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EVALUATING CA-125 FOR OVARIAN CANCER DETECTION: A REVIEW OF DIAGNOSTIC PERFORMANCE

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Abstract: Background: Ovarian cancer remains one of the deadliest gynaecologic malignancies due to its late-stage diagnosis and the lack of effective early screening methods. CA-125, a serum biomarker, has long been used in clinical practice, but its diagnostic accuracy continues to be debated. **Objective:** This review aims to evaluate the diagnostic performance of CA-125 in detecting ovarian cancer across different clinical settings, with attention to variations based on age, ethnicity, and care context. **Methods:** A structured literature review was conducted using PubMed, Scopus, and Google Scholar, covering studies published between 1988 and 2025. From an initial pool of 12 studies, 6 were included based on relevance, methodological rigor, and availability of quantitative diagnostic data. Metrics such as sensitivity, specificity, PPV, NPV, and AUC were extracted and compared.**Results:**CA-125 demonstrated variable diagnostic performance. Sensitivity ranged from 50% to over 90%, while specificity was generally higher in hospital-based settings. One Indonesian study reported an overall accuracy of 94.5% using a 36.5 U/ml cutoff. Ethnicity affected CA-125's predictive value, with lower PPVs observed in Asian and Black women. Longitudinal evidence showed that elevated CA-125 levels can precede clinical diagnosis by several years. However, algorithmic models like ROMA showed only marginal improvement over CA-125 alone. **Conclusion:** While CA-125 is a useful diagnostic tool—especially in secondary care—its limitations in primary care and across diverse populations highlight the need for context-specific interpretation. Integration with imaging, risk algorithms, and emerging biomarkers may enhance early detection and reduce false positives in ovarian cancer diagnostics.

Keywords: Ovarian cancer, CA-125, tumor marker, diagnostic accuracy, sensitivity, specificity, primary care.

Introduction:- Ovarian cancer remains a major global health challenge and is currently the seventh most commonly diagnosed cancer and the eighth leading cause of cancer-related deaths among women (World Health Organization [WHO], 2023). It is often diagnosed at an advanced stage due to the asymptomatic nature of early disease and the lack of effective, widely applicable screening tools, resulting in a poor prognosis for many women (Reid et al., 2021). The five-year survival rate drops dramatically from over 90% for stage I to less than 30% for stage III or IV disease (Siegel et al., 2023).Among the biomarkers studied for the early detection of ovarian cancer, cancer antigen 125 (CA-125) remains one of the most widely used and investigated. First introduced by Bast et al. (1983), CA-125 is a high-molecular-weight glycoprotein expressed by coelomic epithelial tissues including the endometrium, fallopian tubes, and peritoneum. Elevated CA-125 levels are present in approximately 80% of women with advanced epithelial ovarian cancer, but its sensitivity in early-stage disease is significantly lower—often below 50% (Zurawski et al., 1988; Jacobs et al., 1996). Furthermore, the biomarker lacks specificity due to its elevation in numerous

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benign conditions such as endometriosis, menstruation, pelvic inflammatory disease, and even non-gynecologic disorders like liver disease (Funston et al., 2020; Van Gorp et al., 2011). Despite these limitations, CA-125 continues to be a cornerstone in the clinical evaluation of women with pelvic masses or symptoms suggestive of ovarian malignancy. In the United Kingdom, NICE guidelines recommend CA-125 as a first-line test in primary care, particularly for women presenting with persistent bloating, pelvic pain, or other non-specific symptoms (Barlow et al., 2025). In secondary care, CA-125 is used in risk assessment models, such as the Risk of Malignancy Index (RMI) and the Risk of Ovarian Malignancy Algorithm (ROMA), often combined with ultrasound findings and menopausal status to stratify cancer risk (Van Gorp et al., 2011). In recent years, researchers have examined how factors like age, menopausal status, and ethnicity influence CA-125's diagnostic accuracy. For instance, Funston et al. (2020) demonstrated that age-adjusted CA-125 thresholds could more accurately estimate cancer risk, while Barlow et al. (2025) reported that predictive values were lower among Asian and Black women compared to their White counterparts, raising concerns about equity in diagnostic evaluation. Given the variability in CA-125 performance across different settings and populations, there remains significant debate regarding its optimal clinical application, particularly in low-prevalence contexts such as primary care. This review aims to systematically assess the diagnostic accuracy of CA-125 across diverse populations and care settings, with the goal of informing more precise, equitable, and evidence-based decision-making in ovarian cancer diagnosis.

Methodology:-This review was conducted to systematically assess the diagnostic accuracy of serum CA-125 testing for ovarian cancer detection. A comprehensive literature search was performed across databases including PubMed, Scopus, and Google Scholar to identify relevant studies published between 1988 and 2025. The search strategy included combinations of the following keywords: "CA-125," "ovarian cancer," "tumor marker," "diagnostic accuracy," "sensitivity," "specificity," and "screening." Articles were screened by title and abstract, followed by full-text review based on predefined inclusion and exclusion criteria. Studies were included if they reported quantitative diagnostic metrics of CA-125 (sensitivity, specificity, PPV, NPV, AUC) in relation to histologically confirmed ovarian cancer, involved human female subjects aged 18 years and older, and assessed CA-125 either in primary care, hospital-based settings, or screening populations. Excluded were reviews, editorials, case reports, and studies not focused on diagnostic performance, such as those limited to monitoring treatment or prognosis. From an initial pool of 12 eligible studies, 6 were selected for final inclusion based on methodological quality, completeness of diagnostic data, and relevance to clinical diagnostic settings. These studies were conducted across various countries—including the United Kingdom, Indonesia, and Norway—and encompassed a broad range of clinical scenarios, from symptomatic patients in primary care to women undergoing surgery for adnexal masses. Sample sizes ranged from 428 to over 200,000 women. For each study, data on setting, sample size, CA-125 cut-off thresholds, diagnostic performance metrics, and key findings were extracted and tabulated for comparison. Due to heterogeneity in design and outcomes, no meta-analysis was performed. The final synthesis aimed to highlight patterns and clinical implications in the use of CA-125 across diverse patient populations.

Results:-The diagnostic performance of CA-125 varied across clinical settings and populations. In a tertiary Indonesian hospital setting, Pangaribuan et al. (2025) found that a CA-125 cutoff of 36.5 U/ml yielded sensitivity of 86.1%, specificity of 90.1%, and an

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overall diagnostic accuracy of 94.5%, making it a reliable screening tool in patients with suspected malignancy. In contrast, Barlow et al. (2025), using English primary care data, observed that ethnic variations significantly influenced CA-125 performance. White women exhibited higher CA-125 predictive values compared to Asian or Black women. Although these differences were mitigated after adjusting for age and comorbidities, the authors advised against ethnicity-specific thresholds due to a risk of reduced sensitivity.In a landmark prospective study, Jacobs et al. (1996) reported that CA-125 levels ≥30 U/ml increased the relative risk of ovarian or fallopian tube cancer by 35.9 times within one year, and levels ≥100 U/ml increased it by over 200-fold, confirming CA-125's value in long-term risk prediction.Funston et al. (2020), analyzing over 50,000 women in UK primary care, found that a CA-125 level of 53 U/ml corresponded to a 3% probability of ovarian cancer — the threshold for urgent investigation in NICE guidelines. However, the PPV varied significantly with age, from 3.4% in women <50 years to 15.2% in those ≥50 years. Zurawski et al. (1988) showed that elevated CA-125 could precede diagnosis by up to 60 months, with 50% of pre-diagnostic samples (18 months prior) showing levels >30 U/ml. Finally, Van Gorp et al. (2011) evaluated the ROMA algorithm, combining CA-125 with HE4, and found no significant performance gain over CA-125 alone, especially in postmenopausal women (AUC: CA-125 = 0.877, ROMA = 0.898).

Table 1: Summary of Diagnostic Performance of CA-125 Across Studies

Study	**Sample Size**	**Cutoff (U/ml)**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**AUC**	**Key Findings**
Pangaribuan et al. (2025)	Not specified	36.5	86.1	90.1	89.4	86.9	–	High diagnostic accuracy (94.5%) in hospital setting
Barlow et al. (2025)	200k+	Varies	Ethnic differences	Lower specificity in Asian/Black women	Varies	–	–	No ethnicity-specific cutoffs recommended
Jacobs et al. (1996)	22,000	≥30 / ≥100	RR ↑ 35.9x / 204.8x	–	–	0.0012 (<30 U/ml)	–	High predictive power for future cancer
Funston et al. (2020)	50,780	35 / 53 / Age-based	3% risk at 53 U/ml	–	3.4% (<50 yrs), 15.2% (≥50	–	–	Risk thresholds useful for triage

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					yrs)			
Zurawski et al. (1988)	428	30 / 65	50% >30 U/ml (18 mo before Dx)	93% (<30 U/ml in controls)	~25 % (>30 U/ml)	–	–	Detectable elevations long before diagnosis
Van Gorp et al. (2011)	389	ROMA	67.5 (pre-M), 90.8 (post-M)	87.9 (pre-M), 66.3 (post-M)	–	–	0.898 (ROMA), 0.877 (CA-125)	HE4 adds limited value over CA-125

Detectable elevations long before diagnosis Van Gorp et al. (2011) 389 ROMA 67.5 (pre-M), 90.8 (post-M) 87.9 (pre-M), 66.3 (post-M) – – 0.898 (ROMA), 0.877 (CA-125) HE4 adds limited value over CA-125

Discussion:-The findings affirm that CA-125 is a clinically useful tool in detecting ovarian cancer, especially when used in conjunction with patient demographics and clinical presentation. Its performance is strongest in secondary care and postmenopausal populations, where specificity and PPV are notably higher. However, in primary care or screening contexts, the test's low PPV (<5%) in younger women limits its standalone use, necessitating follow-up imaging or repeat testing. The test's sensitivity increases with advancing disease, and its levels may remain normal in early-stage cancers or benign conditions like endometriosis, liver disease, and menstruation. Age-adjusted and algorithm-based models like ROMA can offer incremental improvement but have not consistently outperformed CA-125 alone. Ethnic disparities in test performance highlight the importance of equity in diagnostic thresholds, though implementing ethnicity-specific cutoffs may compromise sensitivity. Longitudinal studies also suggest CA-125 may serve as a risk indicator years before diagnosis, particularly in asymptomatic women.

Conclusion :-CA-125 continues to serve as a valuable diagnostic and risk stratification tool for ovarian cancer, with high sensitivity and specificity in tertiary care settings. However, its limitations in general populations, variability by age and ethnicity, and overlap with benign conditions mean it should be interpreted cautiously. Clinical decisions should integrate CA-125 levels with imaging, risk models, and patient context to improve early detection without increasing false positives. Future research should focus on combinatory biomarkers and artificial intelligence–driven risk models to optimize the early detection of ovarian cancer.

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