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

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HIGHLIGHTS

- Copenhagen Index (CPH-I) can help stratify the risk of ovarian tumor malignancy.
- CPH-I is similarly accurate to but simpler than ROMA.
- CPH-I could replace ROMA in clinical practice.

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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 diagnosed by gynecologic examination / ultrasound who were hospitalized at the Departments of Obstetrics and Gynecology, Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital, Vietnam, between January 2018 and June 2020. ROMA and CPH-I were calculated based on measurements of serum carbohydrate antigen (CA-125) and human epididymis protein (HE4). The final diagnosis was based on clinical features, radiologic and histologic findings, and the International Federation of Gynecology and Obstetrics (FIGO) 2014 stages of ovarian cancer were recorded. Matching the values of ROMA and CPH-I to postoperative histopathology reports resulted in the preoperative prediction values.

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 74.2% and 91.8%, 87.1% and 78.5%, respectively. The optimal cut-off for CPH-I was 1.89%. The areas under the ROC curves (AUCs) of ROMA and CPH-I were 0.882 (95% CI: 0.849–0.909) and 0.898 (95% CI: 0.867–0.924), respectively.

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

1. 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 worldwide, and 184,799 died, with the highest incidence in developed countries [2]. The mortality rate has not changed in the past 30 years, and it is predicted that by 2040, this rate will be significantly increasing [3,4]. 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% [3,5]. Therefore, early detection has important implications for the treatment, quality of life and prognosis of patients [6,7].

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) [8]. In 2009, Moore et al. developed the Risk of Ovarian Malignancy Algorithm (ROMA) by integrating serum CA-125 and HE4 values and menopausal status to differentiate between low- and

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high-risk patients with OC [9]. In 2015, Karlsen et al. developed the Copenhagen Index (CPH-I) based on these two biomarkers and patient age. The areas under the ROC curve (AUCs) 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 of not depending on ultrasound and menopausal status, and the age variable is easy to collect, simple, and objective [10]. Therefore, the Copenhagen Index's advantage promises to be a reliable, objective, and widely applied tool at the grassroots level. The aim of this study was to compare the Copenhagen Index and the ROMA in the preoperative prediction of ovarian cancer.

2. Methods

This was a prospective cohort study conducted at the Departments of Obstetrics and Gynecology, Hue University of Medicine and Pharmacy Hospital and Hue Central 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: the "Z" value for Confidence Interval of 95% ($Z^2_{\frac{\alpha}{2}} = 1.96$ with $\alpha = 0.05$); w (Errors) = 0.04; p_{sp}, the specificity from the study of Yoshida et al (2016) is 0.844 [11]. p_{dis}, the prevalence rate, according to GLOBOCAN (2018), the prevalence rate of OC in Vietnam (p_{dis}) is 7.67 cases/100,000 women = 0.000767 [2]. N_{sp}, the minimum sample size for specificity.

The calculated minimum sample size was 317 subjects. At the end of the study, 475 women who met the selection criteria were included. This number represents most women who were diagnosed and operated on for an ovarian mass during two and half years of the study at two facilities.

After administrative interviews, medical history taking and physical examination, patient having pelvic mass on gynecologic examination was diagnosed with ovarian tumor by transabdominal and transvaginal ultrasonography. An adnexal lesion was described according to the morphological and vascular features as suggested by the consensus opinion from the International Ovarian Tumor Analysis (IOTA) group [12]. Blood serum sample were taken for CA-125 and HE4 tests. The ovarian masses were then removed surgically. Complete histopathological evaluation carried out based on the standard and classification of the World Health Organization (WHO), 2014 [13]. Finally, the parameters were matched with the histopathological results (including benign, borderline and malignant tumors) to calculate the diagnostic values of CPH-I and ROMA.

At Hue University of Medicine and Pharmacy Hospital, serum CA-125 and 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 and HE4 were conducted by chemiluminescent microparticle immunoassay on an 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 Test Standardization Center.

The Copenhagen Index predicts the risk of a preoperative ovarian tumor malignancy (Predicted Probability - PP) according to the algorithm belowe[10]:

$$\mathrm{CPH{-}I} = -14.0647 + 1.0649^{*} \log_2(\mathrm{HE4}) + 0.6050^{*} \log_2(\mathrm{CA{-}125}) + 0.2672^{*}\mathrm{Age}/10$$

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

The ROMA index was calculated to predict the risk of ovarian tumor malignancy before surgery according to the following algorithm: PP = exp.(PI)/[1 + exp.(PI)] * 100 [9].

PI is the Predictive Index, determined as follows:

- Premenopausal women: PI = −12.0 + 2.38*Ln[HE4] + 0.0626*Ln [CA-125]
- Postmenopausal women: PI = −8.09 + 1.04*Ln[HE4] + 0.732*Ln [CA-125]

The ROMA cut-off point values were applied according to the technical instructions of the Cobas 6000 system and the ARCHITECT system. Patients have a high risk of ovarian cancer when:

Test system	Pre-menopausal group	Post-menopausal group
Cobas 6000 (ROMA 1)	≥11.4%	≥29.9%
Architect i1000 (ROMA 2)	≥7.4%	≥25.3%

2.1. Statistical analysis

Data analyses were performed using the statistical software SPSS 20.0 (SPSS, Inc., Chicago, IL, USA), and receiver operative curve (ROC) analysis was performed with MedCalc. Categorical variables were reported as numbers (percentages), and continuous variables were reported as medians (SDs, standard deviations; ranges). The chi-square test ($\chi 2$) was used to evaluate intergroup differences, and $p < 0.05$ was considered significant. The Kruskal-Wallis test was used to compare the differences between three groups that were not normally distributed.

2.2. Ethical approval

Ethical approval for the study protocol was by the Ethics Committee for Biomedical Research at Hue University of Medicine and Pharmacy, Hue, Vietnam (number H2018/359). Informed consent was obtained from all study subjects.

3. Results

Of the 475 patients, 408, 5 and 62 subjects were diagnosed with benign tumors, borderline tumors, 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 that of women in the benign tumor group. There were significant differences in age, menopausal status, and marital status between the two groups ($p < 0.05$). The incidence of OC in the postmenopausal group was 59.7%. (See Table 1.)

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%) had serous cystadenoma, and 37 (9.1%) had endometrioses of the ovary. In the borderline tumor group, 4 of 5 patients had serous borderline tumors. In patients with OC, serous adenocarcinoma was seen in 27 cases (43.5%), followed by 12 (19.7%) with mucinous adenocarcinoma,

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	50.7 ± 15.3		31.8 ± 13.3		36.0 ± 14.9		
(Min – Max)	(11–83)		(16–49)		(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	
Multiparous	39	62.9	3	60.0	207	50.8	

Abbreviations: SD, standard deviation.

6 (9.7%) with poorly differentiated carcinoma, and 6 (9.7%) with dysgerminoma, as shown in Table 2. Clinical staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO): 19 (30.6%) cases were stage I, 8 (12.9%) cases were stage II, 26 (41.9%) cases were stage III, and 9 (14.5%) cases were stage IV.

The 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 median ROMA 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 ($p < 0.05$). The median values of the CPH-I and ROMA of the postmenopausal group were higher than those of the premenopausal group, in both the OC group and the benign tumor group. Specifically, in the premenopausal 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 postmenopausal 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 prognostic values of the Copenhagen Index and the ROMA index in the prediction of OC risk before surgery are shown in Table 4 and Fig. 1. In the study population, the AUCs of CPH-I and ROMA in the prediction of OC were equivalent, being 0.898 (95% CI: 0.867–0.924) and 0.882 (95% CI: 0.849–0.909), respectively. At the optimal cut-off point of 1.89%, the Copenhagen Index had a sensitivity of 87.1% (95% CI: 76.1–94.3%) and specificity of 78.5% (95% CI: 74.2–82.3%). With an optimal cut-off value of 16.5% for ROMA, the sensitivity and specificity were 74.2% (95% CI: 61.5–84.5%) and 91.8% (95% CI: 88.7–94.2%), 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 ($p > 0.05$).

4. Discussions

The present study aimed to compare the Copenhagen Index and the ROMA in the preoperative prediction of ovarian cancer. Our data

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	
CA125	22.46 (12.70–48.29)	198.85 (46.26–729.88)	18.00 (10.77–462.65)	19.83 (12.15–35.10)	0.000
HE4	42.36 (35.10–55.91)	83.81 (51.60–247.73)	45.73 (34.29–66.83)	40.87 (34.50–51.02)	0.000
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	
CA125	22.68 (13.49–43.28)	81.44 (36.00–572.50)	18.00 (10.77–462.65)	21.26 (13.13–36.63)	0.000
HE4	40.00 (33.69–48.57)	60.60 (45.69–170.20)	45.73 (34.29–66.83)	39.67 (33.40–46.69)	0.000
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	
CA125	20.29 (10.23–104.95)	321.30 (61.13–866.10)	–	12.37 (8.03–22.42)	0.000
HE4	60.80 (45.84–94.18)	108.40 (59.67–439.05)	–	54.48 (43.65–66.42)	0.000
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

Abbreviations: Data are shown as median (1st to 3rd quartiles).
Kruskal-Wallis Test.

showed that Copenhagen Index is similarly accurate to but simpler than ROMA to stratify the risk of ovarian tumor malignancy, irrespective of menopausal status.

The rates of OC from several studies were 41.6% [11], 43% [14], and can be up to 57.9% [15] among postmenopausal women, quite similar to those from our study, at 59.7% - higher than the rate of about 30% as stated in some medical textbook; however, the peak age incidence of invasive epithelial ovarian cancer is approximately 60 years (Berek & Novak's Gynecology, 16th ed., 2020) [16]. In Vietnam and in many others low- and middle-income countries, women with ovarian masses were often diagnosed not early, due to the lack of systematic screening program by tumor markers or ultrasound; and the often centrally overweight status of postmenopausal women could lead to late detection of abdominal masses in those women. These facts could explain the higher rate of OC among post-menopausal women found within present study.

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)					
CA125	0.870	44.5	79.0	80.8	<0.05
HE4	0.836	49.0	82.3	72.9	<0.05
CPH–I	0.898	1.89	87.1	78.5	<0.05
ROMA	0.882	16.5	74.2	91.8	<0.05
ROMA 1	0.876	12.4	77.8	83.8	<0.05
ROMA 2	0.886	16.2	77.1	93.9	<0.05
Pre-menopausal (n = 370)					
CA125	0.819	38.8	76.0	76.2	<0.05
HE4	0.776	49.3	72.0	80.0	<0.05
CPH–I	0.840	1.44	84.0	75.4	<0.05
ROMA	0.780	7.65	72.0	79.7	<0.05
ROMA 1	0.743	6.04	88.9	60.3	<0.05
ROMA 2	0.797	7.62	75.0	85.2	<0.05
Post-menopausal (n = 105)					
CA125	0.946	64.6	75.7	98.5	<0.05
HE4	0.793	86.7	59.5	91.2	<0.05
CPH–I	0.916	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.

The median values of CPH-I and ROMA in the OC group, as shown in Table 3, were higher than those of the benign tumor group and borderline tumor group. Compared to previous studies, the median values of CPH-I and ROMA from our research are lower than those of some other studies in the world. According to Adriana Yoshida (2016), the median values of CPH-I for benign tumors and ovarian carcinomas were 1.4% and 83.4%, respectively [11]. 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]. More detailed analysis in the premenopausal and postmenopausal groups, which examined the differences between CPH-I and ROMA, showed that the median values of CPH-I and ROMA were higher in the postmenopausal group than in the premenopausal group (Table 3). The median values of CPH-I and ROMA in the postmenopausal group were higher than those in the premenopausal group. The sensitivity/specificity (Se/Sp) of CPH-I in the absence of marginal ovarian tumors, nonepithelial 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% [11].

The Se/Sp of ROMA and CPH-I in the diagnosis of OC were 74.2%/91.8% and 87.1%/78.5%, respectively. The optimal cut-off point of the CPH-I was 1.89%, and the AUCs of ROMA and CPH-I were 0.882 (95% CI: 0.849–0.909) and 0.898 (95% CI: 0.867–0.924), respectively. The work by T. Nikola (2017) on differential diagnosis between ovarian endometriosis and ovarian carcinoma showed that the accuracy of the

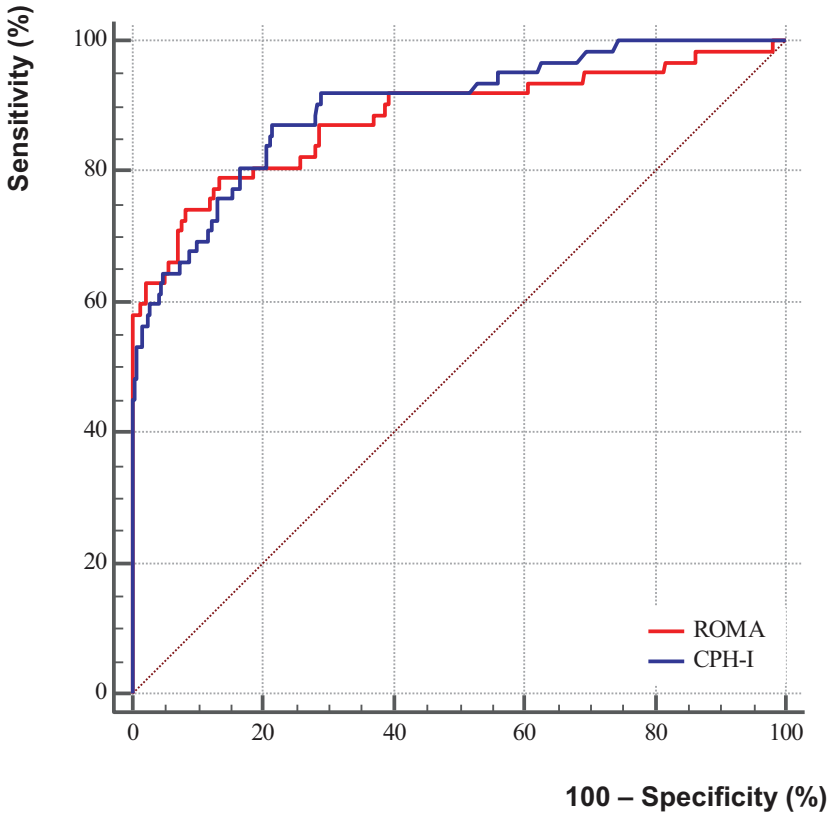

Fig. 1. Comparison of receiver operator characteristic curves for CPH-I and ROMA in the discrimination of benign tumors and borderline ovarian tumors (non-OC) from OC.

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

Index	AUC (95% CI)	Se (%) (95% CI)	Sp (%) (95% CI)	*p*-value
CPH–I	0,898 (0,867–0,924)	87.1 (76.1–94.3)	78.5 (74.2–82.3)	0,4894
ROMA	0,882 (0,849–0,909)	74.2 (61.5–84.5)	91.8 (88.7–94.2)	

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

Copenhagen Index was higher than that of ROMA, 93.75% and 85.42%, respectively [17].

Wang et al. (2019) argued that the HE4 level and ROMA and CPH-I values of epithelial ovarian cancer (EOC) stages I and II (I + II) were all higher than those of borderline ovarian tumor (BOT) stages I + II and benign groups in all premenopausal and postmenopausal groups ($p < 0.01$). When distinguishing BOT I + II from EOC I + II, the AUC-ROCs of CPH-I and HE4 were larger than that of CA-125 ($p < 0.001$). CPH-I is more valuable than CA-125 when distinguishing marginal ovarian tumors from stage I–II ovarian carcinoma, while HE4 may be better than CA-125 in the postmenopausal group; HE4 and CPH-I have been more advantageous than CA-125 when differentiating a borderline ovarian tumor from an early-stage ovarian carcinoma (I + II) in the absence of histology or type of serum fluid. The AUCs of CPH-I and ROMA in the premenopausal group were 0.779 and 0.760, respectively, and those in the postmenopausal group were 0.802 and 0.774, respectively. In the premenopausal group, the Se/Sp of ROMA and CPH-I were 78.69%/64.75% and 70.49%/78.69%, respectively. In the postmenopausal group, the Se/Sp of ROMA and CPH–I were 82.98%/68.18% and 85.11%/68.18%, respectively [18].

According to Høgdall (2016), ROMA and CPH–I can be used for the differential diagnosis between benign and malignant ovarian tumors [19]. Since family doctors might be unable to perform an abdominal ultrasound test, both ROMA and CPH-I could provide the initial reliable information, which helps the patient obtain 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 independent of ultrasound test and menopausal status. Menopausal status can be determined based on age, hormone concentration or amenorrhea per year, so the diagnosis of menopausal status has not been standardized. Therefore, CHP-I could be a simpler method to optimize management when assessing women with suspected OC, including age instead of menopausal status [10,19].

Over 25 years ago, Jacobs et al. proposed an algorithm, the Risk of Malignancy Index (RMI), by combining the values of CA125, ultrasound, and menopause [21]. In 2016, Meys et al. conducted a meta-analysis based on 47 articles (from January 1990 to August 2015), enrolling 19,674 adnexal tumors, the Se and Sp of RMI were 0.75 (95% CI: 0.72–0.79) and 0.92 (95% CI: 0.88–0.94), respectively [22]. According to Karlsen et al., AUCs of CPH-I, ROMA and RMI were 0.960, 0.954 and

Table 5
Diagnostic validity of CPH-I and ROMA from literature.

Authors	Copenhagen Index		ROMA	
	AUC	Se/Sp (%)	AUC	Se/Sp (%)
A. Yoshida (2016) [11]	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) [17]	0.91	81.8/ 97.3	0.90	90.9/ 83.8
Z. Wang (2019) [18]	0.810	78.7/ 74.3	0.807	62.9/ 88.2
Estrid Høgdall (2016) [19]	0.960	–	0.954	–
Nguyen Vu Quoc Huy (2018) [20]	–	–	0.912	86.7/ 88.7
This study	0.898	87.1/ 78.5	0.882	74.2/ 91.8

0.959 respectively in the training study and 0.951, 0.953 and 0.935 respectively in the validation study. Using a Se of 95%, the Sp for CPH-I, ROMA and RMI in the training cohort were 78.4%, 71.7% and 81.5% respectively, and in the validation cohort 67.3%, 70.7% and 69.5% respectively [10]. This suggests that all of these simple indicators, especially the RMI and the CPH-I, were of clinical significance for stratifying the risk of ovarian tumor malignancy.

The Copenhagen Index is a new indicator that has been introduced in several studies around the world. The ROMA algorithm is an index that the US Food and Drug Administration approved for use in clinical practice to distinguish benign and malignant ovarian tumors based on three variables: CA-125, serum HE4, and menopausal status [23]. These two indexes have quite similar values since both are partially based on CA-125 and HE4. Since serum CA-125 and HE4 concentrations are affected by many factors, including age, smoking, uterine fibroids, pregnancy, endometriosis, pelvic inflammatory disease, and gallbladder stones, this will affect the values of the Copenhagen index and ROMA Table 5 [24,25]. In the future, more research on these two indicators on different target groups should be conducted to clarify these differences, aiming to overcome the limitations of these indicators and improve clinical practice.

To the best of our knowledge, this is the first prospective cohort study from Vietnam with large number of ovarian tumor subjects included, examining the validity of CPH-I and comparing it with those from ROMA in risk stratification for ovarian tumor malignancy. Although rigorously designed and implemented, limitations of this study included the limited number of OC cases; and the laboratory equipments were different at the two facilities where the work was done, which could partially affect the homogeneity of the data analysis. Another limitation of the present study was the value of CPH-I of the borderline tumors group was even lower than that of benign tumor (0.42% vs. 0.82%), due to the limited number of borderline tumors - to be separately analyzed and to have statistical power. To overcome this limitation, we combined borderline ones into the non-OC group and to compare with OC group.

5. Conclusions

The introduction of the 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.

Author contributions

TDT, MTL, LC, and VQHN conceived the study, coordinated its planning and implementation, and wrote the manuscript.

TDT, VKV, MTL coordinated data acquisition, participated in the data analysis and interpreted the results.

MTL, LC and VQHN supervised the preparation and revision of the manuscript.

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Declaration of Competing Interest

The authors have no conflicts of interest.

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