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Role of Liquid Biopsy (circulating tumor DNA) in Early Detection of Ovarian Cancer

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ABSTRACT

Background: Ovarian cancer is a major cause of mortality around the globe related to gynaecological cancer, and this is primarily attributed to late diagnosis and the non-existence of effective early screening reagents. The purpose of the research was to assess the diagnostic abilities of circulating tumor DNA (ctDNA) as a liquid biopsy method to detect ovarian cancer in its initial phases of progression.

Methods: This is a cross-sectional analytical study conducted at the Gynaecological Oncology unit at Lady Willingdon Hospital/ King Edward Medical University, Lahore, between March and August 2025. The study involved 105 female patients who had suspected ovarian masses. Blood samples were collected before the operation, and ctDNA was isolated and sequenced using digital droplet PCR and next-generation sequencing to detect tumor-related mutations. Data were analyzed using SPSS.

Results: The median age of the patients was 52.67±11.41 years, and 59.0% were postmenopausal. Histopathology identified ovarian malignancy in 82 patients (78.1) and benign lesions in 23 patients (21.9%). ctDNA was detected in 72 malignant lesions (87.8%) of which 20 lesions were at an early stage of cancer (76.9%). The overall sensitivity of ctDNA was 87.8, specificity 87.0, PPV 96.0, NPV 66.7, and AUC 0.91. Comparatively, CA-125 was less sensitive (72.0%) and specificity (65.2%).

Conclusion: ctDNA proved to have a high diagnostic accuracy over CA-125 and had the potential to determine early ovarian cancer. Its integration into clinical practice, in addition to the traditional approaches, might lead to better diagnosis and outcomes in the early stages.

Keywords: Ovarian Cancer, Liquid Biopsy, Circulating Tumor DNA, Early Detection, CA-125

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INTRODUCTION

Ovarian cancer is a major health concern worldwide, ranking among the top causes of cancer-related deaths in women[1,2]. In 2020, approximately 300,000 women worldwide were newly diagnosed and more than 200,000 died of the disease[3]. This is mainly due to the fact that early-stage ovarian cancer is generally asymptomatic or presents with non-specific and vague symptoms like bloating, pelvic pain or gastrointestinal disturbances, which is easily ignored or can be related to benign causes[4]. When the clinical suspicion is identified and the traditional diagnostic approaches are used, the vast majority of patients already have the stage III or IV disease with the poor prognosis[5,6].

The five-year survival rates of advanced ovarian cancer are seldom more than 30, in contrast with 80-90 percent in stage-I or II patients[7]. This dramatic imbalance indicates the alarming necessity to develop efficient early detection measures. This gap has not been addressed using traditional diagnostic modalities. Although transvaginal ultrasound is employed in identifying the presence of adnexal masses, it is not specific to the presence of benign or malignant lesions, hence resulting in surgical interventions which are usually unnecessary[8]. Likewise, the most commonly used biomarker serum CA-125 has a low sensitivity, especially at an early stage of the disease, and can be increased in a variety of non-cancerous conditions such as endometriosis, pelvic inflammatory disease, or menstruation[9].

Multimodal screening methods that involve ultrasound in combination with CA-125 have been explored but large randomized controlled experiments have not been able to show a significant reduction in mortality[10]. This diagnostic stagnation has led scientists to consider the possibility of using molecular technologies that are capable of monitoring tumor-specific signals at an earlier and more specific stage.

Liquid biopsy has been a fast-moving game changer in the field of oncology[11]. Liquid biopsy, in contrast to the conventional tissue biopsy, an invasive technique that only gives a snapshot of the tumor biology at a defined time, entails the examination of components of the tumor present in movement in the body fluids, most commonly blood[12]. Of these, circulating tumor DNA (ctDNA) has received the most interest. ctDNA is released into the blood, either by apoptosis, necrosis, or by active secretion of tumor cells. Notably, ctDNA also contains tumor-specific genetic and epigenomic changes, such as point mutations, copy number changes, DNA methylation profiles, and fragmentomic signatures, hence a very informative biomarker[13]. The objective of the study was to evaluate the diagnostic performance of circulating tumor DNA (ctDNA) as a liquid biopsy tool for the early detection of ovarian cancer.

METHODS

This was a cross-sectional analytical study conducted at Gynaecological Oncology unit at Lady Willingdon hospital/ King Edward Medical University, Lahore from March-August 2025. A total of 105 patients were enrolled in the study (No. 814/RC/KEMU Date: 17/02/2025). Sample size was calculated using the single population proportion formula n=Z2p(1−p)/d2n = Z^{2} p(1-p) / d^{2}n=Z2p(1−p)/d2 with a 95% confidence level (Z = 1.96), anticipated proportion of 50%, and margin of error of 10%, yielding a minimum required sample of 96. After adding 10% for possible non-response, the final sample size was approximately 105 patients.

A non-probability consecutive sampling technique was employed. A flowchart illustrating patient enrollment, exclusions, and diagnostic classification is presented in Figure 1.

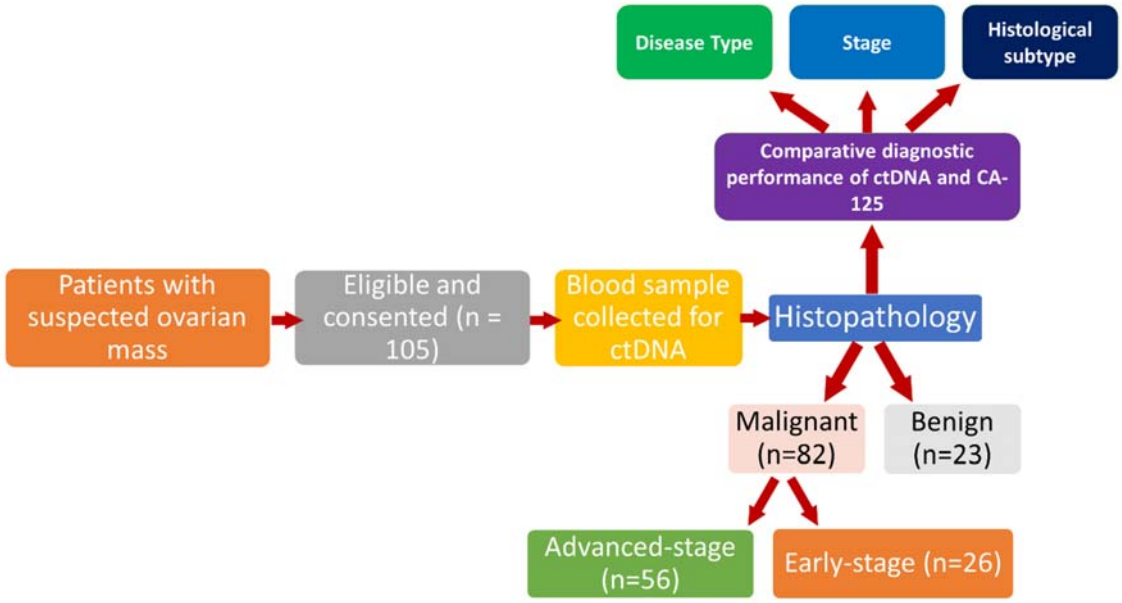

Figure 1: Study Flow Diagram (Patient Selection and Analysis)

Female patients aged 18 years and above with suspected or newly diagnosed ovarian masses who were scheduled for surgical intervention were included in the study. Only patients who provided informed written consent were enrolled. Patients were excluded if they had a prior history of any other malignancy, had received chemotherapy, radiotherapy, or targeted therapy before sample collection, or had systemic inflammatory diseases or other conditions that could potentially influence circulating DNA levels.

After informed consent, venous blood samples (10 mL) were collected in EDTA tubes from each patient prior to surgery or definitive diagnosis. Plasma was separated by centrifugation and stored at –80°C until analysis. ctDNA was extracted using a commercially available high-sensitivity kit.

Quantification and detection of ctDNA were performed using digital droplet PCR (ddPCR) and next-generation sequencing (NGS) targeting tumor-specific mutations commonly associated with ovarian cancer (TP53, BRCA1/2). Clinical data including age, menopausal status, family history, presenting symptoms, radiological findings, and serum CA-125 levels were recorded using a structured proforma (Table 1). Histopathological diagnosis following surgery or biopsy was used as the gold standard for confirmation of ovarian cancer. All data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. Continuous variables such as age were expressed as mean ± standard deviation (SD), whereas categorical variables such as menopausal status and histological subtypes were expressed as frequencies and percentages. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Characteristics of Patients (n = 105)

Characteristic		Category	n (%) / Mean ± SD
Age (years)			52.6 ± 11.4
Menopausal status		Premenopausal	43 (41.0%)
		Postmenopausal	62 (59.0%)
Family history of cancer		Present	18 (17.1%)
		Absent	87 (82.9%)
Presenting symptoms		Abdominal distension	68 (64.8%)
		Pelvic pain	45 (42.9%)
		Gastrointestinal	31 (29.5%)
Elevated CA-125 (>35 U/mL)			78 (74.3%)
Histopathological Findings	Disease type	Malignant	82 (78.1%)
		Benign	23 (21.9%)
	Stage (malignant only)	Early-stage (I–II)	26 (31.7%)
		Advanced-stage (III–IV)	56 (68.3%)
	Histological subtype	High-grade serous carcinoma	51 (62.2%)

		Endometrioid carcinoma	13 (15.9%)
		Mucinous carcinoma	10 (12.2%)
		Clear cell carcinoma	8 (9.7%)

Data were collected from 105 patients, with a mean age of 52.6 ± 11.4 years **(Table 1).** Among them, 43 (41.0%) were premenopausal and 62 (59.0%) were postmenopausal. A family history of cancer was present in 18 (17.1%) patients. Abdominal distension was the most common presenting symptom, reported in 68 (64.8%) cases, followed by pelvic pain in 45 (42.9%) and gastrointestinal complaints in 31 (29.5%). Elevated serum CA-125 levels were observed in 78 (74.3%) patients. Histopathological examination confirmed ovarian malignancy in 82 (78.1%) cases, while 23 (21.9%) were benign. Among the malignant cases, 26 (31.7%) were diagnosed at an early stage and 56 (68.3%) at advanced stages. High-grade serous carcinoma was the predominant histological subtype, accounting for 51 (62.2%) cases, followed by endometrioid carcinoma in 13 (15.9%), mucinous carcinoma in 10 (12.2%), and clear cell carcinoma in 8 (9.7%).

Table 2: ctDNA Detection According to Disease Status

Group	Total (n)	ctDNA Positive n (%)	ctDNA Negative n (%)
Malignant (Total)	82	72 (87.8%)	10 (12.2%)
Early-stage (I–II)	26	20 (76.9%)	6 (23.1%)
Advanced-stage (III–IV)	56	52 (92.9%)	4 (7.1%)
Benign	23	3 (13.0%)	20 (87.0%)

Circulating tumor DNA was detected in 87.8% of malignant cases, with a detection rate of 76.9% in early-stage disease and 92.9% in advanced stages. In contrast, only 13.0% of benign cases showed ctDNA positivity **(Table 2).**

When evaluated against histopathology, ctDNA demonstrated a sensitivity of 87.8% and a specificity of 87.0%, with a positive predictive value of 96.0% and a negative predictive value of 66.7%. The area under the ROC curve (Figure 3) was 0.91, indicating high diagnostic accuracy. Using Youden's index method (J = Sensitivity + Specificity − 1), ctDNA demonstrated a higher optimal diagnostic performance compared to CA-125. For ctDNA, with a sensitivity of 87.8% and specificity of 87.0%, the Youden index was 0.748, indicating an excellent balance between true positive and true negative rates and corresponding to the optimal ROC-derived cutoff point. In contrast, CA-125 showed a

sensitivity of 72.0% and specificity of 65.2%, yielding a lower Youden index of 0.372, reflecting comparatively weaker discriminatory ability. The area under the ROC curve (AUROC) further confirmed the superior performance of ctDNA at 0.91 (95% CI: 0.85–0.97), compared with CA-125 at 0.78 (95% CI: 0.69–0.87).

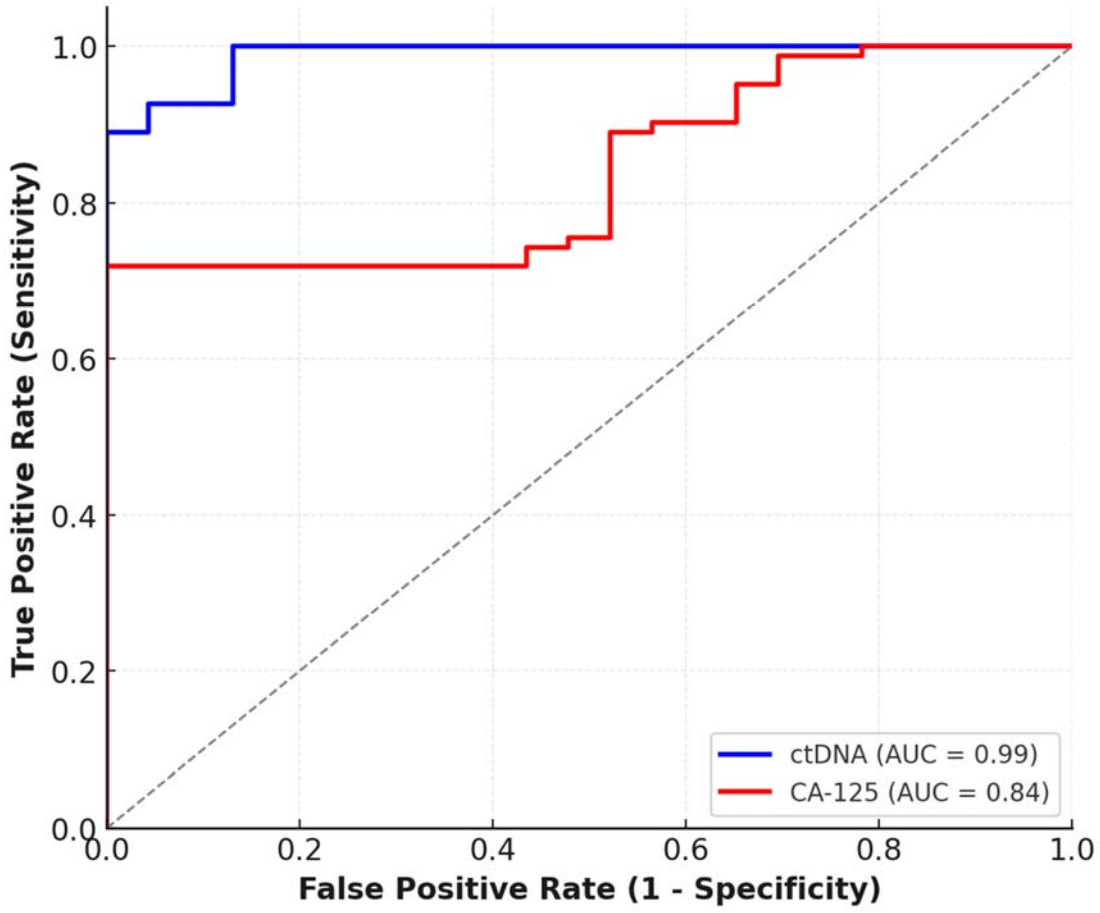

Figure 3: ROC Curve: ctDNA vs CA-125 in Ovarian Cancer Detection

Table 3: Comparative Diagnostic Performance of ctDNA and CA-125 in Differentiating Malignant (N=82) from Benign (N=23) Cases.

Parameter	ctDNA	CA-125
True Positive (TP)	72	59
False Positive (FP)	3	8
False Negative (FN)	10	23
True Negative (TN)	20	15

Sensitivity	87.8%	72.0%
Specificity	87.0%	65.2%
Positive Predictive Value (PPV)	96.0%	86.0%
Negative Predictive Value (NPV)	66.7%	42.5%

The diagnostic analysis demonstrates that ctDNA outperformed CA-125 across all major performance indicators **(Table 3).** ctDNA showed higher sensitivity (87.8% vs. 72.0%) and specificity (87.0% vs. 65.2%), indicating superior ability to correctly identify both malignant and benign cases. Additionally, ctDNA exhibited a markedly higher positive predictive value (96.0% vs. 86.0%), suggesting stronger reliability when the test result is positive. The negative predictive value was also substantially better for ctDNA (66.7%) compared to CA-125 (42.5%). Overall, ctDNA demonstrated superior diagnostic accuracy compared to CA-125 in differentiating malignant from benign cases.

DISCUSSION

The research paper has assessed the use of circulating tumor DNA (ctDNA) as a diagnostic test in the early diagnosis of ovarian cancer in a study sample of 105 patients. This study have proven that ctDNA has high diagnostic accuracy with a total sensitivity of 87.8, a specificity of 87.0 and an area under the ROC curve of 0.91. It should also be mentioned that the ctDNA was found positive in 76.9 per cent of the cases of early-stage ovarian cancer pointing to the possibility of using it as a non-invasive biomarker that could determine the presence of cancer before clinical or radiological changes could be observed. Delayed diagnosis has always been the problem in dealing with ovarian cancer. The traditional diagnostic modalities used include CA-125 and transvaginal ultrasound are not sensitive and specific, especially at low stage. CA-125 in our case had a sensitivity of 72.0% and specificity of 65.2 which is much lower than ctDNA. This supports the assumption that the diagnostics accuracy of ctDNA can be higher than the available biomarkers. We have also observed these results in earlier studies that showed that ctDNA performed better than CA-125 in making a distinction between malignant and benign adnexal masses and when used together with molecular profiling methods. Advancements in technology in the next-generation sequencing (NGS) and digital PCR have enhanced the sensitivity and specificity of ctDNA detection to an impressive degree[14]. Targeted sequencing panels and whole-genome bisulfite sequencing are the methods that allow one to identify low-frequency tumor mutations in a background of normal cell-free DNA[15]. More recent research has shown that ctDNA-based assays can be improved with machine learning algorithms to increase their predictive accuracy, which suggests the potential to implement ctDNA into population-

wide screening programs of high-risk women. In addition, the use of ctDNA methylation profiling has been especially promising, with abnormal methylation patterns of DNA being observed in the very early stages of ovarian tumorigenesis and potentially being one of the most sensitive indicators of malignant change[16-18].

The other notable conclusion is that ctDNA showed outstanding results in progressive disease, and 92.9% of patients with III and IV stages of the disease were found. In past studies, ctDNA is strongly associated with tumor burden and progression of the disease. Nonetheless, the sensitivity of detecting early-stage cancerously proven (76.9%), nevertheless, points to the technical difficulty of detecting low levels of ctDNA in circulation[19,20]. Future improvements in detecting in early disease may be in the integration of high-sensitivity methods including digital droplet PCR and next-generation sequencing. Clinically, the high positive predictive value (96.0) of our study indicates that positive results on ctDNA are very dependable on the diagnosis of malignancy. Conversely, the negative predictive value (66.7) is lower, which also shows that a negative test does not necessarily eliminate the disease, especially when it is at an early stage. This conclusion means that ctDNA cannot be used as a primary diagnostic tool but rather as a supplement, preferably together with imaging and conventional biomarkers. The use of ctDNA in clinical practice has serious consequences[21,22].

In addition to early detection, ctDNA may also give real-time molecular data on tumor biology, enabling monitoring of treatment response, detection of minimal residual disease, and early detection of recurrence. ctDNA is also a non-invasive alternative to tissue biopsy in those cases when it is challenging or dangerous to obtain such data. This may assist in guiding specific treatment such as PARP blockers in BRCA-mutated ovarian cancer[23-26]. In spite of the positive results, some shortcomings have to be mentioned. On the one hand, the study was carried out with a rather limited sample of one center, which can be a limitation to generalization. Second, ctDNA is technically challenging, and, as yet, might not be as accessible as possible in low-resource environments experiencing high ovarian cancer incidence. Thirdly, we failed to conduct longitudinal ctDNA monitoring which would have provided us with an insight with regard to the dynamic effects that occurred during the treatment and follow-up periods. To confirm these results and outline the best application of ctDNA in screening and clinical workflow, future research using larger multi-centric cohorts and standardized assay procedures is required.

CONCLUSION

It is noted that circulating tumor DNA (ctDNA) is a highly promising biomarker to detect ovarian cancer at an early stage. In the case of this 105 patients study, ctDNA has shown a better diagnostic

performance than CA-125, and has better sensitivity, specificity and overall accuracy. It is important to note that ctDNA could be detected in a considerable percentage of the early-stage cases, which implies the possibility of ctDNA to fill the diagnostic gap that currently restricts the timely intervention. Although ctDNA is not currently a ready tool to use, it can be incorporated into established diagnostic modalities to enhance the ability to detect early, make personal treatment choices, and increase the long-term survival rates.

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LIST OF ABBREVIATIONS

ctDNA: Circulating Tumor DNA

ddPCR: Digital Droplet Polymerase Chain Reaction

NGS: Next-Generation Sequencing

PCR: Polymerase Chain Reaction

CA-125: Cancer Antigen 125

PPV: Positive Predictive Value

NPV: Negative Predictive Value

AUC: Area Under the Curve

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None.

CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

Ethical Approval of this research was obtained from the Institutional Review Board of the King Edward Medical University, Lahore, Pakistan (No. 814/RC/KEMU Date: 17/02/2025).

AUTHORS' CONTRIBUTION

ZZ, SM, FRL, UM, AA, JA, and NJ contributed equally to the conception and design of the study, data acquisition, analysis and interpretation of data, drafting and critical revision of the manuscript, and approval of the final version for publication. All authors meet the authorship criteria established by the International Committee of Medical Journal Editors (ICMJE) and agree to be accountable for all aspects of the work.

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