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Review article

Standard and optimal cut-off values of serum ca-125, HE4 and ROMA in preoperative prediction of ovarian cancer in Vietnam

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ABSTRACT

Objectives: To evaluate the validity of serum CA-125, Human Epididymis protein 4 (HE4) and Risk of Malignancy Algorithm (ROMA) at standard and optimal cut-offs, in preoperative prediction of epithelial ovarian carcinoma (EOC) in Vietnam.

Subjects and methods: Cross-sectional, descriptive study on 277 patients with ovarian masses hospitalized at the OBGYN Departments, Hue University Hospital and Hue Central Hospital, Vietnam, from 01/2016 to 11/2017. All patients had measurements of serum CA-125 by Elecsys 2010 system and HE4 by immunoassay ARCHITECT® HE4 kits; ROMA calculated, and preoperative malignancy risk estimated. Matching these values to postoperative histopathology resulted in the preoperative prediction values.

Results: There were 30 (10.8%) cases of EOC. Median values of CA 125, HE4, and ROMA of EOC and benign tumors were 214.20 U/ml, 18.91 U/ml; 90.00 pmol/l, 39.80 pmol/l; and 55.20%, 4.80%, respectively. The sensitivities and specificity of CA125, HE4, and ROMA to distinguish between malignant and benign tumors at standard cut-offs were 83.3% and 78.5%; 50% and 98.38%; 80.0% and 84,6%, and those at optimal cut-offs were 83.3% and 86.6%; 80.0% and 91.5%, 86.7% and 88.7%, respectively. AUCs of CA-125, HE4, and ROMA were 0.872, 0.894, 0.912; and those for the post-menopausal group were 0.900, 0.894 and 0.924, respectively.

Conclusion: Serum CA 125 and HE4 levels and ROMA have good validity in the diagnosis of EOC, of which ROMA gives the best result. The ROMA index should be applied in clinical practice to help in the assessment and management of patients with suspected ovarian cancer.

1. Introduction

Ovarian cancer is one of the most common types of cancer of the female reproduction system, occurring in 5–15 per 100,000 women/year in Western countries. According to GLOBOCAN (2012), the incidence in Vietnam is about 3–4.5 per 100,000 women/year, with a prevalence of around 8–10 cases per 100,000 women per year (Ferlay et al., 2015). About 70% of the cases of ovarian cancer are not diagnosed before reaching the advanced stages, and the five-year survival rate associated with ovarian cancer is < 30% (Rauh-Hain et al., 2011). Early diagnosis of ovarian cancer is a major factor in improving the survival rate. Markers currently used to distinguish between low-risk and high-risk patients with ovarian cancer include CA-125, Human Epididymis protein 4 (HE4), and the recently introduced Risk of Ovarian Malignancy Algorithm (ROMA) (Karlsen et al., 2012).

CA125 is the most widely used biomarker in epithelial ovarian carcinoma (EOC). However, the rather high sensitivity and specificity of CA125 of about 80% in patients in various stages of ovarian cancer drops to 50% or even lower in patients specifically in early stages. Moreover, CA125 level can be elevated in a variety of common benign diseases such as endometriosis and pelvic inflammatory conditions, as well as in borderline tumors of the ovaries (Montagnana et al., 2011a). Recently, HE4 has been repeatedly confirmed as one of the most promising biomarkers for early stage diagnosis. HE4 has been found in more than half of ovarian tumors without CA125 expression (Montagnana et al., 2011b), and less frequently elevated in benign tumors that mimic the biomarker profile of ovarian cancer, which has often been seen in premenopausal women (Moore et al., 2012). The

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combination of HE4 and CA125 values resulted in the algorithm to assess the malignancy of the ovaries – ROMA (Moore et al., 2009), which could provide a high sensitivity and specificity for early detection of ovarian cancer. Since the introduction of ROMA into clinical practice, there have been studies of modified cut-off values of these biomarkers and indices (Winarto et al., 2014). Although numerous studies on HE4 and ROMA have been carried out around the world, there are as yet no data from Vietnam. This study aimed to evaluate the validity of serum CA-125, HE4, and ROMA at standard and optimal cut-offs in the preoperative prediction of EOC in Vietnam.

1.1. Subjects and methods

Study subjects included 277 women with clinically diagnosed ovarian tumors, including benign ovarian tumors and ovarian cancers, admitted to the Departments of Obstetrics and Gynecology, Hue University Hospital and Hue Central Hospital from January 2016 to November 2017. Selection criteria included patients with sufficient personal information, clinical symptoms, data on serum CA125 and serum HE4 levels, and postoperative pathologic findings. Pregnant women, patients with a history of ovarian, primary peritoneal, or any other associated cancer were excluded from the study. Patients were interviewed for demographic characteristics and history, and then underwent gynecologic examination and pelvic ultrasound to evaluate the tumors, and serum was obtained for the measurements of CA125 and HE4 using Elecsys 2010 system immunoassay (Elecsys, 2010) and ARCHITECT i1000SR system respectively (ARCHITECT System User Manual, 2009).

The CA125 cut-off value was 35 U/ml (Bast et al., 1998). The HE4 positive cut-off values for premenopausal and postmenopausal women were > 70 pmol/l and > 140 pmol/l respectively.

ROMA was calculated as described elsewhere (Moore et al., 2010). Briefly, a predictive index (PI) was calculated for premenopausal and postmenopausal patients separately using Eqs. (1) and (3) below, followed by insertion of the calculated PI values into Eqs. (2) and (4), respectively:

$$\text{premenopausal women: PI} = -12.0 + 2.38^{*}\text{LN[HE4]} + 0.0626^{*}\text{LN[CA125]} \quad (1)$$

$$\text{ROMA value (\%)} = \text{exp.(PI)}/[1 + \text{exp.(PI)}]^{*} 100 \quad (2)$$

ROMA values ≥7.4% or < 7.4% are regarded as high-risk and low-risk respectively.

$$\text{postmenopausal women: PI} = -8.09 + 1.04^{*}\text{LN[HE4]} + 0.732\text{LN[CA125]} \quad (3)$$

$$\text{ROMA} = \text{exp.(PI)}/[1 + \text{exp.(PI)}]^{*} 100 \quad (4)$$

ROMA values ≥25.3% or < 25.3% are regarded as high-risk and low-risk respectively.

Based on the ROMA risk estimates and ultrasound-guided tumor malignancy stratification, appropriate surgical interventions were implemented accordingly. The excised ovarian tumors were examined histologically and classified according to WHO classification. Cases with advanced diseases that were considered inoperable and contain positive ascites were excluded. Preoperative CA125, HE4 and ROMA values were matched postoperatively to the histopathological results to calculate the preoperative prediction values.

Data were entered and processed using MedCalc 17.0. Mann-Whitney test was used to compare the two groups having non-standardized distributions. Hanley – McNeil test was used for comparison between two areas under the curves.

Ethics approval for study protocol was obtained from the Ethics Committee for Biomedical Researches at Hue University of Medicine and Pharmacy, Hue, Vietnam. Informed consents were obtained from study's subjects.

Table 1
Demographic characteristics of study's subjects.

	Benign tumor		EOC		p
	n (247)	%	n (30)	%	
Age					
< 20	16	6.5	0	0	< 0.01
20–29	76	30.8	3	10.0	
30–39	66	26.7	2	6.7	
40–49	52	21.1	6	20.0	
≥ 50	37	15.0	19	63.3	
Menopausal status					
Pre-menopausal	217	87.9	13	43.3	< 0.01
Post-menopausal	30	12.1	17	56.7	
Number of children					
Nullipara	70	28.3	7	23.3	0.220
1	48	19.4	4	13.3	
2	52	21.1	4	13.3	
≥ 3	77	31.2	15	50.0	

2. Results

Among the 277 patients included in the study, 247 (89.2%) were diagnosed with benign ovarian tumors and 30 (10.8%) were diagnosed with EOC.

The differences in age and menopausal status were statistically significant, in the cancer group, 63.3% of the patients were older than 50 years, and 56.7% of patients were already menopausal ($p < .01$). The numbers of children were not significantly different between the two groups ($p = .220$) (Table 1).

Median values of HE4, CA125 and ROMA of the cancer group were statistically higher than those of the benign tumor group (Mann-Whitney test) (Table 2). The median value of HE4 in the EOC group was 90.00 pmol/l (57.47–447.97 pmol/l), which was statistically higher than the value from the benign tumor group at 38.50 pmol/l (30.10–45.90 pmol/l) ($p < .01$). The median value of CA-125 of the EOC group was 214.20 U/ml, (60.56–764.42 U/ml), significantly higher than the value of the benign tumor group at 17.45 U/ml (11.88–28.70 U/ml) ($p < .01$). The ROMA median value in the benign tumor group was 4.47% (2.44% - 7.02%), and that of the EOC group was 55.20% (11.89–95.0%); the difference was statistically significant ($p < .01$).

ROMA yielded a higher AUC value than those from CA-125 or HE4 (see Table 3), both in the general group as well as the post-menopausal group, but the differences were not statistically significant (Hanley-McNeil test): ROMA vs. CA125 ($Z = 0.869$; $p = .3851$); and ROMA vs. HE4 ($Z = 1.090$, $p = .27$) (see Graphs 1 and 2). With an optimal cut-off value of 9.52% for ROMA, the sensitivity and specificity were 86.7% and 88.7%, respectively. In both the pre- and postmenopausal groups, optimal cut-off values of ROMA yielded high specificity and negative predictive values.

3. Discussion

This study was conducted to evaluate the validity of serum CA-125, HE4 and ROMA at standard and optimal cut-offs in the preoperative prediction of EOC in Vietnam. Using a cut-off value of 35 U/ml, the sensitivity of CA-125 in our study was 83.3% and the specificity was 78.5%. The area under the ROC curve of CA-125 was 0.872; with the optimal cut-off of 49.4 U/ml, the sensitivity was 83.3% and the specificity was 86.6%.

The level of serum CA-125 can be increased in many clinical cases with benign conditions, including pregnancy, endometriosis, uterine fibroids, pancreatitis, menstruation, pelvic inflammatory disease, and liver disease. On the other hand, serum CA-125 is not elevated in approximately 20% of women with ovarian cancer. In our study, cases of