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ORIGINAL ARTICLE

Association of raised CA 125/ CEA ratio and positive Ascitic fluid cytology with diagnosis of ovarian cancer in patients with adnexal mass.

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ABSTRACT… Objective: To look for the association of raised CA 125/ CEA ratio and positive ascitic fluid cytology with the diagnosis of epithelial ovarian cancer in patients with an adnexal mass. **Study Design:** Comparative Cross-sectional study. **Setting:** Department of Oncology and Gynecology, Sheikh Zayed Hospital Rahimyarkhan. **Period:** September 2021 to February 2022. **Material & Methods:** A total of three hundred patients presenting with adnexal mass were recruited for the study. All patients underwent detailed evaluation, including CA 125 levels, CEA levels and ascitic fluid cytology. After complete staging workup, they underwent surgery and histopathological analysis of adnexal mass. A consultant histopathologist made the diagnosis of ovarian cancer. Association of various factors, including raised CA 125/ CEA ratio and positive ascitic fluid cytology with the diagnosis of ovarian cancer, was established. **Results:** Out of 350 patients of adnexal mass included in analysis, 273 (88%) were diagnosed with ovarian carcinoma, while 77 (22%) were not diagnosed with ovarian cancer after the surgery and had a diagnosis other than ovarian cancer. 179 (51.2%) patients were post-menopausal whereas 171 (48.8%) were pre-menopausal. It was revealed that raised CA-125/CEA ratio and positive ascitic fluid cytology had a statistically significant association with the diagnosis of ovarian carcinoma on histopathology (p-value<0.001). **Conclusion:** Most patients who presented with adnexal mass were diagnosed with ovarian carcinoma in our study. Raised CA 125/ CEA ratio and positive ascitic fluid cytology at baseline predicted a histopathological diagnosis of ovarian cancer in our study participants.

Key words: Adnexal Mass, Cytology, Ovarian Cancer, Tumor Makers.

INTRODUCTION

The number of cancer cases has increased recently, which has high morbidity and mortality and burdens the health system.[1] Epidemiological data regarding neoplastic illnesses is not very accurate for Pakistan, and we have no central national database.[2] Clinicians have been trying hard to look for novel options for diagnosis and management of neoplastic diseases to improve and provide adequate care for oncological patients.[3]

The signs and symptoms of Ovarian cancer are vague and nonspecific and overlap with the clinical presentation of gastrointestinal cancer and metastatic disease.[4] Despite careful pre-operative examination and a risk of malignancy index (RMI) of more than 200, patients with pelvic tumors may prove to have non-ovarian cancer at surgery.[5] Due to unknown origin of tumour, patient performance status, lack of surgical expertise, and financial challenges, upfront surgery or biopsy is not always possible for the treating team.[6] Many studies have been performed to look for the association of various biochemical markers with the diagnosis of ovarian cancer. Lertkhachonsuk et al. In 2020 studied serum CA19-9, CA-125 and CEA for this purpose. They revealed that elevation of these markers at the time of diagnosis of adnexal mass had been associated with the diagnosis of malignant tumour after surgery and histopathology. They advocated the use of these markers, for differentiating between benign, borderline, and malignant ovarian

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tumours.[7] Moru et al. Studied levels of CEA alone and CA 125/CEA ratio in distinguishing primary and secondary ovarian tumours and found CEA levels alone useful for this purpose.[8] Bozkurt et al. Published a study in patients of Turkey regarding levels of various tumour markers in prediction of ovarian cancer. They concluded that CA-125 and CA15-3 were helpful in this regard and helped clinicians differentiate between types of adnexal masses, especially ovarian cancers.[9]

We live in a country with limited resources, and there is always a need to find novel non-invasive and cost-effective methods for diagnosing malignant conditions. A recent local study published data regarding mortality associated with ovarian tumors and other epidemiological findings in the Pakistani population.[10] Limited local data has been available regarding the use of various tumor markers or cytology parameters in distinguishing ovarian tumors from other adnexal masses. This study's rationale is to determine if CA 125/CEA ratio and ascitic fluid cytology preoperatively can be used to differentiate between malignant ovarian disease and malignant non-ovarian disease in the pelvis, with the intent to optimize the selection of patients and timing for surgery and chemotherapy.

MATERIAL & METHODS

This comparative cross-sectional study was conducted at the Oncology and Gynecology Unit of Sheikh Zayed Hospital Rahimyarkhan from September 2021 to February 2022. First, the sample size was calculated, using the WHO sample size calculator by using the population prevalence proportion of ovarian cancer as 1%.[11] Non-Probability purposive sampling technique was used to gather the sample.

As per inclusion criteria, female patient aged 18 to 70 years, both pre-menopausal and post-menopausal, with adnexal mass were included in the study.

Patients with prior history of cancer or those with secondary adnexal mass with primary tumor elsewhere were excluded. Women who were pregnant at the time of diagnosis of adnexal mass were also excluded. Women who refused surgery after the diagnosis or didn't give consent for participation in study were also not recruited in the analysis.

After taking written informed consent from all the potential participants and ethical approval (via letter no 468/IRB/SZMC/SZH) from the hospital's ethical review board, women with adnexal mass were recruited for analysis. Diagnosis of adnexal mass was established by consultant Oncologist and gynaecologist based on clinical and Ultrasound fidnings.[12] All patients underwent detailed evaluation including CA 125 levels, CEA levels and ascitic fluid cytology. After complete workup, patients were discussed in a multidisciplinary team, and surgical intervention was decided. Surgery was carried out in the surgical department of Sheikh Zayed hospital, and Histopathological samples were sent to the Hospital Pathology department. A consultant histopathologist made a diagnosis of ovarian cancer.[13] Association of various factors, including raised CA 125/ CEA ratio and positive ascitic fluid cytology with the diagnosis of ovarian cancer, was established. CA 125/CEA ratio was considered significantly high if it was more than 25.[14]

Data was entered and analyzed by using Statistical package for Social Sciences version 23.0. The qualitative data were presented as frequency distribution and quantitative data were presented as mean ± SD. Relationship of various variables including high CA125/CEA ratio and ascitic fluid cytology with diagnosis of ovarian cancer was analyzed by using Pearson Chi-square test. The p-value ≤ 0.05 was considered statistically significant to establish the association.

RESULTS

Out of 350 patients of adnexal mass included in the analysis, mean age of the women diagnosed with adnexal mass was 44.85 ±8.672 years, 171 (48.8%) were pre-menopausal while 179 (51.2%) had achieved menopause. Table-I summarizes the general characteristics of study participants. Out of total patients recruited in the study, 77 (22%) were not diagnosed with ovarian cancer after the surgery and had diagnosis other than

ovarian cancer while 273 (88%) were diagnosed with ovarian carcinoma on histopathology report.

Study Parameters	N (%)
Age (years) Mean + SD Range (min-max)	 44.85 ±8.672 years 21 years - 65 years
Post-Menopausal No Yes	 171 (48.8%) 179 (51.2%)
Ovarian cancer No Yes	 77 (22%) 273 (88%)
High CA125/CEA ratio No Yes	 60 (17.1%) 290 (82.9%)
Ascitic fluid cytology Negative Positive	 56 (16%) 294 (84%)
Type of ovarian tumor Mucinous Serous Clear cell Endometrioid	 65 (18.6%) 176 (50.3%) 56 (16%) 53 (15.1%)

Table-I. Characteristics of patients with adnexal mass included in the study

Table-II showed the results of Pearson chi-square analysis. It was revealed that raised CA-125/CEA ratio and positive ascitic fluid cytology had statistically significant association with presence of ovarian carcinoma on histopathology among patients diagnosed with adnexal mass. (p-value<0.001).

Blood samples were collected and tested from 350 recruited participants for CA 125 levels and CEA levels, 290 (82.86%) reported high CA 125 / CEA ratio (> 25) as shown in Figure-1 below.

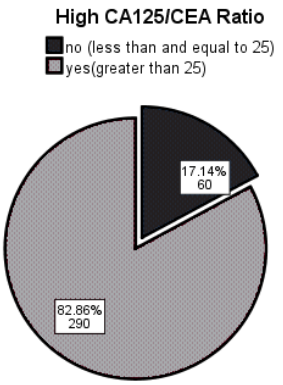

Figure-1. Frequency distribution of high CA 125/CEA ratio

	Negative Biopsy for Ovarian Cancer	Diagnosis of Ovarian Cancer	P-Value
Age < 50 years >50 years	 41 (53.2%) 36 (46.8%)	 130 (47.6%) 143 (52.4%)	0.383
Post-Menopausal No Yes	 42 (54.5%) 35 (45.5%)	 129 (47.2%) 144 (52.8%)	0.258
High CA125/ CEA ratio No Yes	 24 (31.1%) 53 (68.9%)	 36 (13.2%) 237 (46.8%)	<0.001
Positive ascetic fluid cytology No Yes	 23 (29.8%) 54 (70.2%)	 33 (12.1%) 240 (87.9%)	<0.001

Table-II. Association of various parameters with diagnosis of ovarian cancer in patients presenting with adnexal mass

Ascitic fluid cytology revealed that 294(84%) participants reported positive cytology for cancerous cells, as evident from Figure-2.

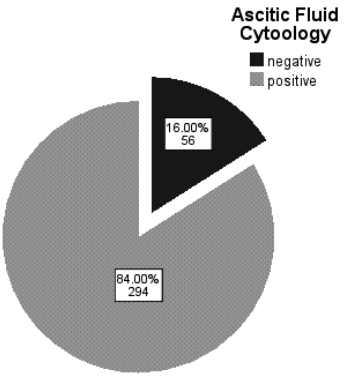

Figure-2. Frequency distribution of ascitic fluid cytology.

DISCUSSION

Two relatively cost-effective and less invasive methods we studied were found associated with the diagnosis of ovarian cancer in our study participants. Ovarian cancer is a relatively common malignant condition among women of all age groups, especially the elderly. The treating team initially picks it as an adnexal mass with multiple differential diagnoses. If any

less invasive and cost-effective investigations can predict future malignancy, it can be helpful to prioritize patients for surgery and work up in resource-limited settings. We conducted this study to look for the association of raised CA 125/ CEA ratio and positive ascitic fluid cytology with the diagnosis of ovarian cancer in patients with an adnexal mass.

Kawahara et al., in 2021, worked on a novel tool for differentiating between endometriosis associated ovarian cancer from ovarian Endometrioma.[15] CEA levels and tumor size were the main components of that tool, and it was concluded that this tool differentiated sufficiently between endometriosis associated ovarian cancer from ovarian Endometrioma. Our study was slightly different from that of Kawahara et al. However, crux remained similar as we also concluded that biochemical markers and cytology could help differentiate ovarian carcinoma from other adnexal masses.

A Turkish study was published in the journal of the college of physicians and surgeons Pakistan in 2021 regarding the initial CA 125 value as a predictive marker for high-grade carcinoma of ovaries.[16] They revealed that initial high levels of CA 125 predict high-grade cancer of ovaries. Our study concluded the same for CA125/CEA ratio in patients presenting with an adnexal mass.

Hermans et al. studied the value of fine needle aspiration cytology diagnosis in ovarian masses in children and adolescents. They concluded that this has low value in predicting the malignant condition of ovaries and should not be used in the routine.[17] Our results were slightly different as we studied the association of both cytology and CA 125/CEA ratio and concluded that many patients who presented with adnexal mass were diagnosed with ovarian carcinoma in our study. Furthermore, raised CA 125/ CEA ratio and positive ascitic fluid cytology at baseline predicted a histopathological diagnosis of ovarian cancer in our study participants.

Choi et al. in 2018 tried to see if serum levels of cancer antigen 125 and carcinoembryonic antigen ratio before the surgery could help clinicians differentiate between mucinous ovarian carcinoma and other epithelial ovarian carcinomas.[18] They came up with the findings that this ratio was quite valuable in differentiating between mucinous ovarian carcinoma and other types of ovarian tumours. Therefore, we tried to look for the usefulness of this ratio in differentiating ovarian cancers from other adnexal masses and found that raised levels of CA125[19] and CEA ratio at the time of diagnosis of adnexal mass is associated with the diagnosis of ovarian cancer after the surgery and histopathology result.

Multiple factors could affect the levels of CA 125 and CEA in women presenting with an adnexal mass, affecting the ratio as well. Therefore, with this study design, we cannot conclude the predictive validity of this ratio for diagnosing ovarian mass in patients presenting with an adnexal mass. Similarly, positive ascitic fluid[20] cytology is a nonspecific investigation and could be positive in any malignancy resulting in ascites.

CONCLUSION

A large number of patients who presented with adnexal mass were diagnosed with ovarian carcinoma in our study. Raised CA 125/ CEA ratio and positive ascitic fluid cytology at baseline predicted a histopathological diagnosis of ovarian cancer in our study participants.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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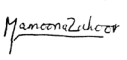
1	Shanzah Shahbaz	Study design conception, data analysis and interpretation, write up and literature search.	
2	Sadia Zahoor	Literature search, data interpretation and analysis, critical review, proof reading.	
3	Mamoona Zahoor	Data interpretation and analysis.	
4	Sadia Zulfiqar	Literature search, Data acquisition and review.