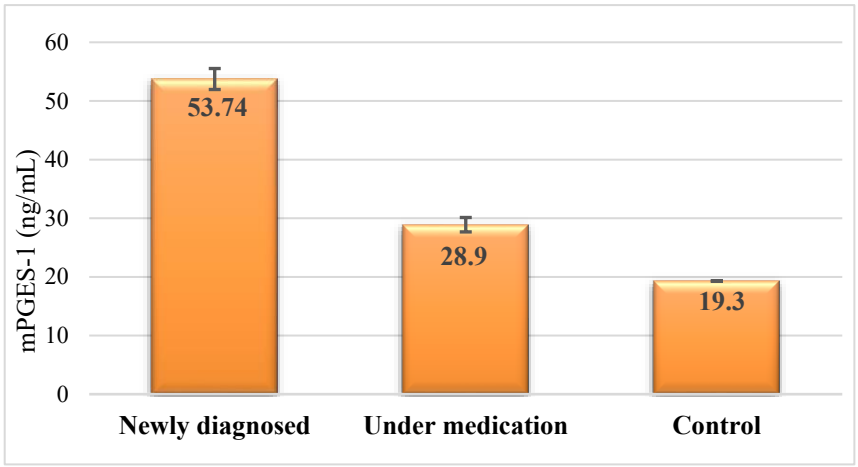

Figure 2 Comparison of serum mPGES-1 levels (ng/mL) among newly diagnosed CRC patients, patients under medication, and healthy controls

4.2 Evaluation of Cyclooxygenase II

Cyclooxygenase II (COX-2) is an essential enzyme in the arachidonic acid pathway, converting arachidonic acid into prostaglandins and thromboxanes. COX-2 mainly functions in inflammatory reactions; however, it also produces pro-resolving metabolites that contribute to the resolving inflammation (Chun et al., 2024; Faki & Er, 2021). In this study, the serum levels of COX-2 were significantly higher in CRC patients compared with healthy controls. The mean COX-2 concentration in newly diagnosed CRC patients was 4.49 ± 0.06, while in patients undergoing treatment, it was 3.27 ± 0.03. In contrast, the mean COX-2 level in the control group was 2.07 ± 0.04. The results revealed highly significant differences among the three groups ($p = 0.0001$). Post-hoc comparisons confirmed significant differences between all groups. Although the differences in COX-2 levels may appear slight potentially due to variations in ELISA kits used, including differences in detection range, sensitivity, and calibration standards they were statistically significant between CRC patient groups and healthy controls ($p = 0.0001$). Comparable findings were reported in a recent Iraqi study (Mowat & Al-Abady, 2025). Additionally, other ELISA-based studies (Cao et al., 2019; Yang et al., 2018; Choosang et al., 2024) were also consistent with these findings. However, as shown in Figure 1, the newly diagnosed patients in this study exhibited higher mean COX-2 level when compared with CRC patients undergoing treatment. This increase may result from COX-2 overexpression in cancer cells, which is associated with tumor

severity and poor clinical outcomes (Szweda et al., 2019). In the same context, a recent study by Shalaby et al., (2025) found that chemo-resistant colon cancer tissues exhibited a significant increase in COX-2 mRNA compared with tissues that did not undergo chemotherapy ($p < 0.001$). In contrast, this study showed a significant decrease in serum COX-2 levels in post-treatment patients. This is consistent with observations that responding tumors exhibit lower COX-2 levels than resistant cases (Rahman et al., 2012; Sophonnithiprasert et al., 2025). While this study used serum ELISA to quantify COX-2, previous studies (Negi et al., 2019; Roelofs et al., 2014) based on immunohistochemistry (IHC) and real-time quantitative polymerase chain reaction (qPCR) reported elevated COX-2 levels in CRC tissues compared with adjacent normal tissue, suggesting a potential link between tissue and circulating concentrations. While this study used serum ELISA to quantify COX-2, previous studies (Negi et al., 2019; Roelofs et al., 2014) based on immunohistochemistry (IHC) and real-time quantitative polymerase chain reaction (qPCR) reported elevated COX-2 levels in CRC tissues compared with adjacent normal tissue, suggesting a potential link between tissue and circulating concentrations. COX-2 expression in healthy colon tissues is typically lower than in CRC tissues. Nevertheless, several studies have reported that COX-2 expression is still detectable in healthy colon tissues, especially in patients with a family history of CRC or other risk factors (Lin et al., 2013).

4.3 Evaluation of mPGES-1

Microsomal prostaglandin E synthase 1 (mPGES-1) is an inducible enzyme that plays a crucial role in the production of PGE_2 under inflammatory conditions (Kojima et al., 2024). As shown in Table 2 and Figure 2, mPGES 1 exhibited highly significant differences among the groups examined ($p = 0.0001$). CRC patients without treatment exhibit higher mPGES-1 levels compared with patients undergoing treatment ($p = \leq 0.001$). Although ELISA-based studies on quantifying mPGES-1 in CRC patients are limited, a parallel study employing real-time polymerase chain reaction (RT-PCR) to measure PTGES expression reported that PTGES levels were markedly increased in CRC cells compared with normal cells (Geng et al., 2023). This finding is in agreement with our results. Moreover, mPGES-1 expression has been linked to the development of polyps that emerge during the early stage of colon cancer (Myung et al., 2006). Subsequent studies have found that mPGES-1 overexpression is associated with significantly poorer prognosis in CRC patients from stages I to III (Seo et al., 2009). The elevated levels of mPGES-1 in CRC patients may result from its strong association with COX-2, which is frequently overexpressed in CRC, thereby leading to higher PGE_2 levels (Stamatakis et al., 2015). Inflammatory signals, such as TNF-α and other cytokines within the tumor microenvironment, further enhance mPGES-1 expression, thereby contributing to disease progression (Kim & Kim, 2021). within the tumor microenvironment, further enhance mPGES-1 expression, thereby higher in both serum and tissue samples of CRC patients than in healthy controls. Furthermore, the present study observed a significant elevation in serum mPGES-1 levels, which mainly participate in PGE_2 synthesis. This evidence further supports the potential utility of mPGES-1 as a non-invasive biomarker for detecting or monitoring CRC. Additionally, the results of this study also indicate that CRC patients who had received chemotherapy and/or radiotherapy exhibited lower blood levels of mPGES-1 compared with untreated individuals. Although the comparison involved two different patient groups rather than longitudinal samples, the distinction indicates that anti-cancer treatment may be associated with reduced mPGES-1 levels.

4.4 Cyclooxygenase II and mPGES-1 Association

Spearman's correlation analysis was performed to determine the potential relationship between Cyclooxygenase II (COX-2) and mPGES-1.

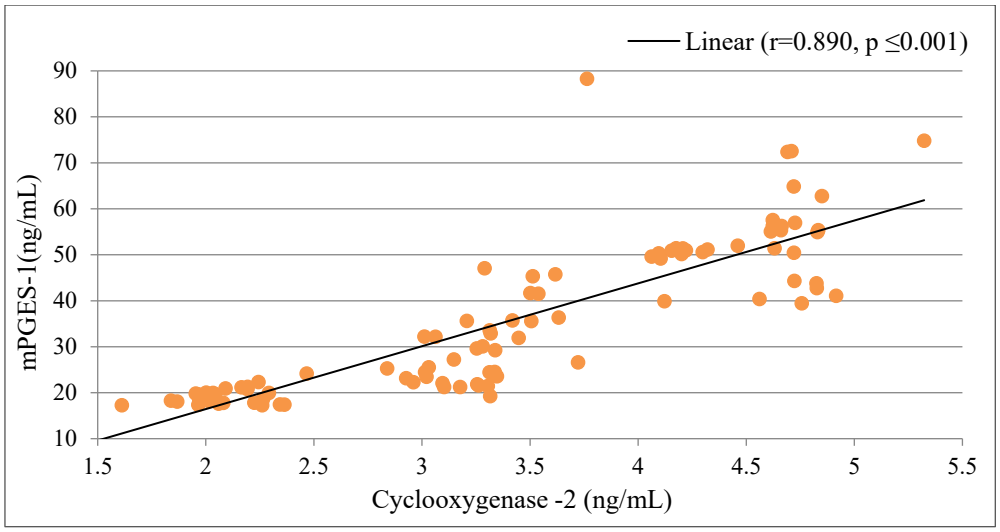

Figure 3 Linear correlation between serum COX-2 and mPGES-1 levels (ng/mL) across all study groups (r = 0.890, $p \leq 0.001$)

Figure 3 illustrates the correlation between those two biomarkers across all study groups. A very strong and highly statistically significant positive correlation was observed (r = 0.890, p = ≤0.001). This association was consistent across newly diagnosed patients, patients undergoing treatment, and healthy individuals.

The findings revealed a significant positive correlation between COX-2 and microsomal Prostaglandin E synthase-1 (mPGES-1) in the studied groups, mainly due to COX-2's function in facilitating tumorigenesis via prostaglandin-mediated signaling pathways.

COX-2 is a crucial enzyme that facilitates the conversion of arachidonic acid (AA) into prostaglandin H_2 (PGH_2), which is subsequently transformed into PGE_2 by mPGES-1. In colorectal cancer, elevated COX-2 expression is commonly observed and is associated with tumor severity and poor clinical outcomes (Finetti et al., 2023). mPGES-1 acts as a final synthase that works downstream of COX-2 to produce PGE_2 (Hyodo et al., 2022). It is highly expressed in CRC and functionally associated with COX-2, particularly under inflammatory conditions (Stamatakis et al., 2015). The regulation of COX-2 and mPGES-1 occurs in a coordinated manner in colorectal cancer. The upregulation of COX-2 leads to increased mPGES-1 expression through an early growth response 1 (EGR1)-dependent mechanism, which is further facilitated by prostaglandins such as $PGF_2\alpha$ produced downstream of COX-2 (Stamatakis et al., 2015). A previous study by Seo et al., (2009) analyzed prostaglandin E synthase (PGES) isomers and COX-2 in CRC tissues using different sample types and detection methods (RT-qPCR, Western blot, and IHC). They reported that mRNA and protein levels of mPGES-1 were overexpressed in CRC tissues compared with paired normal tissues and were correlated with poorer prognosis in stage I-III CRC patients. While their study focused on tissue samples, the present study detected higher serum levels of COX-2 and mPGES-1 in serum using ELISA. Despite the differences in sample types and detection methods, the current study supports their findings, demonstrating significantly higher serum levels of both biomarkers in CRC patients. Additionally, this study observed a strong positive correlation between COX-2 and mPGES-1 (r = 0.89, p ≤0.001; Figure 3), suggesting a coordinated regulation of these enzymes in the systemic circulation of CRC patients. Furthermore, these biomarkers could serve as potential tools for personalized treatment planning. A potentially effective therapeutic strategy may involve targeting the COX-2/mPGES-1 pathway. Although COX-2 inhibitors are effective, they have been associated with cardiovascular and gastrointestinal side effects. Selective mPGES-1 inhibitors are currently being developed as safer therapeutic alternatives (Muthukumaradoss et al., 2022).

5. Conclusion

It can be concluded that serum concentrations of COX-2 and mPGES-1 varied significantly among all participants. Interestingly, the group of newly

diagnosed CRC patients exhibiting the highest levels compared with both undergoing treatment patients and healthy controls. The strong positive correlation between these two biomarkers further highlights their interconnected roles in CRC-associated inflammation and progression. Overall, these data showed that COX-2 and mPGES-1 may serve as potential diagnostic biomarkers for colorectal cancer. Further longitudinal studies with larger cohorts, treatment-specific analyses, and disease-stage stratification are recommended to validate their clinical utility.

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7. CRediT Statement

Zainab I. Abbas: Conceptualization, methodology, data curation, writing, original draft, visualization, resources.
Ahmed Gh. Sabbar: Supervision, formal analysis, investigation, writing, review & editing.
Wajeeh K. Obaid: Supervision, writing, review & editing, project administration, validation.

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