Original Article

Correlation of Pre-Operative CA-125 with Clinico-histological Characteristics in Ovarian Tumor Cases

DOI: dx.doi.org

Tafazzula Tasnim[1*], Nowrin Reza[2]

Received: 7 January 2024
Accepted: 23 January 2024
Published: 10 February 2024

Published by:
Sher-E-Bangla Medical College, Barishal, Bangladesh

*Corresponding Author

Editor: Prof. Dr. HN Sarker

Available Online:
https://bdjournals.org/index.php/planet/article/view/418

ABSTRACT

Introduction: *The clinical presentations of ovarian tumors are non-specific. The measurement of CA-125 levels, often combined with other modalities such as bimanual pelvic examination and transvaginal ultrasonography, is suggested for early detection of ovarian cancer—a key application of this tumor marker.* ***Aim of the study:*** *This study aimed to assess the correlation of pre-operative CA-125 with clinico-histological characteristics in ovarian tumor cases.* ***Methods and materials:*** *This cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Combined Military Hospital, Dhaka, Bangladesh from July 2016 to January 2017. As the study subjects, a total of 100 cases presenting with ovarian tumors were enrolled using a convenience sampling technique. Data analysis was performed using MS Office tools and SPSS Version 23.0.* ***Results:*** *Histological analysis in this study revealed a predominance of benign tumors (58%) over malignant tumors (42%). Among women with benign ovarian tumors, 79.3% had CA 125 levels ≤35 U/ml, whereas in malignant ovarian tumors, 95.2% had levels >35 U/ml (p <0.001). Associations were observed between elevated CA 125 levels and age, menopausal status, ascites, carcinoma presence (p <0.001), and tumor histology. Women with malignant serous histotype exhibited a significant increase in CA-125 levels (818.88 U/ml)* ***Conclusion:*** *Constitutional symptoms like weight loss, appetite loss, and mass effect symptoms such as urinary*

(The Planet 2023; 7(1): 163-171)

1. *Classified Specialist, Department of Gynaecology, Combined Military Hospital (CMH), Rajendrapur, Bangladesh*
2. *Graded Specialist, Department of Radiation Oncology, Cancer Center, Combined Military Hospital (CMH) Dhaka, Bangladesh*

retention and pelvic pressure are indicative of malignant ovarian tumors. Elevated preoperative CA-125 levels were noted in malignant serous histotypes, distinguishing them from benign ovarian tumors and other less common malignancies.

Keywords: *Preoperative CA-125, Ovarian tumor, Malignant, Menopause, Tumor*

INTRODUCTION

Ovarian malignancies pose a significant clinical challenge among gynecologic cancers, often remaining asymptomatic until metastasis occurs. Over two-thirds of patients present with advanced disease [1]. The ovaries, unique in their ability to generate various tumor types, consist of totipotent sex cells and multipotent mesenchymal cells, leading to diverse neoplasms [2]. Epithelial cancers, comprising 90% of ovarian malignancies, exhibit the highest fatality-to-case ratio among gynecologic malignancies [3]. The need for the development of reliable serum biomarkers for early detection and prognosis of ovarian cancer, which are both sensitive and specific, remains a long-awaited priority [4]. CA 125, the first and most widely used serum tumor marker test for epithelial cancer of the ovary, was introduced by Bast et al. in 1983 and was recognized by murine monoclonal antibody [2]. CA 125 levels of less than 35 U/mL are now accepted as normal by most of the authors [4,5]. Although serum CA 125 levels have also been shown to be elevated often in patients with benign adnexal masses, these levels have an established role in the differential diagnosis of ovarian cancer, the monitoring of disease status during treatment, and surveillance during follow-up [6]. Ovarian cancer ranks as the 5th most common cancer in developed countries, constituting 4% of all female cancers and 15-20% of female genital organ cancers [7,8]. In Bangladesh, the annual mortality rate per one hundred thousand people from ovarian cancer has seen a 40.3% increase since 1990, averaging 1.8% per year [9]. With a woman's lifetime risk of ovarian cancer at nearly 1.7%, there is a critical need for a tumor marker aiding in screening, early diagnosis, treatment assessment, and follow-up [3]. Various tumor markers, including CA-125, CEA, CA 19-9, PLAP, CASA, OVX1, OV632, OC125, alpha-fetoprotein, germ cell cancer, and estrogen, androgen, and inhibin (stromal tissue cancer), have been tested for ovarian carcinoma [10]. CA 125 is expressed as a membrane-bound protein on the surface of cells undergoing metaplastic differentiation into a Müllerian-type epithelium [11]. The concentration of CA 125 in body fluids reflects certain physiological conditions. Despite being extensively studied, CA 125 remains a key biomarker for potential use in early ovarian carcinoma detection, proving valuable in both detection and disease monitoring [12]. Elevated CA 125 levels have also been observed in benign conditions such as endometriosis, pregnancy, ovulatory cycles, liver diseases, congestive heart failure, and infectious diseases like tuberculosis [13]. An ideal tumor marker ideally possesses 100% sensitivity, specificity, and positive predictive value. However, CA-125, a widely used marker for ovarian carcinoma of epithelium, demonstrates a sensitivity of 69.8%, specificity of 72.32%, positive predictive value of 49.2%, and negative predictive value of 86.2% [14]. Due to false

positives, especially in premenopausal women, CA-125 is not recommended for routine ovarian carcinoma screening. Postmenopausal women with CA-125 levels exceeding 35 IU/ml or premenopausal women with levels over 200 U/ml should be referred to a gynecologic oncologist [14].

METHODS & MATERIALS

This was a cross-sectional study that was conducted at the Department of Obstetrics and Gynecology, Combined Military Hospital, Dhaka, Bangladesh from July 2016 to January 2017. The study included a total of 50 cases with ovarian tumors, selected through convenience sampling. After obtaining a detailed medical history, clinical examinations, including per abdominal, per speculum, bimanual, and per-rectal exams, were conducted. Pre-operative estimation of CA-125 levels was performed to assess its correlation with various ovarian tumor variables. Additional relevant investigations, such as ultrasound (USG) and, in specific cases, transvaginal ultrasound (TVS), were carried out. Ethical approval for the study was obtained from the hospital's ethical committee, and written consent was obtained from all participants before data collection. The study's exclusion criteria involved patients with a chocolate cyst of the ovary, untreated ovarian tumors, periovarian cysts, pelvic tuberculosis, and pelvic organ malignancies other than ovarian. Demographic and clinical information for all participants was meticulously recorded. Data processing, analysis, and dissemination were conducted using MS Office and SPSS version 23.0, as needed. A P value <0.05 was deemed statistically significant in the analysis.

RESULT

Table I: Per abdominal examination findings of the study patients

Mobility	Benign (29)	Malignant (21)	X^2	P-value
	No. (%)	No. (%)		
Present	25 (86.2)	5 (23.8)	72.55	0
Absent	4 (13.8)	16 (76.2)		
Consistency				
Solid	10 (34.5)	8 (38.1)	72.85	0
Cystic	16 (55.2)	1 (4.8)		
Partly solid	1 (3.4)	10 (47.6)		
Partly cystic	2 (6.9)	2 (9.5)		
Surface				
Regular, Smooth	23 (79.3)	4 (19.0)	70.51	0
Irregular	6 (20.7)	17 (81.0)		
Margin				
Well defined	21 (72.4)	5 (23.8)	63.93	0
Ill-defined	8 (27.8)	16 (16.2)		

Table I presents the per abdominal examination findings of the study patients, comparing the characteristics between benign and malignant ovarian tumors. In the benign group (29 cases), mobility was present in 86.2%, consistency was predominantly cystic (55.2%), surface irregularity was observed in 20.7%, and well-defined margins were present in 72.4% of cases. In contrast, in the malignant group (21 cases), mobility was present in only 23.8%, consistency was more varied with a significant proportion being partly solid (47.6%), surface irregularity was predominant (81.0%), and well-defined margins were observed in only 23.8%. Statistical analysis using Chi-square test (X2) demonstrates significant differences ($p < 0.05$) between benign and malignant groups for all examined characteristics, indicating their potential utility in distinguishing between the two tumor types.

Table II: Association between age and CA-125 level

Age (year)	CA-125 level (U/ml)			t^2	P-value
	n	Mean	95% Confidence Interval		
≤ 40	26	111.84	(13.53, 237.20)	-1.75	0.08
> 40	24	284.17	(129.47, 438.86)		

participants. The table is divided into two age groups: those aged 40 years or younger (≤ 40) and those older than 40 (> 40). For the ≤ 40 age group, the mean CA-125 level was 111.84 U/ml with a 95% confidence interval ranging from 13.53 to 237.20 U/ml, while for the > 40 age group, the mean CA-125 level was notably higher at 284.17 U/ml, with a wider confidence interval spanning from 129.47 to 438.86 U/ml. Statistical analysis using t-test indicates a trend towards a significant difference ($p = 0.08$) between the two age groups in terms of CA-125 levels, suggesting a potential association between age and CA-125 levels, albeit not reaching statistical significance at the conventional level ($p < 0.05$).

Table III: Relationship between CA-125 level and nature of the ovarian tumor

CA-125 level(U/L)	Benign (29)	Malignant (21)	X^2	P-value
	No. (%)	No. (%)		
≤ 35	23 (79.3)	1 (4.8)	85.2	0
>35–65	6 (20.7)	2 (9.5)		
>65	0 (0.0)	18 (85.7)		

Table III depicts the relationship between CA-125 levels and the nature of ovarian tumors, categorizing CA-125 levels into three ranges: ≤ 35 U/L, >35–65 U/L, and >65 U/L. Among patients with benign ovarian tumors (29 cases), the majority (79.3%) had CA-125 levels ≤ 35 U/L, with a small portion (20.7%) falling in the range of >35–65 U/L. None of the benign cases exhibited CA-125 levels above 65

U/L. In contrast, among patients with malignant ovarian tumors (21 cases), only 4.8% had CA-125 levels ≤ 35 U/L, while 9.5% fell within the range of >35–65 U/L. A significant majority (85.7%) of malignant cases had CA-125 levels exceeding 65 U/L. Statistical analysis using Chi-square test (X2) indicates a highly significant association between CA-125 levels and the nature of ovarian tumors ($p < 0.05$), suggesting that CA-125 levels can serve as a useful marker in distinguishing between benign and malignant ovarian tumors.

Table IV: Association between reproductive status and CA-125 level in malignant ovarian tumor cases

Status	CA-125 level (U/ml)			t^2	P-value
	n =21	Mean	95% CI		
Pre-menopause	10	442.22	(138.64, 745.80)	0.19	0.03
Post-menopause	11	572.6	(411.87, 733.33)		

Table IV presents the association between reproductive status and CA-125 levels specifically within malignant ovarian tumor cases. The reproductive status is categorized into pre-menopause and post-menopause groups. Among the pre-menopausal patients (n=10), the mean CA-125 level was 442.22 U/ml, with a 95% confidence interval ranging from 138.64 to 745.80 U/ml. In contrast, among post-menopausal patients (n=11), the mean CA-125 level was slightly higher at 572.6 U/ml, with a narrower confidence interval from 411.87 to 733.33 U/ml. Statistical analysis using the t-test indicates a significant difference ($p = 0.03$) between pre-menopausal and post-menopausal groups in terms of CA-125 levels, suggesting that reproductive status may influence CA-125 levels within malignant ovarian tumor cases.

Table V: Status of ascites in the study patients

Ascites	Patient Status n = 50		X^2	P-value
	Benign (29)	Malignant (21)		
	No. (%)	No. (%)		
Absent	17 (58.6)	7 (33.3)	55.25	0
Present	12 (41.4)	14 (66.7)		

Table V outlines the status of ascites among the study patients, differentiating between benign and malignant ovarian tumor cases. Ascites is categorized as either absent or present. Among the benign cases (n = 29), 58.6% of patients had no ascites, while 41.4% presented with ascites. In contrast, among the malignant cases (n = 21), a smaller proportion (33.3%) had no ascites, whereas a significant majority (66.7%) exhibited the presence of ascites. Statistical analysis using the Chi-square test (X2) demonstrates a highly significant

association ($p < 0.05$) between ascites status and the nature of ovarian tumors, indicating that the presence of ascites is more commonly associated with malignant ovarian tumors.

Table VI: Association between ascites and CA-125 level

Ascites	CA-125 level (U/ml)			t^2	P-value
	n = 50	Mean	95% CI		
Absent	24	92.38	18.55, 203.31)	-2.17	0.04
Present	26	288.87	(131.47, 446.27)		

Table VI displays the association between ascites and CA-125 levels across the study patients. Ascites status is categorized into absent and present groups. Among patients without ascites (n = 24), the mean CA-125 level was 92.38 U/ml, with a 95% confidence interval ranging from 18.55 to 203.31 U/ml. Conversely, among patients with ascites (n = 26), the mean CA-125 level was notably higher at 288.87 U/ml, with a wider confidence interval spanning from 131.47 to 446.27 U/ml. Statistical analysis using the t-test indicates a significant difference ($p = 0.04$) between the CA-125 levels in patients with and without ascites, suggesting that the presence of ascites may be associated with higher CA-125 levels.

Table VII: CA-125 level based on the histopathologic type of malignant ovarian tumor

Tumor type	(n=21)	CA-125(U/ml) (Mean)
Serous cyst adenocarcinoma	12 (24%)	818.88
Mucinous cyst adenocarcinoma	6 (12%)	167.35
Dysgerminoma	2 (4%)	12.75
Granulosa cell tumor	1 (2%)	63.6

Table VII presents the distribution of CA-125 levels based on the histopathologic type of malignant ovarian tumors. The table categorizes malignant ovarian tumors into different histopathologic types, including serous cyst adenocarcinoma, mucinous cyst adenocarcinoma, dysgerminoma, and granulosa cell tumor. Among the 21 malignant ovarian tumor cases, 24% were classified as serous cyst adenocarcinoma, with a mean CA-125 level of 818.88 U/ml. Mucinous cyst adenocarcinoma accounted for 12% of cases, with a mean CA-125 level of 167.35 U/ml. Dysgerminoma and granulosa cell tumor each represented smaller proportions (4% and 2% respectively) with mean CA-125 levels of 12.75 U/ml and 63.6 U/ml, respectively.

DISCUSSION

This study aimed to assess the correlation of pre-operative CA-125 with clinico-histological characteristics in ovarian tumor cases. In this study, the majority of benign tumors exhibited cystic

characteristics (55.2%), mobility (85.2%), and regular surface features (79.3%). In contrast, most malignant tumors were solid (38.1%), partly solid (47.6%), with irregular surfaces (81%) and fixed in position (76.2%). Solid consistency, immobility, irregular surface, and ill-defined margins were identified as significant indicators of malignant ovarian tumors ($p < 0.001$). This study aligns with findings from Rukshana and Rubana [15, 16]. Additionally, the mean CA-125 level in malignant tumors (284.17 U/L) was higher in patients aged >40 years than in those aged <40 years (111.84 U/L). The p-value was not statistically significant, suggesting that serum CA-125 is not influenced by age. This study compared with another study, revealing a mean CA-125 level of 1074.68 U/L, higher among patients aged >45 years [17]. Statistically, this study demonstrated a strong association, suggesting that serum CA-125 levels are influenced by reproductive status, though further evaluation is needed. The International Ovarian Tumor Analysis results in 2007 showed that the average CA-125 level for patients without ascites is 92.38 U/ml, while for those with ascites, it is 288.87 U/ml [18]. With a p-value < 0.05, signifying dissimilarity in the averages at the 5% significance level, a significant association between ascites and CA-125 levels was identified. Bergmann et al. demonstrated a close relationship between high CA125 levels and the presence of ascites, regardless of the origin [19]. In Ivanov S's study, the presence of ascites was associated with median CA125 levels of 897 U/ml [20]. In the present study, the serum CA-125 concentration exceeded 35 IU/ml in approximately 80% of women with ovarian malignancy and 26% of women with benign ovarian tumors [3]. However, none of the benign ovarian tumors had a CA-125 level exceeding 65 U/ml. This finding aligns with Ozoh's study, which suggests that relying on the standard cutoff point of 35 IU/ml to distinguish benign from malignant cases can be misleading, especially in menstruating women [21]. The mean pre-operative CA-125 level in malignant ovarian tumors in this study was 1032.87 U/ml. Comparatively, a previous study reported a mean of (1,049.04 ± 2,052.9 UI/ml) [17]. This study revealed that the mean CA-125 values for malignant tumors, specifically serous cyst adenocarcinoma, mucinous cyst adenocarcinoma, dysgerminoma, and granulosa cell tumor, were 818.88 U/ml, 167.35 U/ml, 12.75 U/ml, and 63.60 U/ml, respectively. Histological findings indicated a significant elevation in CA-125 levels among women with malignant serous histotypes. The serum CA-125 level was significantly higher in serous cyst adenocarcinoma compared to mucinous cyst adenocarcinoma. These results align with observations from Houda B and Ivanov, who reported a strong correlation between preoperative CA-125 levels and histological type, particularly with a serous component in patients with epithelial ovarian cancer [17, 20]. Lindblom et al.'s study in ovarian cancer also suggested that an increase in serum CA-125 concentrations may predict serous adenocarcinoma [22].

LIMITATION OF THE STUDY

The present clinical study was conducted with a limited number of patients, and eligibility was based on having at least one assessment of CA-125 concentration. Consequently, the findings may not accurately represent the broader

community's condition. A more comprehensive study, conducted over an extended period, with a larger patient population and long-term follow-up capabilities, would have provided more precise insights into the incidence, symptoms, and diagnosis, leading to a more definitive conclusion.

CONCLUSION & RECOMMENDATION

Various tumor markers have been explored to aid in the effective management of epithelial ovarian cancers. Currently, serum CA-125 stands as the gold standard tumor marker for this disease. It plays a crucial role in early detection, assessing the adequacy of surgery, evaluating the effectiveness of chemotherapy, facilitating follow-up, and predicting subclinical recurrence, progression, prognosis, and survival. In contemporary ovarian carcinoma management, the investigation is incomplete without considering CA-125 levels.

FUNDING

No funding sources.

CONFLICT OF INTEREST

None declared.

APPROVAL

The study was approved by the Institutional Ethics Committee

REFERENCES

1. *Kumar A Significance of tumor markers in gynecological cancers Obs and Gynae Today 1999, 4(2) 82-85.*
2. *Fritsche HA, Bast RC. CA 125 in ovarian cancer: advances and controversy. Clin Chem. 1998; 44:1379–1380.*
3. *Current Obstetric & Gynaecologic Diagnosis & Treatment 10th edition, Page 849.*
4. *Gupta D, Lis CG. Role of CA125 in predicting ovarian cancer survival-a review of the epidemiological literature. Journal of ovarian research. 2009 Dec;2:1-20.*
5. *Kolwijck E, Thomas CM, Bulten J, Massuger LF. Preoperative CA-125 levels in 123 patients with borderline ovarian tumors: a retrospective analysis and review of the literature. International Journal of Gynecological Cancer. 2009 Nov 1;19(8):1335-8.*
6. *Jacobs IJ, Skates S, Davies AP, et al. Risk of diagnosis of ovarian cancer after raised serum CA 125 concentration: a prospective cohort study.*
7. *Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: A Cancer Journal for Clinicians. 2015; 65:87108.*
8. *Datta DC. Textbook of gynecology. 7th ed. Kolkata: New Central Books Agency (P) Ltd; 2008.p-304.*
9. *Feeley KM, Wells M. Precursor lesions of ovarian epithelial malignancy. Histopathology. 2001; 38:87 –95.*
10. *INGEBORG A. KOELM et al A Comparative Immunohistochemical and Immunocytochemical Study of Two Commercial Monoclonal antibodies.*
11. *Bischof P, Tseng L, Brioschi PA, Herrmann WL. Cancer antigen 125 is produced by human endometrial stromal cells. Hum Reprod. 1986;1 :423.*
12. *Kenemans P, Yedema CA, Bon GG, von Mensdorff-Pouilly S. CA 125 in gynecological pathology--a review. Eur J Obstet Gynecol Reprod Biol. 1993; 49:115-124.*
13. *Spitzer M, Kaushal N, Benjamin F. Maternal CA-125 levels in pregnancy and the puerperium. J Reprod Med. 1998; 43:387–392.*
14. *No GT. Management of suspected ovarian masses in premenopausal women.*

15. *Rukshana J. Correlation of clinical preoperative finding of ovarian tumor (Dissertation), Bangladesh College of Physician and Surgeon January.*
16. *Tabassum R.Study of clinical presentation, management and histological variants of ovarian tumor (Dissertation), Bangladesh College of Physician and Surgeon July 2007.*
17. *Bouanene Houda, HarrabiImed, Factors predictive of elevated serum CA1251evels in patients with epithelial ovarian cancer; Bulletin du Cancer. Volume 94, Numero 7, 10018-22, July 2007, Electronic journal of Oncology30. Nossov Vladimir, Amneus Malaika, The early detection of ovarian cancer: from traditional methods to proteomics. American Journal of Obstetrics and Gynecology Sep2008.215-223.*
18. *Van Calster B, Timmerman D, Bourne T, et al. Discrimination between benign and malignant adnexal masses by specialist ultrasound examination versus serum CA125. J Natl Cancer Inst. 2007; 99(22):1706-1714.*
19. *Liu J, Yang G, Thompson Lanza JA, Glassman A, Hayes K, Patterson A, et al. A genetically defined model for human ovarian cancer. Cancer Res 2004; 64: 1655-63.*
20. *Ivanov S. Epithelial ovarian cancer—preoperative assessment of Cal25 levels as an independent prognostic factor. Akush Ginekol 2003; 42: 16-9.*
21. *Ozoh RF, Schwartz PF Eitel PJ Ovarian Cancer, Fallopian tube carcinoma and peritoneal carcinoma cancer Principles and practice of oncology Philadelphia Lippincott- Raven Publishers 1997 1502-1540.*
22. *Lindblom A, Liljegren A. Tumour marker in malignancies. BMJ2000; 320:424-7.*