

## Correlation of serum CA-125 with histopathological findings in ovarian tumors

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### Abstract

**Introduction:** Primary ovarian neoplasms exhibit a wide range of clinical and histopathological presentations. Tumors showing epithelial differentiation are the most frequent primary ovarian neoplasms. Among the malignant tumors, the most common histological sub-type corresponds to serous adenocarcinoma, whose diagnosis is established in advanced stages of the disease in approximately 75% of the patients in Indian population. Tumor marker CA 125 represents a glycoprotein synthesized mainly by neoplastic cells with epithelial differentiation, and its serum level seems to be associated with the biological potential of these lesions. This study intends to find the correlation between CA125 and histopathology of ovarian tumours.

**Objective:** To estimate the correlation of serum CA-125 with histopathological subtypes of ovarian tumors.

**Materials and Methods:** Fifty two distinct cases of ovarian tumors were selected, between January 2017 and June 2018, from patients undergoing concomitant analysis of serum CA 125 levels. In each case, age, tumor size, histological type and serum CA 125 were determined. The correlation between preoperative CA125 and histopathological type of tumor were evaluated. Chi square analysis was done and p value <0.05 was considered to be statistically significant.

**Results:** 52 ovarian tumor patients were included in the study period. The mean age of presentation was 42.69±14.55 years. Highest levels of serum CA 125 were found in malignant serous tumours. Mean serum CA125 concentration in malignant serous adenocarcinoma patients (n = 26) was 635.36±386.05 IU/ml, showing increased serum levels with raised biologically aggressive behaviour and poor patient outcome. A statistically non significant relationship between CA 125 levels and age (p = >0.05) and other clinico-pathological parameters were found. No relationship between CA 125 levels and tumor size is seen.

**Conclusion:** In our study we found 40 patients with greater than 35 IU/ml of CA 125 and maximum no n=34 (65.4%) belonged to malignant category. Association between malignant potential with CA 125 level (greater than 35 IU/ml) was found to be highly significant (p<0.001).

**Keywords:** CA125, Ovarian tumors.

### Introduction

Primary ovarian tumors exhibit a wide range of clinical and histopathological presentations. Tumors showing epithelial differentiation are the most frequent primary ovarian tumors. Among the malignant tumors, the most common histological sub-type is serous adenocarcinoma, whose diagnosis is confirmed in advanced stages of the disease in approximately 75% of the patients in Indian population. Tumor marker CA-125 represents a glycoprotein synthesized mainly by neoplastic cells with epithelial differentiation, and its serum level is associated with the biological potential of these tumors. In 93% of cases out of the women with ovarian cancer, CA-125 levels were found to be correlated with tumour burden. When CA-125 levels were less than 35 U/ml it was estimated to be normal.<sup>1,2</sup> It has been playing an established role in observing, management and distinguishing recurrence of ovarian cancer. It has also been suggested as an established prognostic marker for advanced stages of ovarian cancer.<sup>3-5</sup> In more than 80% of ovarian cancers cases, CA-125 was over expressed and its levels at presentation were well correlated with the risk of malignancy, stage progression of disease and histology.<sup>6</sup> Thus the aim of this study is to find any correlation, if present between CA125, staging and histopathology of ovarian tumours.

The natural history of malignant ovarian tumours, which included local invasion of tissues deep within the

pelvis and the frequent presence of peritoneal seedling metastases prevents early diagnosis of the disease and once the diagnosis had been made, hindered accurate monitoring of disease status. There was therefore a need for certain serum markers which were good prognostic predictors and were easy to assay. Serum CA125 is one such marker which is commonly used in diagnosis as well as management of epithelial tumours of ovary. Preoperative CA125 levels,<sup>7,8</sup> postoperative levels,<sup>9</sup> absolute levels after chemotherapy<sup>10</sup> and rate of fall<sup>11</sup> after the first cycle of chemotherapy have all been advocated as useful prognostic indicators in epithelial ovarian cancer.

Prognostic significance of early CA125 assay has also been reported in epithelial ovarian carcinoma.<sup>12</sup> Various studies have reported other malignant conditions such as in breast cancer, mesothelioma, non-Hodgkin lymphoma (NHL), gastric cancer, leiomyoma and leiomyosarcoma of gastrointestinal origin, with elevated CA-125 levels. Many benign conditions such as endometriosis, pregnancy, ovulatory cycles, liver diseases, congestive heart failure, as well as infectious disease such as tuberculosis also reveal raised CA-125 levels.<sup>13</sup>

The observational study in question has been planned to correlate serum CA-125 levels with histopathological findings of ovarian tumours.

## Material and Methods

The present Cross-sectional study was conducted over a period of one and half year from Jan 2017 to June 2018. Patient information was collected through a pre-designed proforma. The study was carried out after obtaining clearance from the institutional ethical committee. Total 55 cases were obtained over a period of one and half year which met the inclusion and exclusion criteria. The diagnosis of ovarian tumors was done by thorough clinical, pathological, radiological imaging and histopathological examination. Preoperative serum levels of CA125 were taken from all patients. VIDAS CA 125 II is an automated quantitative test for use on the VIDAS family instruments. Statistical analysis was performed using SPSS version 23. Pearson's Chi Square test and Fisher's exact test were used for comparison of data and p-value of less than 0.05 was considered significant. Present study included patients of age group varying from 2nd to 6th decade.

## Results

In the present study age range of patients with ovarian tumor was seen more commonly in 3rd to 4th decade of life. Mean age of presentation was 42.69±14.55 years.

Various symptoms of the patients were listed and abdominal pain was the most common symptom followed by abdominal mass, Ascites, pain abdomen with mass and menstrual irregularities. Patients presenting with unilateral mass constitute 69.2% cases, out of which 20 cases were malignant, 14 cases were benign and 2 cases were of borderline nature. In bilateral ovarian masses, all of the cases were malignant 30.8%.

Histological findings and distribution of ovarian mass among each of the three categories of patients, Benign, Borderline and Malignant. While among Malignant cases majority of the cases were Serous cystadenocarcinoma followed by Mucinous cystadenocarcinoma. Among all benign tumors, Benign serous cystadenoma, Mucinous cystadenoma and Fibroma showed equal frequency in this

study. Borderline cases constitute only 2 case, which include Borderline serous tumor and Teratoma with borderline epithelial tumor.

Among the benign cases (Table no 1), the mean value of serum CA-125 levels were reported to be 47.09 ± 93.68(IU/ml). Among the borderline cases, the mean value of serum CA-125 level were 101.37±131.58(IU/ml). Among the malignant cases, the mean value of serum CA 125 levels were 572.45±368.48 (IU/ml). There was statistical significant association between malignant potential and mean serum CA 125 Value (p<0.001).

There was a significant correlation (Table no 2) between malignant potential and nature of tumor (p<0.05). Serum CA-125 levels and imaging findings (nature of tumor and ascites) independently correlated with malignancy.

According to distribution of patients mean value of CA-125 and histological findings of malignant potential (Table no 3) highest mean concentration of serum CA-125 levels was seen in Serous cystadenocarcinoma 635.36±386.05 followed by Mucinous cystadenocarcinoma 553.18±141.35 while lowest concentration of serum CA-125 levels was observed in Mucinous cystadenoma 8.17±3.82.

In this study (Table 4) 76.9% of patients with ovarian mass presented with high CA125 levels of greater than 35 IU/ml. Out of these 65.4% were malignant.

Association between malignant potential and CA 125 level (greater than 35 IU/ml) was found to be statistically significant (p<0.001).

Out of 39 women (Table 5) with CA125 score of ≥ 35IU/ml, 34 had malignant lesions on histopathology while 5 women had benign lesions. The sensitivity of CA125 in predicting malignant lesions as compared to histopathology was 87.18% with 81.82% specificity. Highest sensitivity and specificity (table no 6.1 and 6.2) on the basis of serum CA-125 levels of our studied patients and the cut off value of serum CA 125 for this was ≥43.4 IU/ml sensitivity 94.4% & Specificity 81.2%.

**Table 1:** Correlation between malignant potential and Serum CA 125 Value

	n	CA 125			P value
		Mean ± SD	Median	Range	
<b>Benign</b>	14	47.09±93.68	14.02	4.0–362.6	<0.001
<b>Borderline</b>	2	101.37±131.58	101.37	8.33–194.42	
<b>Malignant</b>	36	572.45±368.48	528.10	8.26–1420	

**Table 2:** Correlation between malignant potential and nature of tumor

	Malignant Potential			P value*
	Borderline (n=2)	Benign (n=14)	Malignant (n=36)	
<b>Solid (n=4)</b>	0	2	2	<0.001
<b>Mix (n=38)</b>	2	3	33	
<b>Cystic (n=10)</b>	0	9	1	

\*Pearson Chi-Square

**Table 3:** Distribution of patients mean value of CA-125 and histological findings of malignant potential

Histological findings		Frequency		Mean±SD CA 125 Value
		n	%	
<b>Benign (n=14)</b>	Fibroma	3	5.8%	136.13±197.03
	Serous cystadenoma	4	7.7%	16.39±13.8
	Mucinous cystadenoma	3	5.8%	8.17±3.82
	Benign cystic lesion	1	1.9%	88.6
	Mature monodermalteratoma	1	1.9%	21.8
	Mature Teratoma	2	3.8%	25.24±15.5
<b>Borderline (n=2)</b>	Borderline serous tumor	1	1.9%	8.33
	Teratoma with borderline epithelial tumor	1	1.9%	192.42
<b>Malignant (n=36)</b>	Immature Teratoma	1	1.9%	455
	Metastatic signet ring cell carcinoma	1	1.9%	359.8
	Mucinous cystadenocarcinoma	5	9.6%	553.18±141.35
	Serous cyst adenocarcinoma	26	50.0%	635.36±386.05
	Malignant Brenner's tumor	2	3.8%	26.63±25.98
	Granulosa cell tumor	1	1.9%	134.2

**Table 4:** Comparison between malignant potential and mean CA 125 Value

Malignant Potential	Serum CA 125 (IU/ml)				Total (%)		P value
	≤ 35	%	>35	%	N	%	
<b>Benign</b>	9	17.3%	5	9.6%	14	26.9%	<0.001
<b>Borderline</b>	1	1.9%	1	1.9%	2	3.8%	
<b>Malignant</b>	2	3.8%	34	65.4%	36	69.2%	
<b>Total</b>	12	23.1%	40	76.9%	52	100.0%	

Kappa = 0.573

**Table 5:** Showing prediction of malignant tumor according serum CA 125 level

Malignant Potential	Serum CA 125 level	
	>35 (Diseased) (n=39)	≤ 35 (Non-Diseased) (n=11)
<b>Yes (n=36)</b>	34(True Positive)	2 (False negative)
<b>No (n=14)</b>	5 (False positive)	9(True Negative)

Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
<b>87.18</b>	<b>81.82</b>	<b>94.44</b>	<b>64.29</b>	<b>86.0</b>

**Table 6.1:** Serum CA 125 level

Benign Tumor	Serum CA 125 level	
	False positive	True negative
<b>Yes (n=14)</b>	5	9

**Table 6.2:** Serum CA 125 level

Malignant Tumor	Serum CA 125 level	
	False Negative	True positive
<b>Yes (n=36)</b>	2	34

**Table 7:** Showing Comparison of sensitivity and specificity of CA125 in prediction of malignant tumors

Parameters	Present Study	Jacobs et al. <sup>26</sup> (1990)	Snehal. A. Shintre et al <sup>27</sup> (2017)	Chhanda Das et al <sup>28</sup> (2014)
Sensitivity (%)	94.44%	71.0%	93.33%	100.0%
Specificity (%)	81.82%	83.0%	87.75%	86.0%
PPV (%)	87.18%	-	70.0%	-
NPV (%)	64.29%	-	97.73%	-

## Discussion

Epithelial ovarian neoplasms and tumors of mesothelial origin express carbohydrate antigen – 125 which is a high molecular-weight glycoprotein. Besides this, CA -125, a glycoprotein is also found in normal tissues which is originally derived from coelomic epithelium such as peritoneum, pericardium, pleura, fallopian tubes and endometrium and therefore the levels are raised in various benign and malignant conditions that engage these tissues.<sup>15</sup> Some researches have also shown that levels of soluble CA-125 are elevated in numerous other malignant conditions such as mesothelioma, breast cancer, non-Hodgkin lymphoma, gastric cancer, leiomyoma and leiomyosarcoma of gastrointestinal origin. A few benign conditions such as pregnancy, ovulatory cycles, liver diseases, endometriosis, and congestive heart failure, as well as infectious disease such as tuberculosis also reveal raised CA-125 levels.<sup>16</sup> Hogdall EV et al, in their study showed that elevated levels of CA-125 were more strongly related with serous, rather than mucinous tumors.<sup>17</sup> In the present study, Serous tumours showed highest levels of serum CA-125 compared to other tumours ( $635.36 \pm 386.05$ U/ml).

The serum CA-125 levels is elevated in ovarian tumors associated with ascites.<sup>18</sup> In our study serum CA-125 was elevated in non-epithelial tumors as well as in epithelial tumors although the levels were less in non-epithelial ovarian tumors.

Kolwijck et al.<sup>19</sup> described that the pre-operative serum CA 125 levels are significantly higher in serous tumors ( $p < 0.001$ ). In the present study, the mean age of patients were  $42.69 \pm 14.55$  years similar to study by Priya et al<sup>20</sup> and Nalini et al<sup>21</sup>, reported the mean age of 42 years and 42.3 years respectively.

In the present study majority of patients 73.1% presented with symptoms of abdominal pain followed by abdominal mass in 65.4%, Ascites in 57.7%, Pain abdomen with mass in 48.1%, while menstrual irregularity was seen in 38.5% cases. These findings were similar to a study conducted by Nalini et al<sup>21</sup> who reported abdominal mass to be the most common presentation, present in 58.9% of cases. However in a study carried out by Priya et al,<sup>20</sup> pain abdomen was reported as the most common finding present in 71% of cases.

In the present study, majority of the patients presented with unilateral mass comprising of 69.2% cases whereas bilateral masses were seen in 30.7% cases. Karet al<sup>22</sup> obtained similar results in his studies in which majority of the cases were unilateral (73.13%) and rest were bilateral. In the studies undertaken by Nalini et al,<sup>21</sup> and Nishal et al<sup>23</sup> majority of the cases 90.6% and 83% were unilateral and rest were bilateral respectively.

In the present study, out of 52 cases of ovarian tumors, 73.2% cases showed mixed solid cystic areas while 19.1% cases presented as cystic mass. Only 7.7% patients presented as solid mass. In the study conducted by Priya et al<sup>20</sup> reported solid mass only 2.7%, 32.8% mixed mass and 64.5% cystic mass. Another study done by Manoj V et al<sup>24</sup>

also reported 4.2% solid, 24.2% mixed and 71.6% cystic masses in their study.

In the present study, out of 52 studied patients there was 69.3% malignant cases on the basis of histological findings & majority of them 50% cases were serous cyst adenocarcinoma. Among 52 cases there were 26.9% benign tumor among which most common was serous cystadenoma, followed by mucinous cystadenoma and Fibroma, both of which showed equal incidence 5.77% each. Borderline cases were only 3.8%. Study conducted by Nalini et al<sup>21</sup> study for 141 tumors, 83.01% were benign, 4.9% were borderline and 12.1% were malignant, Serous cystadenoma was the most common benign lesion 39.7% followed by mucinous cystadenoma 32.6%. Out of the total malignant cases 12.1%, serous cystadenocarcinoma 9.22% was the most common followed by mucinous cystadenocarcinoma and one case of clear cell carcinoma and one case of endometrioid carcinoma. Out of the 7 cases of borderline lesions 4 were mucinous followed by 3 serous type cases. A mixed epithelial tumor with serous cystadenofibroma along with a minor component of Brenner tumor was also seen in their study.

The present study aimed to find the correlation between malignant potential and Serum CA 125. It was seen that all the malignant cases demonstrated high mean serum value of CA 125 measuring 572.45 (IU/ml) which ranges from 8.26 – 1420 IU/ml. For two Borderline cases, the mean value of Serum CA 125 was 101.37 (IU/ml) which ranged between 8.33–194.42 IU/ml. In benign category the mean value of Serum CA 125 was 47.09 (IU/ml) ranges between 4 -362.6 IU/ml. There was significant association between malignant potential and mean Serum CA 125 ( $p < 0.05$ ). Correlation between Preoperative clinicopathological findings and serum CA-125 was found to be non-significant association ( $p > 0.05$ ). Similar study was done by Yuthana et al<sup>25</sup> who also found similar results reported mean CA 125 level of Benign tumor was 37.5 IU/mL and for malignant was 165 IU/mL.

The results of present study suggest that tumor marker, the most extensively studied molecule CA-125, seems to be the most promising biomarker to predict the probability for ovarian cancer in a given patient<sup>29</sup>

## Conclusion

To conclude, among ovarian masses incidence of ovarian carcinoma was 69% in the present study. Maximum number of cases was noted in 3<sup>rd</sup> to 4<sup>th</sup> decade and most of the patients (73.1%) presented with pain in abdomen. In present study we found 40 patients with greater than 35 IU/ml of CA 125 and maximum number of patients ( $n=34$ , 65.4%) belonged to malignant category. A highly significant ( $p < 0.001$ ) association was seen between malignant potential and CA 125 level (greater than 35). The sensitivity of serum CA-125 level in predicting malignant lesions as compared to histopathology was 87.18% with 81.82% of specificity. It may be concluded that, patients with high serum CA-125 levels having good accuracy in predicting malignant masses and useful in clinical practice.

### Limitations

Study was undertaken in only for those cases which have fulfilled the criteria of pre operative CA-125 and operated in SRMS IMS. Most of the cases turned out to be malignant because of advanced pre-operative workup before surgery.

**Conflict of Interest:** None.

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