The Efficacy of HE4 and ROMA in Prediction of Ovarian Malignancy in Comparison to CA-125 and RMI

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Abstract

Introduction: Cancer of the Ovary is one of the most communal gynecologic malignancy. It has the highest fatality due to its vague and unspecific clinical presentation.

Aim of the Study: Is the evaluation of CA-125, RMI, HE4, and ROMA as diagnostic concert amongst women with nonfunctional ovarian cysts for cancer recognition.

Methods: It is a prospective clinical study in females presented by ovarian cysts ≥ 4 cm who were prepared for surgery at Zagazig University hospital, Egypt between April 2018 and July 2019. Ultrasound findings and blood sample assembly were accomplished pre- operative. All information and pathologic results were achieved and were evaluated statistically under SPSS software version 21.

Results: 140 females with ovarian cysts were assessed. (75.7%) were benign and (24.3%) were malignant. HE4 had the lowest sensitivity(51.2%) and the highest specificity (96.9%). In comparison to CA125, it had NPV (90.3% vs. 94.1%) and PPV (89.2% vs. 27.9%) in distinguishing between malignant and benign ovarian tumors. ROMA of postmenopausal women had sensitivity (90.1%) which is slightly more than that of CA125 (88.1%) and NPV (91.6%) which is slightly lower than that of CA125 (94.1%). Also, higher specificity (72.1% vs.(43.7%) {postmenopausal} and (89.2%vs 43.7%) {premenopausal} and PPV (46.9% vs. 27.9%). HE4 at 70 pMol/L, would provide the sensitivity (71.2%) and specificity (84.3%) to distinguish between benign and malignant ovarian tumors which were analogous to diagnostic value of ROMA.

Conclusion: CA-125 and RMI had lesser performance than ROMA and HE4 as they had (higher specificity, PPV) when matched to CA-125 and RMI. Also 70 pMol/L of HE4 could be the firsthand cutoff value for ovarian cysts differentiation.

Keywords: *Cancer; Ovary; CA125; RAI; ROMA; HE4*

Introduction

Two-thirds of the cancer ovary cases were diagnosed at advanced stage [1]. As its symptoms are ambiguous and unspecific; it results in diminishing the five-year survival rate from up to 90% in stage I to less than 30% in advanced stage So, the early stage of diagnosis leads to Improved survival outcome [2]. CA-125 level and transvaginal ultrasonography are the diagnostic approaches of ovarian cancer at present-day. (RMI) Risk of Malignancy Index is an algorithm that services the findings of ultrasound and constructions features of a pelvic mass, CA-125 levels, and menopausal status to estimate a numeric score for classifying patients with epithelial ovarian cancer

(EOC) to high- and low-risk groups [3]. Nevertheless, the sensitivity and specificity of CA-125 are low [4]. As its level does not raise in half of early-stage EOC patients. Conversely, it upraises in several benign gynecologic disorders such as PID, endometriosis, and even in menstruation [5].

Therefore, it is important to search for other marker which has the ability to identify cancer at early-stage with high specificity to improve clinical decision. Human epididymis protein 4 (HE4) is a possible new biomarker to attain high sensitivity and specificity for epithelial ovarian cancer recognition in comparison to CA-125 [6]. Risk of Ovarian Malignancy Algorithm (ROMA) is a quantitative test that syndicates; CA-125, HE4 and menopausal status into a mathematical score to classify an ovarian adnexal mass to high or low probability of malignancy [7].

Objective of the Study

The objective of this study was the evaluation of the diagnostic value specificity, of CA-125, RMI, HE4 and ROMA for perception of ovarian cancer in females with nonfunctional ovarian cysts.

Patients and Methods

Prospective analytic study was done on 140 females aged ≥ 19 years old who were presented by ovarian cysts ≥ 4 cm and arranged for surgery between April 2018 and July 2019 after the approval of Research Ethics Committee of the Faculty of Medicine, Zagazig University, Egypt and Written informed Consent which was obtained from all of them. We excluded anyone had previous history of cancer; ovarian, or anywhere, pregnancy, functional cysts or previous bilateral oophorectomy. The demographic criteria of patients [age, parity, contraception, and menopausal status] were assessed. Pre-operative; blood sample was taken from each one (10 ml) for HE4 and CA-125 investigation by electrochemiluminescence immunoassay (ECLIA) with the same team cast (MODULAR ANALYTICS E170, cobas e601 and cobas e602 analyzers). [CA-125, RMI, HE4, ROMA], results and findings of ultrasound (Size, bilateral, multiloculation, solid part, ascites, and confirmation of metastasis) sideways with pathologic results was also attained. Score of ultrasonogram before admission, CA 125 value and menopause status were attained and calculated the RMI. Automatically, ROMA score was considered by the computer program. Postoperative, the operative finding and pathologic results were compared to the RMI and the other parameters. Statistical analysis was done through using SPSS version 21 (SPSS Inc, Chicago, IL, USA). General features were presented and studied in median, percentage and range. Sensitivity, specificity, NPV and PPV of CA-125, RMI, HE4 and ROMA were evaluated as diagnostic performances in comparison with the pathologic result which was Considered as gold standard.

Results

140 females with ovarian cysts were assessed. Table 1 represented the demographic data of all participants. Range of the age was from 19 to 72 years old with the mean 46 years old (SD ± 11.14 years). 40% of the participants were nulliparous, (7.1%) had history of different methods of Contraception, 21.4% were Postmenopausal. Pathological diagnosis was benign in (75.7%) and malignant in (24.3%). Table 2 represented the values of CA-125, HE4, RMI, and ROMA of all the participants in median and Range. HE4 had the lowest sensitivity (51.2%) and the highest specificity (96.9%). In comparison to CA125, it had NPV (90.3% vs. 94.1%) and PPV (89.2% vs. 27.9%) in distinguishing between malignant and benign ovarian tumor. ROMA of postmenopause had sensitivity (90.1%) which is slightly more than that of CA125 (88.1%) and NPV (91.6) which is slightly lower than of CA125 (94.1%).

Also, higher in specificity (72.1% vs. 43.7%) {postmenopausal} and (89.2%vs 43.7%) {premenopausal} and PPV (68.5% vs. 27.9%) (46.9% vs. 27.9%) (Table 2). Table 3 showed comparison between the sensitivity, specificity, PPV and NPV of CA- 125, HE4 and ROMA concentrating on the cut of level of HE4 at 70 pMol/L, it would provide the sensitivity (71.2%) and specificity (84.3%) to distinguish between benign and malignant ovarian cancer which were analogous to diagnostic value of ROMA.

Character	N (%)
Age	(Mean ± SD) 46.13 ± 11.14 (Range) 19 - 72
Parity	
Nullipara	56 (40.0%)
Multipara	84 (60%)
Contraception	10 (7.1%)
Menopausal status	
Postmenopause	30 (21.4%)
Premenopause	110 (78.57%)
Pathological	
Benign	106 (75.7%)
Malignancy	34 (24.3%)
Early-stage ovarian cancer	18 (12.8%)
Advanced-stage ovarian cancer	16 (11.5%)

Table 1*: Demographic criteria of the Patients and the pathological result of the ovarian cysts.*
Values are presented as mean ± SD, No. (percentage %).

Item	Median	Sensitivity (%)	Specificity (%)	PPV	NPV
CA-125 (> 35 IU/ml)	46.1 (32.3 - 132.8)	88.1	43.7	27.9	94.1
HE4 (> 150 pMol/L)	38.9 (19.8 - 70.9)	51.2	96.9	89.2	90.3
RMI (> 250)	36.8 (1.0 - 179.8)	67.3	88.7	63.3	89.4
ROMA (postmenopause)	42.8 (9.9 - 75.2)	90.1	72.1	68.5	91.6
ROMA (premenopause)	12.8 (4.1 - 12.1)	65.7	89.2	46.9	95.2

Table 2: *Diagnostic value of CA-125, RMI, HE4, and ROMA.*
Median(Range), Sensitivity, Specificity, PPV and NPV.

	CA-125 (> 35 IU/mL)	HE4 (> 150 pMol/L)	HE4 (> 70 pMol/L)	ROMA
Sensitivity (%)	88.1	51.2	71.2	80.6
Specificity (%)	43.7	96.9	84.3	78.9
PPV (%)	27.9	89.2	60.1	58.1
NPV (%)	94.1	90.3	92.7	92.9

Table 3*: Comparison of sensitivity, specificity, PPV and NPV of CA-125, HE4 and ROMA.*

Discussion

This current study assessed the diagnostic concert of [HE4, and ROMA] and (CA-125, RMI) in females with ovarian cysts. HE4 and ROMA while had higher specificity and PPV in differentiating between benign and malignant ovarian tumor.

This agreed with study of Kondalsamy., et al. [8] and Romagnolo., et al. [9] they found that ROMA had the paramount concert in discriminating benign ovarian cyst from malignant one.

Also agreed with studies of Gorp., et al. [10], Karen., et al. [11] and Molina., et al. [12] previous studies [13]. The cutoff value of HE4was 150 pMol/L but in this study we can alter it to 70 pMol/L as at that level it provides the sensitivity at 71.2% and specificity at 84.3% comparable to sensitivity and specificity of ROMA. HE4 is definitely cheaper than ROMA since it needs both CA 125 and HE4. So, HE4 at the cutoff level at 70 pMol/L had equivalent diagnostic value with lower cost than ROMA. Using it at this value could affect the opinion to choose diagnostic devices in the prediction of cancer ovary and the best suitable management [14]. At the end, we think using HE4 at cutoff level 70 pMol/L and ROMA can help in differentiating benign from malignant ovarian cysts. Since they have higher sensitivity and specificity to do than using CA-125 and RMI.

Conclusion

CA-125 and RMI had lesser performance than ROMA and HE4 as they had (higher specificity, PPV) when matched to CA-125 and RMI. Also 70 pMol/L of HE4 could be the firsthand cutoff value for ovarian cysts differentiation.

Conflicts of Interest

Authors declare that they have no conflicts of interest.

Data Availability

data used to support the findings of this study are available from the corresponding author upon request.

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