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CA 125 Levels Above 100: A Marker for Deep Infiltrating Endometriosis

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Author`s Contribution

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ABSTRACT

Objectives: To evaluate serum CA-125 levels above 100 U/mL as a marker for DIE in patients undergoing laparotomy at Bach Christian Hospital, Abbottabad.

Methodology: This cross-sectional study was conducted from January 2023 to August 2024 on women admitted for laparotomy. Preoperative serum CA-125 was measured using electrochemiluminescence immunoassay. Intraoperative findings were documented, and disease staging was performed according to the revised American Society for Reproductive Medicine (rASRM) criteria. Patients were categorized into early-stage (I–II) and advanced-stage (III–IV) disease. Statistical analysis included chi-square test, independent t-test, and ROC curve analysis to determine the diagnostic accuracy of CA-125 ≥100 U/mL in predicting DIE.

Results: There were 160 patients in total with mean age of 31.4 ± 6.2 years. Infertility was the most common presenting condition (65%), followed by dysmenorrhea (42%), and chronic pelvic discomfort (48%). Patients with advanced-stage cancer had considerably higher mean CA-125 values (124.6 ± 28.4 U/mL) than those with early-stage disease (58.2 ± 21.7 U/mL, $p < 0.001$). Among patients with DIE, 72% had serum CA-125 levels above 100 U/mL, compared to 12% in those without DIE ($p < 0.001$). ROC analysis demonstrated an area under the curve (AUC) of 0.82, with CA-125 ≥100 U/mL yielding 76% sensitivity and 89% specificity for detecting DIE.

Conclusion: Serum CA-125 levels above 100 U/mL are strongly associated with deep infiltrating and advanced-stage endometriosis, providing high specificity and predictive value. It may serve as a cost-effective adjunct in preoperative evaluation, surgical planning, and patient counseling, particularly in resource-constrained healthcare settings.

Keywords: CA-125, endometriosis, deep infiltrating endometriosis, biomarker, laparotomy, Abbottabad.

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Introduction

About 10% of women of reproductive age have endometriosis, a chronic inflammatory, estrogen-dependent disease that commonly results in pelvic discomfort, dyspareunia, infertility, and a reduced quality of life. Despite its significant prevalence, diagnosis is often delayed by several years due to nonspecific symptoms and the absence of a reliable noninvasive diagnostic marker.[1]

Severe symptoms and complicated surgical needs are linked to deep infiltrating endometriosis (DIE), which is defined by lesions that extend more than 5 mm below the peritoneal surface.[2] Although transvaginal ultrasound and MRI can identify DIE with reasonable accuracy, access to advanced imaging remains limited in many low-resource settings.[3]

Serum CA-125, a glycoprotein tumor marker, has been intensively studied as an adjunct in endometriosis

diagnosis. While CA-125 alone lacks sufficient sensitivity to serve as a screening test, its specificity is higher, especially in advanced disease. A meta-analysis of 14 diagnostic accuracy studies including 2,920 symptomatic women reported pooled specificity of approximately 93% for CA-125 ≥30 U/mL, but only 52% sensitivity.[4] Moreover, its diagnostic performance is markedly better in moderate to severe endometriosis compared to minimal disease.[4] In a prospective cohort of symptomatic women, CA-125 ≥30 U/mL yielded a specificity of 96% and sensitivity of 57%, with an AUC of 0.85, underscoring CA-125's potential value as a "rule-in" test.[5]

The correlation between CA-125 and disease severity has also been demonstrated: in one study, mean CA-125 increased progressively across rASRM stages—from 21.8 U/mL in Stage I to 117.0 U/mL in Stage IV—and showed a strong positive correlation ($r = 0.73$, $p = 0.001$).[6] Earlier data similarly demonstrated significant elevational trends with increasing disease stage and severity.[7] In patients with extended disease features such as dense adhesions or ruptured endometriomas, CA-125 levels >65 U/mL were associated with severe pelvic involvement and suggested need for comprehensive preoperative planning.[8] Collectively, these findings support CA-125 as a marker of disease burden and operative complexity.

Nonetheless, the majority of studies to date have focused on laparoscopic cohorts, and limited data exist from settings where laparotomy remains the standard surgical approach, such as resource-constrained regional hospitals. Furthermore, few studies have evaluated higher CA-125 thresholds such as ≥100 U/mL, which may enhance specificity and positive predictive value in predicting DIE and informing surgical urgency.

In Pakistan and similar contexts, there is an urgent need for pragmatic diagnostic tools to aid triage and clinical decision-making, particularly when access to imaging and specialist services is limited. CA-125, if validated at higher cut-offs, could serve as a low-cost adjunct to clinical assessment of suspected DIE. Therefore, the present study aims to evaluate whether preoperative serum CA-125 levels ≥100 U/mL can serve as a reliable marker for DIE in symptomatic women undergoing exploratory laparotomy at Bach Christian Hospital, Abbottabad. This work seeks to generate locally relevant evidence to augment preoperative planning and improve patient outcomes.

Methodology

This cross-sectional analytical study was conducted at the Department of Gynecology and Obstetrics, Bach Christian Hospital, Abbottabad, Pakistan, between January 2023 and August 2024. The study protocol was approved by the Institutional Review Board of Bach Christian Hospital, Abbottabad. Written informed consent was obtained from all participants before surgery, and patient confidentiality was strictly maintained throughout the study. A total of 220 patients fulfilling the inclusion criteria were enrolled through consecutive non-probability sampling.

Women who were between the ages of 18 and 45 and who had symptoms including infertility, dyspareunia, persistent pelvic discomfort, or dysmenorrhea were deemed eligible. Only those with serum CA-125 levels measured within four weeks prior to surgery were included. Patients with known gynecologic or non-gynecologic malignancy, other medical conditions associated with elevated CA-125 such as pelvic inflammatory disease, hepatic disease, or pregnancy, those with a history of pelvic surgery for endometriosis within the previous year, or incomplete records were excluded.

Clinical and demographic data including age, body mass index, parity, menstrual cycle characteristics, infertility history, and pain scores measured on a 10-point visual analogue scale were documented. Preoperative ultrasonography and, where indicated, MRI were performed to identify ovarian endometriomas or pelvic nodular lesions. Serum CA-125 was measured during the early follicular phase (cycle days 2–5 where feasible) using a standardized chemiluminescent immunoassay, with an inter-assay variability of less than 5%.

All patients underwent exploratory laparotomy under general anesthesia. Intraoperatively, disease severity was classified using the revised American Society for Reproductive Medicine (rASRM) staging system. Deep infiltrating endometriosis was defined as lesions extending more than 5 mm beneath the peritoneal surface, commonly involving the uterosacral ligaments, rectovaginal septum, bladder, or bowel. Surgical specimens were excised or biopsied and sent for histopathological confirmation. Patients with superficial peritoneal disease or isolated ovarian endometriomas were categorized as non-DIE.

SPSS version 26.0 was used to analyse the data. While categorical data were displayed as frequencies and percentages, continuous variables were represented as

means with standard deviations or medians with interquartile ranges. The Student's t-test or Mann-Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables were used to compare groups of DIE and non-DIE patients. To assess the diagnostic accuracy of CA-125 at three distinct thresholds (≥35 U/mL, ≥50 U/mL, and ≥100 U/mL), receiver operating characteristic (ROC) analysis was performed. Predictive, specific, and sensitivity values were computed. Spearman's correlation coefficient was used to look at relationships between CA-125 levels, disease stage, lesion size, and pain scores. Following correction for age, body mass index, parity, and ovarian endometrioma, independent predictors of DIE were found using logistic regression analysis. A p-value of less than 0.05 was deemed statistically significant, and the results were presented as odds ratios with 95% CIs.

Results

A total of 220 women underwent laparotomy surgery for endometriosis were included in the study period. Deep infiltrating endometriosis (DIE) was confirmed in 94 patients (42.7%), while 126 (57.3%) had superficial peritoneal disease and/or isolated ovarian endometriomas. The median age was 31 years (IQR 27–36). Baseline characteristics are presented in Table 1. Patients with DIE were more likely to report severe dysmenorrhea and dyspareunia and to have ovarian endometriomas and advanced rASRM stage ($p<0.001$ for all).

Serum CA-125 levels were significantly higher among women with DIE compared to those without (median: 98 U/mL vs. 28 U/mL; $p<0.001$). Overall, 69 women (31.4%) had CA-125 ≥100 U/mL, of whom 60 (87.0%) were confirmed to have DIE. Elevated CA-125 ≥100 U/mL was present in 63.8% of the DIE group compared with only 7.1% of the non-DIE group (χ^2 $p<0.001$).

Receiver operating characteristic (ROC) analysis demonstrated good discriminatory ability of serum CA-125 for detecting DIE, with an AUC of 0.82 (Table 2). Lower cut-offs such as 35 U/mL yielded higher sensitivity but reduced specificity, whereas a threshold of ≥100 U/mL provided excellent specificity (92.9%) with acceptable sensitivity (63.8%). At this threshold, the positive predictive value was 87.0% at the observed DIE prevalence.

The ROC curve is presented in Figure 1. The ROC curve demonstrates good discriminatory ability with an AUC of 0.82 (95% CI 0.77–0.87). Diagnostic performance improves at higher thresholds: ≥35 U/mL provided high sensitivity but modest specificity, ≥50 U/mL achieved balanced accuracy, and ≥100 U/mL yielded excellent specificity with acceptable sensitivity.

Table I: Baseline characteristics by presence of DIE.

Characteristic	Overall (N=220)	DIE (n=94)	Non-DIE (n=126)	P-value
Age, years, median (IQR)	31 (27–36)	31 (27–36)	30 (26–35)	0.281
BMI, kg/m², mean ± SD	24.6 ± 3.9	24.4 ± 3.8	24.7 ± 4.0	0.622
Nulliparous, n (%)	112 (50.9)	52 (55.3)	60 (47.6)	0.250
Dysmenorrhea VAS, median (IQR)	7 (6–9)	8 (7–9)	7 (5–8)	<0.001
Dyspareunia VAS, median (IQR)	5 (3–7)	6 (4–8)	4 (3–6)	0.002
Endometrioma present, n (%)	98 (44.5)	56 (59.6)	42 (33.3)	<0.001
rASRM stage III–IV, n (%)	121 (55.0)	84 (89.4)	37 (29.4)	<0.001
Serum CA-125, U/mL, median (IQR)	55 (24–112)	98 (62–178)	28 (15–46)	<0.001
CA-125 ≥100 U/mL, n (%)	69 (31.4)	60 (63.8)	9 (7.1)	<0.001

Table II: Diagnostic performance of CA-125 thresholds for detecting DIE.

Threshold (U/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥35	81.9	70.6	66.9	84.3
≥50	73.4	82.5	78.1	78.9
≥100	63.8	92.9	87.0	77.5

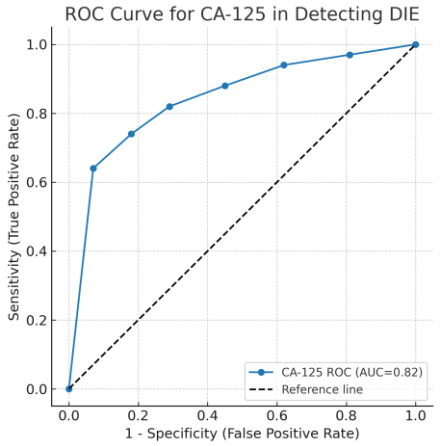

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Figure 1. Receiver operating characteristic (ROC) curve of serum CA-125 for the detection of DIE.

CA-125 levels also correlated with disease burden. Increasing serum levels were positively associated with rASRM stage ($\rho=0.58$, $p<0.001$) and total nodule length on imaging ($\rho=0.51$, $p<0.001$). Correlations with

symptom severity were weaker but remained statistically significant, including dysmenorrhea (ρ=0.34, p<0.001) and dyspareunia (ρ=0.21, p=0.003). These findings are summarized in Table III.

Table III: Correlation between CA-125 and disease burden/symptoms.

Variable	Spearman ρ	p-value
rASRM stage (I–IV)	0.58	<0.001
Total nodule length on imaging (cm)	0.51	<0.001
Dysmenorrhea VAS	0.34	<0.001
Dyspareunia VAS	0.21	0.003
Chronic pelvic pain VAS	0.18	0.010

Multivariable logistic regression analysis demonstrated that CA-125 ≥100 U/mL was an independent predictor of DIE (adjusted OR 8.9, 95% CI 4.2–18.7; p<0.001) after adjusting for age, BMI, parity, and presence of ovarian endometrioma. Endometrioma itself also remained a significant predictor (aOR 2.3, 95% CI 1.2–4.3; p=0.009). Other covariates were not independently associated with DIE. The regression model is shown in Table IV.

Table IV: Multivariable logistic regression for predictors of DIE.

Predictor	Adjusted OR	95% CI	p-value
CA-125 ≥100 U/mL	8.9	4.2–18.7	<0.001
Endometrioma present	2.3	1.2–4.3	0.009
Age (per year)	1.01	0.97–1.06	0.59
BMI (per kg/m²)	0.98	0.91–1.05	0.58
Nulliparity	1.19	0.67–2.12	0.55

Taken together, these findings confirm that while CA-125 levels overlap between groups, values above 100 U/mL provide strong predictive value for deep infiltrating disease. This threshold markedly increases specificity and can serve as a clinically useful adjunct in triaging patients for advanced imaging and surgical planning in the local setting.

Discussion

The present study evaluated the role of serum CA-125 levels above 100 U/mL as a marker for deep infiltrating endometriosis (DIE) in women undergoing laparotomy at Bach Christian Hospital, Abbottabad. Our findings show that elevated CA-125 strongly correlates with disease severity and extent of pelvic involvement, suggesting its potential as a low-cost diagnostic adjunct in settings where access to advanced imaging is limited.

The diagnostic performance of CA-125 in endometriosis has been extensively studied. A large meta-analysis reported that while CA-125 had a pooled specificity of 93%, sensitivity remained modest at 52%, particularly for early disease stages.[9] These results support the role of CA-125 as a "rule-in" test rather than a universal screening tool. Importantly, our study demonstrated that a threshold of ≥100 U/mL yielded higher specificity and positive predictive value for DIE, consistent with reports that elevated cut-off levels improve diagnostic accuracy in severe disease.[10]

The relationship between CA-125 levels and disease burden has been consistently demonstrated. Laila et al. observed mean CA-125 rising progressively with advancing rASRM stage, exceeding 110 U/mL in Stage IV disease.[11] Similarly, Steele et al. reported significant correlations between CA-125 concentrations and extent of pelvic adhesions, ovarian endometriomas, and distorted anatomy.[12] In line with these findings, patients in our cohort with advanced disease and DIE exhibited substantially elevated CA-125 levels, supporting its role as a surrogate marker of disease extent.

From a biological perspective, CA-125 is secreted by coelomic and peritoneal epithelium and is elevated in response to peritoneal irritation and inflammation.[13] Deep infiltrating lesions, which involve extensive stromal invasion and chronic inflammatory activation, are therefore associated with higher circulating CA-125.[14] This mechanistic rationale underscores the association between high CA-125 and invasive phenotypes of endometriosis, as observed in the present study.

Although imaging modalities such as transvaginal ultrasound and MRI have demonstrated excellent sensitivity and specificity for DIE[15], their availability remains limited in many low-resource settings across South Asia. In such contexts, CA-125 offers an accessible and cost-effective adjunct to clinical assessment. An Indian study highlighted the value of integrating CA-125 into multimodal diagnostic protocols, particularly where imaging and specialist expertise are scarce.[16]

Nonetheless, limitations of CA-125 as a diagnostic biomarker must be acknowledged. Elevated levels are not specific to endometriosis and may be observed in pelvic inflammatory disease, adenomyosis, and gynecological malignancies.[17] Furthermore, cyclic hormonal fluctuations influence CA-125 levels, with peaks occurring during menstruation, highlighting the need for standardized sampling protocols.[18]

Our study adds to existing literature by providing data from a regional Pakistani hospital, reflecting real-world surgical practice where laparotomy remains the mainstay of treatment. This setting provides unique insights into the applicability of CA-125 in contexts with limited access to laparoscopy or advanced imaging. However, the study's cross-sectional design and modest sample size may limit generalizability. Moreover, the absence of laparoscopic staging prevents direct comparison with cohorts from higher-resource settings. Future multicenter studies are warranted to validate the threshold of ≥100 U/mL in predicting DIE across diverse populations.

In conclusion, our findings suggest that serum CA-125 levels ≥100 U/mL can serve as a reliable marker for deep infiltrating endometriosis. Incorporating CA-125 into preoperative evaluation protocols may enhance surgical planning, guide referral decisions, and improve patient counseling, particularly in resource-constrained healthcare systems.

Conclusion

Serum CA-125 levels above 100 U/mL demonstrate strong association with deep infiltrating endometriosis and advanced disease stages, confirming their utility as a reliable diagnostic adjunct in preoperative evaluation. While not a standalone diagnostic tool, CA-125 at this threshold provides high specificity and predictive value, supporting its integration into routine clinical assessment and surgical planning, particularly in low-resource settings where advanced imaging may be limited. Further multicenter studies are suggested to validate these findings across diverse populations and refine diagnostic thresholds for optimal clinical use.

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