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Review Article

Role of multi-biomarkers and algorithms for diagnosis of early-stage ovarian cancer

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ABSTRACT

Our reviews intend to provide a comprehensive update for the diagnosis of ovarian cancer using biomarkers (CA125) and ultrasonography algorithm RMI and ROMA and how to improve our approaches to identify and diagnose ovarian cancer in early stage and improve the survival rate This meta-analysis done in the Department of Obstetrics and Gynaecology Swaroop Rani hospital Prayagraj, Uttar Pradesh. Source of literature was all the standard online articles available in last 3years and also the departmental records of the last 1year following criteria CA125, HE4, RMI, ROMA for screening or diagnosis. Our result on the basis of ODDS ratio and confidence interval (CI) of tumour marker like CA125, HE4, RMI, ROMA from different study. Overall estimation and pooled estimation determined by forest plot and our pooled estimation is present between the 0.8 OR to 1.0 OR and 95 % of confidence interval of the result. Our study concludes that RMI has comparatively good OR ratio and pooled effect of forest plot is in favour of RMI 0.8 OR to 1.0 OR and had good opportunity to identify early-stage ovarian cancer. Our study concludes that RMI score has comparatively good OR ratio and it can be used to identify early-stage ovarian cancer which can help in on time intervention and improved outcomes in such patients.

Keywords: Diagnosis of ovarian cancer, Biomarkers, Ultrasonography algorithms

INTRODUCTION

Ovarian cancer is the eighth most commonly occurring cancer worldwide[1] contributing to 313959 new cases and expected number of death due to ovarian cancer was 207252 globally in 2020. According to WHO ovarian cancer is the 5th leading cause of death in women worldwide. According to the data from 2013-2015, there is a chance of about 1.3% of women to be diagnosed with ovarian cancer during their lifetime. In addition, 2011 to 2015 data report 11.6 per 100,000 annual case of women and 7.2 per 100,000 deaths per year with ovarian cancer.[2] Ovarian cancer most likely asymptomatic in early stage and symptoms becomes more obvious as the cancer advances. For this reason, ovarian cancer have the highest mortality rate in various gynecological diseases. Therefore, the strategy should be to identify biomarkers for the diagnosis of ovarian cancer at early stage with high specificity and sensitivity.[3] ovarian cancer can be categorized into germ cell, sex cord-stromal cell and epithelial cell types Epithelial ovarian cancer constitute above 95% of the disease.[4] In recent year, only biomarker cancer antigen CA125 is most commonly in routine use for the management of patient with epithelial ovarian/fallopian tube or primary peritoneal cancer. The reference Interval of CA125 is 35ku/L or less. in case of ovarian cancer, serum CA125 level may be elevated, but this marker has a low sensitivity in early stage of ovarian cancer.[5] So other biomarkers have been developed in order to improve specificity for ovarian carcinomas such as human epididymis protein 4 {HE4}. This biomarker reported to be overexpressed in ovarian cancer. Although specificity of this marker is rather reliable but low sensitivity.[4] For these reasons, algorithm, RMI (risk of

malignancy index) and ROMA (risk of ovarian malignancy algorithm) included their menopausal status in an attempt to improve the inherent characteristics of these biomarkers. Another study performed in 2012 that the ultrasound assessment was superior according to IOTA (international ovarian tumor analysis) criteria compared to RMI. IOTA (international ovarian tumor analysis) reported 20,000ovarian tumor with better results with the use of ultrasound criteria (sensitivity 93%, specificity 80%).[6] Our reviews intend to provide a comprehensive update for the diagnosis of ovarian cancer using biomarkers (CA125) and ultrasonoghraphy algorithm RMI and ROMA and how to improve our approaches to indentify and diagnose ovarian cancer in early stage and improve the survival rate. If we diagnose the ovarian cancer in early stage 1 and 2 survival rate is 70% after 5 years.

METHODOLOGY

This review study done in the Department of Obstetrics and Gynaecology Swaroop Rani hospital, Prayagraj, Uttar Pradesh. All literature reviewed from 2010 to till date were included and analysed. literature was searched by medline database following criteria CA125, HE4, RMI, ROMA for screening or diagnosis.

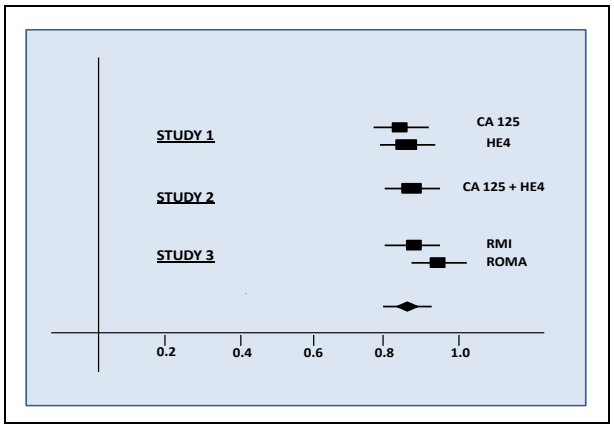

Figure 1: Forest plot showing overall estimate and pooled estimate of different study.

Conclusions were derived regarding How to improve survival rate of ovarian cancer patient by early-stage diagnosis and differentiation of nature (benign/malignant) of ovarian mass using different algorithms. This study is a result of reviews regarding algorithms determining status of ovarian mass and the source of literature was all the standard online articles available in last 3 years and also the departmental records of the last 1 year. So we have concluded our result on the basis of ODDS ratio and confidence interval (CI) of tumor marker like CA125, HE4, RMI, ROMA from different study. Overall estimation and pooled estimation determined by forest plot and our pooled estimation is present between the 0.8 OR to 1.0 OR and 95 % of confidence interval of the result. Our study concludes that RMI has comparatively good OR ratio and pooled effect of forest plot is in favor of RMI 0.8 OR to 1.0 OR and had good opportunity to identify early stage ovarian cancer.

SUMMARY AND DISSCUSION

Overall,102 studies were identified. out of these 6studies met the inclusion criteria and were thus selected and other were excluded. Out of 7 studies, 2 were cohort studies and 4 were systemic review/metanalysis. Various methods such as imaging, tumor marker and different algorithms have been proposed for Identification and confirmation of early ovarian cancer. Recent advances include molecular approach like whole genome analysis, transcription profiling, micro RNA profiling proteomic profiling etc. A study performed by Braga et al shows the comparison between human epididymis 4 vs. carbohydrate antigen CA125 for the diagnosis of ovarian cancer.[7] It demonstrated that sensitivity of CA125 is 79% and specificity of CA125 for detecting ovarian cancer was 78% (95% ci 76-80) and HE4 has sensitivity of 79% and specificity of HE4 was 93%.

Another study of European group on tumor markers tells that screening for ovarian cancer based on CA125 is not recommended among asymptomatic women due to low of sensitivity both for stage 1 and mucinous epithelial ovarian tumor.so we found that in our hospital setting in which we analysed data for 3 years. also suggested that a multivariant approach is better to diagnose ovarian cancer in comparison to single biomarker CA125.[7] According to Drapkin et al proposed that gene coding HE4 is commonly amplified in ovarian cancer.it is a secreted protein that is absent in normal ovarian epithelium but expressed specifically in 100% of the 16 human endometriod epithelian ovarian cancer screened and 93% of the 60 serous ovarian cancer stained for HE4.[8] Due to financial constraints this test was not included in our study. A review literature given by Dodge et al recommended that a standalone modality serum cancer antigen CA125 is not recommended for distinguishing between benign and malignant adenexal mass.[10] According to them ultrasonoghraphy based morphology scoring system like ROMA and RMI can be used to differentiating benign from malignant adenexal masses. Similar results were found in our study where women with adenexal mass were evaluated using scoring systems RMI/ROMA and biomarker CA 125.

A study done by Nolen et al recommended that CA125 with HE4 gave best result among all biomarker in distinguishing the benign cells from early stage of ovarian cancer at 74.2 % sensitivity and 85% specificity.[15] A another study done by Visintin et al used panel of six biomarkers consisting of CA-125, osteopontin, leptin, prolactin, MIF and IGF-II improved the sensitivity at 95.3% and specificity at 99.4% for ovarian cancer.[16] Jacob et al in suggested to use RMI algorithm by using CA125, ultrasound finding and menopausal status according to the formula: RMI =U xMx CA125.[17]

Table 1: Diagnostic biomarkers of early-stage ovarian cancer.

Biomarkers	Sensitivity (%)	Specificity (%)	Methods	Reference
HE4+CA125	45.9	95	Mesomark™ Assay	Moore et al.[9]
Human kallikrein 6 (hK6)+CA125	42	90	Immunoassay	Diamandis et al.[11]
CA-125, HE4, CEA, and VCAM-1	86	98	Bead-based xMAP immunoassays	Yurkovetsky et al.[12]
ApoA1+CA-125+TTR	93.9	95	multiplex liquid assay system	Kim et al.[13]
β2-microglobulin (β2-M), ApoA1 and CA-125	94	98	Multiplexed fluorescence spectroscopic, and Surface Plasmon Resonance spectroscopy	Pal et al.[14]

Table 2: Studies included in our discussion.

First author	Year	Study design	Main result
Tanha et al.[18]	2021	A systematic review and metanalysis	Most commonly reported genetic factor were MTFHR c677(OR= 1.077; 95% CI (1.032,1.124) p<0.001), BMSLrs1544410 (OR=1.078; 95%CI (1.024,1.153), (p=0.004) and FOKLRS2228570 (OR=1.123;95% CI (1.089,1.153)
Tuya et al.[19]	2009	A systematic review and metanalysis	The pooled proportion of MSI-H ovarian cancer was 0.12 (95% CI ,0.08-0.17) from 18 studies with 977 cases.
Wang et al[20]	2014	A metanalysis	Three tests yielded similar performance in ovarian cancer diagnosis (95% CI)-0.89 (0.86-0.92) for HE4; 0.87 (0.84-0.90) for CA125; 0.91 (0.88-0.93) for ROMA.
Suri et al[21]	2021	A metanalysis	A diagnostic ODD ratio for ROMA (postmenopausal female) OR=44.04, 95%CI- 31.27- 62.03), ROMA (Premenopausal OR=18.93 95% CI 13.04-27.48, CA 125 OR=13.44 95%CI (9.97-18.13), HE4 OR=41.03 95% CI (27.96- 60.21)
Meys et al[22]	2016	A metanalysis	We analysed 47 articles, enrolling 19,674 adenexal tumors; 13953 (70.9%) benign and 5721 (29.1 %) subjective assessment by experts performed best with pooled sensitivity of 0.93 (95% CI (0.92-0.95) and specificity 0f 0.89 (95% CI (0.86-0.92)
Cui et al[23]	2019	A metanalysis	The pooled estimate for ROMA index sensitivity 0.90 (95% CI (0.88-0.93), Specificity 0.90(95% CI 0.89-0.94) Positive predictive 0.90 (95% CI (0.88-0.95), Negative predictive 0.93 95% CI (0.91-0.95).

Another study performed in 2012 demonstrated that the ultrasound assessment was superior according to IOTA (international ovarian tumor analysis) criteria compared to RMI. A score above 200 proved that high risk of malignancy (sensitivity 85.4% and specificity 96.9%). Our study of almost 50 ovarian tumor reported better results with use of ultrasound criteria (sensitivity 93% and specificity 80%).

CONCLUSION

In view of growing health concerns regarding biomarkers development for early detection of ovarian cancer, we need wide cohort study in future may help in the identification of the best biomarker panels in improving the sensitivity of the biomarkers and in achieving the required sensitivity, specificity and accurate positive predictive value. In our hospital setting we analyzed CA125 is one of the commonly used serum biomarkers in diagnosis for the ovarian cancer but significant increase in level of CA125 was found in ademyosis, uterine myoma, endometriosis of ovary. Moreover, CA125 not only increased in 80% of ovarian cancer but also 50% rises are observed in early stage ovarian cancer. In recent year in our institute that ultrasound with RMI scoring combined CA125 has a better predictive value compared with CA125 alone. In our hospital settings most of the patient do not afford the amount of extensive serum biomarker/molecular marker testing which has been recently developed. Although in future we can try to improve the diagnostic accuracy for early-stage ovarian cancer with combination of new serum biomarkers/molecular markers detection using technologies like nucleic acid including whole genom analysis, free DNA, mRNA, miRNA and circulating tumor DNA (ctDNA) gene wide transcriptomic profiling may help to determine the aberrant genes to identify the novel biomarker of ovarian cancer in future.

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