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Original Research Article

# Serum Mesothelin Level in Patients with Epithelial Ovarian Cancer

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**Abstract:** The aim of the study is to determine serum mesothelin level in patients with ovarian cancer and its level indifferent histopathological subtypes. The ultimate goal is to know if we can set serum mesothelin as a marker for ovarian cancer. The method was serum samples were collected from 39 women as cases attending the gynecological oncology clinic at El Shat by Maternity University Hospital, after their diagnosing as ovarian cancer. And another serum samples were collected from 45 women as a control group attending El-Shat by Maternity University Hospital for other therapeutic reasons after applying the exclusion and inclusion criteria. A sandwich ELISA tech. was used to detect the level of mesothelin in the sera of cases and control groups. The results from the receiver operating characteristic (ROC) curve analysis, we found that mesothelin is a good indicator for diagnosis and anticipation of ovarian cancer.The best cut-off that maximizes (sensitivity + specificity) is 2.32 (ng/ml). At this level, the sensitivity is 56.41 and specificity is 82.22. In conclusion using a quantitative ELISA for serum mesothelin detection found to be elevated in 69.8 %of ovarian cancer patients; these results have identified serum mesothelin a potential biomarker for these cancers. However studies involving much larger patients' samples are needed to fully characterize the sensitivity and specificity of the assay.
**Keywords:** Ovarian Cancer, ROC curve, ELISA.

## INTRODUCTION

Ovarian cancer is the second most common cancer in women (affecting about 1/70) and the leading cause of death from gynecologic cancer, (1% of all women die of it) [1]. In 2014, the incidence rate for women in developed countries was approximately 9.4 per 100,000, compared to 5.0 per 100,000 in developing countries [2].

Ovarian cancer is classified according to the histology of the tumor, obtained in a pathology report. Histology dictates many aspects of clinical treatment, management, and prognosis [3].

Signs and symptoms of ovarian cancer are frequently absent in early stages and when they exist they may be subtle, in most cases the symptoms persist for several months before being recognized and diagnosed. Most typical symptoms include: bloating, abdominal or pelvic pain, difficulty eating, and possibly urinary symptoms [4].

In most cases, the exact cause of ovarian cancer remains unknown. The risk of developing ovarian cancer appears to be affected by several factors [5]. Older women who have never given birth, and those who have a first or second degree relative with the disease, have an increased by mutations in specific genes (most notably BRCA1 and BRCA2, but also in genes for hereditary non- polyposis colorectal cancer) [5].

Diagnosis of ovarian cancer starts with a physical examination (including a pelvic examination), a blood test for CA-125 and sometimes other markers, and transvaginal ultrasound. The diagnosis must beconfirmed with surgery to inspect the abdominal cavity, and look for cancer cells in the abdominal fluid [6]. A widely recognized method of estimating the risk of malignant ovarian cancer based on initial workup is the risk of malignancy index (RMI) [7].

It is recommended that women with an RMI score over 200 should be referred to a center with experience in ovarian cancer surgery. The RMI is calculated as follows [7].

RMI = ultrasound score x menopausal score x CA-125 level in U/ml [7]. Under physiological conditions, the expression of Mesothelin is limited. However, overexpression of normal Mesothelin has been described in many types of malignancies, such as mesothelioma, ovarian cancer, and pancreatic cancer. Mesothelin is detectable in many biological fluids, such as serum and urine [8].

Quantification of Mesothelin in these biological fluids may serve as a useful biomarker for cancer diagnosis, prognosis, and monitoring response to therapy in patients with mesothelioma and ovarian cancer. Furthermore, due to its low expression in normal tissues and high expression in tumor cells, Mesothelin is an attractive candidate for cancer immunotherapy. Additionally, Mesothelin can elicit an autoimmune response in cancer patients. These therapies include agents that target cell surface Mesothelin or elicit an immune response against Mesothelin [8].

Surgical treatment may be sufficient for malignant tumors that are well-differentiated and confined to the ovary [9]. The type of surgery depends upon cancer stage, as well as the presumed type and grade of cancer, (stage 1, low grade or low-risk disease), for the only involved ovary and fallopian tube will be removed (unilateral salpingooophorectomy, USO), especially in young females who wish to preserve their fertility [9]. Borderline tumors, even following spread outside of the ovary, are managed well with surgery, and chemotherapy is not seen as useful, Surgery is the preferred treatment and is frequently necessary to obtain a tissue specimen for differential diagnosis via its histology [9].

For patients with advanced disease a combination of surgical reduction with a combination chemotherapy regimen is standard [9].

Ovarian cancer usually has a relatively poor prognosis.bIt is disproportionately deadly because it lacks any clearearly detection or screening test, meaning that mostcases are not diagnosed until they have reached advanced stages. Women with advanced ovarian cancer or a relapses hould get palliative care immediately and if appropriatea referral to a palliative care physician [10].

## METHODS

### Subjects and study design:

This study was conducted on 84 patients (39 cases ovarian cancer and 45 cases healthy control admitted to El-Shat by Maternity University Hospital. After explanation of the study protocol and agreement then signing a well-informed written consent as approved by ethical committee, Inclusion criteria were**:**

All stages of ovarian cancer, all histopathological types of ovarian cancer, patients fit for surgery, any age.

Our study groups subjected to the following

1. Detailed history including.
2. Physical examination: A fixed, solid, irregular pelvi-abdominal mass may be felt during palpation of the abdomen. Ascites could be felt.
3. Laboratory Testing: Measurement of the serum level of mesothelin in both patients and control.
4. Transvaginal Sonography: The features suggestive of ovarian malignancy on ultrasound include: Septations greater than 3 mm, mural nodularity, and papillary projections.
5. Staging laparatomy Surgery for ovarian cancer requires that the abdominal incision be adequate to explore the entire abdominal cavity.
6. Biopsy: Histopathology for the ovarian mass.

### Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

## RESULTS

**Table 1: Distribution of the studied cases according to different parameters (n=39)**

| | **No. (%)** |
|---|---|
| **Age of menarche** | |
| Early | 19(48.7%) |
| Late | 20(51.3%) |
| **Complaints** | |
| Pain | 17(43.6%) |
| GIT symptoms | 16(41.0%) |
| Menstrual disturbance | 4(10.3%) |
| Dyspnea | 2(5.1%) |
| **CA125** | 167.0 (9.60 – 1378.0) |
| **CEA** | 3.0 (0.59 – 203.0) |
| **Border line or malignant** | |
| Border line | 13 (33.3%) |
| Malignant | 26 (66.7%) |
| **Histopathological typing** | |
| Serous | 17(43.6%) |
| Mucinous | 18 (46.2%) |
| Endometroid | 2(5.1%) |
| Brenner | 2(5.1%) |
| **Grading** | |
| Highly differentiated (1) | 21(53.8%) |
| Moderately differentiated (2) | 17(43.6%) |
| Poorly differentiated (3) | 1(2.6%) |
| Undifferentiated (4) | 0(0.0%) |
| **Stage** | |
| **I** | **35(89.7%)** |
| IA | 25(64.1%) |
| IB | 2(5.1%) |
| IC | 8(20.5%) |
| **II** | **4(10.3%)** |
| IIA | 1(2.6%) |
| IIB | 2(5.1%) |
| IIC | 1(2.6%) |
| **Omentum** | 6(15.4%) |
| **Ascitic Fluid** | 6(15.4%) |
| **Peritoneal biopsy** | 2(5.1%) |

Qualitative data were described using number and percent abnormally distributed data was expressed using Median (Min. – Max.)

**Table 2: Comparison between the two studied groups according to different parameters**

| | Cases (n = 39) | Control(n = 45) | p |
|---|---|---|---|
| **Age (years)** | 49.44 ± 13.41 | 27.42 ± 5.59 | <0.001* |
| **BMI** | 33.72 ± 3.17 | 29.82 ± 1.70 | <0.001* |
| **Obstetric history** | | | |
| Gravidity | 4.0(0.0 – 11.0) | 0.0(0.0 – 5.0) | <0.001* |
| Parity | 3.0(0.0 – 10.0) | 0.0(0.0 – 3.0) | <0.001* |
| Abortion | 0.0(0.0 – 5.0) | 0.0(0.0 – 5.0) | 0.650 |
| **Menstrual history** | | | |
| Still menstruating | 19(48.7%) | 45(100.0%) | <0.001* |
| Post menopausal | 20(51.3%) | 0(0.0%) | |
| **Mesothelin** | 2.39(0.44 – 9.68) | 1.07(0.46 – 4.53) | 0.002* |

Qualitative data were described using number and percent and was compared using Chi square test normally quantitative data was expressed as Mean ± SD and compared using student t-test . While abnormally distributed data was expressed using Median (Min. – Max.) and was compared using Mann Whitney test.
*: Statistically significant at $p \leq 0.05$

**Table 3: CA125, CEA and mesothelin correlation in patients (borderline and malignant)**

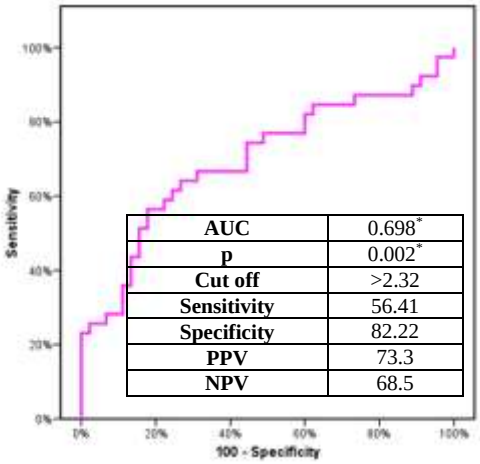
| | Border line (n = 13) | Malignant (n = 26) | p |
|---|---|---|---|
| **CA125(u/ml u)** | 123.0(19.50 – 934.0) | 342.30(9.60– 1378.0) | 0.065 |
| **CEA(ng/ml u)** | 2.0(0.59 – 203.0) | 3.45(0.66 – 201.0) | 0.112 |
| **Mesothelin(ng/ml u)** | 1.09 (0.64 – 6.47) | 2.78 (0.44 – 9.68) | 0.009* |

Abnormally distributed data was expressed using Median (Min. – Max.) and was compared using Mann Whitney test.
*: Statistically significant at $p \leq 0.05$

**Table 4: Relation between mesothelin, CA125 and CEA with histopathological typing, grading, ascitic fluid affection, omentmal deposits and peritoneal biopsy affection**

| | N | Mesothelin | CA125 | CEA |
|---|---|---|---|---|
| **Histopathological typing** | | | | |
| Serous tumor | **17** | 3.06(0.69 – 9.68) | 640.0(20.0 - 1378.0) | 2.0(0.66 – 210.0) |
| Mucinous tumor | **18** | 1.20(0.44 – 6.47) | 92.35(9.60 – 1300.0) | 5.12(0.59 - 203.0) |
| Endometroid tumor | **2** | 2.12(1.81 – 2.44) | 415.50(71.0 - 760.0) | 2.50(2.0 - 3.0) |
| Brenner tumor | **2** | 3.61(2.10 – 5.12) | 704.0(500.0 - 908.0) | 3.50(2.0 – 5.0) |
| **p** | | 0.013* | 0.037* | 0.519 |
| **Grading** | | | | |
| Highly differentiated (1) | **21** | 1.63(0.56 – 7.26) | 150.0(9.60 - 1300.0) | 2.25(0.59 – 203.0) |
| Moderately differentiated (2) | **17** | 2.79(0.44 – 9.68) | 240.0(20.0 - 1378.0) | 3.40(0.66 – 103.0) |
| Poorly differentiated (3) | **1** | 6.16 | 850.0 | 3.0 |
| Undifferentiated (4) | **0** | - | - | - |
| **p** | | 0.076 | 0.268 | 0.952 |
| **$r_s$ (p)** | | -0.355* (0.026*) | -0.254 (0.118) | -0.051 (0.758) |
| **Ascitic Fluid** | | | | |
| Not affected | **33** | 2.10(0.44 – 7.26) | 135.0(9.60 - 1300.0) | 3.0(0.59 – 203.0) |
| Affected | **6** | 6.25(3.60 – 9.68) | 662.0(240.0 - 1378.0) | 2.25(0.66 – 103.0) |
| **p** | | 0.001* | 0.022* | 0.290 |
| **Omentum** | | | | |
| Not affected | **33** | 2.35(0.44 – 9.68) | 135.0(9.60 - 1378.0) | 3.0(0.59 – 201.0) |
| Affected | **6** | 4.16(0.64 – 6.60) | 474.50(167.0- 1157.0) | 9.63(2.0 – 203.0) |
| **p** | | 0.330 | 0.087 | 0.137 |
| **Peritoneal biopsy** | | | | |
| Not affected | **37** | 2.35(0.44 – 7.26) | 150.0(9.60 - 1300.0) | 3.0(0.59 – 203.0) |
| Affected | **2** | 8.14(6.60 – 9.68 ) | 824.80(271.60- 1378.0) | 1.58(0.66 – 2.50) |
| **p** | | 0.026* | 0.143 | 0.200 |

Abnormally distributed data was expressed using Median (Min. – Max.) and was compared using Mann Whitney test or Kruskal Wallis test, $r_s$: Spearman coefficient, *: Statistically significant at $p \leq 0.05$




| | |
|---|---|
| **AUC** | 0.698* |
| **p** | 0.002* |
| **Cut off** | >2.32 |
| **Sensitivity** | 56.41 |
| **Specificity** | 82.22 |
| **PPV** | 73.3 |
| **NPV** | 68.5 |

**Fig-1: ROC curve for Mesothelin to diagnose cases**

## DISCUSSION

In Egypt, ovarian cancer is the most common gynecological cancer and the fourth most common cancer in women [11]. The incidence rates are highest in Central America and Northern Europe and lowest in some parts of Africa and Asia. In Egypt the crude rate of ovairan cancer reported is 4.6% and the age specific rate (ASR) is 6.3% [11].

In the present study, we aimed to study serum mesothelin level in patients with epithelial ovarian cancer and to compare it with levels in normal population. The ultimate goal is to test the efficacy of serum Mesothelin as a screening tool for ovarian cancer.

In the present study the mesothelin level was significantly higher in cases (2.94 ± 2.28) compared to control (1.53 ± 1.04) groups. This is in accordance to Sasaki A., et al. (2015) [12].

From the Receiver Operating Characteristic (ROC) Curve analysis, we found that mesothelin is a good indicator for diagnosis and anticipation of ovarian cancer. The best cut-off that maximizes (sensitivity + specificity) is 2.32 (ng/ml). At this level, the sensitivity is 56.41 and specificity is 82.22.

Obulhasim G. *et al* [13], in 2010 found that mesothelin was expressed in 100% of serous cystadenocarcinoma and 100% of serous borderline tumor of the ovary. In accordance to our results, we found that mesothelin level was significantly higher in cases (2.94 ± 2.28 ng/ml) compared with control group (53 ± 1.04 ng/ml).

In this study, in order to determine serum mesothelin level in patients with adnexal mass suspicious for ovarian cancer to set a cut-off level of serum mesothelin as a marker for ovarian, 84 women (39 cases with adnexal mass suspicious for ovarian carcinoma, and 45controls) whom meet the inclusion criteria were recruited from Gyne-oncology unit in El Shatby Maternity University Hospital.

In the present study the mean CA-125 level in the 39 suspected ovarian cancer patients was 411.05 ± 439.07 U/ml, that is much higher than levels reported bySzatkowski W. *et al.* [14], who reported that only 22.9% of their patients had CA-125 level≥285.5 U/ml. The mean level of CEA in the present study was 20.25 ± 47.42 ng/ml, Bian J *et al*, [15] reported that the mean CEA in patients with ovarian cancer was 12.3 ± 3.6 ng/ml and mean CA-125 level is 210.8 ± 78.6 U/ml. This difference in levels of CA-125 and CEA may be attributed to difference in populations.

In the present study 26 (66.7%) of cases were malignant. As regard histopathological typing, serous and mucinous were 43.6% and 46.2% respectively. Szatkowski W. *et al.*, [14] reported 40.9% of serous and 6.1 for mucous.

As regards grading of the tumour in the present study, highly differentiated (G1) was in 53.8% of cases, moderately differentiated (G2) in 43.6% of cases, poorly differentiated in 2.6% of cases. Szatkowski W. *et al.*, [14] reported 70% of cases as G3. This difference may be attributed to the difference in selection criteria between the two studies.

According to the International Federation of Gynecology and Obstetrics (FIGO) surgical staging system for ovarian cancer [16] our study found that 35 (89.7%) of cases were stage I, and 4 (10.3%) stage II. Lu, Y. *et al*. in their systematic review, concluded that for comprehensive staging surgery, laparoscopy was equivalent to or even better than conventional laparotomy for early ovarian cancer.

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