Serum CA-125 and Serum CEA Ratio to Distinguish between Ovarian Malignancies and Non-ovarian Malignancies

Anju Radhakrishnan[1], Neeta Malukar[2], Shilpa Jain[3]

Abstract

Introduction: Globally, ovarian carcinoma is the 7th most common cancer. Cancer antigen 125 (CA-125) is the most frequently used biomarker for ovarian cancer (OC). Carcinoembryonic antigen (CEA) is present only at very low levels in healthy adults and is raised in colon cancer, pancreatic malignancies, pancreatitis, cirrhosis, etc. The present study is to evaluate the ability of CEA in combination with CA-125 to differentiate epithelial ovarian malignancies from non-ovarian malignancies.

Aims and objectives: To study, compare, and calculate the ratio of serum CA-125 and serum CEA levels in cases of epithelial ovarian malignancies and non-ovarian malignancies.

Materials and methods: Thirty patients of epithelial ovarian malignancies in group I and 30 female patients of non-ovarian malignancies in group II are included.

Results: Specificity and positive predictive value (PPV) increase when CA-125 to CEA ratio increases and both are 100% if the ratio is >50. When CEA (<5 ng/mL) alone is used for distinguishing an ovarian malignancy from a non-ovarian malignancy, sensitivity is only 93%, specificity 67%, PPV 74%, negative predictive value (NPV) 91%, respectively.

Conclusion: When CA-125/CEA ratio increases, the sensitivity and NPV fall but the specificity and PPV increase and became 100% when it is >50. By knowing the ratio we can have an early diagnosis of OC. We cannot always consider the cut-off for CEA as <5 ng/mL because in smokers the reference value is up to 10 ng/mL.

Keywords: Cancer antigen 125, Cancer antigen 125 to carcinoembryonic antigen ratio, Epithelial ovarian malignancies.

Indian Journal of Medical Biochemistry (2020): 10.5005/jp-journals-10054-0161

Introduction

Globally, ovarian carcinoma is the 7th most common cancer and the 8th most common cause of death from cancer in women.[1] According to NICPR, in India, it is the 4th most common cancer in women. Ovarian cancer (OC) often has no symptoms at the early stages, so the disease is generally advanced when it is diagnosed.[2] Ovarian cancer is the deadliest cancer among women placing it in 4th place for all the fatal diseases among women. Cancer statistics from 2019 show that the estimated number of new cases is 22,240 with deaths around 14,170 cases.[3] There are three histological types associated with the disease. The most common is epithelial OC (EOC). Patients with this fatal disease have only a 45.6% 5-year survival rate.[4] The survival rate in general increases up to 70% if effective early-stage detection is possible. The early-stage detection rate for this disease is as low as 20%.[5]

Several tumor markers are nowadays used to aid in diagnostic and prognostic evaluation. Of these cancer antigen 125 (CA-125/carbohydrate antigen/mucin-16) is the most frequently used biomarker for OC.[6] Carcinoembryonic antigen (CEA) is usually present only at very low levels in the blood of healthy adults. It is raised in malignancies like colon cancer, pancreatic cancer, and lung cancer, and in benign conditions like pancreatitis, cirrhosis.[7,8] By doing the markers alone, we could not correctly identify the primary site of the malignancy as both these markers are raised in several benign conditions also. Their ratio (CA-125/CEA) is a better predictor pointing toward ovarian malignancy as ovarian tumor presents with non-specific symptoms, rather than other organ tumors.

A patient presenting with an abdominal or pelvic mass might complain of various symptoms but a significant majority will have no guiding/obvious symptoms at the first visit, although the final disease may be life-threatening. The pelvic mass may be a primary tumor arising from the uterine corpus, ovaries, urinary bladder, or colon. In other cases, the tumor may be an ovarian metastasis derived from breast, gastric, pancreatic, or lung cancer. In such cases, the patient undergoes unnecessary surgery and is exposed to a risk of morbidity, and the appropriate treatment is delayed.

The present study was to evaluate the ability of the tumor marker, CEA in combination with CA-125 to differentiate epithelial ovarian malignancies from non-ovarian malignancies.

Aims and Objectives

Aims

To find out the significance of serum CA-125/CEA ratio in distinguishing epithelial ovarian malignancies from non-ovarian malignancies.

[1]Department of Biochemistry, Sree Narayana Institute of Medical Sciences, North Paravur, Kerala, India

[2,3]Department of Biochemistry, Medical College, Vadodara, Gujarat, India

Corresponding Author: Anju Radhakrishnan, Department of Biochemistry, Sree Narayana Institute of Medical Sciences, North Paravur, Kerala, India, Phone: +91 8980020660, e-mail: dranju2904@gmail.com

Objectives

- To study serum CA-125 and serum CEA levels in cases of epithelial ovarian malignancies and non-ovarian malignancies.
- To compare the serum CA-125 and serum CEA levels in cases of epithelial ovarian malignancies and non-ovarian malignancies.
- To find out the ratio of CA-125 to CEA and its importance in distinguishing epithelial ovarian malignancies from non-ovarian malignancies.

MATERIALS AND METHODS

An analytical cross-sectional study carried out at Clinical Chemistry Laboratory, Medical College Baroda and Sir Sayajirao General (S.S.G.) Hospital, Vadodara after obtaining permission from the institute's scientific and ethical committee. This study includes two groups: 30 diagnosed cases of epithelial ovarian malignancies in group I and 30 diagnosed female cases of non-ovarian malignancies in group II.

Inclusion Criteria

All clinically, radiologically, and histopathologically diagnosed cases of ovarian malignancies in group I and diagnosed female cases of non-ovarian malignancies in group II.

Exclusion Criteria

All histopathologically diagnosed cases of benign ovarian and non-ovarian tumors.

Male patients in group II.

As this is a pilot study, benign conditions causing raised CA-125 and CEA levels, conditions like a vulval abscess, vaginal prolapse, spontaneous abortion, extrauterine pregnancy are excluded. Benign conditions will also be included later.

Sample Collection

Three milliliters of blood was collected through venipuncture and kept for half an hour to clot, at room temperature. Serum was separated through centrifugation at 3,000 rpm for 3 minutes and was transferred to plain vacutainer for serum CA-125 and serum CEA estimation.

Biochemical Analysis

Estimation of serum CA-125 and serum CEA levels was done by Sandwich ELISA.

Statistical Analysis

Statistical analysis was done by using unpaired Student's *t*-test for the parameters which are normally distributed and Mann–Whitney *U* test for the parameters which are not normally distributed to find out the significance of the difference between two groups and interpretation done according to *p* values. *p* value < 0.005 is considered as significant. Diagnostic (2×2) tables were drawn and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. All statistical analyses were done using MedCalc software 19.5.3.

Sensitivity = True Positive/(True Positive + False Negative)
Specificity = True Negative/(True Negative + False Positive)
PPV = True Positive/(True Positive + False Positive)
NPV = True Negative/(True Negative + False Negative)

RESULTS

An analytical cross-sectional study with 30 diagnosed patients of ovarian malignancies and 30 diagnosed female patients of non-ovarian malignancies between the age group of 40 years and 80 years were enrolled in my study. Results of routine laboratory tests of the two groups show no statistically significant difference.

"The serum CA-125 levels, serum CEA levels and serum CA-125/ CEA ratios were found out, and showed statistically significant difference in two groups (Table 1)". Sensitivity, specificity, PPV, NPV of serum CEA alone, and CA-125/CEA ratio at different cut-off levels were calculated. "It showed that sensitivity of CEA <10 ng/mL was 100%, <5 ng/mL was 93% while that of CA-125/CEA ratio >20 was 100%, >30 was 96%, >50 was 90%, >100 was 76%, respectively. Specificity of CEA <10 ng/mL was 50%, <5 ng/mL was 67% while that of CA-125/CEA ratio >20 was 77%, >30 was 90%, >50 was 100%, respectively, and PPVs were 66%, 74%, 81%, 90%, 100%, respectively (Table 2)".

So, in the present study, all the 60 patients have raised CA-125 (>35 U/L), and CEA (>5 ng/mL) levels are raised only in 2 out of 30 in group I and 20 out of 30 in group II. The rest 28 patients in group I and 10 patients in group II have raised CA-125 levels but normal CEA levels. We found that specificity and PPV increase when CA-125 to CEA ratio increases and both are 100% if the ratio is >50, and the sensitivity is 90%, NPV is 91%. When CEA (<5 ng/mL) alone is used for distinguishing an ovarian malignancy from a non-ovarian malignancy, sensitivity is 93%, specificity 67%, PPV 74%, NPV 91%, respectively. Cancer antigen 125/CEA ratio when increases, the sensitivity and NPV fall but the specificity and PPV increase and became 100% when CA-125/CEA ratio is >50. We cannot always consider the cut-off for CEA as <5 ng/mL because in smokers the reference value is up to 10 ng/mL. So, it is better to use the CA-125 to CEA ratio for the best diagnosis and further management.

DISCUSSION

A cross-sectional study of 30 cases of ovarian malignancies in group I and 30 female cases of non-ovarian malignancies in group II have been included. Group II has 10 cases of colon cancer, 5 cases of breast cancer and 5 cases of pancreatic cancer, 4 cases of gastric malignancy, 3 cases of carcinoma lung, 2 cases of carcinoma bladder, and 1 case of uterine cancer.

Table 1: Serum CA-125, Serum CEA, and CA-125/CEA levels in group I and group II

Column 1		Column 2	Column 3	Column 4
Parameter		Group I	Group II	p value
CA-125 (U/L)	Median	523.5	87.0	*p* < 0.0001
	Interquartile range	(326–729)	(55–354)	
CEA (ng/mL)	Median	2.95	10.10	*p* < 0.0001
	Interquartile range	(2.20–3.90)	(4.70–20.0)	
CA-125/CEA ratio	Median	159	12	*p* < 0.0001
	Interquartile range	(119–232)	(6.67–20.2)	

Table 2: Sensitivity, specificity, PPV, NPV of serum CEA, and CA-125/CEA

Column 1		Column 2	Column 3	Column 4	Column 5
		Sensitivity	Specificity	PPV	NPV
Serum CEA		100%	50%	66%	100%
(<10 ng/mL)	CI	(88.43–100)	(31.3–68.7)	(51.0–63.2)	(78.2–100)
Serum CEA		93%	67%	74%	91%
(<5 ng/mL)	CI	(77.9–99.1)	(47.1–82.7)	(56.9–86.6)	(70.8–98.8)
CA-125/CEA >20		100%	76.60%	81.00%	100%
	CI	(88.4–100)	(57.5–90.0)	(64.8–92.0)	(85.1–100)
CA-125/CEA >30		96%	90%	90%	96%
	CI	(82.7–99.9)	(73.4–97.9)	(74.9–98.0)	(81.6–99.9)
CA-125/CEA >50		90%	100%	100%	91%
	CI	(73.4–97.8)	(88.4–100)	(87.2–100)	(75.6–98.1)
CA-125/CEA >100		76%	100%	100%	81%
	CI	(57.7–90.0)	(88.4–100)	(85.1–100)	(64.8–92.0)

In the study, the maximum numbers of individuals were under the age group 50–59 years in both groups. In my study, specificity and PPV were 90% and sensitivity is 96% when CA-125/CEA ratio was >30. When CEA alone is used, the sensitivity and NPV are 93 and 91%, respectively, but the specificity is only 67% and PPV is 74%. This matched with Buamah et al.'s study which showed, the CA-125/CEA ratio appeared to be excellent for differentiation between OC and non-OCs since all 47 patients with OC had a ratio of >30.[9] Yedema et al. published a study based on 71 patients: 47 with OC and 24 with colorectal cancer, CA-125/CEA ratio >25 showed a sensitivity of 91% and a specificity of 100% for detection of OC.[10] Sorensen et al. predicted OC in 82.0% (CI 76.3–86.8%; $p < 0.001$) when the CA-125/CEA ratio was >25.[11]

The limitations of the present study were a small sample size; most of the cases were in advanced stages, only malignant cases were taken, no benign pelvic masses had not been included. To reach an optimum conclusion, this study should be carried on in the future with more cases, sufficient number in all stages, including both benign and malignant tumors.

Conclusion

Serum CA-125 levels, a known marker for ovarian malignancies, are raised in all patients of ovarian malignancies and non-ovarian malignancies. Serum CEA levels are raised in the majority of the patients with non-ovarian malignancies and are raised in some patients with ovarian malignancies. In all the malignancies, serum CA-125 levels and serum CEA levels are found to be increasing as the stage of the disease advances. Serum CA-125/CEA ratio calculated is found to be significantly different when compared between ovarian malignancies and non-ovarian malignancies. Since serum CA-125 levels and serum CEA levels are not up to the mark for distinguishing ovarian malignancies from non-ovarian malignancies their ratio (CA-125/CEA) is a better marker for differentiating the same. Sensitivity and NPV are 100% when the CA-125/CEA is >20. But specificity and PPV are not so good. When the ratio is increased from 20 to 50 the specificity and NPV reach 100% but the sensitivity and PPV are fallen. CA-125/CEA at >30, the sensitivity, specificity, and both the predictive values are better and I recommend a ratio of >30 for distinguishing epithelial ovarian malignancies from non-ovarian malignancies in my study population.

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