Assessment of carcinoembryonic antigen as a prognostic marker in ovarian malignancies treated in a rural hospital of West Bengal

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ABSTRACT

Background: Ovarian neoplasms are the second most common cause of gynecological malignancy both worldwide as well as in India. Innocuous clinical presentation and late diagnosis contribute to the mortality toll of this neoplasm. Thus, early diagnosis remains the cornerstone to increase the survival rate of ovarian neoplasms. Though, cancer antigen 125 (CA-125) is a time-tested marker for ovarian neoplasm diagnosis yet its increment in benign gynecological conditions questions its own diagnostic specificity. Carcinoembryonic antigen (CEA), the conventional marker for colorectal cancer detection, is found to be associated with epithelial ovarian cancer. **Aims and Objectives:** This study was aimed to find the efficacy of CEA along with CA-125 in the early detection of ovarian neoplasm and predicting the outcome. **Materials and Methods:** This hospital-based longitudinal study was conducted in the Biochemistry department of Bankura Sammilani Medical College. Established cases of ovarian neoplasm were recruited as study population using pre-defined inclusion and exclusion criteria. Serum CEA and CA-125 were estimated at the time of diagnosis, 6 weeks, 6 months, and 12 months after surgery. **Results:** There was no significant difference between the median concentration of CEA among the four phases of treatment. Serum CEA was positively correlated to CA-125 during all phases of treatment (P = 0.653, P = 0.000). The binary logistic regression revealed that CEA (odds ratio = 1.2, 0.83–1.69) had higher chances to be associated with ovarian stages associated with cancers beyond Stage IC. CEA had a lower sensitivity and specificity in comparison to CA-125. **Conclusion:** This study suggested CEA, a theranostic marker, can supplement the present biochemical diagnostic modalities to improve diagnostic and prognostic efficacy cost-effectively.

Key words: Cancer Antigen 125; Carcinoembryonic antigen; Epithelial ovarian cancer

INTRODUCTION

Ovarian neoplasm is the second most common cause of gynecological malignancy having a high mortality rate in the world as well as in India. Cancer registries have shown that even in India the mortality has increased to 3.8% (2020) from 3.34% (2018).[1] This clearly identifies how the burden of ovarian malignancy is escalating with time. The disease epidemiology varies with age, race, ethnicity, geographical location, and socioeconomic status. The median age for diagnosis of this disease is 50–79 years.[2] Although the highest prevalence is within Caucasian population but mortality of ovarian cancer is highest among the African population probably due to their poor socio-economic status.[3,4] Although the exact etiopathogenesis of ovarian malignancy in innocuous, yet relevant literature about interplay of the following risk factors like nulliparity, early menarche, late menopause, family history of ovarian cancer and association of BRCA1 and BRCA2 mutation, Lynch syndrome, and

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breast malignancy is available.[5,6] This fatality burden is mainly due to late diagnosis. The array of non-specific clinical symptoms is a hindrance to prompt diagnosis. Literature review suggests that the disease is diagnosed in 60% of patients suffering with ovarian neoplasm where the disease has aggravated to a terminal stage and prognosis is very poor.[7] Thus, early diagnosis remains the corner stone to increase the survival rate of ovarian neoplasms. Cancer antigen 125 (CA-125), a glycoprotein, is a time tested marker for the past 30 years in diagnosis as well as in predicting the recurrence of ovarian neoplasm but its associated with various non-ovarian neoplasms such as endometrial cancer, pancreatic cancer, cervical cancer challenges its role as a specific marker.[8] Carcinoembryonic antigen (CEA) is a glycoprotein synthesized by fetal tissues and conventionally used as diagnostic as well as prognostic marker of colorectal cancer.[9] Research has depicted that CEA concentration is raised in about 35% of patients suffering with ovarian malignancy.[10] Relevant literature has cited that CEA has a tendency to be higher in the stage IB to IIIC and ratio of CA-125/CEA along with malignancy risk index may reduce the cost of investigations such as tomography and colonoscopy.[11] With the burgeoning rise of Ovarian neoplasm in this part of subcontinent too, the rationale of this study is to find the efficacy of CEA in correlation to CA-125 with early detection of ovarian neoplasm and predicting the outcome. The hypothesis of this study was to evaluate the role of CEA as a prognostic indicator compared to the existing gold standard CA-125.

Aims and objectives

The aim of this study was to evaluate the role of CEA as a prognostic indicator compared to the existing gold standard CA-125. This hospital-based longitudinal study was aimed to find the efficacy of CEA in correlation to CA-125 in early detection of ovarian neoplasm and predicting the outcome. The serum concentration of CEA and CA-125 was measured at diagnosis and at intervals of 6 weeks, 6 months and 12 months after surgical intervention, and association between the tumor markers were estimated.

MATERIALS AND METHODS

This hospital-based non-interventional longitudinal study was conducted in the Department of Biochemistry of Bankura Sammilani Medical College in collaboration with the Department of Radiotherapy from April 2020 to June 2021. The prospective study was initiated after receiving ethical clearance from the Institutional ethics committee. (Memo no. BSMC/Aca:-288 Dated 27/01/2020). The sample size was calculated based on a formula used for cohort study: N (SS)=(Z/e) 2, Where, Z=1.96 (two tailed) at 95% Confidence Interval (CI), e=Allowable error around the expected/reported incidence of event of interest (here, it is the prevalence of recurrence of Ovarian Cancer). Considering 20%=0.2 error the sample size was 96 (approximately). Assuming 10% non-response/drop-out, the revised SS will be 96+10% of 96=106. However, due to the COVID-19 pandemic few patients were unable to follow up; final 98 patients were included in the study. Each patient was evaluated in a methodical manner and medical records were scrutinized. Patients attending the Radiotherapy clinic having confirmed ovarian malignancy were enrolled in the study. Patients who were known cases of Colorectal carcinoma, Pancreatic carcinoma, Gastric carcinoma, Non-Squamous Cell Lung cancer, Uterine cancer, Chronic Liver disease, and Smoking addiction were excluded from the study. The venous blood sample was collected from study participants with a standard aseptic procedure after obtaining informed consent. The serum CEA and CA-125 concentration were using Centaur CP immunoassay analyzer using chemiluminescence technology.

Statistical analysis

Data of the study were compiled; tabulated and analyzed using appropriate statistical methods in Microsoft excel 2010 and IBM SPSS 21 statistical package. The biological data of the individual were checked for Gaussian distribution using the Kolmogorov Smirnov test and was considered in Gaussian(normal) distribution if $P>0.05$. The Binary logistic regression was done and odd's ratio (OR) was calculated to assess the risk of association The performance parameters such as sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio of CEA and CA-125 was calculated.

RESULTS

The mean age of the study cohort was 48.6 ± 11.2 years. The socio-demographic evaluation of the study population (n=98) revealed that about 97.9% (n=96) and 94.9% (n=93) were married and multiparous. Among the study population, 36.7% had tobacco addiction. The most common histopathological variant among the study population was the epithelial variant. However, a fairly large number (n=9) of metastatic variant of ovarian malignancy was noticed. The most common sub-histological variant among the epithelial variety was serous type. The Kolmogorov-Smirnov test revealed that the distribution of concentration of both CEA and CA-125 deviated significantly from the normal distribution

(P<0.005) and thus the Kruskal-Walis non-parametric test was done. There was a significant difference among the mean rank of Concentration of CA-125. However, no significant difference was there among the mean rank of concentration of CEA (Table 1). A non-parametric Correlation test was done between CEA and CA-125 was done and Spearman's rho (ρ) co-efficient was calculated. From Table 2, it is evident that there is a significant correlation among the CEA and CA-125 throughout the course and treatment of the disease. However, a strong (r=0.653) and significant (P=0.000) correlation co-efficient existed during the post-12 months phase of treatment. The evaluation of the performance parameters like sensitivity, specificity revealed that CEA has a weaker potential in comparison to CA-125 (Table 3). However, the binary logistic regression analysis was performed (excluding the metastatic histopathological variant, as they behave like the tumor of primary origin) and taking Stage IC as the cut-off criteria for Surgical spill (FIGO Classification).[12] It was found that CEA had a higher odd's ratio of 1.2 (95% CI=0.83–1.69) in comparison to CA-125 (OR=1.005, 95% CI=0.99–1.02).
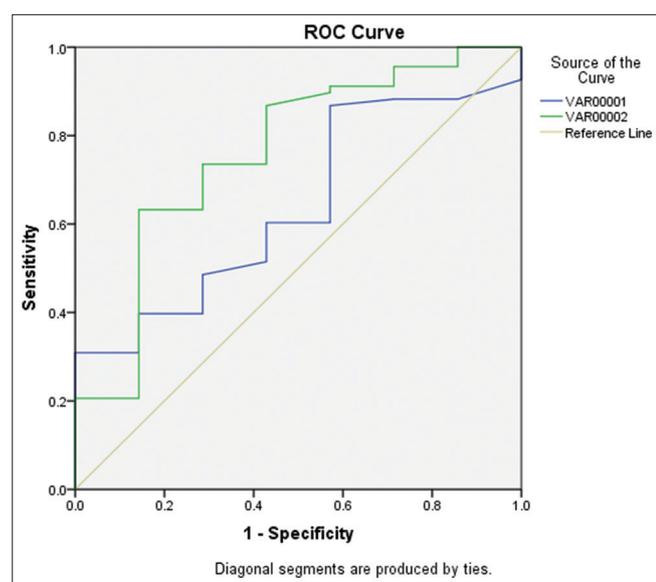

Figure 1: The receiver operating curve of carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125). The area under the curve for CEA and CA-125 is 0.639 and 0.761. Green color for CEA and blue color for CA-125

DISCUSSION

In the present study, we can find that the mean age of disease diagnosis is 48.6±11.2 years, which is a little earlier compared to a study by Burger et al.,[13] in the Caucasian population, where the mean age of diagnosis of the disease was seen to be 50–79 years. The mean age is lower than data obtained from the cohort study of Saini et al., and Murthi et al.[14,15] The research work of Murthi et al., demonstrated that the mean age at diagnosis ranged between 52.2 and 59.5 years.[15] However, the mean age of our cohort population is in concordance with the findings of Basu et al., and associates. Their study reported mean age of 48.8±11.2 years.[16] These demographic details may give us an idea to conduct an ovarian screening program in high-risk woman beyond the age of 45 years. As the survey of Doufekas and associates clearly pointed out that there are higher chances of malignant transformation with age, so this gives an idea to conduct an ovarian screening program in high-risk woman beyond the age of 45 years.[17] The proportion of epithelial ovarian cancer in our study is 76.53% and these findings are in agreement with the findings of Basu et al.[16] There was a significant difference in the median CA-125 concentration among the patients at the time of diagnosis and during various phases of treatment. However, there was no significant difference in the median Concentration of CEA. The median CEA concentration 2.4 ng/ml at the time of diagnosis. This value is quite similar to the findings of study Bashizadeh et al., in Irani women, where the mean concentration of CEA was 2.6 ng/ml.[18] A study by Tholander et al., and his associates suggest that Serum CEA is raised in about 35% of all ovarian malignancy patients and varies with histopathological gradings such as 88% in mucinous and 19% in serous tumors.[10] However, in our present study, the number of cases of mucinous carcinoma is less (6.7%) in comparison to serous cases (52%). This may alter the data finding. Thus, the presence of non-epithelial variety and metastatic variety may have masked the actual data distribution of CEA concentration. Moreover, there is a strong significant correlation of CEA and CA-125 during 12 months past treatment, this clearly identifies that CEA has an important role in prognosis or recurrence as shown in Table 2. A retrospective study by Ayhan

Sl.no	Analyte	Pre-treatment Median Concentration	Median Concentration 6 weeks after surgery	Median Concentration 6 months after surgery	Median Concentration 12 months after surgery
1.	CA-125 (U/ml)	124.1	36.1	45.5	61.9
2.	CEA (ng/ml)	2.4	2.1	2.6	2.7

Table 1: The median concentration of CA-125 and CEA in the study population across various phases of follow-up

CA: Cancer antigen 125, CEA: Carcinoembryonic antigen

Table 2:The correlation between CA-125 during various phases of the study with concomitant CEA

sl.no	Parameters	Spearman's-rho correlation Coefficient (ρ)	P value#
1.	Pre-treatment CEA	0.418	0.000*
2.	CEA concentration 6 weeks after treatment	0.410	0.000*
3.	CEA-concentration 6 months after treatment	0.493	0.000*
4.	CEA-concentration 12 months after treatment	0.653	0.000*

(#Spearman's rho[ρ] non-parametric correlation Coefficient was estimated and considered statistically significant if *P*<0.05* and insignificant if *P*>0.05†), CA: Cancer antigen 125, CEA: Carcinoembryonic antigen

Table 3: Performance parameters of CEA and CA-125 at the point of diagnosis of ovarian malignancy

Sl.no	Diagnostic performance	CEA	CA-125
1.	Sensitivity% and 95% CI	45.33 (33.79-57.25)	96.00 (88.75-99.17)
2.	Specificity% and 95% CI	50.00 (23.04-76.96)	57.14 (28.86-82.34)
3.	Positive Predictive value and 95% CI	82.93 (73.12%-89.66)	92.31 (86.74%-95.65)
4.	Negative Predictive value and 95% CI	14.58 (8.86-23.05)	72.73 (44.59-89.83)
5.	Positive Likelihood ratio & 95% CI	1.09 (051-1.62)	2.24 (1.22-4.11)
6.	Negative Likelihood ratio & 95% CI	0.91 (0.62-1.92)	0.07 (0.02-0.23)

CA: Cancer antigen 125, CEA: Carcinoembryonic antigen

et al., on Turkish women clearly suggested that raised preoperative CA 125 concentrations are associated with positive peritoneal washing cytological findings in the case of Borderline ovarian malignancy.[19] Moreover, their study also suggested that increased CA-125 and CA-19-9 in pre-operative stage may be associated with large tumor size in case of Serous variant. However, our study has shown a positive correlation between CEA and CA-125 indirectly pointing out that a correlation between serum tumor markers panel may act as a surrogate tool for predicting the prognosis. However, low sensitivity clearly identifies the weakness of CEA alone as diagnostic parameter. Literature review clearly demonstrates the elevation of CEA in non-ovarian malignancy too, thus strengthening our finding.[17] In our study, the positive predictive value of CEA and CA-125 was 82.93% and

92.31%, respectively. The negative predictive value of CEA was 14.58% and that of CA-125 was 72.73%. The positive likelihood ratio for CEA and CA-125 was 1.09 and 2.24, respectively while the negative likelihood ratio for CEA and CA-125 was 0.91 and 0.07, respectively. Therefore, it can be concluded that CA-125 has better diagnostic performance compared to CEA. This finding correlates with the study done by Lertkhachonsuk et al.[20] Moreover, in a study by Sorensan, CA-125/CEA ratio >25 had an association of Ovarian cancer in 82% cases. The CA-125/CEA ratio detected 63% of the non-ovarian neoplasms accurately. The specificity raised to85% when the cut-off value of the CA-125/CEA ratio was raised beyond 25.[18,21] It was found that taking Stage IC as the surgical spill criteria, CEA had higher odds ratio (OR=1.2, 95% CI=0.83–1.69) this clearly points out that CEA had a clear correlation with prognostic outcome. This means that patients with elevated CEA had a higher chance of having poor prognosis as compared to those with elevated CA-125. The results correspond to the studies by Cho and Kelly.[22] However, the risk ratio was lower than the study by Lertkhachonsuk et al., who demonstrated a risk ratio of 1.58 (95% CI=1.10–2.29).[20] In our study, both CEA and CA-125 provided diagnostic accuracy with area under the curve (AUC) of 0.693 and 0.761 to differentiate between stages of epithelial ovarian cancer with poor prognosis (stages beyond IC) (Figure 1). The predictive performance of this CEA cut-off value AUC was 0.791 (95% CI, 0.711–0.870) by a study by Moro et al.[23] This clearly identifies that CEA has an important role to predict prognosis or recurrence. However, low sensitivity and specificity clearly identifies the weakness of CEA alone as diagnostic parameter of ovarian neoplasm. However, its role as diagnostic marker can be strengthened using an algorithm like Risk of Ovarian Malignancy Algorithm and multiple markers. In this longitudinal study, we have tried to establish an additional tool to supplement the present diagnostic modalities to improve diagnostic and prognostic accuracy in cost-effective manner.

Limitations of the study:
The sample size was small so the further study is required for generalising the results. Literature reviews suggest that CEA is associated with mainly mucinous variety of ovarian neoplasm. However, the presence of serous, germ cell and metastatic variety of ovarian neoplasm in study population may affect the actual presentation of data.

CONCLUSION

With a limited sample size and resource setting, the study identified that CA-125 cannot be used as a sole parameter

for diagnosis of ovarian neoplasms. CA-125 along with CEA may increase the diagnostic accuracy as well can also be used a tool to predict the outcome too. Our cohort study identified that CEA along with CA-125 can be used a pre-operative tool to plan the line of treatment. Moreover, this study also finds a scope that CEA itself can be used as a criterion in the evaluation of Malignancy risk score if with stringent follow-up and exclusion of information bias, selection bias.

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