Copenhagen Index versus ROMA in the preoperative ovarian malignancy risk stratification: result from the first Vietnamese prospective cohort study

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Abstract

Objectives: This study aimed to evaluate the diagnostic performances of the Copenhagen Index (CPH-I) and Risk of Ovarian Malignancy Algorithm (ROMA) in the preoperative prediction of ovarian cancer.

Methods: In a prospective cohort study, data were collected from 475 patients with ovarian masses who were hospitalized at the Departments of Obstetrics and Gynecology, Hue Central Hospital and Hue University of Medicine and Pharmacy Hospital, Vietnam, between January 2018 and June 2020. ROMA and CPH-I were included for the women who had measurements of serum carbohydrate antigen (CA-125) and human epididymis protein (HE4). Matching these values to postoperative histopathology resulted in the preoperative prediction values. The final diagnosis was based on clinical features, histologic, radiologic findings, and the International Federation of Gynecology and Obstetrics (FIGO) 2014 stages of ovarian cancer were recorded.

Results: Among the 475 women, 408 had benign tumors, 5 had borderline tumors and 62 had malignant tumors. The two indices showed similar discriminatory performances with no significant differences ($p > 0.05$). At an optimal cut-off, the sensitivities/specificities of ROMA and CPH-I for ovarian cancer diagnosis were 76.1% and 87.0%, 83.6% and 78.7%, respectively. The optimal cut-off for CPH-I was 1.89%. The areas under the ROC curves (AUCs) of ROMA and CPH-I were 0.860 (95%CI: 0.825 – 0.890) and 0.868 (95%CI: 0.833 – 0.896), respectively.

Conclusions: The introduction of the Copenhagen Index to help stratify the malignancy risk of ovarian tumor, irrespective of menopausal status might be applied as a simple alternative with a similar efficacy to ROMA in clinical practice.

Introduction

Ovarian cancer (OC) is one of the ten most commonly diagnosed cancers in women and has the highest mortality rate and the worst prognosis of all gynecological cancers (1). In 2018, 295,414 cases of OC were detected in the world, and 184,799 died, with the highest incidence in developed countries (2). In 2019, about 22,530 cases of OC were diagnosed in the United States, ranked second in pelvic cancers after cancer of the uterus, of which there were 13,980 deaths (3). The mortality rate has not changed in the past 30 years, and it is predicted that, by the year 2040, this rate will be significantly increasing (4,5). Since 70% of ovarian cancers are diagnosed in an advanced stage (stage III – IV), when the disease has spread to the pelvic and abdominal region, the 5 – year survival rate is 20–25%, but if detected in the early stage, this rate is increased to 90% (4,6). Therefore, early detection had important implications on treatments, quality of life and prognosis of patients (7,8).

In the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), there were 78 ovarian cancer cases in 1,590 adnexal tumors, which were detected after screening 48,230 women by transvaginal ultrasound and 50,078 women using biochemical markers (CA-125, HE4) (9). In 2009, Moore et al. developed the Risk Ovarian Malignancy Algorithm (ROMA) by integrating serum CA-125, HE4 values,

and menopausal status for differentiating between low- and high-risk patients with OC (10). In 2015, Karlsen et al. developed the Copenhagen Index (CPH-I) based on these two biomarkers and patient's age. The areas under the ROC curve (AUC) that predicted OC by CPH-I and ROMA were 0.960 and 0.954, respectively, thereby showing that the values of these two indicators were equal. The Copenhagen Index has the advantage not depending on ultrasound and menopausal status, the age variable is easy to collect, simple, and objective (11). Therefore, the Copenhagen Index 's advent promises to be a reliable, objective, and widely applied tool at the grassroots level.

The purpose of this study was to compare the Copenhagen Index and the ROMA in the preoperative prediction of ovarian cancer.

Methods

The study was conducted on women diagnosed with ovarian tumors, who were hospitalized at the Departments of Obstetrics and Gynecology, Hue Central Hospital and Hue University of Medicine and Pharmacy Hospital, Vietnam, between January 2018 and June 2020.

The sample size was calculated according to the formula to estimate the specificity in two steps:

Step 1

Calculate *FP + TN*

$$FP + TN = \frac{Z^2_{\frac{\alpha}{2}} x p_{sp} x \left(1 - p_{sp}\right)}{w^2}$$

Step 2

Calculate sample size

$$N_{sp} = \frac{FP + TN}{1 - p_{dis}}$$

Abbreviations: FP, False Positive; TN, True Negative, Z_(α/2)^2 = 1.96 with α = 0.05; w = 0,04. The p_{sp} value from the study of Adriana Yoshida (2016) is 0.844 (12). According to GLOBOCAN (2018), the prevalence rate of OC in Vietnam (p_{dis}) is 7.67 cases/ 100,000 women = 0.000767 (2). The minimum sample size (N_{sp}) calculated by the formula was 317 patients. At the end of the study, 475 women who met the disease selection criteria were included.

In this prospective cohort study, the research steps include administrative interviews, medical history, physical examination as well as quantitative assay of serum CA-125, HE4. At Hue University of Medicine and Pharmacy Hospital, serum CA-125, HE4 tests were conducted using an Electrochemiluminescence Immunoassay on the COBAS 6000 system, Roche, Switzerland. Test results were controlled by the

Internal Quality Control (IQC) system with RANDOX's standard control samples and programs. Calibration samples were performed daily on the system of testing machines before being tested. At Hue Central Hospital, tests for CA-125, HE4 were conducted by Chemiluminescent Microparticle Immunoassay on Architect i1000 system (Abbott Diagnostics). The tests were quality checked daily (internal inspection) and were subjected to external inspection at the Ho Chi Minh City Standardization Center.

The Copenhagen Index predicts the risk of a preoperative ovarian tumor malignancy according to the algorithm below (11):

$$\text{CPH-I} = -14{,}0647 + 1{,}0649 * \log_2(\text{HE4}) + 0{,}6050 * \log_2(\text{CA-125}) + 0{,}2672 * \text{Age}/10$$

$$\text{PP} = e^{(\text{CPH-I})} / (1 + e^{(\text{CPH-I})})$$

- Calculating the ROMA index to predict the risk of ovarian tumor malignancy before surgery according to the algorithm: ROMA (%) = exp(PI) / [1 + exp(PI)] * 100 (10)

PI is the prediction index, determined as follows:

- - Pre-menopausal women: PI= -12,0 + 2,38*Ln[HE4] + 0,0626*Ln[CA-125]
- - Post-menopausal women: PI= -8,09 + 1,04*Ln[HE4] + 0,732*Ln[CA-125]

The ROMA cut-off point values are applied according to the Technical Instructions of the Cobas 6000 system and the ARCHITECT system. Patients are supposed to have a high risk of ovarian cancer when:

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Test system	Pre-menopausal group	Post-menopausal group
Cobas 6000 (ROMA 1)	≥ 11,4%	≥ 29,9%
Architect i1000 (ROMA 2)	≥ 7,4%	≥ 25,3%

The patients were then surgically managed and diagnosed with histopathology according to the World Health Organization (WHO) 2014 (13). Finally, the parameters were compared with the histopathological results (including benign and malignant ovarian tumors) to calculate and compare with the diagnostic values of CPH-I and ROMA. Based on these two indicators, the patients were classified into the benign tumor group or malignant tumor group (borderline and malignant tumors).

Statistical analysis

Data analyses were performed using the statistical software SPSS20.0 (SPSS, Inc., Chicago, IL, USA), and receiver operative curve (ROC) analysis was done with Medcalc. Categorical variables were reported as number (percentage) and continuous variables as median (SD, standard deviation; range). The Chi-square test (c2) was used to evaluate inter-group differences, and $p < 0.05$ was considered significant. Use the Kruskal – Wallis test to compare the difference between three groups that are not normal distributions.

Ethical Approval

Ethic approval for the study protocol was by the Ethics Committee for Biomedical Research at Hue University of Medicine and Pharmacy, Hue, Vietnam (decision number H2018/359, issued on June 22, 2018). Informed consent was obtained from the study's subjects.

Results

Of the 475 patients, 408, 5 and 62 were diagnosed with benign tumor, borderline tumor, and OC, respectively. The main characteristics of individual patient subgroups according to histopathologic diagnosis are shown in Table 1. The mean age of women in the OC group was higher than the benign tumor group. There were significant differences in age, menopausal status, marital status between the two groups ($p < 0.05$). The incidence of OC in the post-menopausal group was 59.7%.

Histological classification of participants was demonstrated as follows: among the 408 women diagnosed with benign tumors, 171 (41.9%) had mature cystic teratoma, 165 (40.4%) serous cystadenoma, 37 (9.1%) endometrioses of ovary. In the borderline tumor group, 4 of 5 cases with serous borderline tumor. In patients with OC, serous adenocarcinoma was seen in 27 cases (43.5%), followed by 12 (19.7%) with mucinous adenocarcinoma, 6 (9.7%) with poorly differentiated carcinoma, and 6 (9.7%) with dysgerminoma. Clinical staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO): 19 (30.6%) cases in stage I, 8 (12.9%) cases in stage II, 26 (41.9%) cases in stage III, and 9 (14.5%) cases in stage IV.

Median values of CPH-I and ROMA of the OC group were statistically higher than those of the benign tumor group (Kruskal – Wallis test) (Table 3). In the study sample, the median value of CPH-I in the OC group was 24.81% (3.49 – 81.21%), which was statistically higher than the value from the benign tumor group at 0.82% (0.44 – 1.76%) ($p < 0.05$). The ROMA median value in the benign tumor group was 5.03% (3.46 – 8.71%), and that of the OC group was 49.93% (12.78 – 81.22%); the difference was statistically significant ($p < 0.05$). Median values of the CPH-I and ROMA of the post-menopausal group were higher than those of the pre-menopausal group, both in the OC group as well as the benign tumor group. Specifically, in the pre-menopausal group, the median values of CPH-I for the OC group, benign tumor, and borderline tumor group were 4.87% (1.49 – 45.72%), 0.72% (0.41 – 1.43%) and 0.42% (0.29 – 24.39%) respectively; the median values of ROMA for the OC group, benign tumor group, and borderline tumor group were 12.18% (6.11 – 62.06%), 4.58% (3.06 – 6.76%) and 5.84% (3.28 – 16.38%) respectively. For the post-menopausal subjects, the median values of CPH-I for the OC group and benign tumor group were 45.49% (8.35 – 91.62%) and 1.49% (0.87 – 3.65%) respectively; the median values of ROMA for the OC group and benign tumor group were 72.37% (37.41 – 95.16%) and 10.59% (7.49 – 18.88%), respectively.

The values of the Copenhagen Index and the ROMA index in the prediction of OC risk before surgery are shown in Table 4 and Graph 1. In the study population, the AUC of CPH-I and ROMA in the prediction of OC are equivalent, being respectively 0.868 (95% CI: 0.833 – 0.896) and 0.860 (95%CI: 0.825 – 0.890). At the optimal cut-off point of 1.89%, the Copenhagen Index had a sensitivity of 83.6% (95%CI: 72.5 – 91.5%) and specificity of 78.7% (95%CI: 74.4 – 82.6%). With an optimal cut-off value of 12.1% for ROMA, the sensitivity and specificity were 76.1% (95%CI: 64.1 – 85.7%) and 87.0% (95%CI: 83.4 – 90.1%), respectively. The Copenhagen Index and the ROMA index are of equivalent value in the differential diagnosis of benign and malignant ovarian tumors; the difference was not statistically significant ($p > 0.05$).

Discussions

The continuous variables ROMA and CPH-I in this study have several non-standard distributions. Therefore, the statistics of ROMA and CPH-I will be presented as median values (Q25% – Q75%).

The median values of CPH-I and ROMA in the OC group, as shown in the Table 3, are higher than those of the benign tumor group, and borderline tumor group. Specifically, for the study population (n = 475), the median value of CPH-I in the malignant group was 24.81% (3.49 – 81.21%), whereas in the benign tumor group it was 0.42% (0.29 – 24.39%), and those in the borderline tumor was 0.42% (0.29 – 24.39%). The median values of ROMA in the cancer group, borderline group, and the benign group were 49.93% (12.78 – 81.22%), 5.48% (3.28 – 16.38%), and 5.03% (3.46 – 8.71%), respectively ($p < 0.05$). Compared to previous studies, the median values of CPH-I and ROMA from our research are lower than those some other studies in the world. According to Adriana Yoshida (2016), the median values of CPH-I for benign tumors, ovarian carcinomas were 1.4%, and 83.4%, respectively (12). Meanwhile, in Lubos Minar's study, the median values of CPH-I in the benign and malignant groups were 2.2% and 75.4%, respectively (14) (Table 5). More detailed analysis in the pre-menopausal and post-menopausal groups, which examine the differences between CPH-I and ROMA, showed that the median values of CPH-I and ROMA were higher in the post-menopausal group, compared with the pre-menopausal group (Table 3). Median values of CPH-I and ROMA in the post-menopausal group were higher than what in the pre-menopausal group. The Sensitivity/Specificity (Se/Sp) of CPH-I in the absence of marginal ovarian tumors, non-epithelial OC, and OC metastasis, was 89.7%/ 85.3%, but if the above objects were included, the corresponding Se/ Sp became lower at 73.1%/ 84.4% (12).

The Se/Sp of ROMA and CPH-I in the diagnosis of OC were 76.1%/ 87.0% and 83.6%/ 78.7% respectively. The optimal cut-off point of the CPH-I was 1.89%, the AUCs of ROMA and CPH-I were respectively 0.860 (95%CI: 0.825 – 0.890) and 0.868 (95% CI: 0.833 – 0.896). Research by T. Nikola (2017) differential diagnosis between ovarian endometriosis and ovarian carcinoma showed that the accuracy of the Copenhagen Index was higher than ROMA, 93.75% and 85.42%, respectively (15).

Zhiheng Wang et al. (2019) argued that the HE4 level, ROMA and CPH-I values of epithelial ovarian cancer (EOC) stages I and II (I + II) were all higher than that of borderline ovarian tumor (BOT) I + II and

benign groups whether in all, pre-, or postmenopausal groups ($p < 0.01$). When distinguishing BOT I+II from EOC I+II, the AUC-ROC of CPH-I and HE4 were larger than CA-125 ($p < 0.001$). CPH-I is more valuable than CA-125 when distinguishing marginal ovarian tumors with stage I – II ovarian carcinoma, while HE4 may be better than CA-125 in post-menopausal group; HE4 and CPH-I have been more advantageous than CA-125 when differentiating a borderline ovarian tumor with an early-stage ovarian carcinoma (I + II) in the absence of histology or type of serum fluid. The AUC of CPH-I and ROMA in the pre-menopausal group are respectively 0.779 and 0.760, and in the post-menopausal group are 0.802 and 0.774. In the pre-menopausal group, the Se/ Sp of ROMA and CPH-I are respectively 78.69%/ 64.75% and 70.49%/ 78.69%. In the postmenopausal group, the Se/ Sp of ROMA and CPH–I are respectively 82.98%/ 68.18% and 85.11%/ 68.18% (16).

According to Estrid Høgdall, ROMA and CPH–I can be used to the differential diagnosis between benign and malignant ovarian tumors [13]. Since family doctors might be unable to perform an ultrasound test, therefore both ROMA and CPH-I could provide the initial reliable information which helps the patient to get early diagnosis and proper treatment from specialized centers. In general, CPH-I and ROMA have similar sensitivity and accuracy. CPH-I is not identical to ROMA and RMI because it is not independent from ultrasound test and menopausal status. Menopausal status can be determined based on age, hormone concentration or amenorrhea per year, so that, the diagnosis of menopausal status has not been standardized. Therefore, CHP-I could be a simpler method to optimize the management when assessing women with suspected OC, including age instead of menopausal status (11,17).

Table 5

Diagnostic validity of CPH-I and ROMA from literature.

Authors	Copenhagen Index		ROMA	
	AUC	Se/Sp (%)	AUC	Se/Sp (%)
A. Yoshida (2016) [12]	0.84	73.1/ 84.4	0.82	71.2/ 83.5
L. Minar (2017) [14]	0.81	69.0/ 85.0	0.83	71.0/ 88.0
T. Nikolova (2017) [15]	0.91	81.8/ 97.3	0.90	90.9/ 83.8
Z. Wang (2019) [16]	0.810	78.7/ 74.3	0.807	62.9/ 88.2
Estrid Høgdall (2016) [17]	0.960	–	0.954	–
Nguyen Vu Quoc Huy (2018) (18)	–	–	0.912	86.7/ 88.7
This study	**0.862**	**80.4/ 80.3**	**0.848**	**69.5/ 92.2**

The Copenhagen Index is a new indicator, which has been introduced in several studies around the world. The ROMA algorithm is an index that the US Food and Drug Administration has introduced in clinical practice to distinguish benign and malignant ovarian tumors, based on the three variables: CA-125, serum

HE4, and menopausal status (19). These two indexes have quite similar values since both are partially based on CA-125, HE4. Since the serum CA-125, HE4 concentrations were affected by many factors including age, smoking, uterine fibroids, pregnancy, endometriosis, pelvic inflammatory disease, gallbladder stone, this will affect the values of the Copenhagen index and ROMA (20,21). In the future, more research about these two indicators on different target groups to clarify these differences, aiming to overcome the limitations of these indicators and avail in clinical practice.

To the best of our knowledge, this is the first cohort study from Vietnam with large number of ovarian tumor subjects included, examining the validity of CPH-I and comparing with those from ROMA in risk stratification for ovarian tumor malignancy. Although being rigorously designed and implemented, the OC cases were still limited, and the laboratory equipements were different at the two facilities where the works were done, this could partially affect the homogeneity of the data analysis.

Conclusions

The introduction of Copenhagen Index to help stratify the risk of ovarian tumor malignancy, irrespective of menopausal status, is similarly accurate to but simpler than ROMA, and could therefore replace ROMA in clinical practice.

Declarations

Author contributions

TDT, LMT, LC, and NVQH conceived the study, coordinated its planning and implementation, and wrote the manuscript.

TDT, VVK, LMT coordinated data acquisition, participated in the data analysis and interpreted the results

LMT, LC and NVQH supervised preparation and revision of the manuscript.

All authors have approved the submitted version of the manuscript.

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Conflicts of interest

The authors have no conflicts of interest.

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Tables 1-4

Table 1

Demographic characteristics of study's subjects.

Parameter	Ovarian cancer		Borderline		Benign tumor		*p-value*
	n (62)	%	n (5)	%	n (408)	%	
Age (year)							
< 20	3	4.8	1	20.0	41	10.0	< 0.0001
20 – 29	1	1.6	1	20.0	122	29.9	
30 – 39	10	16.1	1	20.0	95	23.3	
40 – 49	11	17.7	2	40.0	74	18.1	
50 – 59	22	35.5	-	-	40	9.8	
≥ 60	15	24.2	-	-	36	8.8	
Mean ± SD (Min – Max)	50.7 ± 15.3 (11 – 83)		31.8 ± 13.3 (16 – 49)		36.0 ± 14.9 (4 – 86)		
Menopausal status							
Post-menopausal	37	59.7	-	-	68	16.7	< 0.0001
Pre-menopausal	25	40.3	5	100.0	340	83.3	
Marital status							
Single	9	14.5	-	-	106	26.0	< 0.0001
Married	53	85.5	5	100.0	302	74.0	
Number of children							
Nulliparous	14	22.6	1	20.0	136	33.3	> 0.05
Primiparous	9	14.5	1	20.0	65	15.9	
Parity of two	21	33.9	2	40.0	106	26.0	
Multiparous	18	29.0	1	20.0	101	24.8	

Abbreviations: SD, standard deviation.

Table 2

Histological classification and FIGO stages.

	Ovarian cancer		Borderline		Benign tumor	
	n = 62		n = 5		n = 408	
Pathologic finding						
Epithelial-stromal tumor	Serous adenocarcinoma	27 (43.5)	Serous borderline tumor	4 (80.0)	Serous cystadenoma	165 (40.4)
	Mucinous adenocarcinoma	12 (19.4)	Mucinous borderline tumor	1 (20.0)	Endometriosis of ovary	37 (9.1)
	Endometrioid adenocarcinoma	4 (6.5)			Mucinous cystadenoma	29 (7.1)
	Malignant Brenner tumor	1 (1.6)			Brenner tumor	1 (0.2)
	Clear cell adenocarcinoma	2 (3.2)				
	Poorly differentiated carcinoma	6 (9.7)				
Germ cell tumor	Dysgerminoma	6 (9.7)	-	-	Mature cystic teratoma	171 (41.9)
	Endodermal sinus tumor	1 (1.6)				
Sex cord-stromal tumor	Granulosa theca	3 (4.8)	-	-	Fibroma	5 (1.2)
FIGO stage (n = 62)						
	Stage I	19 (30.6)				
	Stage II	8 (12.9)				
	Stage III	26 (41.9)				
	Stage IV	9 (14.5)				

Abbreviations: FIGO, the International Federation of Gynecology and Obstetrics.

Table 3

Values of CPH-I and ROMA of study's subjects.

	Median (Q25% – Q75%)				*P**
	Total	**Ovarian cancer**	**Borderline**	**Benign tumor**	
Study sample	**n = 475**	**n = 62**	**n = 5**	**n = 408**	
CPH – I	0.96 (0.49 – 2.72)	24.81 (3.49 – 81.21)	0.42 (0.29 – 24.39)	0.82 (0.44 – 1.76)	< 0.05
ROMA	5.49 (3.57 – 10.77)	49.93 (12.78 – 81.22)	5.84 (3.28 – 16.38)	5.03 (3.46 – 8.71)	< 0.05
Pre-menopausal	**n = 370**	**n = 25**	**n = 5**	**n = 340**	
CPH – I	0.78 (0.42 – 1.75)	4.87 (1.49 – 45.72)	0.42 (0.29 – 24.39)	0.72 (0.41 – 1.43)	< 0.05
ROMA	4,63 (3.19 – 7.22)	12.18 (6.11 – 62.06)	5.84 (3.28 – 16.38)	4.58 (3.06 – 6.76)	< 0.05
Post-menopausal	**n = 105**	**n = 37**	**-**	**n = 68**	
CPH – I	3.39 (1.22 – 16.65)	45.49 (8.35 – 91.62)	-	1.49 (0.87 – 3.65)	< 0.05
ROMA	18.71 (8.93 – 46.47)	72.37 (37.41 – 95.16)	-	10.59 (7.49 – 18.88)	< 0.05

Data are shown as median (1st to 3rd quartiles)

* Kruskal-Wallis Test

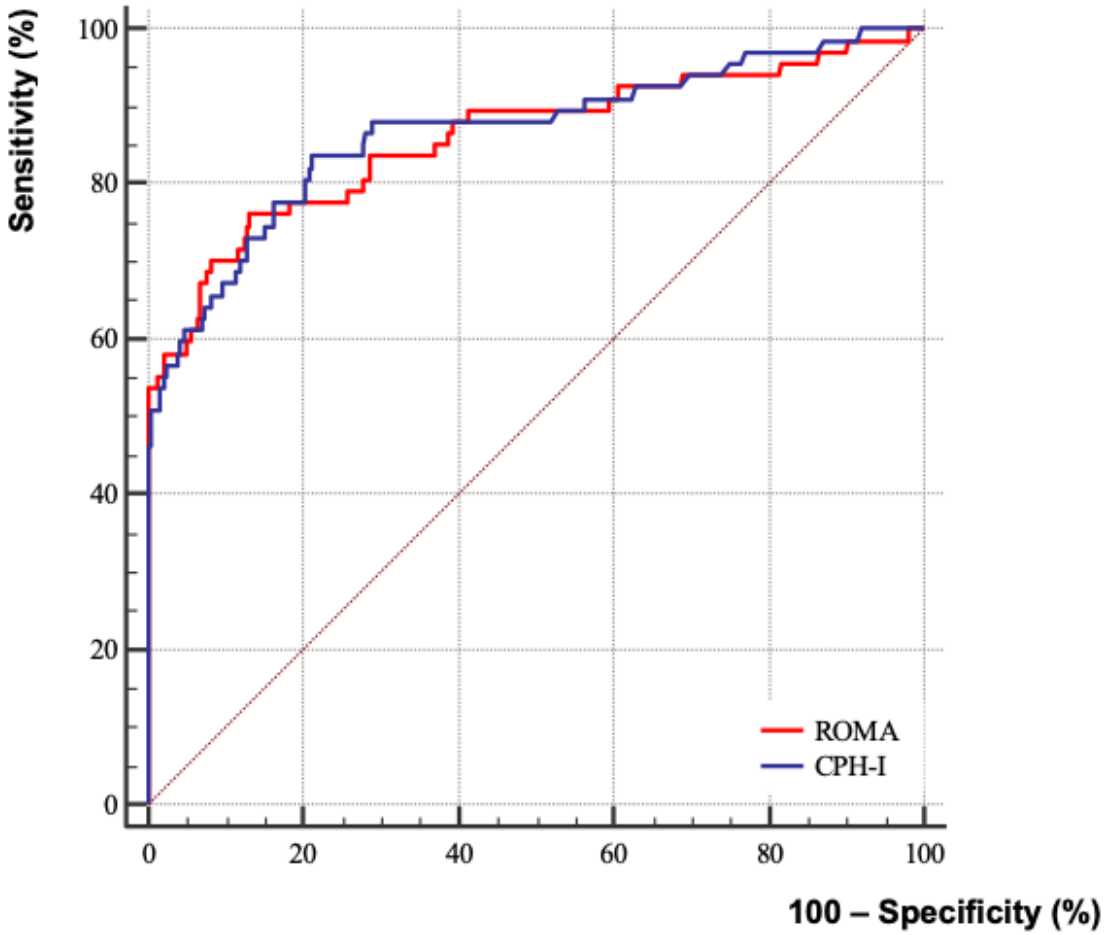
Table 4

The Validity of CPH-I and ROMA for preoperative diagnosis of ovarian cancer at optimal cut-off.

	AUC	Optimal cut-off (%)	Se (%)	Sp (%)	*p*
Study group (n = 475)					
CPH–I	0.868	1.89	83.6	78.7	< 0.05
ROMA	0.860	12.1	76.1	87.0	< 0.05
ROMA 1	0.844	12.1	74.2	83.5	< 0.05
ROMA 2	0.864	16.2	75.0	93.9	< 0.05
Pre-menopausal (n = 370)					
CPH–I	0.875	1.44	76.7	75.6	< 0.05
ROMA	0.757	7.65	66.7	80.0	< 0.05
ROMA 1	0.732	5.67	84.6	56.6	< 0.05
ROMA 2	0.758	7.62	70.6	85.1	< 0.05
Post-menopausal (n = 105)					
CPH–I	0.757	15.4	72.9	95.6	< 0.05
ROMA	0.927	43.3	75.7	98.5	< 0.05
ROMA 1	0.946	43.3	77.8	100.0	< 0.05
ROMA 2	0.913	30.2	78.9	96.2	< 0.05

Abbreviations: CPH-I, Copenhagen Index; ROMA, Risk of Ovarian Malignancy Algorithm; AUC, Area Under the Curve; Se, Sensitivity; Sp, Specificity

Figures



Graph 1. ROCs of CPH-I and ROMA values in the study group.

Index	AUC (95% CI)	Se (%) (95% CI)	Sp (%) (95% CI)	*p*-value
CPH–I	0.868 (0.833 – .896)	83.6 (72.5 – 91.5)	78.7 (74.4 – 82.6)	0.7374
ROMA	0.860 (0.825 – 0.890)	76.1 (64.1 – 85.7)	87.0 (83.4 – 90.1)	

Abbreviations: CPH-I, Copenhagen Index; ROMA, Risk of Ovarian Malignancy Algorithm; AUC, Area Under the Curve; Se, Sensitivity; Sp, Specificity; CI, confidence interval;

Figure 1

Comparison of receiver operator characteristic curves for CPH-I and ROMA in the discrimination of benign tumors from borderline ovarian tumors and OC.