Cyclooxygenase-2 concentration and prostaglandin E_2 levels in sera and urine of women with breast cancer

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Abstract. Breast cancer is the most prevalent malignant neoplasm and the leading cause of cancer-related mortality among women worldwide. From arachidonic acid and other fatty acids, the cyclooxygenase (COX) pathway generates a variety of prostaglandins. However, there are limited studies available on serum cyclooxygenase and prostaglandin E_2 (PGE_2) levels in patients with breast cancer globally, and none on urinary concentrations worldwide, at least to the best of our knowledge. The present study thus investigated the association between serum and urinary COX and PGE_2 levels in women with breast cancer in an aim to assess urine as a potential alternative to serum analysis. The fasting sera and urine COX and PGE_2 concentrations were determined in 29 patients with breast cancer, 29 first-degree relatives and 30 age-matched women without breast cancer as the controls. Enzyme linked immunosorbent assay was used to the measure sera and urine COX and PGE_2 concentrations. All three groups were statistically similar in terms of age and body mass index. A significant difference in the serum level of COX-2 was observed among the groups, with the breast cancer group manifesting the highest level (P<0.001). In urine, the COX-2 levels portrayed an opposite trend to that of the serum levels: The control group displayed notably higher levels (P<0.001). The sera and urine levels of PGE_2 among the three groups do not exhibit a statistically significant difference. On the whole, the present study demonstrates that COX-2 levels are elevated in the early stages of breast cancer, indicating its potential role in disease progression.

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Introduction

Worldwide, breast cancer is the most prevalent malignant tumor and the leading cause of cancer-related mortality among women (1,2). Although there is evidence of an association with estrogen-receptor (ER)-positive tumors, the association between weight and breast cancer risk is often greater for ER-positive breast malignancies (3,4). According to the Iraqi Cancer Registry (ICR) in 2023, breast cancer affects 20.5% of all patients with cancer (https://storage.moh.gov.iq/2024/11/24/2024_11_24_12127028949_4299728097670824.pdf). Arachidonic acid and other fatty acids are converted by the cyclooxygenase (COX)-2 pathway into a variety of prostaglandins, prostacyclins and thromboxanes (5). Prostaglandin (PG) E_2 (PGE_2) stimulates E-type prostanoid receptor activation, which in turn enhances cellular proliferation, promotes angiogenesis, inhibits apoptosis, stimulates invasion and motility, and suppresses immunological responses (6). PGE_2 and its receptors play a prominent role in driving cancer progression (7). PGs belong to the eicosanoid family and are produced by the majority of cells in the human body (8). COX-2 overexpression induces cancer by promoting angiogenesis, reducing tumor immunity and promoting PGE_2 production (6). Different functions are performed by COX isoforms in healthy and pathological circumstances. In the majority of tissues, COX-1 is typically produced constantly, regulating physiological processes, including vascular homeostasis or cellular responses to hormone stimulation. When growth factors or inflammation are stimulated, COX-2 is primarily expressed, and this frequently results in an increased synthesis of PGE_2 in tumor or inflammatory tissue (9). The inducible enzyme COX-2 is linked to inflammatory illnesses and cancer. Furthermore, it may also promote angiogenesis, tumor tissue invasion and resistance to apoptosis (10). Up to 40% of the expression of COX-2 enzyme in human breast cancer is connected with numerous factors, including age, tumor size, a high grade, a negative hormone receptor status, a high proliferation rate and the presence of human EGFR-2 oncogene amplification (11).

The aim of the present study was to examine the association of the COX-2 and PGE_2 concentrations in the sera and urine of women with breast cancer, as well as to evaluate the levels of these parameters to determine their potential use in predicting disease occurrence. Furthermore, the present study aimed to evaluate whether the urine test for COX-2 and PGE_2 can be used as an alternative to the sera test.

Patients and methods

Patient selection. The present study included 88 women that were classified into three groups, as follows: Group 1 included 29 patients with breast cancer prior to surgery and without pharmaceutical treatment, group 2 was comprised of 29 first-degree relatives, and group 3 included 30 healthy subjects as the controls; the age of the participants ranged from 25 to 57 years. All patients and first-degree relatives attended the Oncology Teaching Hospital in Medical City (Baghdad, Iraq) during the time of September, 2024 to April, 2025. All women with breast cancer had invasive ductal carcinoma and did not suffer from any other malignant diseases; 45% of them had a family history of tumors, and 55% of them had no family history. All patients were ER-positive, human epidermal growth factor receptor 2 (HER2)-negative, and had grade II, and stage I and II disease. All the patients were non-smokers, not pregnant, and had not taken any anti-inflammatory or non-steroidal anti-inflammatory drugs. First-degree relatives of the patients with breast cancer were included as a distinct study group to represent individuals with familial predisposition and a potentially increased risk of developing breast cancer. This group was included in an aim to explore whether COX-2 levels demonstrate differential patterns across healthy controls, individuals with familial risk and patients with a confirmed breast cancer. This group was included for exploratory and hypothesis-generating purposes and was not intended to support screening or clinical risk stratification. The research Ethics Committee of Mustansiriyah University (Baghdad, Iraq) reviewed and approved the present study (approval no. BCSMU/0924/0042C). Ethics approval was obtained from the author's institution as the governing document. This approval was presented to the administrations of Oncology Teaching Hospital in Medical City. As these are affiliated teaching hospitals with established inter-institutional collaboration protocols, they granted administrative site permission for sample collection based on the university's central ethics clearance. Every patient who took part in the research provided written, informed consent. It was made clear to the participants that participation was completely voluntary and that there would be no consequences if participants opted to withdraw from the study at any moment.

Samples. A total of 5 ml fasting blood and 10 ml midstream random spot urine in the morning was collected after the study subjects gave their agreement and completed the face to face questionnaire, which included (full name, age, weight, hight, family history of cancer, any other diseases, any medications, marriage status, number of children, smoking status, and the use of any contraceptives). At room temperature, blood was allowed to stand for 30 min to allow complete clotting. Urine samples were collected from all the women participating in the study into disposable screw cup containers for the estimation of the study parameters. The collected specimens were centrifuged at 4,000 rpm for 10 min. The creatinine concentration was measured in the urine samples immediately. The sera and the second part of the urine was separated into small aliquots and stored at -20˚C until use to measure the COX-2 and PGE_2 concentrations.

Calculation of body mass index (BMI). BMI was calculated by dividing the weight by the square of the height, as follows: BMI=weight (kg)/height (m^2).

Sera and urine marker analysis. With the use of enzyme-linked immunosorbent assay (ELISA), the serum and urinary COX-2 concentrations were measured using the Human PTGS2/COX-2 ELISA kit [cat. no. ELK2096, Elk (Wuhan) Biotechnology Co., Ltd.]. The assay has a reported lower limit of detection of 0.125 ng/ml and a detection range of 0.32-20 ng/ml. The manufacturer states that the coefficients of variation within and between assays are <8 and 10%, respectively. The PGE_2 levels were quantified using the Human PGE_2 ELISA kit [cat. no. ELK9315, Elk (Wuhan) Biotechnology Co., Ltd.]. This competitive ELISA has a reported sensitivity of 0.97 pg/ml and a detection range of 3.13-200 pg/ml, with high specificity and minimal cross-reactivity. At a wave-length of 450 nm, the optical density (OD) was determined on a 96-well microplate reader and the COX-2 and PGE_2 concentrations are expressed in pg/ml. Urine creatinine concentrations were measured by colorimetric assay using the automatic Roche/Hitachi cobas c111 System and the concentrations are expressed in mg/dl. The COX-2 and PGE_2 concentrations in urine were divided by the level of creatinine in urine for the purpose of providing a representative sample, enabling us to analyzed these parameters without the need for collecting urine for 24 h.

Statistical analysis. The data were analyzed using SPSS software version 25 (IBM Corp.). Data are presented as the mean ± SD, and analyzed using one-way ANOVA, followed by Tukey's honest significant difference (HSD) test for post hoc pairwise comparisons to control type I error. Pearson's correlation analysis was performed to correlations among all parameters (12). To assess the accuracy of COX-2 and PGE_2 parameters, receiver operating characteristic (ROC) analysis was performed and the area under the curve (AUC) was calculated (13). Cut-off values for serum and urinary COX-2 and PGE_2 were determined using ROC curve analysis and the Youden index, based on the study cohort. No internal or external validation procedures were applied. A value of $P<0.05$ was considered to indicate a statistically significant difference.

Results

In total, 45% of the patients in the present study some had a family history of tumors, with the remainder having no family history. Some physical features of the study groups are presented in Table I. The difference in age and BMI between these groups was not statistically significant ($P>0.05$). The post hoc comparison indicated that all three groups were statistically similar in terms of age and BMI.

The data presented in Table II revealed a significant difference in the serum levels of COX-2 among the groups, with the breast cancer group manifesting the highest levels (40.21±7.66), followed by the first-degree relatives (30.91±2.63) and the control group (21.97±5.74). This finding was substantiated by a P-value of 0.001 underscoring the statistical significance. The

Table I. Age and BMI among all the study groups.

Parameter	Breast cancer (n=29)	First-degree relatives (n=29)	Control (n=30)	P-value[a]	P-value[b]	P-value[c]	P-value[d]
Age (years)	43.62±8.36	40.35±10.51	40.96±7.01	0.365	0.964	0.471	0.334
BMI (kg/m2)	28.68±3.66	26.99±3.12	27.07±2.67	0.147	0.996	0.138	0.090

Data are presented as the mean ± SD. Data were analyzes using one-way ANOVA followed by Tukey's post hoc test. [a]P-value between patients with breast cancer and first-degree relatives. [b]P-value between first-degree relatives and the control group. [c]P-value between patients with breast cancer and the control group. [d]P-value among all study groups. BMI, body mass index.

Table II. COX-2 enzyme level in sera and the urine ratio of COX-2 by the level of creatinine in the urine of patients with breast cancer, first-degree relatives and healthy controls.

Parameter	Breast cancer (n=29)	First-degree relatives (n=29)	Control (n=30)	P-value[a]	P-value[b]	P-value[c]	P-value[d]
COX-2 sera (pg/ml)	40.21±7.66	30.91±2.63	21.97±5.74	0.030*	0.001	0.001	0.001
COX-2 urine (pg/ml)	20.55±3.94	16.87±1.06	39.14±1.77	0.001	0.001	0.001	0.001
COX-2/creatinine in urine ($x10^9$)	2.0±0.92	1.62±0.53	3.58±1.81	0.516	0.001	0.001	0.001

Data are presented as the mean ± SD. Data were analyzes using one-way ANOVA followed by Tukey's post hoc test. [a]P-value between patients with breast cancer and first-degree relatives. [b]P-value between first-degree relatives and the control group. [c]P-value between patients with breast cancer and the control group. [d]P-value among all study groups. Values in bold font indicate statistically significant differences (P<0.05). COX-2, cyclooxygenase 2.

Table III. Comparison of the sera and urine level of PGE_2 and the ratio of PGE_2 by the level of creatinine in urine in all study groups.

Parameter	Breast cancer (n=29)	First-degree relatives (n=29)	Control (n=30)	P-value[a]	P-value[b]	P-value[c]	P-value[d]
PGE_2 sera (pg/ml)	14.41±7.24	15.99±11.82	18.88±8.23	0.806	0.495	0.153	0.173
PGE_2 urine (pg/ml)	52.57±16.10	48.75±15.59	56.02±16.83	0.678	0.250	0.698	0.281
PGE_2/creatinine in urine ($x10^9$)	5.14±2.56	4.69±2.31	4.98±2.95	0.816	0.921	0.969	0.830

Data are presented as the mean ± SD. Data were analyzes using one-way ANOVA followed by Tukey's post hoc test. [a]P-value between patients with breast cancer and first-degree relatives. [b]P-value between first-degree relatives and the control group. [c]P-value between patients with breast cancer and the control group. [d]P-value among all study groups. PGE_2, prostaglandin E2.

post hoc analysis labels further demonstrated the distinction among all three groups.

Notably, the COX-2 urine levels portrayed an opposite trend to those of the serum levels. The control group displayed markedly higher levels (39.14±1.77) as compared to the breast cancer group (20.55±3.94) and first-degree relatives (16.87±1.06). The difference was statistically significant (P<0.001). The post hoc analysis indicated there were significant differences between the groups (Table II).

The ratio of COX-2 in urine by the level of creatinine in urine is demonstrated in Table II. The results revealed that there was a highly significant difference (P<0.001) between the breast cancer and control groups, and no significant differences were observed between the breast cancer first-degree relatives group (P=0.516).

A detailed investigation of the serum and urine levels of PGE_2 across the three different groups was performed. The results are summarized in Table III. The serum levels of PGE_2 across the breast cancer, control and first-degree relatives groups displayed mean values of (14.41±7.24, 18.88±8.23 and 15.99±11.82 pg/ml, respectively. Despite these numerical variations, statistical analysis yielded a P-value of 0.17, indicating that these differences were not statistically significant.

Similarly, the urinary levels of PGE_2 among the three groups do not exhibit a statistically significant difference (P-value=0.28). Table III also presents the ratio of the PGE_2

Table IV. Correlations among the levels of all studied parameters in serum in all study groups.

Parameter	COX-2 BC group	PGE_2 BC group	COX-2 FR group	PGE_2 FR group	COX-2 control group	PGE_2 control group
Age (years)						
r	-0.368	-0.162	-0.755[b]	-0.163	0.221	0.156
P-value	0.049[a]	0.402	0.001	0.456	0.250	0.418
BMI (kg/m^2)						
r	0.253	-0.169	-0.351	0.236	0.086	0.121
P-value	0.185	0.379	0.101	0.278	0.656	0.531

[a]Correlation is significant at the 0.05 level (two-tailed). [b]Correlation is significant at the 0.01 level (two-tailed). BC, breast cancer; FR, first-degree relatives; BMI, body mass index; COX-2, cyclooxygenase 2; PGE_2, prostaglandin E2.

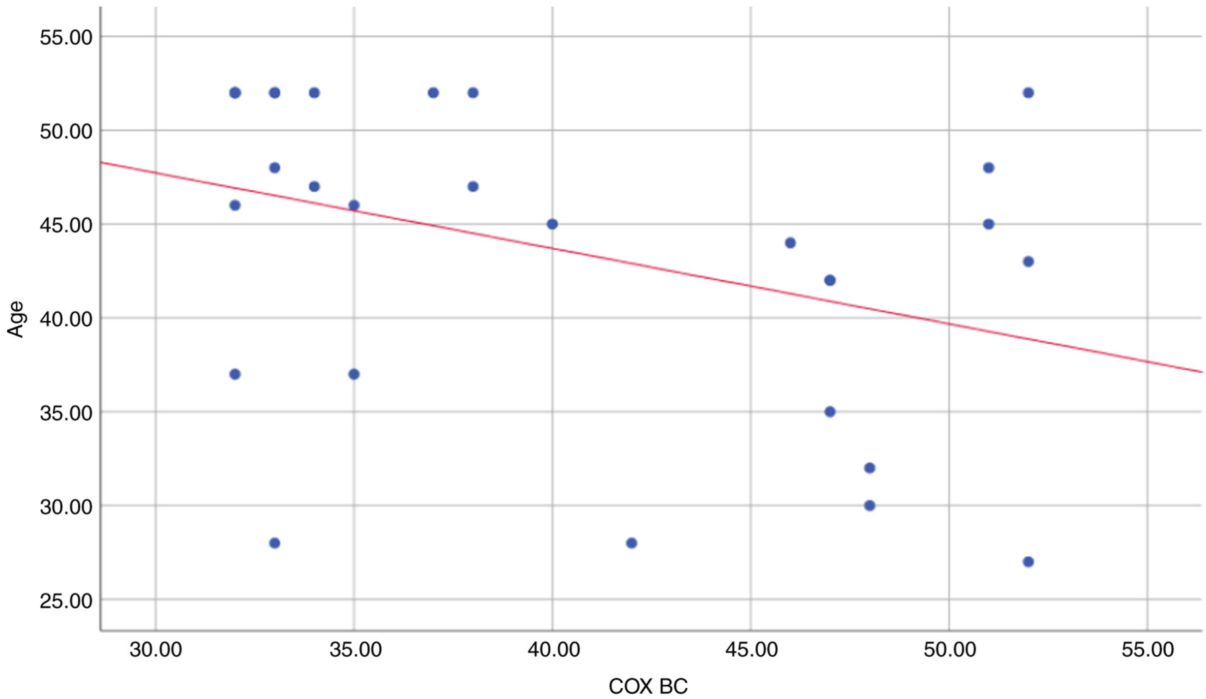

Figure 1. Correlation between age and COX-2 concentrations in serum among patients with breast cancer. Age and serum COX-2 levels in the breast cancer group exhibited a significant negative correlation (r=-0.368, P=0.049). COX, cyclooxygenase; BC, breast cancer.

level in urine by the level of creatinine in urine; the results revealed that there were no significant differences among the three groups.

Pearson's correlation analysis (Table IV) provided valuable insight into the correlations between multiple variables in the context of sera in all the study groups. According to the results presented in Table IV and Fig. 1, age and serum COX-2 in the breast cancer group exhibited a significant negative correlation (r=-0.368, P=0.049). Furthermore, there was no correlation observed between other parameters. In first-degree relatives group, there was a strong negative correlation between age and serum COX-2 (r=-0.755, P=0.001), as demonstrated in Table IV and Fig. 2. In the control group, there was no correlation among all parameters.

The diagnostic performance of various biomarkers in differentiating between cases of breast cancer and controls is illustrated in Figs. 3 and 4. Sera and urine COX-2 exhibited exceptional diagnostic accuracy, as indicated by a sensitivity and specificity of 100% and an AUC of 1.00. These findings suggest that these particular markers are extremely reliable for distinguishing patients with breast cancer from controls. On the other hand, the serum and urine PGE_2 ROC curve demonstrated a considerably similar efficacy, with a sensitivity of 38%, specificity of 93%, and an AUC of 0.66 for serum with a cut-off value of 9.93, and a sensitivity and specificity of 59%, and an AUC of 0.57 for urine with a cut-off value of 48.77.

Discussion

Given the increasing prevalence of breast cancer and the absence of reliable biomarkers for early prediction, the present study was conducted in an aim to contribute to the

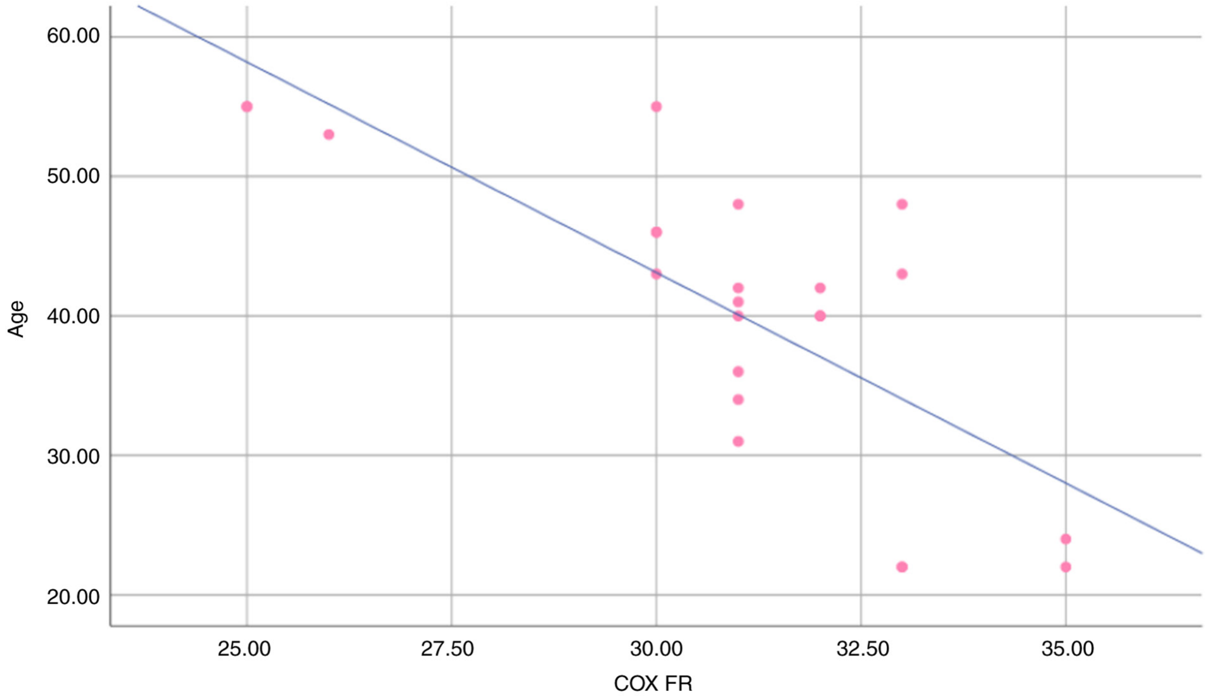

Figure 2. Correlation between age and COX-2 concentrations in serum among the first-degree relatives group. In first-degree relatives group, there was a strong negative correlation between age and serum COX-2 (r=-0.755, P=0.001). COX, cyclooxygenase; FR, first-degree relatives.

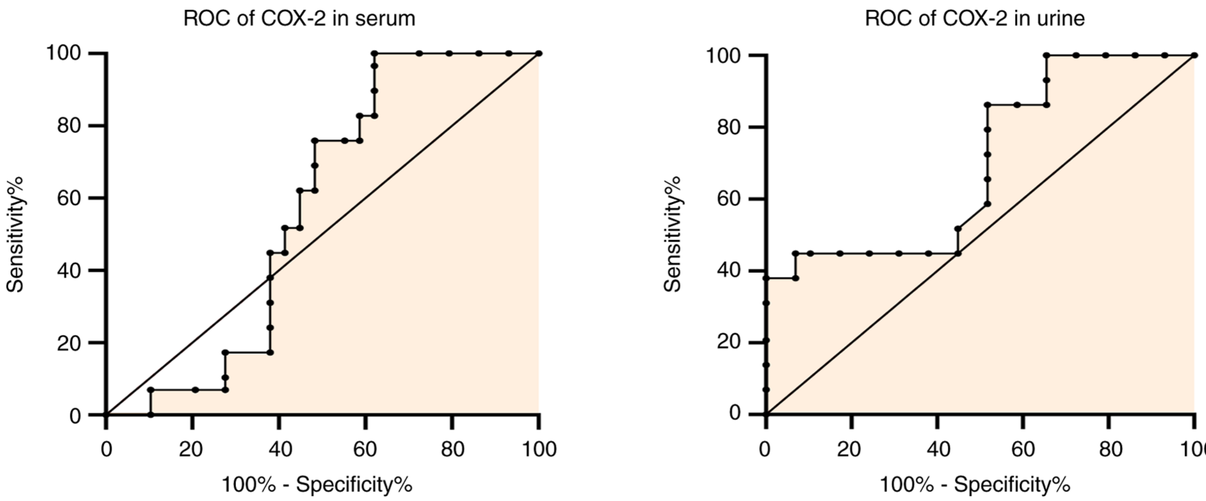

Figure 3. ROC curves for COX-2 concentrations in the sera and urine of patients with breast cancer. ROC, receiver operator characteristic; COX-2, cyclooxygenase-2.

identification of novel markers in serum and urine that may assist in the early detection of breast cancer. The mean ± SD age of the patients in the present study was 40.62±12.36 years. As previously demonstrated, the risk of acquiring breast cancer increases with age as follows: A 1.5% risk at age 40, 3% at age 50, and >4% at age 70 years (14). Women who have had long-term estrogen circulation in their bodies are more susceptible to developing breast cancer (15). An increased number of menstrual cycles also increases the risk of developing breast cancer. Women who menarche early and menopause at a later stage are more likely to develop breast cancer (16).

BMI is classified as follows: Underweight (<18 kg/m^2) and normal weight (18.5-24.9 kg/m^2). While overweight (BMI between 25.0 and 29.9 kg/m^2), class I obesity (BMI of 30.0 to 34.9 kg/m^2), class II obesity (BMI of 35.0 to 39.9 kg/m^2) and class III or severe obesity (BMI of 40 kg/m^2) are all examples of obesity, the medical risk increases gradually as the degree of obesity increases (17,18). In the present study, the results summarized in Table I demonstrate that the BMI the patients in all the groups was >25 kg/m^2, indicating that the population in the present study was overweight. Epidemiological data indicate that obesity increases the risk of developing breast cancer (19). According to the study by Fontvieille *et al* (20) women >50 years of age with a higher BMI are at a greater risk of developing cancer compared to those with a lower BMI. Additionally, it has been found that a higher BMI is linked to

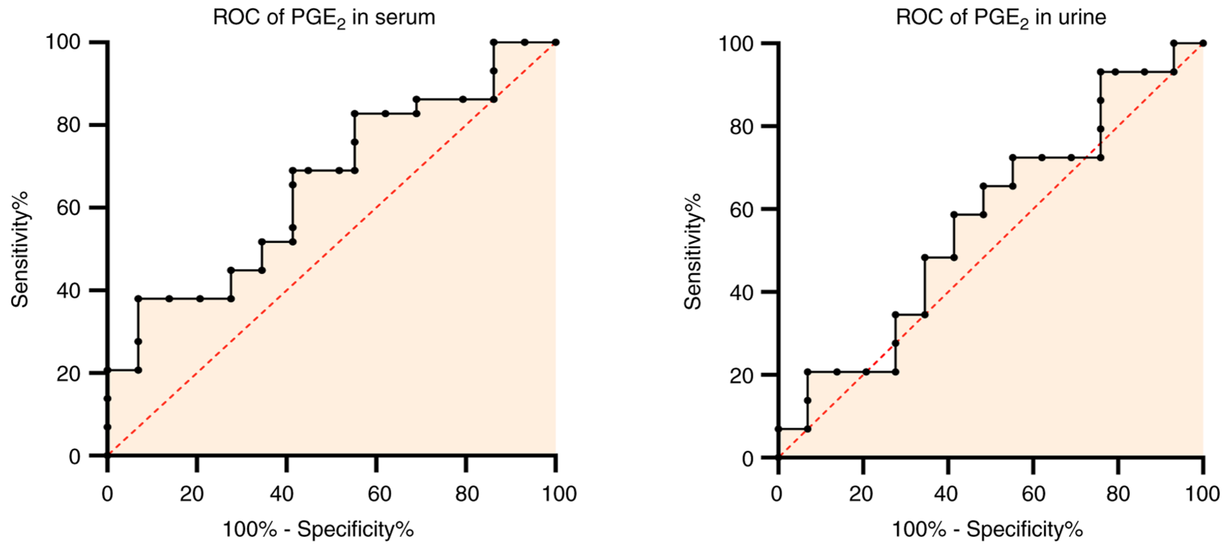

Figure 4. ROC curves for PGE_2 concentrations in the sera and urine of patients with breast cancer. ROC, receiver operator characteristic; PGE_2, prostaglandin E_2.

more aggressive biological characteristics of the tumor, such as a larger size and a higher percentage of lymph node metastasis. According to the meta-analysis by Smith *et al* (21), there was a low positive association between the risk of developing breast cancer and BMI, with an increase in BMI of 5 kg/m^2 being associated with an increase in the risk of developing breast cancer of 2%. Nonetheless, among premenopausal women, a higher BMI reduces the risk of developing breast cancer. Obesity and overweight are considered to provide protection against premenopausal breast cancer, with the exception of women having a family history of breast cancer. Therefore, body fat may be a better measure of breast cancer risk in postmenopausal women than BMI or body weight. Body fat distribution may also influence the risk of developing breast cancer (22). According to observational data, women with and without a family history of breast cancer may have a similar link between their BMI and the risk of developing the disease (23).

The results of the present study demonstrated a significant increase in serum COX-2 in patients with breast cancer compared with the first-degree relatives and the controls. These results are in line with those of the study by Habeeb (24). Moreover, in urine, there were highly significant differences between the control group and patients with breast cancer and, first-degree relatives ($P<0.001$). Previous research has revealed a correlation between COX-2 expression and the ER (25), progesterone receptor and HER-2 positive status (26). The enzyme aromatase, which converts testosterone to estrogen, is expressed and activated to a greater extent when PGs are present. Through the activation of the ER and its target genes, estrogen can promote the development of cancer cells (27). According to the study by Jana *et al* (28), COX-2 may promote the growth and angiogenesis of breast tumors through this mechanism. According to that study, COX-2 expression was detected in invasive and *in situ* ductal carcinoma, but not in normal breast tissue (28). In 2014, in the USA, the overexpression of COX-2 was repeatedly reported in all stages of breast cancer by molecular biologists from numerous independent laboratories (29). In 2021, in India, Bhutani *et al* (30) examined the spectrum of COX-2 expression in normal breast tissue, and compared COX-2 expression with histological prognostic factors and hormone receptor status in ductal carcinoma in situ next to and inside invasive carcinoma. They found that the reduction of COX-2 may provide a potential target for the prevention of breast cancer oncogenesis and as an adjuvant treatment following surgery to minimize local recurrence (30). In the present study, the results of ROC curve analysis (Fig. 3) demonstrated that sera and urine COX-2 had the high diagnostic efficacy in the diagnosis of BC (AUC=1).

COX-2 expression inhibits GSK3β enzyme activity, which is a major Wnt component that phosphorylates β-catenin and stimulates its eventual destruction via proteasome (31,32). In urine, the reduced concentration of COX-2 may cause the activation of β-catenin mediated transcriptional signaling and the disruption of the balance between cell proliferation and differentiation thus paving the way for tumorigenesis (33).

In the present study, there were no significant differences in the PGE_2 concentration in serum and urine among the three groups. The relative rates of 15-hydroxyprostaglandin dehydrogenase dependent breakdown and COX-2/PGE synthase dependent production determine the steady state cellular levels of PGE2. Ilyan *et al* (34) examined the association between the serum levels of PGE_2, COX-2, and 25-hydroxyvitamin D in patients with breast cancer in Indonesia. They demonstrated that serum PGE_2 and vitamin D levels varied according to the stage of breast cancer; the PGE_2 serum level and breast cancer stage were not significantly associated with serum 25(OH) D levels (34). Herein, there was no significant association between COX-2 levels in blood and urine; therefore, urine cannot be used as a substitute for blood, and vice versa.

There are certain limitations to the present study, which should be mentioned. The statistical power may have been diminished by the comparatively small sample size, particularly for diagnostic accuracy analyses such as ROC curves. In addition, the study population was limited to patients with ER-positive, HER2-negative, grade II, early-stage breast cancer, which represents a highly selected cohort and limits the generalizability of the results to other molecular subtypes and disease stages.

In conclusion, the results of the present study demonstrated an elevation in COX-2 levels during the early stages of breast cancer, indicating its potential role in disease progression. The ROC analysis further suggested that this enzyme may serve as an effective diagnostic biomarker. Moreover, the measurements of the PGE_2 concentration revealed the absence of severe inflammation among patients, consistent with their classification in the early stages of the disease.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HQM edited the manuscript, and was also involved in the conceptualization and design of the study. TJT and RSM collected and analyzed data. MIH oversaw the study, participated in data curation, and reviewed and edited the report. The final text has been reviewed and approved by all authors. HQM and TJT confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was examined and authorized by the Research Ethics Committee of Mustansiriyah University, Baghdad, Iraq (approval no. BCSMU/0924/0042C), and subsequently authorized by THE Oncology Teaching Hospital/Medical City administration per standard institutional collaboration procedures. Every patient who took part in the study provided written, informed consent. It was made to the participants that their participation was completely voluntary and that there would be no consequences if they opted to withdraw from the study at any moment. By using coded IDs instead of names or medical record numbers, anonymity and confidentiality were protected. The study upheld high ethical standards in accordance with international ethical norms, such as the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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