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Original Article

Serum biomarkers associated with disease stage and pain severity among women with endometriosis in Indonesia

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Abstract

Endometriosis is a chronic estrogen-dependent disease characterized by the presence of endometrial-like tissue outside the uterine cavity, resulting in chronic inflammation, recurrent pain, and infertility, and affecting approximately 190 million women worldwide. Chronic inflammation in endometriosis may stimulate overexpression of cyclooxygenase-2 (COX-2), which catalyzes prostaglandin E2 production, whereas cancer antigen 125 (CA-125) is a glycoprotein biomarker released by endometrial and mesothelial cells in response to inflammatory processes. The aim of this study was to analyze the correlations between serum COX-2 and CA-125 levels and the degree of endometriosis, based on the revised American Society for Reproductive Medicine classification, and between these levels and pain severity, based on the Numeric Rating Scale. A cross-sectional study was conducted among patients with endometriosis at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. The levels of COX-2 and CA-125 were measured using enzyme-linked immunosorbent assay and chemiluminescence immunoassay, respectively. Spearman correlation and ordinal logistic regression were used for statistical analysis. The median age of the participants was 36 years (range: 19-51 years), and most patients had Stage IV endometriosis (78.6%). COX-2 showed a significant positive correlation with both the degree of endometriosis (r=0.526; p<0.001) and pain severity score (r=0.769; p<0.001). CA-125 also showed a significant positive correlation with the degree of endometriosis (r=0.433; p=0.004), but not with pain severity (r=0.256; p=0.102). Receiver operating characteristic curve analysis showed that COX-2 had good discriminative ability for severe endometriosis (AUC=0.865) and for severe pain (AUC=0.864). In the multivariable model, COX-2 and CA-125 were also significantly associated with pain severity. These findings suggest that COX-2 was more strongly associated with pain severity, whereas CA-125 was more closely related to the degree of endometriosis. Further studies with larger sample sizes and prospective designs are needed to validate these findings and clarify the clinical utility of these biomarkers in endometriosis management.

Keywords: Endometriosis, endometriosis stage, pain severity, cyclooxygenase-2, CA-125

Introduction

Endometriosis is a chronic, estrogen-dependent disease characterized by the growth of glandular and stromal endometrial tissue outside the uterine cavity, which triggers chronic inflammation that leads to adhesions and fibrosis in the pelvic cavity [1]. According to the World

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Health Organization (WHO) in 2021, endometriosis affects approximately 10% of women of reproductive age, or about 190 million women globally, with prevalence ranging from 5–50% in infertile women to 5–21% in hospitalized patients with pelvic pain [2]. In Indonesia, the incidence among infertile women ranges from 13.6% to 69.5%, with endometriosis contributing 10–25% of gynecological consultations at Dr. Zainoel Abidin Hospital in Banda Aceh, Aceh Province [3].

The pathogenesis of endometriosis involves multiple mechanisms, including retrograde menstruation, coelomic metaplasia, stem cell theory, and genetic/epigenetic factors. Chronic inflammation activates nuclear factor kappa B (NF-κB), stimulating pro-inflammatory cytokine production and activating peritoneal macrophages [4]. This ongoing inflammatory state stimulates cyclooxygenase-2 (COX-2) expression, causing elevated prostaglandin E2 (PGE2) levels in endometriotic lesions [4]. COX-2 is a key rate-limiting enzyme that catalyzes the conversion of arachidonic acid to PGE2 and other prostanoids, playing critical roles in endometriosis progression through stimulation of aromatase expression (CYP19A1), activation of matrix metalloproteinases (MMP-2 and MMP-9), and promotion of angiogenesis [5]. Previous studies have demonstrated overexpression of COX-2 in endometriotic tissues compared with the normal endometrium [5,6]. Elevated COX-2 concentrations lead to high cell proliferation, low apoptosis rates, high invasion, and angiogenesis in endometriosis [5]. A study confirmed that *PTGS2* mRNA expression (encoding COX-2) in endometrial and ovarian lesions correlated significantly with serum CA-125 levels and endometrioma diameter [6].

CA-125 is a high-molecular-weight glycoprotein released by mesothelial and endometrial cells in response to irritation and inflammation. A study found that mean CA-125 levels for American Society for Reproductive Medicine (ASRM) stages I, II, III, and IV were 18.8±0.9, 40.3±2.8, 77.1±3.5, and 182.4±14.0 IU/mL, respectively, increasing significantly with advanced stages [7]. A meta-analysis involving 22 observational studies (N=3,626 women) showed CA-125 has a pooled sensitivity of 52% and specificity of 93% for endometriosis diagnosis [8].

Despite the established individual roles of COX-2 and CA-125, evidence regarding their combined diagnostic value for assessing endometriosis stage and pain severity simultaneously remains limited. The relationship between disease stage and pain intensity is paradoxical — severe pain can occur in minimal endometriosis while extensive disease may present with mild pain [9]. Understanding the distinct pathophysiological roles of COX-2 as an active inflammatory mediator and CA-125 as an anatomical disease marker may provide complementary clinical value. Therefore, the aim of this study was to analyze the correlation between COX-2 and CA-125 levels and the degree of endometriosis and pain severity, and to evaluate their combined diagnostic value for clinical stratification of patients with endometriosis.

Methods

Study design and setting

An observational analytical study with a cross-sectional design was conducted at the Obstetrics and Gynecology Clinics of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, from February to October 2025. The study was designed to evaluate the association of serum COX-2 and CA-125 levels with endometriosis stage and pain severity among patients with endometriosis. Eligible patients who were scheduled to undergo laparotomy or laparoscopy were recruited during the study period. Blood samples for biomarker measurement were collected before surgery, while endometriosis stage was determined intraoperatively using the revised American Society for Reproductive Medicine (rASRM) classification, and pain severity was assessed using the Numeric Rating Scale NRS). The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cross-sectional studies.

Participants criteria

Eligible participants were patients diagnosed with endometriosis based on clinical examination and supporting imaging, including transvaginal ultrasonography or magnetic resonance imaging, who were scheduled to undergo laparotomy or laparoscopy. Participants were included if they agreed to undergo serum COX-2 and CA-125 measurements, had not consumed analgesics within 24 hours before blood sampling, and provided consent to participate. Patients were excluded if

there were clinical or imaging findings suggestive of malignancy, a history of previous laparotomy, pregnancy, active inflammatory disease such as pelvic infection, autoimmune disease, or inflammatory bowel disease, or use of hormonal therapy within the preceding 3 months, including gonadotropin-releasing hormone agonists or hormonal contraceptives. Participants were further excluded after surgery if histopathological examination did not confirm endometriosis, demonstrated ovarian malignancy, or if the data were incomplete or the blood sample was hemolyzed.

Sample size and sampling

The required sample size was calculated using Cohen's formula for correlation studies, assuming a two-sided significance level of 5%, a statistical power of 90%, and an expected correlation coefficient of 0.5. Based on this calculation, the minimum sample size was 38 participants. After accounting for a potential 10% dropout rate, the final minimum required sample size was 42 participants. Patients were recruited consecutively during the study period until the required sample size was achieved.

Study procedures

All eligible patients underwent standardized study procedures during the preoperative and intraoperative periods. At the initial evaluation, patients attending the Gynecology Clinic underwent history taking, general physical examination, gynecological examination, and supporting imaging, including transvaginal ultrasonography or magnetic resonance imaging, to establish the clinical diagnosis of endometriosis. Patients who were scheduled for laparotomy or laparoscopy and fulfilled the eligibility criteria were invited to participate and provided written informed consent before enrollment.

Before surgery, a 5 mL venous blood sample was collected in the morning for measurement of serum COX-2 and CA-125 levels. Pain severity was also assessed preoperatively using the NRS scale based on the patient's pain experience during the preceding three months. During surgery, the degree of endometriosis was assessed intraoperatively using the rASRM classification. Excised tissue specimens were subsequently sent for histopathological examination to confirm the diagnosis. Only participants with complete clinical, laboratory, operative, and histopathological data were included in the final analysis.

Laboratory measurements

Venous blood samples (5 mL) were collected in the morning before surgery for measurement of serum COX-2 and CA-125 levels. For CA-125 assessment, serum samples were analyzed at the Clinical Pathology Laboratory of Dr. Zainoel Abidin Hospital using a chemiluminescence immunoassay on the ADVIA Centaur analyzer, and the results were reported in U/mL, with a reference value of <35 U/mL. For COX-2 assessment, serum was separated after centrifugation at 3,000 rpm for 15 minutes and stored at -80°C until analysis. Serum COX-2 levels were then measured using the Human PTGS2/COX-2 Enzyme-Linked Immunosorbent Assay kit (Elabscience Bionovation, Texas, USA) according to the manufacturer's instructions. The assay had a detection range of 0.16–20 ng/mL and a sensitivity of 0.19 ng/mL. All biomarker results were expressed in ng/mL for COX-2 and U/mL for CA-125.

Assessment of outcome variables

The primary outcome variables were endometriosis stage and pain severity. Endometriosis stage was assessed intraoperatively using the rASRM classification, which categorizes disease severity into Stage I, Stage II, Stage III, and Stage IV based on the extent of lesions, adhesions, and anatomical involvement observed during laparotomy or laparoscopy. Pain severity was assessed preoperatively using the NRS, in which patients rated their pain on a scale from 0 to 10 based on the intensity of symptoms experienced over the previous 3 months. Pain scores were then categorized as mild (1–3), moderate (4–6), and severe (7–10). Histopathological examination of excised tissue was performed to confirm the diagnosis of endometriosis in all included participants.

Statistical analysis

Descriptive statistics were presented as median (range) for non-normally distributed variables. Associations of COX-2 and CA-125 with outcomes were assessed using Spearman's rank correlation test. Receiver operating characteristic (ROC) curve analysis, together with the Youden index, was performed to determine the optimal diagnostic cut-off values. The area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were also calculated. Multivariable analysis was performed using ordinal logistic regression after assessment of multicollinearity. Statistical significance was defined as $p<0.05$. Data were analyzed using SPSS version 24 (IBM, Armonk, NY, USA).

Results

Characteristics of study subjects

A total of 42 patients with confirmed endometriosis were enrolled, and their detailed characteristics are presented in **Table 1**. The median age was 36 years (range: 19–51 years). Most subjects were married (90.5%) and had completed secondary education (senior high school, 57.1%). All subjects (100%) reported dysmenorrhea, followed by infertility (52.4%) and dyspareunia (4.8%). Regarding pain severity, 23.8% of subjects had mild pain, 50.0% had moderate pain, and 26.2% had severe pain. Based on rASRM classification, stage IV was the most common (78.6%), followed by stage III (21.4%), whereas no subjects were classified as stage I or II, which may reflect the tertiary referral nature of the study setting. The median COX-2 level was 0.57 ng/mL (range: 0.19–17.64 ng/mL), and the median CA-125 level was 69.18 U/mL (range: 8.40–389.40 U/mL).

Table 1. Characteristics of patients with confirmed endometriosis included in the study (n=42)

Characteristics	Frequency (%)
Age, median (range), years	36 (19–51)
Marital status	
Married	38 (90.5)
Unmarried	4 (9.5)
Clinical symptoms	
Dysmenorrhea	42 (100.0)
Infertility	22 (52.4)
Dyspareunia	2 (4.8)
COX-2, median (range), ng/mL	0.57 (0.19–17.64)
CA-125, median (range), U/mL	69.18 (8.40–389.40)
Pain severity (Numeric Rating Scale)	
Mild (1–3)	10 (23.8)
Moderate (4–6)	21 (50.0)
Severe (7–10)	11 (26.2)
Endometriosis stage (rASRM)	
Stage I	0 (0)
Stage II	0 (0)
Stage III	9 (21.4)
Stage IV	33 (78.6)

rASRM: revised American Society for Reproductive Medicine classification

Correlation between COX-2 and CA-125 with degree of endometriosis and pain severity

Correlation between COX-2 and CA-125 with degree of endometriosis and pain severity are presented in **Table 2**. Spearman correlation analysis demonstrated significant positive correlations between COX-2 and the degree of endometriosis ($r=0.526$; $p<0.001$), as well as between CA-125 and the degree of endometriosis ($r=0.433$; $p=0.004$). In addition, COX-2 showed a strong positive correlation with pain severity ($r=0.769$; $p<0.001$). No significant correlation was observed between CA-125 and pain severity ($r=0.256$; $p=0.102$) (**Table 2**).

Table 2. Spearman correlation between cyclooxygenase-2 (COX-2) and cancer antigen 125 (CA-125) with endometriosis degree and pain severity in patients with confirmed endometriosis

Biomarker	Endometriosis degree		Pain severity	
	r	*p*-value [a]	*r*	*p*-value [a]
COX-2 (ng/mL)	0.526	<0.001*	0.769	<0.001*
CA-125 (U/mL)	0.433	0.004*	0.256	0.102

[a]Spearman's rank correlation test
*Statistically significant ($p<0.05$)

Diagnostic performance of COX-2 and CA-125

The diagnostic performance of COX-2 and CA-125 is presented in **Table 3**; the diagnostic performance of CA-125 on pain severity was not performed. ROC analysis demonstrated that COX-2 had excellent discriminative ability for predicting severe pain, with an AUC of 0.864 (95%CI: 0.742–0.985). The optimal cut-off value was 1.54 ng/mL, yielding a sensitivity of 87.50%, specificity of 88.24%, positive predictive value of 63.64%, negative predictive value of 96.77%, and accuracy of 88.10%. For predicting severe endometriosis (Stage IV), COX-2 also showed excellent discriminative ability, with an AUC of 0.865 (95%CI: 0.747–0.984) and an optimal cut-off value of 0.395 ng/mL, corresponding to a sensitivity of 96.30%, specificity of 53.33%, and accuracy of 80.95%. In comparison, CA-125 showed good discriminative ability for predicting severe endometriosis, with an AUC of 0.805 (95%CI: 0.670–0.940). The optimal cut-off value for CA-125 was 64.90 U/mL, which yielded a sensitivity of 95.65%, specificity of 42.11%, and accuracy of 71.43% (**Table 3**).

Table 3. Diagnostic performance of cyclooxygenase-2 (COX-2) and cancer antigen 125 (CA-125) using receiver operating characteristic (ROC) curve analysis in patients with confirmed endometriosis

Parameter	AUC	95%CI	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
COX-2 vs. severe pain	0.864	0.742–0.985	1.54 ng/mL	87.50	88.24	63.64	96.77
COX-2 vs. severe stage	0.865	0.747–0.984	0.395 ng/mL	96.30	53.33	78.79	88.89
CA-125 vs. severe stage	0.805	0.670–0.940	64.90 U/mL	95.65	42.11	66.67	88.89

AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value

Multivariate analysis showing associations between COX-2 and CA-125 with endometriosis degree and pain severity

Multicollinearity testing confirmed no multicollinearity between COX-2 and CA-125 (tolerance=0.985; VIF=1.016). Adjusted analysis ordinal logistic regression showed COX-2 and CA-125 did not significantly predict endometriosis degree when both were analyzed simultaneously (COX-2: estimate=34.418, $p=0.168$; CA-125: estimate=0.236, $p=0.199$). However, adjusted ordinal logistic regression analysis indicated that both COX-2 and CA-125 were significantly associated with pain severity (**Table 4**). COX-2 showed a significant positive association with pain severity (estimate=1.244; $p=0.018$), indicating that higher COX-2 levels were associated with greater pain severity. Similarly, CA-125 was also significantly associated with pain severity (estimate=0.013; $p=0.016$). The Nagelkerke R^2 value of 0.456 indicated that the model explained 45.6% of the variation in pain severity.

Table 4. Multivariate ordinal logistic regression analysis showing the association of cyclooxygenase-2 (COX-2) and cancer antigen 125 (CA-125) levels with pain severity in

Variable	Estimate	Standard error	Wald	*p*-value
COX-2	1.244	0.527	5.575	0.018*
CA-125	0.013	0.005	5.771	0.016*
Nagelkerke R^2	0.456			

*Statistically significant ($p<0.05$)

Discussion

This study demonstrated that COX-2 and CA-125 have distinct yet complementary roles in endometriosis. COX-2 appeared to be more closely related to pain severity, whereas CA-125 more strongly reflected the anatomical extent of disease. The significant positive correlation between COX-2 and the degree of endometriosis supports the role of COX-2 in disease progression. This finding is biologically plausible because PGE2 has been shown to stimulate aromatase (CYP19A1) expression through the cyclic adenosine monophosphate-protein kinase A pathway, thereby establishing a positive feedback loop between estradiol production and COX-2 activation that may promote lesion proliferation and invasion [5]. In addition, A previous study showed that DNA hypomethylation at the PTGS2 promoter was strongly associated with endometriosis-related pathological processes, suggesting that COX-2 overexpression may also be influenced by epigenetic mechanisms [10].

The strong positive correlation between COX-2 and pain severity represented one of the most clinically relevant findings of this study. The COX-2/PGE2 pathway has been reported to reduce nociceptor thresholds and increase the excitability of sensory nerve fibers through activation of transient receptor potential vanilloid-1 and voltage-gated sodium channel Nav1.9, thereby contributing to peripheral sensitization [5]. A previous preclinical study also demonstrated increased COX-2 expression in the spinal dorsal horn, thalamus, and anterior cingulate cortex in endometriosis, supporting the involvement of central sensitization in pain hypersensitivity [11]. These mechanisms may explain why COX-2 showed a stronger association with pain severity than with disease stage. This interpretation is further supported by evidence indicating that endometriosis-associated pain is influenced not only by lesion burden, but also by inflammation, neuroangiogenesis, peripheral sensitization, and central sensitization [12-14]. A previous study likewise reported that severe pelvic pain was more closely associated with deeply infiltrating lesions at specific anatomical sites than with ovarian endometrioma alone, suggesting that lesion location and neural involvement may contribute more directly to pain generation than rASRM stage alone [15]. In this context, the excellent discriminative ability of COX-2 for severe pain, as shown by an area under the curve of 0.864 with sensitivity of 87.50% and specificity of 88.24% at a cut-off value of 1.54 ng/mL, suggests that COX-2 may have clinical utility for identifying patients at risk of greater symptom burden.

CA-125 also showed a significant positive correlation with the degree of endometriosis, which is consistent with its recognized role as a marker of peritoneal disease burden. Previous studies have shown that CA-125 concentrations are higher in women with ovarian endometrioma, deep infiltrating endometriosis, and more extensive surgical disease, whereas only limited elevation is observed in superficial peritoneal disease [16-18]. This pattern supports the interpretation that CA-125 reflects greater tissue involvement and inflammatory burden in more advanced disease. In the present study, CA-125 showed good discriminative ability for predicting Stage IV endometriosis, with an area under the curve of 0.805 and an optimal cut-off value of 64.90 U/mL. This value was higher than the conventional 35 U/mL threshold, which may indicate that advanced-stage disease is associated with greater peritoneal destruction and a more pronounced inflammatory response. This finding is also consistent with previous evidence showing that CA-125 performs better in moderate-to-severe endometriosis than in minimal disease [19].

In contrast, no significant correlation was observed between CA-125 and pain severity. This finding is consistent with A previous study showing no meaningful association between CA-125 levels and the type or severity of pain in endometriosis [20]. Such a finding is biologically plausible because CA-125 appears to reflect tissue irritation and peritoneal involvement rather than direct activation of nociceptive pathways. Given that pain in endometriosis is multifactorial and may involve peripheral sensitization, central sensitization, neuroinflammation, and psychosocial influences, CA-125 alone may not adequately represent symptom severity. However, its significant contribution to the adjusted model for pain severity suggests that peritoneal inflammation may still contribute indirectly to the overall pain burden.

The adjusted model of COX-2 and CA-125 explained 45.6% of the variation in pain severity, indicating that the two biomarkers may provide complementary information. COX-2 appears to reflect active inflammatory signaling and nociceptive sensitization, whereas CA-125 appears to

capture the extent of peritoneal involvement. This interpretation is in line with previous recommendations advocating the use of multi-biomarker approaches to improve diagnostic and prognostic assessment in endometriosis [21]. At the same time, CA-125 alone remains insufficient as a standalone biomarker because of its limited specificity and lower sensitivity in early-stage disease [22,23]. Therefore, its clinical value may be greater when interpreted together with COX-2 rather than in isolation.

From a clinical perspective, the findings of this study may have therapeutic relevance. The COX-2 cut-off value of 1.54 ng/mL may help identify patients who are more likely to require intensive pain management. This interpretation is supported by previous evidence showing that selective COX-2 inhibitor therapy was associated with significant improvement in pelvic pain and dyspareunia [24,25]. Taken together, the present findings further support the importance of inflammatory pathways in endometriosis-associated pain and suggest that COX-2, particularly when interpreted alongside CA-125, may provide useful information for assessing both symptom severity and disease extent.

This study should be interpreted in light of several limitations. The relatively small sample size may have reduced the statistical precision of the estimates and limited the stability of the multivariable model. In addition, the study was conducted in a tertiary referral center, where more advanced or clinically complex cases are more likely to be encountered. As a result, the study population may not fully represent the broader spectrum of endometriosis, especially milder disease seen in primary or secondary care settings. This pattern may also explain the predominance of severe-stage disease in the present sample and may have influenced the observed diagnostic performance of both COX-2 and CA-125. Additional limitations arise from the biological and clinical complexity of endometriosis. Biomarker levels were measured at a single time point, and potential fluctuations related to menstrual cycle phase, hormonal exposure, or dynamic inflammatory activity could not be assessed. Such variation may have affected the measured concentrations of both COX-2 and CA-125 and may partly account for interindividual differences. Pain severity in endometriosis is also multifactorial and cannot be explained solely by inflammatory biomarkers. Central sensitization, psychological distress, comorbid pain syndromes, lesion location, and individual pain perception may all influence symptom severity, yet these factors were not comprehensively evaluated in the present study. Consequently, the combined model explained only part of the variability in pain severity, indicating that additional biological and clinical determinants remain unaccounted for. These limitations suggest that the present findings should be interpreted with caution and should ideally be confirmed in larger prospective studies involving more diverse patient populations, longitudinal biomarker assessment, and broader characterization of pain-related factors.

Conclusion

Serum COX-2 and CA-125 were both positively correlated with the degree of endometriosis, indicating their relevance as biomarkers of disease severity. COX-2 showed stronger discriminative performance for pain severity, whereas CA-125 more closely reflected anatomical disease severity. In addition, the combined assessment of COX-2 and CA-125 explained a substantial proportion of the variation in pain severity, supporting their complementary clinical value in endometriosis stratification. These findings suggest that serum COX-2 may have potential as a non-invasive biomarker for pain risk stratification and for identifying patients who could benefit from targeted anti-inflammatory management.

Ethics approval

This study was approved by the Health Research Ethics Committee of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia (053/ETIK-RSUDZA/2025). Written informed consent was obtained from all participants prior to enrollment.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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