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**Short Communication**

# Associations of VEGF and CA125 with disease stage and pain among women with endometriosis: A cross-sectional study in Indonesia

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## Abstract

Endometriosis is a chronic gynecological disease characterized by the presence of endometrial tissue outside the uterine cavity, affecting approximately 10% of women of reproductive age. Vascular endothelial growth factor (VEGF) and cancer antigen 125 (CA125) have been proposed as potential biomarkers in endometriosis; however, evidence regarding their association with disease stage and pain severity remains limited, particularly in the Indonesian population. The aim of this study was to evaluate the relationship between peritoneal fluid VEGF and serum CA125 levels with endometriosis stage and pain severity. A cross-sectional study was conducted involving patients with surgically and histopathologically confirmed endometriosis who underwent laparoscopy or laparotomy at Dr. Zainoel Abidin Hospital, Banda Aceh, between February and July 2025. Peritoneal fluid VEGF and serum CA125 levels were measured using enzyme-linked immunosorbent assay and chemiluminescence immunoassay, respectively. Endometriosis stage was classified according to the revised American Society for Reproductive Medicine (rASRM) criteria, and pain severity was assessed using the Numeric Rating Scale. Statistical analyses included Spearman's correlation and receiver operating characteristic (ROC) curve analysis. Our data suggested no significant correlation between VEGF levels and endometriosis stage ($r$=0.042; $p$=0.813). Peritoneal fluid VEGF levels showed a moderate positive correlation with pain severity ($r$=0.505; $p$<0.05), and ROC analysis identified an optimal cut-off value of 39.45 pg/mL, with a sensitivity of 73.68% and specificity of 73.33% for distinguishing severe pain from mild-to-moderate pain. Serum CA125 levels demonstrated a significant positive correlation with endometriosis stage ($r$=0.422; $p$=0.013), and ROC analysis yielded an optimal cut-off value of 32.45 U/mL, with a sensitivity of 86.95% and a specificity of 63.64% for distinguishing stage IV endometriosis from lower stages. No significant correlation was observed between CA125 levels and pain severity ($r$=0.186; $p$=0.292). This study represents the first report from Indonesia to simultaneously evaluate peritoneal fluid VEGF and serum CA125 in relation to endometriosis stage and pain severity. This study highlights that CA125 is primarily associated with endometriosis stage, whereas VEGF is more closely related to pain severity, supporting their complementary roles in endometriosis assessment.

**Keywords**: Endometriosis, VEGF, CA125, endometriosis stage, pain severity

## Introduction

Endometriosis is a complex benign gynecological condition characterized by the presence of endometrial-like glandular and stromal tissue outside the uterus [1]. The pathogenesis of



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endometriosis is not fully understood, and the treatment options include hormonal therapy and surgical procedures aimed at relieving symptoms, suppressing disease progression, and improving fertility [2]. Inflammation plays an important role in the pathogenesis of endometriosis [1,2]. Endometriosis affects approximately 10% of women of reproductive age, with prevalence increasing to 20–50% among women with infertility [3]. The condition is found in up to 80% of women experiencing infertility accompanied by pelvic pain, dyspareunia, or dysmenorrhea [3,4]. In Indonesia, endometriosis affects 10.2–23.8% of women of childbearing age, while in Banda Aceh, endometriosis accounts for approximately 10–25% of gynecological consultations, with infertility reported in 30–50% of affected patients [5,6].

Laparoscopy remains the gold standard for diagnosing endometriosis. However, laparoscopy is an invasive surgical procedure that carries risks of morbidity and mortality for patients. Among various non-invasive methods using biomarkers, cancer antigen 125 (CA125), an antigen expressed on cell surfaces derived from coelomic epithelium, has emerged as the most representative glycoprotein biomarker for endometriosis [7,8]. Nevertheless, its sensitivity and specificity for endometriosis vary when combined with other biomarkers [7,8]. Its diagnostic value as a single biomarker remains limited. Generally, CA125 demonstrates a specificity of 90% but a sensitivity of no more than 52% [9-11]. Elevated preoperative CA125 levels are frequently associated with benign gynecological conditions, particularly ovarian endometriomas and deep infiltrating endometriosis. CA125 levels are typically elevated in endometriosis, especially in moderate to severe stages of the disease [9-11].

In addition, vascular endothelial growth factor (VEGF) has been explored as a promising biomarker for diagnosing endometriosis. Evidence suggests that measuring VEGF levels, in combination with other biomarkers such as CA125, may enhance the diagnostic accuracy of non-invasive approaches [12,13]. Studies have reported significant differences in VEGF levels between women with and without endometriosis, indicating its potential utility in clinical practice [12,13]. However, the role of VEGF in endometriosis remains contentious, with conflicting results reported in the literature.

Although these biomarkers have been extensively studied in isolation, their combined association with disease severity and pain intensity in endometriosis cases remains poorly characterized, especially in Indonesian populations. The aim of this study is therefore to evaluate the role of peritoneal fluid VEGF and serum CA125 levels in relation to endometriosis stage and pain severity among endometriosis patients undergoing surgical intervention.

# Methods

## Study design and setting

A cross-sectional study was conducted to investigate the correlation between biomarker levels and disease severity and pain intensity among endometriosis patients. The study was conducted at Dr. Zainoel Abidin General Hospital, a provincial reference hospital in Banda Aceh, Indonesia, between February and July 2025.

## Participants

The study population consisted of women with clinically suspected endometriosis scheduled to undergo surgical management through laparoscopy or laparotomy. The inclusion criteria of the patients were: (1) clinically suspected endometriosis and planned to have surgical intervention; (2) had preoperative transvaginal ultrasound results; (3) no previous laparotomy or laparoscopy history; and (4) no hormonal therapy received in the last three months. Those who had ultrasonographic features suggesting malignancy, had concurrent chronic inflammatory conditions, and were pregnant were excluded from the study. Drop-out criteria were established to exclude patients if their histopathological findings indicated ovarian malignancy or pathology other than endometriotic cysts.

## Sample size and sampling method

The sample size was determined using the formula for a correlation study: $n=((Z\alpha+Z\beta)^2 (1-r^2))/r^2$, where $Z\alpha=1.96$ (95% confidence level), $Z\beta=1.28$ (90% power), and $r=0.5$ (moderate

correlation cut-off). The calculation indicated a minimum of 31 participants required for a minimal sample size, which was adjusted to 34 to account for potential drop-outs. Purposive sampling was employed to select participants based on established inclusion, exclusion, and dropout criteria.

## Study procedures and laboratory analysis

Eligible patients who met the inclusion criteria were consecutively recruited, and written informed consent was obtained prior to study participation. Preoperatively, venous blood samples (5 mL) were collected aseptically from the cubital vein using serum separator tubes to measure CA125 levels. Samples were allowed to clot at room temperature for 30 minutes, then centrifuged at 3,000 rpm for 15 minutes. Serum aliquots were stored at −80°C until analysis. Serum CA125 levels were quantified using a chemiluminescence immunoassay (CLIA) using Cobas Elecsys CA 125 II (Roche Diagnostics GmbH, Mannheim, Germany). Pain severity was also assessed preoperatively using the Numeric Rating Scale (NRS), where patients rated their pain intensity on a scale from 0 (no pain) to 10 (worst pain imaginable).

At the initiation of surgery, to measure VEGF levels, the peritoneal fluid samples (5–10 mL) were aspirated aseptically from the pouch of Douglas immediately after abdominal entry and before any intraperitoneal manipulation. Samples were centrifuged at 2,500 rpm for 10 minutes to remove cellular debris, and the supernatant was aliquoted and stored at −80°C for subsequent analysis. Peritoneal fluid VEGF levels were measured using a commercially available ELISA kit (Quantikine, R&D Systems Inc., Minneapolis, USA). All laboratory analyses were performed at Prodia Laboratory, Indonesia, in accordance with the manufacturers' protocols.

During surgery, endometriosis diagnosis and staging were established intraoperatively using the revised American Society for Reproductive Medicine (rASRM) classification system to ensure consistency and minimize inter-observer variability. All clinical, laboratory, and surgical data were recorded using standardized data collection forms and anonymized prior to statistical analysis to maintain participant confidentiality.

## Study variables

The primary independent variables in this study were serum CA125 level and peritoneal fluid VEGF level measured using chemiluminescence immunoassay (CLIA) (Elecys CA 125 II, Cobas, Roche Diagnostics GmbH, Mannheim, Germany) and enzyme-linked immunosorbent assay (ELISA) Quantikine ELISA Human VEGF Immunoassay (R&D Systems, Minneapolis, USA), respectively. The dependent variables in this study were endometriosis severity and pain severity. Endometriosis severity was defined intraoperatively according to revised American Society for Reproductive Medicine (rASRM) score classification system. It evaluates the location, size, and depth of endometriotic lesions, as well as the extent and type of pelvic adhesions involving the ovaries and fallopian tubes. Each lesion and adhesion is assigned a weighted score, and the total score determines disease stage: stage I (minimal, 1–5 points), stage II (mild, 6–15 points), stage III (moderate, 16–40 points), and stage IV (severe, >40 points). Pain severity was assessed using the Numeric Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain). For analytical purposes, pain was categorized as mild (1–3), moderate (4–6), or severe (7–10).

## Statistical analysis

Statistical analysis was conducted using SPSS version 24.0 software (IBM, New York, USA). The normality of variables was assessed using the Shapiro-Wilk test. The strength and direction of associations between biomarker concentrations (CA125 and VEGF) and clinical characteristics (endometriosis stage and pain severity) were assessed using Spearman's rank correlation coefficient, as the data were nonparametric. The discriminative ability of biomarkers was assessed using receiver operating characteristic (ROC) curve analysis, with diagnostic thresholds established using the Youden Index to maximize sensitivity and specificity. Statistical significance was set at $p$=0.05 for all analyses.

# Results

## Demographic and clinical characteristics

A total of 34 women with histopathologically confirmed endometriosis were enrolled, and their demographic and clinical characteristics are presented in **Table 1**. The median age of patients was 37 years (range: 19–51 years), and the majority were married (88.2%). Regarding educational attainment, two patients (5.9%) had completed elementary school, two (5.9%) had completed junior high school, 19 (55.9%) had completed senior high school, five (14.7%) held a diploma, and six (17.6%) had a bachelor's degree. All patients reported dysmenorrhea (100%), making it the most prevalent symptom, followed by infertility in 47.1% and dyspareunia in 17.6% of cases (**Table 1**). Pain intensity associated with dysmenorrhea and dyspareunia was assessed using the Numeric Rating Scale (NRS) and classified as mild in 2.9% of patients, moderate in 44.1%, and severe in 52.9%. According to surgical staging, advanced disease predominated, with stage IV endometriosis observed in 70.6% of patients, followed by stage III in 20.6% and stage II in 8.8%. No cases of stage I endometriosis were identified in this cohort (**Table 1**).

Table 1. Demographic and clinical characteristics of women with histopathologically confirmed endometriosis included in this study (n=34)

| Characteristics | Frequency (percentage) |
|---|---|
| Age (year), median (range) | 37 (19–51) |
| Marriage | |
| Married | 30 (88.2) |
| Not married | 4 (11.8) |
| Clinical features | |
| Dysmenorrhea | 34 (100) |
| Dyspareunia | 6 (17.6) |
| Infertility | 16 (47.1) |
| Pain severity | |
| Mild | 1 (2.9) |
| Moderate | 15 (44.1) |
| Severe | 18 (52.9) |
| Endometriosis stage (based on revised American Society for Reproductive Medicine (rASRM) classification) | |
| I | 0 (0.0) |
| II | 3 (8.8) |
| III | 7 (20.6) |
| IV | 24 (70.6) |

## Biomarker levels and correlations with endometriosis stage and pain severity

Correlation analysis in 34 patients revealed distinct patterns of association between biomarker levels and clinical manifestations of endometriosis, as presented in **Table 2**. Peritoneal fluid VEGF levels showed no significant correlation with endometriosis stage ($r$=0.042; $p$=0.813). In contrast, VEGF levels showed a moderate positive correlation with pain severity ($r$=0.505; $p$=0.002), indicating that higher VEGF concentrations were associated with greater pain intensity in patients with endometriosis (**Table 2**).

Table 2. Correlation between biomarker concentrations of vascular endothelial growth factor (VEGF) and cancer antigen 125 (CA125) with endometriosis stage and pain severity (n=34)

| Biomarker | Endometriosis stage | | Pain severity | |
|---|---|---|---|---|
| | Correlation coefficient | $p$-value | Correlation coefficient | $p$-value |
| VEGF | 0.042 | 0.813 | 0.505 | 0.002* |
| CA125 | 0.422 | 0.013* | 0.186 | 0. 292 |

*Statistically significant at $p<0.05$

Serum CA125 levels demonstrated a different correlation profile (**Table 2**). CA125 showed a moderate positive correlation with endometriosis stage ($r$=0.422; $p$=0.013), suggesting an association between elevated CA125 levels and more advanced disease. However, no significant correlation was observed between CA125 levels and pain severity ($r$=0.186; $p$=0.292), indicating a weak and statistically non-significant relationship (**Table 2**). Overall, these findings suggest

distinct clinical implications for the two biomarkers: VEGF appears more closely associated with pain-related symptomatology, whereas CA125 is more strongly correlated with disease stage and the anatomical severity of endometriosis.

## Diagnostic performance of peritoneal fluid VEGF for predicting severe pain

To evaluate the diagnostic performance of peritoneal fluid VEGF in predicting severe pain, the ROC curve analysis was conducted (**Figure 1A**). This analysis assessed the ability of VEGF levels to discriminate between endometriosis patients with mild-to-moderate pain and those with severe pain. The ROC analysis yielded an area under the curve (AUC) of 0.792 (SE: 0.076; 95%CI: 0.642–0.941; $p$=0.004), indicating good discriminative accuracy.

At the identified cut-off, the predictive performance of peritoneal fluid VEGF showed a positive predictive value of 77.78%, indicating that most patients with VEGF levels above the threshold had severe pain. The negative predictive value was 68.75%, reflecting that a substantial proportion of patients with VEGF levels below the cut-off experienced mild-to-moderate pain. Overall, peritoneal fluid VEGF at a threshold of 39.45 pg/mL achieved a diagnostic accuracy of 73.53%.

The optimal cut-off value for peritoneal fluid VEGF was determined using the Youden Index (**Table 3**). A threshold of 39.45 pg/mL provided the best balance between sensitivity and specificity for identifying severe pain. At this cut-off, VEGF demonstrated a sensitivity of 73.68% and a specificity of 73.33%, reflecting a balanced ability to correctly identify patients with severe pain and those with mild-to-moderate pain (**Table 3**).

Table 3. Optimal cut-off value of vascular endothelial growth factor (VEGF) in predicting severe pain among women with confirmed endometriosis

| Biomarker | Youden index cut-off | Sensitivity | Specificity | Negative predictive value | Positive predictive value | Accuracy |
|---|---|---|---|---|---|---|
| VEGF (pg/mL) | 39.45 | 73.68 | 73.33 | 77.78 | 68.75 | 73.53 |

## Diagnostic performance of serum CA125 for predicting severe endometriosis

To evaluate the diagnostic performance of serum CA125 in predicting severe endometriosis, ROC curve analysis was performed (**Figure 1B**). This analysis assessed the ability of CA125 levels to discriminate patients with stage I–III endometriosis (mild to moderate) from those with stage IV disease. The ROC analysis yielded an AUC of 0.752 (95%CI: 0.564–0.940; $p$=0.022), indicating statistically significant discriminative ability.

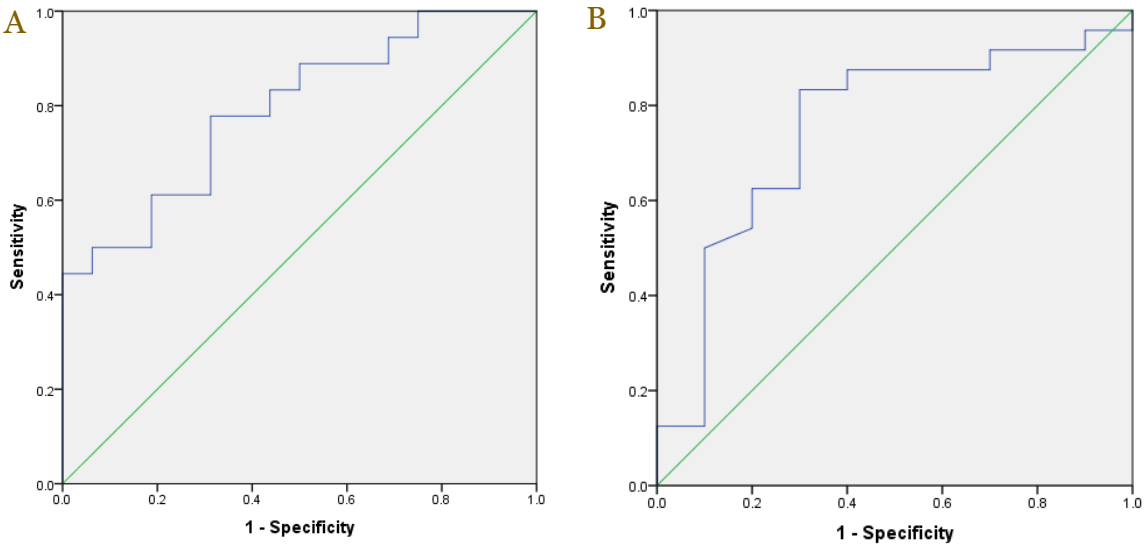


Figure 1. Diagnostic performance of vascular endothelial growth factor (VEGF) and cancer antigen 125 (CA125) biomarker concentrations in predicting severe pain and disease severity among women with histopathologically confirmed endometriosis. (A) The receiver operating characteristic (ROC) curve of VEGF predicts the severity of pain in endometriosis. (B) ROC curve of CA125 in predicting disease severity of endometriosis.

The optimal cut-off value for serum CA125 was determined using the Youden Index and is presented in **Table 4**. A threshold of 32.45 U/mL provided the best balance between sensitivity and specificity for identifying stage IV endometriosis. At this cut-off, CA125 demonstrated a sensitivity of 86.95% and a specificity of 63.64% (**Table 4**).

At the identified cut-off, serum CA125 showed a positive predictive value of 83.3%, indicating that most patients with CA125 levels above the threshold had stage IV endometriosis. The negative predictive value was 70%, reflecting that a substantial proportion of patients with CA125 levels below the cut-off were classified as having non-severe disease. Overall, CA125 at a threshold of 32.45 U/mL achieved a diagnostic accuracy of 79.41% (**Table 4**).

Table 4. Optimal cut-off value of cancer antigen 125 (CA125) in predicting severe endometriosis among women with confirmed endometriosis

| Biomarker | Youden index cut-off | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Accuracy |
|---|---|---|---|---|---|---|
| CA125 (U/mL) | 32.45 | 86.95 | 63.64 | 83.3 | 70 | 79.41 |

## Discussion

This study aimed to evaluate the association of peritoneal fluid VEGF and serum CA125 levels with endometriosis stage and pain severity among surgically confirmed endometriosis patients. The main findings demonstrate that VEGF is more closely associated with pain severity, whereas CA125 correlates primarily with disease stage, indicating complementary roles of these biomarkers in endometriosis assessment. The demographic and clinical characteristics of the study population, including age distribution, predominance of reproductive-age patients, high prevalence of dysmenorrhea, and substantial proportion of infertility, are broadly comparable with findings reported in previous studies and international guidelines [7,14-17]. In addition, the predominance of advanced-stage disease observed in this cohort is consistent with reports from tertiary referral and infertility-centered populations, where patients with moderate-to-severe endometriosis are more frequently represented due to greater symptom burden and surgical indication [18,19]. Collectively, these similarities indicate that the study population is representative of clinically managed endometriosis cases, providing an appropriate context for interpretation of the subsequent biomarker analyses.

This study found no significant association between peritoneal fluid VEGF levels and endometriosis severity, indicating that VEGF elevation does not consistently reflect disease stage and is therefore not a reliable marker for staging in this population. This finding is consistent with a previous study reporting that peritoneal VEGF levels do not increase in parallel with advancing disease severity [20]. These observations suggest that VEGF expression may be influenced more strongly by biological variability and host-related factors than by the extent of anatomical disease. The lack of correlation between VEGF and disease stage may reflect the complex interplay between local inflammatory responses, angiogenic signaling, and individual genetic susceptibility, which collectively modulate VEGF production independently of lesion burden or surgical stage.

A positive correlation was observed between peritoneal fluid VEGF levels and pain severity in endometriosis ($r$=0.505; $p$=0.002), supporting the role of VEGF in pain pathogenesis through angiogenic and neuroinflammatory mechanisms. An AUC value of 0.792 falls within the good diagnostic accuracy category according to standard ROC interpretation criteria, in which values between 0.7 and 0.9 indicate acceptable to excellent discriminative performance. A previous study demonstrated that enhanced angiogenesis contributes to endometrial lesion formation and progression, with elevated levels of angiogenic factors, including VEGF and TNFα, detected in the peritoneal fluid of patients with endometriosis [21]. Neuroangiogenesis is regulated by estrogen and immune-mediated mechanisms, particularly involving macrophages, which serve as important sources of VEGF and nerve growth factor, both of which are elevated in endometriosis and may explain the direct association between increased VEGF levels and pain intensity through concurrent stimulation of vascular and neural growth [22]. Another study reported that VEGF, a highly responsive angiogenic factor modulated by activin A and IL-1β, shows increased mRNA expression in ovarian endometriotic lesions under hypoxic conditions characterized by elevated

HIF-1α levels [23]. These findings suggest that peritoneal fluid VEGF has substantial discriminative capacity for differentiating pain severity in endometriosis.

This study also demonstrated a moderate positive correlation between serum CA125 levels and endometriosis severity ($r$=0.422; $p$=0.013), indicating that elevated CA125 levels are associated with more advanced disease stages. An AUC value of 0.752 falls within the fair-to-good diagnostic accuracy category based on standard ROC curve interpretation, in which values between 0.7 and 0.8 generally indicate acceptable diagnostic performance for clinical application. This finding is consistent with the pathophysiology of endometriosis, in which increased inflammatory activity and ectopic endometrial tissue proliferation promote the release of antigens into the circulation, resulting in elevated CA125 levels.

A previous study reported significant correlations between endometriosis stage, lesion size, adhesion scores, and preoperative plasma CA125 concentrations [11]. A recent study from Indonesia has similarly confirmed the predictive value of CA125 for moderate-to-severe endometriosis staging [24]. Another study also demonstrated a close association between CA125 levels and disease severity in laparoscopically confirmed cases, with progressive increases observed across advancing stages, supporting its role as an adjunctive biochemical marker in preoperative evaluation [25]. These findings underscore the clinical utility of CA125 as a practical biomarker for endometriosis staging stratification in clinical settings.

This study found no statistically significant association between serum CA125 levels and pain severity in patients with endometriosis ($r$=0.186; $p$=0.292). Although a weak positive trend was observed, the strength of the correlation was insufficient to indicate meaningful clinical relevance, suggesting that CA125, despite its widespread use in diagnosing and monitoring endometriosis, does not reliably reflect pain severity. A previous study similarly demonstrated that among patients reporting dysmenorrhea, CA125 was unable to discriminate endometriosis cases from controls using a 35 U/mL cut-off, with limited diagnostic performance [26]. Consistent with these findings, another study reported that although CA125 is associated with disease stage, it shows no significant correlation with pain intensity [24].

Several limitations of this study should be acknowledged. First, the relatively small sample size and single-center design may limit the generalizability of the findings to broader endometriosis populations, particularly those managed in primary or secondary care settings. Second, the cross-sectional design precludes causal inference regarding the relationships among biomarker levels, disease stage, and pain severity, and longitudinal changes in VEGF and CA125 in relation to symptom progression could not be assessed. Third, peritoneal fluid VEGF was measured at a single intraoperative time point, which may not fully capture temporal or cyclical variations influenced by menstrual phase, hormonal milieu, or acute inflammatory activity. In addition, pain severity was assessed using a subjective scale, which, although widely validated, may be influenced by individual pain perception and psychosocial factors. Finally, other potentially relevant inflammatory and neuroangiogenic mediators were not evaluated, limiting a more comprehensive characterization of the biological pathways underlying pain and disease progression. Despite these limitations, this study provided novel evidence from an Indonesian cohort supporting the complementary roles of VEGF and CA125 in pain and disease severity stratification in endometriosis.

## Conclusion

This study assessed the association between peritoneal fluid VEGF and serum CA125 levels with endometriosis stage and pain severity, and the findings demonstrated that VEGF and CA125 serve complementary yet distinct roles in endometriosis assessment. Peritoneal fluid VEGF was more closely associated with pain severity, reflecting underlying neuroinflammatory and angiogenic processes, whereas serum CA125 correlated primarily with disease stage and anatomical progression.

### Ethics approval

The study protocol was approved by the Ethics Committee of Dr. Zainoel Abidin Hospital, Banda Aceh, Aceh, Indonesia (341/ETIK-RSUDZA/2024). Written informed consent was obtained from all patients prior to participation.

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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**

This study used artificial intelligence (AI) tools in manuscript writing support. AI-based language models, Quillbot and Claude, were employed to technical writing assistance. We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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