Section: Obstetrics & Gynaecology

Original Research Article

A STUDY OF CA 125 AS A SCREENING TOOL FOR OVARIAN TUMORS

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Received : 26/06/2025
Received in revised form : 12/08/2025
Accepted : 30/08/2025

Keywords:
CA 125, ovarian tumors, screening.

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DOI: 10.47009/jamp.2025.7.5.145

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (5); 754-759

ABSTRACT

Background: Ovarian tumours are abnormal growths arising from different cells in the ovary. They can be benign, borderline or malignant and are categorized based on the cell type they originate from. Neoplasms of epithelial origin accounts majority of ovarian tumours, germ cell and Sex cord-stromal tumours are much less frequent. Ovarian cancer is second most common malignant gynaecologic neoplasm word wide, and it accounts for more mortality than all other female genital tumours. CA 125 is an epithelial marker derived from coelomic epithelium and it reflects the relative volume of the ovarian tumour. **Objective:** To assess the sensitivity and specificity of CA 125 in screening of ovarian tumours. **Materials and Methods:** A cross-sectional study of 180 patients was conducted over 18 months at RIMS, Imphal. The study included ovarian tumor patients who attended Gynae OPD and were admitted in Gynae ward. Serum CA 125 levels were measured using ELISA. ROC curve analysis was used to determine diagnostic performance. **Result:** Out of 180 cases, 153 (85%) were benign and 27 (15%) were malignant. CA 125 was elevated (>35 U/mL) in 88.9% of malignant tumors and 76.5% of benign tumors. Sensitivity was 88.9%, specificity 23.5%, PPV 17%, and NPV 92.3%. **Conclusion:** CA 125 has high sensitivity but low specificity in detecting ovarian tumors. It may be a useful screening tool when combined with other clinical and diagnostic parameters.

INTRODUCTION

Ovarian tumors are a heterogenous group of neoplasms that may arise from any of three cell types in a normal ovary- multipotent coelomic epithelium, totipotent germ cells, and sex cord-stromal cells. Neoplasms of epithelial origin account for the majority of ovarian tumors and, in their malignant forms, account for almost 90% of ovarian cancers. Germ cell and sex cord-stromal tumors are much less frequent; although they constitute 20% to 30% of ovarian tumors, they are collectively responsible for less than 10% of malignant tumors.[1]

Ovarian cancer is the second most common malignant gynecologic neoplasm worldwide, and it accounts for more mortality than all other female genital tumors. According to the new 2020 World Health Organization classification, five main types of ovarian carcinomas are identified based on histopathology, immune profile, and molecular analysis: high-grade serous carcinoma (HGSC, 70%), endometrioid carcinoma (EC, 10%), clear cell carcinoma (CCC, 6–10%), low-grade serous carcinoma (LGSC, 5%), and mucinous carcinoma (MC, 3–4%). Some rare entities have been introduced (e.g., mesonephric-like carcinoma and mixed carcinoma), while others have been removed (e.g., seromucinous carcinoma).[2]

Despite of advancements in oncology, ovarian cancers continues to have poor prognosis, largely due its insidious onset and lack of early symptoms. The estimated number of new cases in 2022 is 19880, which accounts for 1% of all new cancer cases. Five year survival rate is 49.7 % based on 2012 to 2018 data. Ovarian tumors are the second most common and most lethal gynecologic malignancy reported in the United States of America.[3]

CA 125 is an epithelial marker derived from coelomic epithelium. It is a high molecular weight glycosylated membrane protein that can be detected in serum. Serum CA 125 levels reflect the relative volume of the ovarian tumor. It is elevated in 90% of advanced ovarian cancers and 50% of early ovarian

ISSN (O): 2687-5365; ISSN (P): 2753-6556

cancers. However, 20% of ovarian cancers have low or no expression of CA 125.[4]

CA 125 is widely used in clinical practice not only for the diagnosis but also for monitoring treatment response and recurrence in ovarian cancer. Neverthless, elevated CA 125 levels are not specific to malignancy. They can also be seen in benign conditions such as menstruation, endometriosis, pelvic inflammatory disease, liver disease and non gynecologic cancers such as pancreas, lung, breast, and colon.[5] Ascitis, pleural effusion or pericardial effusions, recent laparotomy may also result in increased serum CA 125 levels.[6]

Ovarian cancer has a worse prognosis due to its asymptomatic nature, its lack of active screening and early detection techniques. Ovarian cancer is the 18th most deadly disease worldwide.[7] The late-stage diagnosis of ovarian cancer is moderately accredited. The relative survival rate of ovarian cancer is generally 45%. However, if identified early, the mortality can be reduced significantly. CA 125 is the only biomarker that has proven to detect ovarian cancer before the onset of clinical symptoms and most commonly used in clinical practice.[8] Despite of poor sensitivity and specificity, CA125 is a most helpful marker for detecting and monitoring nonmucinous epithelial tumors of the ovary.[9] But as the level is also elevated in the benign conditions of the ovary, there is a need to consider the possibility of other conditions in addition to Ovarian cancer in women with high CA 125 levels. Furthermore no comprehensive study has been conducted in this region of India. Hence the present study was designed to assess the role of serum CA 125 in screening of ovarian tumors.

MATERIALS AND METHODS

This cross-sectional study was conducted from December 2022 to May 2024 at Regional Institute of Medical Sciences, Imphal, Manipur, involving 180 participants with ovarian tumors using covenient sampling.

Inclusion Criteria: Patients with ovarian tumors

Exclusion Criteria: Endometrial Carcinoma, Breast Carcinoma, Endometriosis, Pelvic inflammatory disease, Liver disease, Ascites, pleural or pericardial effusions, recent laparotomy.

Data collection: Prior to data collection, ethical approval was sought from the Research Ethics Board of Imphal. Informed written consent was taken from all the participants. Data were collected in predesigned proforma. The collected data were checked for completeness and consistency.

1. Medical history was taken from patients with ovarian tumors
2. Detailed clinical examination and imaging- Ultrasonography, Magnetic resonance imaging, Computed tomography.
3. Blood samples were collected in a plain tube - centrifuged- to collect the serum - CA 125 was estimated using the ELISA (Enzyme Linked Immunosorbent assay) technique.

Statistical Analysis: Data collected were entered in IBM SPSS 21.0 after checking for consistency and completeness. Descriptive statistics like mean and SD were used for continuous variables, and frequency proportion was used for categorical variables to express the data. The association between serum CA125 and tumor type (benign and malignant) was analyzed by chi-square test. The software assessed sensitivity, Specificity, and Positive and Negative likelihood ratios for CA 125. The ROC curve was drawn through software. A P value < 0.05 was considered statistically significant.

RESULTS

A total of 180 ovarian tumor cases were included in the study to assess the sensitivity and specificity of CA125 in the screening of ovarian tumors in the Department of Obstetrics and Gynaecology. The results of this study are depicted as follows:

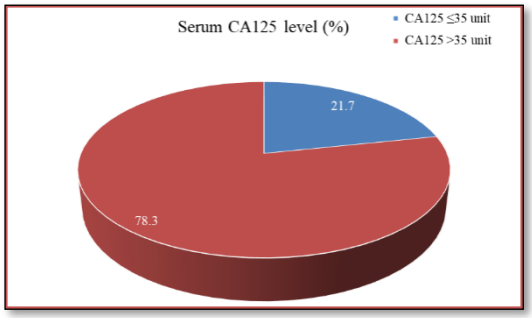

Figure 1: Serum CA125 level among the participants (N=180):

Figure 1 shows that the majority of patients had raised CA 125 levels >35 U/mL comprising 141(78.3%) of total participants and 39 (21.7%) patients had normal CA 125 levels <35 U/m.

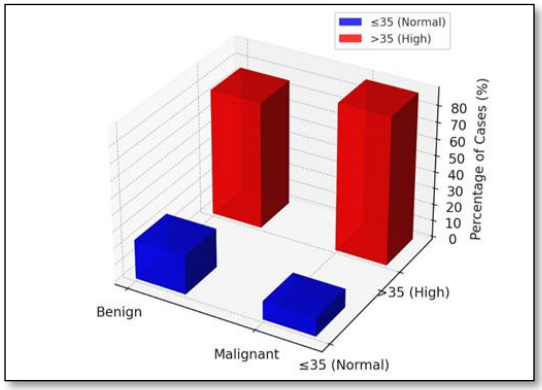

Figure 2: Relation between CA 125 level and ovarian tumor type (N=180):

Figure 2 shows that CA 125 level was raised (> 35 U/mL) in 76.5% of benign ovarian tumors and 88.9% of malignant ovarian tumors.

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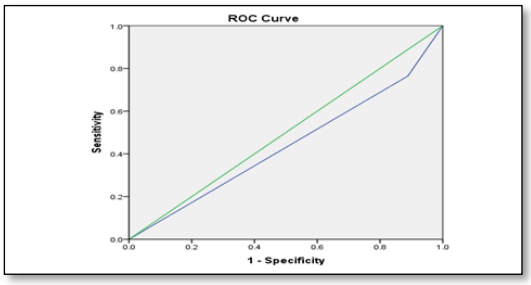

Figure 3: ROC (Receiver operating Charateristics) curve:

Figure 3 shows that the green diagonal line is the reference line (AUC = 0.5), which represents a test with no discriminative ability.The blue curve represents the true ROC curve for CA 125 which falls below the diagonal line is a sign of poor test performance, The study shows AUC of 0.438 indicating that serum CA125 is not reliable test for differentiating between benign and malignant ovarian tumors.

Table 1: Sociodemographic profile of study participants (N= 180):

Parameter	Category	Frequency (N)	Percent (%)
Age group (years)	≤ 21	21	11.7
	21–30	33	18.3
	31–40	56	31.1
	41–50	34	18.9
	51–60	7	3.9
	> 60	29	16.1
Religion	Hindu	131	72.9
	Muslim	26	14.3
	Christian	23	12.9
Educational qualification	Illiterate	21	11.7
	Up to 5th standard	20	11.1
	Up to 10th standard	51	28.4
	Up to 12th standard	63	35
	Graduate and above	25	13.9
Occupation	Self-employed	135	75
	Employed	27	15
	Student	18	10

Table 1 shows sociodemographic profile of study participants, Majority of patients belongs to 31 to 40 years age group comprising of 56 (31%) of total cases, Majority of cases were hindus -131 (72%), educated upto 12th standard -63 (35%) and self-employed -135 (75%).

Table 2. Variables associated with ovarian tumors (N= 180):

Parameter	Category	Frequency (N)	Percent (%)
Body Mass Index	Normal	83	46.1
	Overweight	33	18.3
	Obese	64	35.6
Parity	Nullipara	77	42.8
	Para 1	26	14.4
	Para 2	33	18.3
	Para 3	15	8.3
	Para 4	18	10
	Para ≥ 5	11	6.1
Menopausal status	Premenopausal	138	76.7
	Postmenopausal	42	23.3
Family history of ovarian tumor	Yes	13	7.2
	No	167	92.8
Tobacco use	Yes	34	18.9
	No	146	81.1
Oral contraceptive pill use	No history	159	88.3
	≤ 6 months	6	3.3
	1–2 years	11	6.1
	> 2 years	4	2.2

Table 2 depicts different variables associated with ovarian tumors, Majority of patients had raised BMI (overweight or obese) comprising of 97 (53.9%) of total cases, most of the patients were nullipara -77 (42.8%) and belongs to premenopausal group -138 (76.7%), Only 13 (7.2%) patients had family history of ovarian tumors and 34 (18.9%) patients had history of taking tobacco, Majority of patients didn't use oral contraceptive pills - 159 (88.3%).

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Table 3: Relation between CA 125 level and ovarian tumor type (N=180):

Ovarian tumor type	Serum CA level (units/ml)		Total	P value
	≤35 level: Normal N(%)	>35 level: High N(%)		
Benign	36 (23.5)	117 (76.5)	153	.206
Malignant	3 (11.1)	24 (88.9)	27	
Total	39	141	180	

Table 3 shows that

- The sensitivity of Serum CA125 to identify ovarian tumors was 88.9%.
- The positive predictive value (PPV) was 17.0%
- The negative predictive value (NPV) was 92.3%
- The specificity of the serum CA125 to detect ovarian tumors was 23.5%.
- P value of 0.206, statistically not significant.

Table 4: Relation between Risk of malignancy index score and ovarian tumor (N=180):

Risk of malignancy index score	Tumor type		Total	P value
	Benign N (%)	Malignant N (%)		
No significant risk	102 (66.6)	4 (14.9)	106	.04
Significant risk	51 (33.4)	23 (85.1)	74	
Total	153	27	180	

Table 4 shows that

- The sensitivity of the Risk of malignancy index score (RMI) to predict tumor was 85.1%.
- The specificity of the Risk of malignancy index score (RMI) to predict tumor was 66.6%.
- The positive predictive value was 31.1%,
- The negative predictive value was 96.2%
- P value was 0.04 which was statistically significant

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DISCUSSION

Ovarian cancer is the second most common gynecological malignancy and the most lethal worldwide. Most patients are diagnosed with advanced disease, which carries significant mortality. Multi-modal ovarian cancer screening using a serial CA125 algorithm has resulted in diagnosis at an earlier stage, both in average and high-risk women.[10-11]

Table 1 shows that the age group most affected was 31–50 years (50%), as supported by the the study conducted by Scully RE,[12] Labidi SI et al,[13] and Barnhill DR et al.[14] The present study shows that ovarian tumors are more prevalent among Hindus (72.9%) which may be because it was conducted in a Hindu-dominated city. The majority of the participants were educated up to the 12th standard (35%), followed by class 10th (28.4%) and only 13.9% were graduates and above. Educational status plays a very important role in terms of awareness about the signs and symptoms of disease, early diagnosis, and treatment. The study shows that 75% of cases (135) were self-employed, followed by employed 15% (27) and students 10% (18). In our study, we did not come across any high-risk occupations related to ovarian tumors.

Table 2 dipicts that 35.6%(64) of cases were obese, and 18.3%(33) of cases were overweight, suggesting the role of high levels of estrogen leading to ovarian cysts. The finding is supported by the study conducted by Tworoger SS et al,[15] where they found that higher BMI was associated with certain histologic types of ovarian cancer like low-grade serous and invasive mucinous tumors.The substantial proportion of cases belong to the nulliparous group. Since there is more ovulation, there will be more metaplasia of the surface epithelium of the ovary, which further increases the risk of ovarian tumors. The finding is supported by the study conducted by Negri E et al,[16] where they found that ovarian cancer is associated with low parity and infertility. Parity is inversely proportional to the risk of ovarian cancer.The present study shows that most cases belong to the premenopausal group (76.7%). The finding is supported by the study conducted by Franceschi S et al,[17] where they found that early menarche and late menopause increase the risk of ovarian cancer. We also found that 7.2% had a family history of ovarian tumors. Similar findings were found in a study conducted by Frank TS et al,[18] which stated that most hereditary ovarian cancers result from mutations in BRCA1 or BRCA2 genes. Many studies have found that at least 15% of women with high-grade nonmucinous ovarian cancer have germline mutations. The degree of risk is difficult to determine precisely without performing a full pedigree analysis. It is important to note that 40% of women with BRCA-related ovarian cancer do not have a family history.

In our study 18.9% had a history of tobacco consumption; among that, 75% of patients had malignant tumors. The finding is supported by the study conducted by Hathaway CA et al,[19] and Sancutti C et al,[20] where they found that early-life tobacco exposure may increase the risk of developing

ISSN (O): 2687-5365; ISSN (P): 2753-6556

ovarian tumors. The present study shows that 11.7% of cases consumed OCP in the past for a varied period, and the remaining 88.3% of patients did not use OCPs. The OCPs provide protection against ovarian tumors by inhibiting ovulation. Oral contraceptive pills are the only documented method of chemo-prevention for ovarian cancer, and it is essential for women with a strong family history of ovarian cancer. This finding is supported by a study conducted by Negri E et al,[16] which they found that OCP reduces the risk of epithelial ovarian cancer.

In this cross-sectional study of 180 women with ovarian tumors the clinical utility of serum CA125 in differentiating benign from malignant tumors was evaluated. The majority of cases (85%) were benign, and only 15% were malignant (Figure-1) consistent with previous literature by Das MK et al,[21] Couto et al,[22] Ganga SP et al.[23]

Table 3 shows that serum CA125 demonstrated a high sensitivity (88.9%) for detecting malignant ovarian tumors, but the specificity was low (23.5%). This reflects the well-known limitation of CA125, which may be elevated in several benign gynecological conditions such as endometriosis and PID reducing its discriminative ability as quoted by Bast RC Jr et al,[24] Cramer DW et al,[25] Lertkhachonsuk AA et al,[26] Henderson, JT et al.[27] The positive predictive value (17%) was poor, whereas the negative predictive value (92.3%) was high, indicating that a normal CA125 level reliably excludes malignancy. Similar findings were noted in a study conducted by Matsas A et al,[28] and Jacobs IJ et al.[29]

ROC curve analysis (Figure-3) further confirmed the limited diagnostic role of CA125 in this cohort, with an AUC of 0.438, suggesting performance inferior to chance. This can be attributed to the substantial overlap in CA125 levels between benign and malignant cases.

In contrast, the Risk of Malignancy Index (RMI) showed better diagnostic balance, (Table 4) with sensitivity of 85.1% and specificity of 66.6%. The NPV was excellent (96.2%), and the p value (0.04) indicated statistical significance. By integrating ultrasound features, menopausal status, and CA125 levels, RMI reduced false positives while maintaining high sensitivity, similar to studies conducted by Winarno GN et al,[30] and Mustafin C et al.[31] Clinically, these findings support the use of RMI over CA125 alone for preoperative evaluation of ovarian tumors, especially in settings with a high prevalence of benign disease. However, the low PPV of both tests highlights the need for complementary diagnostic approaches, including advanced imaging and additional biomarkers.

Limitations: The small sample size was an issue in the present study. Subjects were selected using convenient sampling, which allows for selection bias. Serum CA125 also responds to other tumors, which was not considered and, of course, beyond the scope. A case-control or randomized control trial study would be better.

CONCLUSION

The present study concluded that ovarian tumors had high serum CA125 levels. High serum CA125 (>35 U/mL) was higher in malignant-form ovarian tumors than in benign tumors. The study also showed that sensitivity of the test is 88% but has weak specificity to identify malignant form. Finally, the study concluded that CA125 is a good screening tool (high sensitivity but low specificity), so it may be used along with other tools or in combination to be more specific in screening ovarian tumors.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556