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Research Article

# CLINICAL UTILITY OF CA125, HE4 AND RISK OF OVARIAN MALIGNANCY ALGORITHM (ROMA) FOR EARLY DETECTION OF OVARIAN CARCINOMA

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**ABSTRACT**

Ovarian cancer is the leading cause of mortality from gynaecological cancer in worldwide. Majority of patients with advanced disease face relapse following primary treatment. Early diagnosis of ovarian cancer is difficult due to its asymptomatic nature and the lack of sensitive screening methods. So, the challenge still exists to develop appropriate serum markers for the screening and detection in early stages of cancer progression. Patient in advanced phase undergo continuous biomarker monitoring and follow-up for proper treatment. In past decades, numbers of potential serum biomarkers have been assessed in diagnosing of ovarian cancer. These includes structural as well as functional component of the cell and tissue such as various Cytokines, biological factors (coagulation, growth and apoptosis factors), hormones and adhesion molecules, but none of them have been applied to everyday clinical practice. Nowadays, serum cancer antigen 125 (also called as carbohydrate antigen 125 or CA125) and human epididymis 4 protein (HE4) are clinically approved biomarkers with reliable sensitivity and specificity of diagnosis. Next step in the diagnosis is the utilization of Risk of Ovarian Malignancy Algorithm (ROMA) which incorporates the results of HE4 and CA125 levels and menopausal status becoming more and more widespread in clinical practice for the evaluation of ovarian cancer. This review will focus on the utility of the combination of CA125 and HE4 as ROMA and the comparison of ROMA with alone CA125, HE4 and RMI with the future directions in ovarian cancer screening.

**Keywords:** Ovarian cancer, epithelial ovarian Carcinoma (EOC), biomarker CA125; HE4, ROMA

## INTRODUCTION

Ovarian cancer shows higher morbidity and mortality rates among gynaecological malignancies worldwide. The problem is the late diagnosis due to the lack of sensitive screening methods and the absence of recognizable physical symptoms in early stages. Although, the present medical treatments have decreased death rate by 1.9% per year, ovarian cancer still accounts for 3% of all malignancies among women. Current prevalence data recommended that ovarian tumors of epithelial origin (EOC) are the most common type of ovarian cancer[1].

Currently, well known mechanisms of pathogenesis, histological subtypes of different ovarian cancer are already at hand. Thus, future biomarker panels should take into consideration for their implication in clinical diagnosis of molecular patterns and biological behaviour of various subtypes of ovarian cancer. The choice of the most informative biomarkers is the challenging and crucial aspect in biomarker development. It should be measurable, reliable and informative for all histological and pathological subtypes of a given cancer[2].

Biomarker development efforts to date suggested that no single biomarker can provide sufficient sensitivity with high specificity for the early detection of ovarian cancer. Therefore, in order to devise a robust multimarker algorithm, it is necessary to identify additional informative biomarkers that complement with existing classical biomarker CA-125. Early Detection Research Network (National cancer institute- NIH) recommend five phases for development of biomarkers; preclinical exploratory Phase I, clinical development and validation in Phase II, validation in a retrospective longitudinal study in Phase III, prospective screening in Phase IV and randomized clinical trials in Phase V[3].

## EPIDEMIOLOGY OF OVARIAN CANCER

Ovarian cancer accounts for approximately 4% of all female cancers and is the seventh most commonly diagnosed female cancer worldwide[4]. As per the data from SEER stat fact sheets by National cancer institute of health (NIH), a total of 22,440 new cases of ovary cancer and more than 14,080 deaths are expected in India in 2017. The prevalence of ovarian cancer in the population of women aged over 50 is 40/100,000. The age-standardized incidence rates (ASR) for ovarian cancer varied from 0.9 to 8.4/100,000 person years among various registries[4]. Table1 shows the international statistical incidence of cancer in Indian women.

On the basis of the cell for the beginning of ovarian cancer, it is subdivided into three subgroups. In which merely 1% of the ovarian cancer patients belongs to gonadal stromal cell cancer that begins development from structural tissue cells which hold the ovary together and produce the female hormones oestrogen and progesterone[5]. Germ cell cancer occurs in <2% of ovarian cancer patients and starts development from the cells that produce the ovum[6-7]. Ovarian Surface Epithelial Carcinoma (EOC) is the fourth most common malignant ovarian tumor.

Among all gynecological malignancies, EOC accounts for almost 5% of all cancers, and 4.2% of cancer deaths in women worldwide[8]. Ovarian tumors of epithelial origin (EOC) are characterized and classified mainly into four major histological subtypes, these include: serous, mucinous, clear cell and endometriosis carcinoma[9-10]. The stages of ovarian cancer at diagnosis critically determine the five year survival of the patients. If patients diagnosed and treated by conventional surgery with chemotherapy while localized (FIGO stage I and II), 5 year survival can reach over approximately 90%. However, only 15% of all cases are detected at this stage[11]. In contrast, the majority of cases (63%) are diagnosed after dissemination or in late stage (FIGO stage III and IV) that decreases 1, 5, and 10 year relative survival rates[12-15]. Commonly, ovarian cancer patients with advanced stage also experience disease recurrence within a few years from the time of diagnosis. Despite, available tools and medication, the survival rate of women diagnosed with ovarian cancer has remained comparatively unchanged over the past three decades[16].

Due to the anatomical location of ovaries in deep down the small pelvis and the nature of the disease which spread in the form of diffused carcinosis, tumour related abnormal functioning of the ovaries is asymptomatic until the tumour becomes enlarged or disseminates. These conditions become worst for postmenopausal women, because ovaries dysfunctional and aging play crucial role in cancer. Therefore, ovarian cancer is more likely to be detected in an advanced rather than an early stage[17]. Indeed, if the malignancy arises in the ovary and is localized for enough time to allow effective screening, then the probability for survival is considerably higher[18]. Therefore, the ultimate purpose of any successful therapeutic strategy is the early detection of ovarian cancer to improve long-term survival of patients and to obtain significant reduction of risk. For that reason, there is greater need to discover novel biomarker or biomarker panels for the detection of ovarian cancer prior to its advanced or metastatic state[19].

## DIAGNOSIS

A broad spectrum of potential single serum biomarkers and multiple panels (as cytokines, growth factors, adhesion molecules, proteases, hormones, coagulation factors, acute phase reactants, and apoptotic factors) have been examined in the last years for diagnosis of ovarian cancer. In addition, imaging exams and combination algorithms have also been used to discriminate benign from malignant epithelial ovarian cancer[20]. About 202 types of different protein biomarkers and only 1 gene and 1 genetic biomarker have been identified yet[2].

CA-125 (Carcinoma antigen 125, also known as mucin 16 or MUC16) is a protein that in humans is encoded by the MUC16 gene. CA-125 is the most frequently used biomarker for ovarian cancer detection [16]. Clinical evidence suggested that apart from CA125, other biomarker gives ambiguous test results and poor diagnosis. This may cause harmful and unnecessary health care than they are likely to detect ovarian cancer in women who are at average risk of developing it[21-22]. Moreover, serum levels of CA125 have a significant lead-time prior to clinically detectable recurrence[23-25]. Though, CA125, as a single biomarker has the modest sensitivity and positive predictive value for early detection of EOC[25-26]. More efforts have been made to discover new biomarkers which could improve the sensitivity and specificity for the diagnosis of ovarian cancer during early stages[27]. HE4 (human epididymis protein 4) is another most interesting marker which is a secreted glycoprotein and over expressed by serous and endometrioid EOC.[28-29]. Numerous studies have defined the utility of HE4 in the diagnosis of ovarian cancer either as a single biomarker or in combination with CA125 as a risk of malignancy algorithm called ROMA (Risk of Ovarian Malignancy Algorithm) [31-32].

**CA125**: CA125 is a high molecular weight (>1M Da) glycoprotein with an extracellular, transmembrane and intracellular domain and frequently used biomarker for ovarian cancer detection[33]. First time, Bast et al (1983) investigated CA125 in advanced stage ovarian cancer patient with OC125 murine monoclonal antibody in a double determinant radioimmunoassay[34]. CA125 is normally expressed in variety of epithelial cell types as in fetal amniotic and coelomic epithelium[35]. Other than this, it is also expressed in the tissues derived from Mullerian epithelia as tubal, endometrial and endocervical; and coelomic epithelia as pericardium, peritoneum and mesothelial cells of the pleura[36]. CA125 has shown 50-60% sensitivity with 90% specificity in early stage postmenopausal women[37-39]. The expression of CA125 is elevated in 90% of EOC patients (85% of serous, 65% of endometrioid, 40% of clear cell, 36% of undifferentiated and only 12% of mucinous ovarian cancer)[41].

**HE4**: Another clinically verified biomarker is Human epididymal 4, which is a secreted glycoprotein with WAP-type four disulfide cores and is encoded by WFDC2 (whey acidic four disulfide core domain protein 2) gene found on chromosome 20q1213.1[42]. Initially, it was identified as mRNA transcript specific to the distal epididymal tissue. Interestingly, HE4 is absent in ovarian surface epithelium but it is present in fallopian tube epithelium, endothelium and endocervical glands[43]. The exact role of HE4 is not elucidated yet, but probably it takes part in immune response[44]. One study has revealed that HE4 moderately expressed in the epithelium of the respiratory tract (especially tracheal region), breast carcinoma, transitional cell endometrial carcinomas and pancreatic carcinoma. Despite of this, consistent high expression of HE4 has been observed in ovarian carcinoma[45]. Moreover, different over expression of HE4 was depend upon the pathological as well as histological distribution in specific subtypes of ovarian cancer[46]. Generally, HE4 biomarker was found 93-100% in serous, 80-100% in endometrioid and 50-83% in clear cell carcinomas of the ovary and none of HE4 was detected in mucinous ovarian cancer[47]. Since, HE4 is a relatively specific biomarker for the serous subtype of epithelial ovarian cancer (EOC) and also noted as a potential marker for adenocarcinoma of the endometrium[48], it possibly distinguishes among several tumour types. Several diagnostic kits have already been commercialized for the detection of HE4 as Fujirebio Diagnostics Inc. (Malvern, PA) has developed a diagnostic assay kit for HE4 and FDA (Food and drug administration, U.S) has approved the use of HE4 for monitoring of recurrence, relapse or progression of EOC[49]. Several researchers have confirmed that HE4 can be compared with CA125 as both showing 80% sensitivity and 95% specificity to classify blinded late stage cases and healthy controls[48].

Cumulative case studies of ovarian cancer patients have found that HE4 is a reliable biomarker for detection of ovarian cancer alone and in combination with CA125. Results from one of these case study revealed that, out of the 37 serum samples from diseased women HE4 alone effectively detected cancer in 30, while the CA125 alone detected in 29 cases. Interestingly, apart from this when combination of both biomarkers CA125 as well as HE4 taken, total 33 case were confirmed out of the 37 cancer cases[50]. Additional research also observed HE4 as less

frequently positive in non-malignant diseased patients that may be advantageous over CA125. Furthermore, HE4 were also used in the evaluation of premenopausal women[51]. HE4 elevated in over 50% of ovarian cancer patients whose tumours do not express CA125 or CA125 level in normal limits[52]. To differentiate borderline tumors from healthy controls/benign disease HE4 alone was the better test in comparison with CA-125, with specificities of 81.8 and 85.9%, and sensitivities of 62.5 and 62.5%, respectively. Clinical data suggested that HE4 is also a better test to differentiate a benign pelvic mass.
In a study of 1042 women with benign disease there was less elevated level of HE4 than CA125 (8 vs. 29%)[53].

In 2007, Moore et al. recognized the diagnostic potential for circulating levels of 9 biomarkers (CA125, mesothelin (SMRP), HE4, CA72–4, activin, inhibin, osteopontin, EGFR and ERBB2). They analysed the serum and urine samples from 67 patients with invasive epithelial ovarian cancers and 166 with benign ovarian neoplasm (233 women with a pelvic mass)[54]. In this cumulative study, alone HE4 had shown the highest sensitivity (72.9% sensitivity at 95% specificity). Apart from this HE4 had shown a sensitivity of only 45.9% at 95% specificity as a single marker to differentiate the benign from stage I cancer[55]. Hence, it has been proven that HE4 shows greater sensitivity among early stage ovarian cancer and greater specificity in concern with benign ovarian lesions. Moore et al then used HE4/CA125 combination in a forthcoming multicentre study involving 531 patients with 93.8% of ovarian cancer patients correctly classified into the high risk group[56]. Consistently, the superior performance of the CA 125/HE4 combination over either biomarker alone has been supported by numerous subsequent studies[57]. Cumulative study suggested that, two proteins which are C125 as well as HE4 may play at least in part different roles in epithelial ovarian carcinoma diagnosis[58]. Although HE4 seems more efficient than CA125 in ruling in EOC patients in the disease group, also in early stages tumours, both in pre and post menopause[59].

## ROMA: PREDICTIVE PROBABILITY ALGORITHM

Based on the encouraging results of HE4 in the diagnosis of ovarian cancer, especially in combination with CA125, Moore et al. have developed the Risk of Ovarian Malignancy Algorithm (ROMA). Authors of this algorithm evaluated 472 patients with pelvic mass (89 of which were found to have ovarian cancer) in a prospective, multicentre, blinded clinical trial and developed ROMA as the more effective tool to stratify women presenting with pelvic mass as low and high risk of malignancy for detection of ovarian cancer from benign pelvic masses even in early stages. ROMA includes serum levels of HE4 and CA125 with menopausal status[60]. ROMA represents mathematical predictive probability algorithm-

Pre-menopausal: Predictive index (PI) = –12.0 + 2.38 × LN (HE4) + 0.0626 × LN (CA125)
Postmenopausal: Predictive index (PI)=-8.09 + 1.04 x LN (HE4) + 0.732 x LN (CA125
Predictive probability (ROMA) = exp (PI) / [1 + exp (PI)] × 100%

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) has to be calculated for each of both markers, with cut-off values of 35 U/ml for CA125 and 70 or 140 pmol/l (for premenopausal or postmenopausal patients, respectively) for HE4, as previously determined. There is an established cut off values of ROMA as >13.1% for premenopausal women and >27.7% for postmenopausal women qualified them to a group with a high risk of ovarian tumour malignancy. Although these cut-off values differ slightly depending on the manufacturer of the diagnostic kit but approximately 75% specificity thresholds for the ROMA predictive probability is generally considered. Literature and previous data has suggested that ROMA works well particularly in the premenopausal patient with 100% sensitivity (SN) and the specificity (SP) of 74.2%. Moreover, ROMA has assessment power with ability to classify and differentiate cancer from endometriosis with greater specificity and sensitivity[61].

## COMPARISON WITH RMI

Apart from FDA approved ROMA for use in determining the risk of ovarian cancer in pre and postmenopausal women with a pelvic mass, Gemini et al have made attempts in the development of many diagnostic algorithms by combining CA125 with the ultrasound imaging. Risk of malignancy index (RMI) is one of them as a diagnostic tool in clinical practice and still used in the diagnosing of ovarian tumours. And both algorithms have been compared with unpredictable results[62]. Clinical evidences suggested that ROMA has higher sensitivity of 94.3% in comparison to RMI (84.6%) at 75% specificity in the diagnosis of ovarian cancer. These two diagnostic tools showed more remarkable and clear difference at early stage of ovarian cancer (FIGO I/II) as 85.3% sensitivity for ROMA and 64.7% sensitivity for RMI at a specificity of 75%[63]. However, in a separate cohort study of 432 women with pelvic mass consequently found that RMI outperformed ROMA among both pre- and postmenopausal women[64]. On the basis of these results, FDA approved ROMA for use in determining the risk of ovarian cancer in pre and postmenopausal women with a pelvic mass. Out of four variations of RMI, RMI I is found to be more efficient[63-66], calculated with the following formula:

**RMI = U × M × CA125,**
Where,
U – Ultrasound image (1 point for each of the features: solid, multilocular, bilateral tumour, ascites, intra-abdominal metastases); U = 0 (0 points), U = 1 (1 point), U = 3 (2-5 points)
M – Menopausal status; M = 1 (premenopausal), M = 3 (postmenopausal)
CA125 – Serum CA125 concentration (U/ml).

Being a simple scoring system, ROMA is effective and shows very high specificity, but less sensitivity than CA-125 and RMI in premenopausal women. However, they are of comparable sensitivity in postmenopausal women[66]. Hence, it can be said that ROMA is an excellent diagnostic and useful tools for the detection of EOC in post-menopausal women rather than in pre-menopausal women. Moreover, ROMA has also been shown well balanced and valuable diagnostic performance in distinguishing benign ovarian tumors or endometriosis from ovarian cancer[67].

**Table 1: International statistical incidence of cancer in Indian woman in 2012**

| Cancer | Incidence | | | Mortality | | | 5-year prevalence | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | (%) | ASR (W) | No. | (%) | ASR (W) | No. | (%) | Prop. |
| Lip, oral cavity | 23161 | 4.3 | 4.3 | 5631 | 4.8 | 3 | 35194 | 3.1 | 8.2 |
| Nasopharynx | 991 | 0.2 | 0.2 | 742 | 0.2 | 0.1 | 2479 | 0.2 | 0.6 |
| Other pharynx | 6956 | 1.3 | 1.3 | 5782 | 1.8 | 1.1 | 10006 | 0.9 | 2.3 |
| Oesophagus | 14622 | 2.7 | 2.8 | 13513 | 4.1 | 2.6 | 8139 | 0.7 | 1.9 |
| Stomach | 19711 | 3.7 | 3.7 | 18320 | 5.6 | 3.4 | 14340 | 1.3 | 3.3 |
| Colorectum | 27415 | 5.1 | 5.1 | 20789 | 6.4 | 3.8 | 36789 | 3.3 | 8.6 |
| Liver | 10180 | 1.9 | 1.9 | 10008 | 3.1 | 1.9 | 4786 | 0.4 | 1.1 |
| Gallbladder | 11172 | 2.1 | 2.1 | 9450 | 2.9 | 1.8 | 13630 | 1.2 | 3.2 |
| Pancreas | 5354 | 1 | 1 | 4894 | 1.5 | 0.9 | 3020 | 0.3 | 0.7 |
| Larynx | 2546 | 0.5 | 0.5 | 1755 | 0.5 | 0.3 | 5050 | 0.4 | 1.2 |
| Lung | 16547 | 3.1 | 3.1 | 15062 | 4.6 | 2.9 | 7991 | 0.7 | 1.9 |
| Melanoma of skin | 895 | 0.2 | 0.2 | 506 | 0.2 | 0.1 | 2335 | 0.2 | 0.5 |
| Kaposi sarcoma | 11 | 0 | 0 | 8 | 0 | 0 | 15 | 0 | 0 |
| Breast | 144937 | 27 | 25.8 | 70218 | 21.5 | 12.7 | 396991 | 35.3 | 92.6 |
| Cervix uteri | 122844 | 22.9 | 22 | 67477 | 20.7 | 12.4 | 308901 | 27.4 | 72 |
| Corpus uteri | 12325 | 2.3 | 2.3 | 4773 | 1.5 | 0.9 | 44980 | 4 | 10.5 |
| **Ovary** | 26834 | 5 | 4.9 | 19549 | 6 | 3.6 | 55231 | 4.9 | 12.9 |
| Kidney | 3038 | 0.6 | 0.6 | 1919 | 0.6 | 0.3 | 6112 | 0.5 | 1.4 |
| Bladder | 3122 | 0.6 | 0.6 | 1859 | 0.6 | 0.4 | 7112 | 0.6 | 1.7 |
| Brain, nervous system | 6976 | 1.3 | 1.2 | 5578 | 1.7 | 1 | 10157 | 0.9 | 2.4 |
| Thyroid | 9944 | 1.9 | 1.7 | 2337 | 0.7 | 0.4 | 39977 | 3.6 | 9.3 |
| Hodgkin lymphoma | 2694 | 0.5 | 0.5 | 1404 | 0.4 | 0.3 | 5129 | 0.5 | 1.2 |
| Non-Hodgkin lymphoma | 7918 | 1.5 | 1.5 | 5526 | 1.7 | 1 | 9138 | 0.8 | 2.1 |
| Multiple myeloma | 2689 | 0.5 | 0.5 | 2285 | 0.7 | 0.4 | 4600 | 0.4 | 1.1 |
| Leukaemia | 12913 | 2.4 | 2.3 | 10644 | 3.3 | 1.9 | 10088 | 0.9 | 2.3 |
| All cancers excl. non-melanoma skin cancer | 537452 | 100 | 97.4 | 326100 | 100 | 60.2 | 1125960 | 100 | 262.5 |

**Note**: Incidence and mortality data for all ages, 5-year prevalence for adult population only.
Age Standard Rate (W): It is the number of new cases or deaths per 100, 000 persons per year.
Source: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx, accessed on 27/03/2017

## CONCLUSION AND FUTURE PERSPECTIVE

Epithelial ovarian cancer (EOC) is the most deadly gynaecologic problem worldwide. Being of advances in surgery and chemotherapy, the survival rate for this disease remains low. Majority of case is detected in advanced stage with bad prognosis which results in high mortality. The crucial part in clinical practice is early detection for its prevention and treatment. CA125 is the most used tumour marker since three decades for diagnosis as well as follow up of EOC patients. Moreover, other biomarkers are not reliable as much as CA125 for the diagnosis of ovarian cancer. However, CA125 have diagnosis limitations like, it is negative in 20% of EOC, and more than half of early cases, and it is often elevated (CA125 >35 U/ml), in different benign gynaecological conditions such as endometriosis, pregnancy and pelvic inflammatory disease. In the past decade, Human epididymis protein 4 (HE4) has emerged as a promising biomarker in EOC. In addition HE4 has equally detection performance as CA125 but with a better capacity to differentiate healthy women and women with benign disease. Clinically approved different algorithms are available for diagnostic purpose with their merits and demerits. Thus all possible different algorithms should be used for diagnosing OC.

Regarding the future, the combination of ROMA with other markers may be more precise for diagnosing ovarian cancer as the addition of progesterone with ROMA has been considered as the better detection method than ROMA or CA-125 or HE4 alone. Irrespective of the menopausal status, considerably higher levels of median CA-125 and HE4 found in patients of OC compare with women with benign ovarian tumours. Moreover, the median progesterone levels occurred highest in premenopausal women with benign ovarian tumours, compared with premenopausal women with OC with or without benign ovarian disease. Thus, it is concluding that the different algorithms should be used for diagnosing OC and the addition of progesterone might improve the performance of ROMA for the diagnosis of pelvic masses in premenopausal women. Further scientific data and link between clinical practice resources would help in clinically validation. These resources will most likely identify novel protein, genetic and low-molecular-weight cancer markers, which may effect on cancer care.

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