Short Communication

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Evaluating serum cyclooxygenase-2 and vascular endothelial growth factor as biomarkers for endometriosis severity in reproductive-age women

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Abstract

Endometriosis affects approximately 10–15% of reproductive-age women and up to 70% of those with chronic pelvic pain, with diagnosis typically relying on invasive laparoscopy with histopathological confirmation. Cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF) are central mediators of the inflammatory and angiogenic pathways underpinning endometriosis pathogenesis, making them promising candidates for non-invasive biomarkers. This study aimed to analyze the correlation between serum COX-2 and VEGF concentrations and endometriosis severity to evaluate their potential utility as non-invasive biomarkers. A cross-sectional study was conducted among women with confirmed endometriosis at Dr. Zainoel Abidin General Hospital in Banda Aceh, Indonesia, in 2025. Peripheral blood samples were collected preoperatively, and serum COX-2 and VEGF concentrations were quantified using ELISA. Endometriosis severity was classified according to the American Society for Reproductive Medicine staging system. Correlation analyses were performed to assess associations between biomarker levels and disease stage, and diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis to determine the area under the curve (AUC) values, optimal cut-off points, sensitivity, and specificity. Twenty-eight patients were included, with the mean COX-2 and VEGF levels being 1.16±1.28 ng/mL and 266.50±72.91 pg/mL, respectively. VEGF demonstrated a strong and statistically significant correlation with endometriosis staging (r=0.744, p<0.001), while COX-2 showed a limited correlation that did not reach statistical significance (r=0.367, p=0.055). The ROC analysis further highlighted VEGF's superior diagnostic performance, with an AUC of 0.975 (95%CI: 0.926–1.000, p<0.001) compared with COX-2 (AUC 0.734; 95%CI: 0.518–0.950, p=0.057). The optimal VEGF threshold of 221 pg/mL yielded 90% sensitivity and 100% specificity, whereas the COX-2 threshold of 0.675 ng/mL provided 80% sensitivity and 62.5% specificity. These findings indicate that VEGF is a highly promising non-invasive biomarker for assessing endometriosis severity and may support the development of improved diagnostic approaches for endometriosis management.

Keywords: Endometriosis, COX-2, VEGF, biomarkers, angiogenesis

Introduction

Endometriosis is a complex gynecological condition characterized by the presence of ectopic endometrial tissue outside the uterine cavity. This inflammatory, angiogenic, and invasive

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disorder affects approximately 10–15% of women of reproductive age and up to 70% of those experiencing chronic pelvic pain, representing a major contributor to infertility and diminished quality of life [1,2]. Despite its high prevalence, diagnostic delays of approximately 6–7 years are common due to the absence of accurate and reliable non-invasive diagnostic methods. The current diagnostic gold standard—laparoscopic visualization with histopathological confirmation—remains invasive, costly, and associated with procedure-related risks. These limitations highlight the urgent need for validated serum biomarkers capable of improving both diagnostic accuracy and severity assessment in endometriosis [3,4].

The pathogenesis of endometriosis involves an intricate interplay of inflammatory, immune, and angiogenic mechanisms that collectively facilitate ectopic lesion establishment and progression [5]. Cyclooxygenase-2 (COX-2) is a central enzyme in the inflammatory cascade, catalyzing prostaglandin E2 (PGE2) synthesis, a major mediator of inflammation and pain in endometriosis. Elevated COX-2 expression has been consistently reported in endometriotic tissues, correlating with enhanced disease activity [5,6]. Beyond its role in inflammation, COX-2 contributes to ectopic implantation, lesion growth, angiogenesis, and local immunosuppression, making it a biologically plausible candidate biomarker for disease severity [5,6].

Vascular endothelial growth factor (VEGF), the principal regulator of angiogenesis and lymphangiogenesis, is essential for the vascular support required by developing endometriotic lesions [7,8]. Overexpression of VEGF in endometriotic tissues and peritoneal fluid promotes neovascularization and facilitates the survival of ectopic endometrial cells [8]. Increased VEGF levels have been associated with larger endometrioma size and greater angiogenic activity, suggesting its potential role as a severity indicator [8].

A growing body of evidence suggests a bidirectional regulatory relationship between COX-2 and VEGF mediated through interconnected signaling pathways. COX-2-derived PGE2 upregulates VEGF through cAMP/PKA/CREB activation, whereas VEGF enhances COX-2 expression via the PI3K/Akt/NF-κB pathway [9,10]. This reciprocal regulation may amplify inflammatory and angiogenic pathways, contributing to lesion progression, and thus supports the rationale for evaluating both molecules as prognostic biomarkers [9,10].

The American Society for Reproductive Medicine (ASRM) classification system categorizes endometriosis from stage I (minimal) to stage IV (severe), reflecting disease extent and progression [11]. Higher ASRM stages are typically associated with more intense inflammatory and angiogenic activity. Based on this biological framework, we hypothesized that serum COX-2 and VEGF concentrations positively correlate with endometriosis severity, offering potential as non-invasive markers for disease staging. However, studies exploring this correlation remain limited, particularly within the Indonesian population. This study aimed to analyze the correlation between serum COX-2 and VEGF levels and the severity of endometriosis, as classified by the ASRM system, to evaluate their potential roles as non-invasive biomarkers for disease staging. Establishing reliable serum biomarkers would strengthen early detection algorithms, improve monitoring of disease progression and therapeutic response, and enhance prognostic evaluation in affected patients. Furthermore, elucidating the mechanistic roles of COX-2 and VEGF may facilitate future development of targeted therapeutic strategies with greater specificity and effectiveness.

Methods

Study design and setting

This analytical cross-sectional study investigated the association between circulating COX-2 and VEGF levels and the severity of endometriosis. The study was conducted in the Department of Obstetrics and Gynecology, Dr. Zainoel Abidin General Hospital in Banda Aceh, Indonesia—a tertiary referral center providing advanced gynecologic surgical services. All clinical assessments, surgical staging, and biological sample collection were performed at the hospital. Laboratory analyses of COX-2 and VEGF were conducted at a certified external reference laboratory (Prodia Laboratory).

Patients and characteristics

The source population comprised all women presenting to Dr. Zainoel Abidin General Hospital with clinical suspicion of endometriosis. Consecutive patients scheduled for laparoscopic or open gynecologic surgery were screened for eligibility. Women were included if they met all of the following criteria: (1) suspected endometriosis based on clinical and imaging findings; (2) had not received hormonal therapy; (3) agreed to undergo COX-2 and VEGF testing; (4) underwent laparoscopy or laparotomy; and (5) provided written informed consent. Patients were excluded if (1) histopathological evaluation did not confirm endometriosis or (2) ultrasonography revealed features suggestive of malignancy.

Sample size and sampling method

The sample size was calculated using the Lemeshow formula for proportion estimates, assuming p=0.5, α=0.05, and relative precision (ε) of 0.30. The minimum required sample was 22; after adjusting for a projected drop-out rate of 25%, the final target sample size was 28. A consecutive sampling strategy was used, whereby all eligible patients presenting sequentially during the study period were enrolled until the target sample size was achieved.

Study variables and measurements

The study assessed two independent variables—serum COX-2 concentration and serum VEGF concentration—both quantified using enzyme-linked immunosorbent assay (ELISA). During surgery, 10 mL of peritoneal fluid was aspirated and collected into serum separator tubes, centrifuged within 1–2 hours at 2000×g for 10 minutes, and the resulting supernatant was aliquoted and stored at −80°C before transport to Prodia Laboratory for ELISA-based analysis. Serum COX-2 concentrations were measured using the Human PTGS2/COX-2 ELISA Kit (Elabscience, Houston, USA). The assay has an analytical sensitivity of <0.094 ng/mL and a detection range of 0.156–10 ng/mL. Serum VEGF levels were quantified using the Human VEGF ELISA Kit (Elabscience, Houston, USA) with sensitivity <18.75 pg/mL; detection range 31.25–2000 pg/mL. All ELISA analyses were performed once per sample following the manufacturer's protocol. Calibration curves and internal controls supplied in the Elabscience kits were used to verify assay validity, and measurements were accepted only when standard curve performance met the manufacturer's quality criteria.

Demographic and clinical data—including age, reproductive history, and presenting symptoms—were also systematically collected for all patients. Age was recorded in years and summarized as mean±SD and range. Marital status was categorized as married or unmarried. Clinical symptoms at presentation included the presence or absence of dysmenorrhea and a documented history of infertility. Reproductive characteristics were assessed through parity, classified as nullipara, primipara, or multipara.

The dependent variable was the severity of endometriosis and confirmed intraoperatively during diagnostic and therapeutic laparoscopy using the American Society for Reproductive Medicine (ASRM) Revised Classification of Endometriosis. During the procedure, multiple anatomical and pathological components were systematically assessed and scored according to the ASRM scoring sheet. The evaluation included the location, depth, and size of endometriotic lesions on the peritoneum and ovaries, distinguishing between superficial and deep implants measuring <1 cm, 1–3 cm, or >3 cm. The degree of posterior cul-de-sac obliteration was documented as partial or complete. Adhesions involving the ovaries and fallopian tubes were scored according to their density (filmy vs. dense) and extent of enclosure (<1/3, 1/3–2/3, or >2/3 enclosure of the adnexa). Tubal fimbrial involvement and enclosure were also recorded, applying ASRM adjustments when the fimbrial end was completely occluded. Additional endometriotic lesions and associated pelvic pathology were documented descriptively when present. The total ASRM score was calculated, and disease severity was classified into Stage I (minimal), Stage II (mild), Stage III (moderate), or Stage IV (severe), as defined by established scoring thresholds.

Study procedures

Eligible patients were informed of the study objectives, procedures, and risks, and written informed consent was obtained. Surgical confirmation of endometriosis was performed via laparoscopy or laparotomy. During the procedure, peritoneal fluid sampling was conducted

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before extensive manipulation. All samples were processed according to standardized laboratory procedures to maintain biochemical stability. Clinical staging of endometriosis was performed intraoperatively by the attending gynecologic surgeon according to ASRM criteria. Data collection continued sequentially until the predetermined sample size was met.

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), depending on distribution assessed by normality testing. The relationship between serum COX-2 and VEGF concentrations and endometriosis stage (ordinal scale) was evaluated using the Spearman rank correlation test.

Receiver operating characteristic (ROC) curve analysis was performed to determine the discriminative accuracy of each biomarker for identifying severe endometriosis (Stage III–IV) and to estimate optimal cut-off values, sensitivity, specificity, and area under the curve (AUC). A two-tailed $p<0.05$ was considered statistically significant.

Results

Participant characteristics

A total of 28 patients with surgically confirmed endometriosis were included in the analysis. The demographic data and clinical characteristics of the patients are presented in **Table 1**. The mean age of participants was 38.54±8.09 years (range: 23–51). The majority were married (96.4%), and most reported dysmenorrhea (85.7%) and infertility (64.3%) as primary clinical manifestations. With respect to reproductive history, 67.9% of patients were nulliparous, followed by 25.0% multiparous and 7.1% primiparous individuals. Based on the ASRM classification, severe endometriosis (Stages III–IV) predominated (71.4%), while 28.6% presented with mild disease (Stages I–II) (**Table 1**).

Table 1. Characteristics of patients with confirmed endometriosis included in the study (n=28)

Characteristic	Frequency (percentage)
Age (years), mean±SD	38.54±8.09
Age range (years)	23–51
Marital status	
Married	27 (96.4)
Unmarried	1 (3.6)
Clinical symptoms	
Dysmenorrhea	24 (85.7)
Infertility	18 (64.3)
Parity	
Nullipara	19 (67.9)
Primipara	2 (7.1)
Multipara	7 (25.0)
Endometriosis stage (ASRM classification)	
Mild (I-II)	8 (28.6)
Severe (III-IV)	20 (71.4)

Serum COX-2 and VEGF concentrations

Serum biomarker quantification demonstrated considerable inter-individual variability. The COX-2 levels ranged from 0.23 to 7.23 ng/mL, with a mean concentration of 1.16±1.28 ng/mL (**Table 2**). The VEGF levels ranged from 163 to 394 pg/mL, with a mean of 266.50±72.91 pg/mL (**Table 2**). These distributions indicate higher VEGF levels overall and wider variability in COX-2 expression.

Table 2. Levels of COX-2 and VEGF among patients with confirmed endometriosis included in the study (n=28)

Biomarker	Minimum	Maximum	Mean	Standard deviation
COX-2 (ng/mL)	0.23	7.23	1.16	1.28
VEGF (pg/mL)	163	394	266.50	72.91

Correlation between serum COX-2 and VEGF levels with endometriosis severity

Spearman correlation analysis showed a moderate positive correlation between serum COX-2 concentration and endometriosis staging (r=0.367); however, this correlation did not reach statistical significance (p=0.055) (**Table 3**).

VEGF demonstrated a strong and statistically significant correlation with disease severity (r=0.744, p<0.001) (**Table 3**). Patients with elevated VEGF levels had more severe endometriosis compared with those with mild disease. This finding reflects VEGF's mechanistic role as the principal angiogenic mediator supporting neovascularization and lesion progression. The magnitude of correlation indicates that circulating VEGF may reliably reflect underlying angiogenic activity and lesion burden.

Table 3. Correlation of serum COX-2 and VEGF levels with endometriosis severity

Biomarker	Correlation coefficient	p-value	Interpretation
COX-2	0.367	0.055*	No significant correlation
VEGF	0.744	0.000*	Significant correlation

*Spearman correlation test

Predictive performance of COX-2 and VEGF for severe endometriosis

The ROC analysis was performed to evaluate the diagnostic performance of both biomarkers in predicting severe endometriosis (Stages III–IV). The VEGF had excellent discriminative ability, with an AUC of 0.975 (95%CI: 0.926–1.000, p<0.001) (**Table 4** and **Figure 1**), indicating near-perfect classification. The optimal VEGF cut-off value was 221 pg/mL, yielding a sensitivity of 90.0% and specificity of 100%. In contrast, COX-2 demonstrated limited discriminative capacity, with an AUC of 0.734 (95%CI: 0.518–0.950, p=0.057) (**Table 4** and **Figure 1**). The optimal COX-2 threshold of 0.675 ng/mL produced a sensitivity of 80.0% and specificity of 62.5%.

Table 4. Receiver operating characteristic (ROC) curve analysis of the levels of cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF) for predicting severe endometriosis (stages III-IV)

Parameter	AUC (95%CI)	p-value	Cut-off point	Sensitivity (%)	Specificity (%)
COX-2 (ng/mL)	0.734 (0.518–0.950)	0.057	0.675	80.0	62.5
VEGF (pg/mL)	0.975 (0.926–1.000)	0.000	221	90.0	100

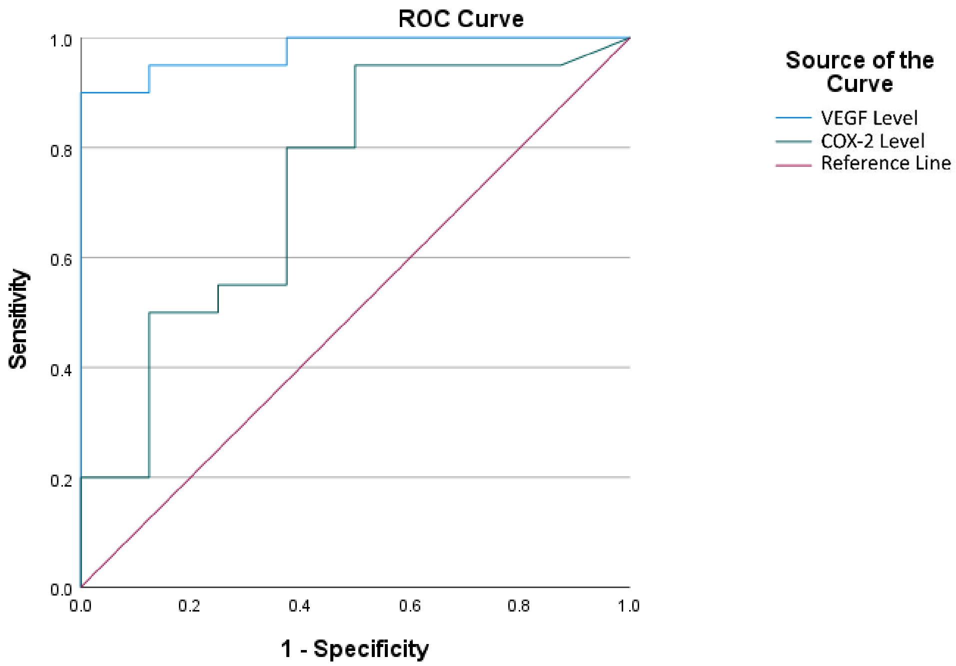

Figure 1. Receiver operating characteristic (ROC) curve of the levels of cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF) for predicting severe endometriosis.

Discussion

This study examined the association between serum COX-2 and VEGF concentrations with endometriosis severity. A strong and statistically significant correlation was observed between VEGF levels and ASRM staging, whereas COX-2 demonstrated a limited correlation.

The demographic characteristics of participants, including the mean age of 38.54±8.09 years, were consistent with typical endometriosis profiles described in previous studies, which generally report onset during reproductive age and rare occurrence before menarche or after menopause [12]. The predominance of dysmenorrhea and infertility among participants aligns with previous findings showing these as the most frequent manifestations of endometriosis [13]. The staging distribution in this investigation, with a predominance of severe disease (71.4%), contrasts with earlier reports that documented a higher proportion of early-stage presentations [14]. This discrepancy may reflect delayed diagnosis and the referral nature of tertiary care settings, where patients commonly present with more advanced disease. The high proportion of nulliparous participants further supports existing evidence regarding the link between endometriosis and subfertility [15].

Although the correlation between COX-2 levels and endometriosis severity did not reach significance, the near-threshold *p*-value (p=0.055) suggests that a meaningful association may become evident with a larger sample. Previous studies have reported increased *COX-2* expression in endometriotic lesions and have shown that *inflammatory cytokines drive COX-2 upregulation*, increased prostaglandin E2 synthesis, enhanced aromatase activity, and local estrogen production—mechanisms that intensify in more advanced stages of the disease [16–18]. COX-2 also contributes indirectly to angiogenesis through stimulation of VEGF expression, further linking it to disease progression [18].

VEGF demonstrated a markedly stronger association with disease severity (r=0.744, p<0.001). This is biologically plausible given VEGF's central role in angiogenesis. Studies have consistently shown that VEGF levels rise in response to hypoxia, inflammatory cytokines, and local estrogen production—factors that are amplified in advanced endometriotic lesions [19,20]. The ROC analysis confirmed VEGF's excellent discriminative capacity, showing an AUC of 0.975 and a threshold of 221 pg/mL with high sensitivity and specificity. Patients with VEGF ≥221 pg/mL had a substantially increased risk of severe endometriosis, supporting its utility as a potential severity biomarker. A previous study similarly demonstrated that elevated VEGF levels were associated with more extensive lesions and higher recurrence risk [21].

Across all analytical parameters, VEGF outperformed COX-2. Its superior AUC, sensitivity, and specificity suggest that angiogenesis may reflect disease severity more directly than inflammation alone. While COX-2 remains mechanistically relevant to endometriosis pathophysiology, its expression is influenced by multiple pathways and may be less specific to disease staging. Nevertheless, given their complementary biological roles, combined assessment of COX-2 and VEGF may offer a more comprehensive approach to evaluating disease severity. A biomarker panel strategy has been proposed in previous studies and could enhance diagnostic and prognostic accuracy [22].

These findings have several clinical implications. Although laparoscopy remains the diagnostic gold standard, its invasiveness and cost represent substantial limitations. Serum biomarkers such as VEGF may provide a non-invasive triage tool for identifying patients at high risk of severe disease before surgical confirmation [22]. Elevated VEGF may also identify individuals at greater risk of recurrence, supporting more individualized follow-up strategies and therapeutic planning [2]. Furthermore, understanding the biological roles of VEGF highlights opportunities for targeted medical therapies. Selective anti-angiogenic agents have shown promising results, underscoring the potential for integrating biomarker-guided treatment approaches [23]. Finally, VEGF may serve as a marker of treatment response and early recurrence, with reductions following therapy reflecting favorable outcomes and subsequent elevations indicating possible relapse [24].

The sample size was relatively small, which may have limited the statistical power to detect significant associations, particularly for COX-2. The cross-sectional design restricts causal inference and does not allow assessment of biomarker fluctuations over time or in response to treatment. Biomarker levels were measured only once, and serial measurements might provide more robust insight into temporal dynamics. As this study was conducted at a tertiary referral center where patients typically present with advanced disease, the generalizability of findings to earlier-stage populations may be limited. The absence of additional inflammatory or angiogenic markers restricted broader comparative analysis. Potential confounders—such as menstrual cycle phase, hormonal fluctuations, and body mass index (BMI)—were not controlled for and may influence serum COX-2 and VEGF concentrations, warranting consideration in future studies.

Conclusion

This study demonstrates a significant correlation between serum VEGF concentrations and endometriosis severity. Overall, VEGF demonstrated superior predictive performance compared to COX-2, as reflected by its higher AUC, sensitivity, and specificity. These findings support the potential utility of VEGF as a non-invasive biomarker for assessing endometriosis severity and highlight opportunities for biomarker-guided diagnostic and therapeutic strategies. Future research should incorporate larger sample sizes, inclusion of control groups, longitudinal follow-up, and expanded biomarker panels to strengthen clinical applicability and validate these results.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and adhered to national ethical standards for human biomedical research. Ethical approval was obtained from the Institutional Ethical Committee, Dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia (No. 075/ETIK-RSUDZA/2025) prior to study initiation. All participants were fully informed about the study objectives, procedures, risks, and confidentiality safeguards, and provided written informed consent before enrollment. Surgical tissue samples and peritoneal fluid were collected only after consent was obtained, and all data were anonymized to ensure participant privacy and data protection.

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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

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