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Diagnostic Performance of the International Ovarian Tumor Analysis Simple Rules with CA125 in Differentiating between Benign and Malignant Adnexal Masses

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ABSTRACT

Objectives: To evaluate the diagnostic performance of the International Ovarian Tumor Analysis (IOTA) simple rules in combination with serum tumor marker Cancer Antigen 125 (CA125).

Materials and Methods: This secondary analysis was based on a previous prospective diagnostic single-center study conducted at Siriraj Hospital, Thailand, between May 1, 2018, and May 31, 2019. Gynecological patients scheduled for an elective adnexal surgery at Siriraj Hospital were recruited. Preoperative ultrasound was performed within 120 days before surgery. The assessment included IOTA simple rules, IOTA simple rules with subjective assessment, and IOTA simple rules with CA125. The sensitivity, specificity, positive predictive value, negative predictive value and area under the receiver operating characteristic curve (AUC) were assessed.

Results: A total of 357 patients from the original study cohort were included, and all were found eligible. The IOTA simple rules were applicable in 316 cases (88.5%), and achieved an AUC of 0.938 (95% CI 0.897-0.979). The IOTA simple rules along with subjective assessment demonstrated a similar AUC, 0.933 (95% CI 0.892-0.975). Integrating CA125 with the IOTA simple rules reduced the AUC to 0.825 (95% CI 0.776–0.875). When CA125 was applied exclusively to the inconclusive group, the AUC was 0.909 (95% CI 0.866–0.953). The optimal cutoff value of CA125 calculated from our cohort was 115 U/ml.

Conclusion: The IOTA simple rules are an excellent model for differentiating benign and malignant adnexal masses. Selective use of CA125 or subjective assessment in inconclusive cases can support decision-making.

Keywords: adnexal diseases, ovarian neoplasms, international ovarian tumor analysis (IOTA), simple rules, CA125

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การศึกษาประสิทธิภาพในการวินิจฉัยแยกแยะก้อนที่ปีกมดลูกชนิดไม่ร้ายแรงและมะเร็งของเกณฑ์การวิเคราะห์ IOTA Simple Rules ร่วมกับการตรวจค่า CA125

กมลลักษณ์ ลิ้มสุวรรณ, ประสงค์ ตันมหาสมุทร, วิชา บุญยกรณ

บทคัดย่อ

วัตถุประสงค์: เพื่อประเมินประสิทธิภาพของ International Ovarian Tumor Analysis (IOTA) simple rules เมื่อใช้ร่วมกับสารบ่งชี้มะเร็ง Cancer antigen 125 (CA125)

วัสดุและวิธีการ: การวิจัยนี้เป็นการวิเคราะห์หัตถ์วิทยุจากการศึกษาแบบไปข้างหน้าเดิมที่จัดทำขึ้นที่โรงพยาบาลศิริราชระหว่างวันที่ 1 พฤษภาคม 2561 ถึงวันที่ 31 พฤษภาคม 2562 ผู้ป่วยนรีเวชที่มีกำหนดการเข้ารับการผ่าตัดสำหรับรังไข่และท่อนำไข่จะถูกคัดเลือกเข้าร่วมการศึกษา โดยผู้ป่วยจะได้รับการตรวจอัลตราซาวนด์ภายในเวลาไม่เกิน 120 วันก่อนการผ่าตัด การประเมินประกอบด้วย IOTA simple rules, IOTA simple rules ร่วมกับ subjective assessment และ IOTA simple rules ร่วมกับ CA125 ได้มีการประเมินค่าความไว (sensitivity) ความจำเพาะ (specificity) ค่าทำนายผลบวก (positive predictive value) ค่าทำนายผลลบ (negative predictive value) การวิเคราะห์เส้นโค้ง (Receiver operating characteristic - ROC) และ พื้นที่ใต้เส้นโค้ง (area under the curve - AUC)

ผลการศึกษา: ผู้ป่วยทั้งหมดจากศึกษาเดิมจำนวน 357 คนเข้าเกณฑ์การศึกษา โดยไม่มีการคัดออก เครื่องมือ IOTA simple rules สามารถใช้ได้กับผู้ป่วย 316 ราย คิดเป็น 88.5% และมีค่า AUC เท่ากับ 0.938 (95% CI 0.897–0.979) และ IOTA simple rules ร่วมกับการประเมินแบบ subjective assessment ให้ค่า AUC เท่ากับ 0.933 (95% CI 0.892–0.975) ซึ่งใกล้เคียงกัน เครื่องมือ IOTA simple rules ที่ใช้ร่วมกับ CA125 ทำให้ค่า AUC เท่ากับ 0.825 (95% CI 0.776–0.875) และเมื่อใช้ CA125 เฉพาะกับกลุ่มที่ไม่สามารถสรุปผลได้ (inconclusive group) ค่า AUC เท่ากับ 0.909 (95% CI 0.866–0.953) ค่าจุดตัด CA125 ที่เหมาะสม ที่คำนวณได้จากกลุ่มตัวอย่างคือ 115 U/ml

สรุป: IOTA simple rules มีประสิทธิภาพที่ดีในการจำแนกกระหว่างก้อนรังไข่และปีกมดลูกที่เป็นมะเร็งและไม่เป็นมะเร็ง การใช้ CA125 หรือการประเมินแบบ subjective assessment ในกรณีที่ผลไม่สามารถสรุปได้ (inconclusive) สามารถเข้ามาช่วยในการตัดสินใจวางแผนการรักษาผู้ป่วยได้

คำสำคัญ: โรคของปีกมดลูก, เนื้องอกรังไข่, International Ovarian Tumor Analysis (IOTA), Simple Rules, สารบ่งชี้มะเร็ง CA125

Introduction

Ovarian cancer is one of the most common gynecological cancers globally⁽¹⁾. In 2020, the Global Health Research Group of Association of Pacific Rim Universities reported that 207,252 women died from ovarian cancer, with increasing incidence in lower-income countries⁽²⁾. A systematic review, published in August 2015, demonstrated that patients with advanced ovarian cancer particularly benefit from medical care provided by subspecialist gynecologic oncologists. Surgery performed by subspecialist gynecologic oncologists was associated with higher survival rates, reduced need for repeat surgery, and more frequent lymphadenectomy procedures compared with surgeries performed by non-subspecialists⁽³⁾. Similarly, a study conducted in the Netherlands found that subspecialist-performed surgery was associated with higher 5-year survival rates in patients with epithelial ovarian cancer⁽⁴⁾.

Conversely, unnecessary surgery leading to early surgical menopause can have detrimental long-term effects, including increased long-term cardiovascular and metabolic complications, lower bone mass, and altered sexual function and sexual desire^(5, 6). Therefore, accurately distinguishing between benign and malignant adnexal masses is crucial. Various scoring systems and screening tools have been developed to distinguish between benign and malignant adnexal tumors using characteristics and biomarkers, including the Risk of Malignancy Index (RMI), International Ovarian Tumor Analysis Simple Rules (IOTA SR), Cancer antigen 125 (CA125), Human Epididymis protein 4 (HE4), Ovarian-Adnexal Reporting and Data System (O-RADS), and the Assessment of Different Neoplasias in the adnexa (ADNEX).

The International Ovarian Tumor Analysis (IOTA) group introduced the simple rules in 2008,

which rely exclusively on ultrasonographic features to support clinical decision-making. These rules consist of five benign and five malignant ultrasonographic features⁽⁷⁾. The IOTA SR showed high diagnostic accuracy in previous study⁽⁸⁾ and were significantly better than RMI-2⁽⁹⁾. The authors believe that the IOTA SR offers a straightforward, effective, and practical approach, suitable even for non-expert ultrasonographers.

CA125 is one of the most widely utilized biomarkers for epithelial ovarian cancer, particularly in non-mucinous histological subtypes. However, its role in screening is limited due to poor sensitivity for early-stage disease⁽¹⁰⁾. Despite this limitation, CA125 remains valuable for assessing suspected malignancies and borderline tumors. Elevated CA125 levels may also be seen in several benign conditions, such as leiomyoma, pregnancy, endometriosis, and pelvic inflammatory disease⁽¹¹⁾. To address this limitation, HE4 has been developed as a complementary biomarker with higher specificity for ovarian cancer. However, due to its higher cost and limited availability, HE4 has not replaced CA125 as the primary biomarker in routine clinical practice^(12, 13).

Although numerous studies have investigated the most effective methods for distinguishing benign from malignant adnexal lesions, the optimal diagnostic approach remains a subject of debate⁽¹⁴⁻¹⁶⁾. Early and accurate detection is essential to guide appropriate management, minimize complications and avoid unnecessary surgical interventions. While the IOTA SR is a straightforward and effective diagnostic tool, its limitation lies in cases with inconclusive results. To overcome this limitation without compromising simplicity, the present study aimed to assess the diagnostic performance of IOTA SR in combination with CA125 for preoperative differentiation between benign and malignant ovarian tumors.

Materials and Methods

This was a secondary analysis of a previous prospective diagnostic study performed at the Gynecologic Ultrasonography Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University. The study was performed at a single tertiary care hospital between May 1, 2018, and May 31, 2019⁽¹⁷⁾. Ethical approval was obtained from the Institutional Review Board of Siriraj Hospital (Protocol No.161/2567(IRB3), CoA no. Si 275/2024).

Patients presenting at Siriraj Hospital with adnexal masses scheduled for surgical intervention, who underwent ultrasound evaluation within 120 days prior to surgery, were recruited. None of the patients had a diagnosis of the adnexal mass through laparoscopy or previous surgery. Transvaginal ultrasonography was the primary technique used, while transabdominal ultrasonography was performed in selected cases when transvaginal ultrasonography was inadequate (GE Voluson E6 BT13.5, Milwaukee, WI, USA, equipped with 3.5-MHz and 8.0-MHz transducers). If more than one lesion was identified, the most complex lesion was included in the study. No patients were excluded from the original dataset.

The prevalence of ovarian cancer at Siriraj Hospital was 17%⁽¹⁷⁾. Drawing on pilot data from our previous prospective study⁽¹⁷⁾, the sensitivity and specificity of the IOTA SR combined with CA125 were 85.71% and 63.64%, respectively. Applying diagnostic accuracy formulas, the minimum required sample size was determined to be 48 for malignant and 277 for benign adnexal masses. Accounting for a 10% allowance for incomplete records, a total of 308 subjects was required. Consequently, the 357 participants recruited in our previous study provided sufficient data for this secondary analysis. A flow

diagram of patient recruitment and exclusion is provided in Fig. 1.

Unadjusted sample size:

Sensitivity: $NSe(unadj) =$

$$[(Z\alpha/2)^2 Se(1 - Se)]/d^2$$

Specificity: $NSp(unadj) =$

$$[(Z\alpha/2)^2 Sp(1 - Sp)]/d^2$$

Adjusted sample size: Sensitivity: $NSe(prev adj) = NSe(unadj)/P$

Specificity: $NSp(prev adj) = NSp(unadj)/(1-P)$

$\alpha = 0.05$, $Z(0.975) = 1.96$, $p = \text{prevalence} = 0.8571$, $d = \text{margin of error} = 0.10$

$Se(unadj)$, unadjusted sensitivity; $Sp(unadj)$, unadjusted specificity;

$Se(prev.adj)$, prevalence-adjusted sensitivity; $Sp(prev.adj)$, prevalence-adjusted specificity

Case record forms were reviewed for demographic and clinical data, including age, menopausal status, parity, and underlying diseases, with all identifiers removed. Ultrasonographic features were assessed and categorized using IOTA SR, which is a classification system used for the preoperative diagnosis of ovarian cancer⁽⁹⁾. According to these rules, adnexal masses are categorized as benign, malignant, or inconclusive based on the presence of benign features (B-features) or malignant features (M-features), shown in Table 1. A mass was classified as benign if one or more B-features were present in the absence of M-features. Conversely, it was classified as malignant if one or more M-features were present without any B-features. If both B-features and M-features were present, or if neither feature applied, the mass was deemed inconclusive.

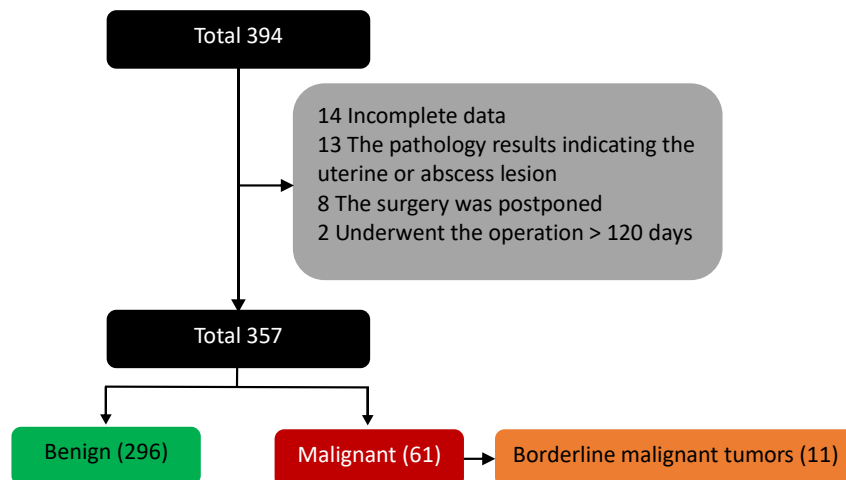


Fig. 1. Flow diagram of the patient recruitment and exclusion.

Table 1. Features of the international ovarian tumor analysis simple rules (IOTA SR)⁽¹⁾

Rules for predicting malignant tumor (M-rules)	Rules for predicting benign tumor (B-rules)
M1 Irregular solid tumor	B1 Unilocular cyst
M2 Presence of ascites	B2 Presence of solid components where the largest solid component has a largest diameter < 7 mm
M3 At least four papillary structures	B3 Presence of acoustic shadow
M4 Irregular multilocular-solid tumor with the largest diameter > 100 mm	B4 Smooth multilocular tumor with the largest diameter < 100 mm
M5 Very strong blood flow (color score 4)	B5 No blood flow (color score 1)

The initial ultrasonography was performed and recorded by expert gynecologists in the Gynecologic Ultrasonography Unit, with experience in gynecologic ultrasound ranging from 5 to 18 years. In cases of inconclusive results, subjective assessment was adjudicated by two experienced ultrasonographers in the Gynecologic Ultrasonography Unit. Discordant results were resolved through consultation with a third ultrasonographer of equivalent expertise.

According to Bast and colleagues, a threshold

of 35 U/mL has widely been adopted as the standard for early detection of ovarian cancer in postmenopausal women⁽¹⁸⁾. Applying the same threshold to premenopausal women leads to a significantly higher incidence of false-positive results. Menopausal status is the primary clinical variable influencing CA125 levels; consequently, a higher diagnostic threshold of 50 U/mL is required for premenopausal women, whereas the conventional 35 U/mL was validated for postmenopausal women⁽¹⁹⁾. For the combined model

of IOTA SR and CA125, lesions categorized as benign by the IOTA SR with a negative CA125 result were classified as benign. Lesions categorized as benign with a positive CA125 result were reclassified as malignant. Lesions categorized as malignant by the IOTA SR, regardless of CA125 status, were classified as malignant.

For IOTA SR inconclusive group with CA125, stratified by menopausal status, lesions that could be directly categorized as benign or malignant required no additional assessment. Lesions classified

as inconclusive by the IOTA SR with a negative CA125 result were considered benign, whereas those with a positive CA125 result were considered malignant.

Our new optimal CA125 value, derived from the dataset, was applied to the IOTA SR with the new optimal CA125 and to the IOTA SR inconclusive group with the new optimal CA125. The analysis was conducted in the same manner. Table 2 and Fig. 2 provide a summary of the interpretation of each diagnostic approach.

Table 2. Interpretation of each diagnostic approach.

Diagnostic method	The IOTA simple rules	CA 125/ Optimal CA125	Subjective assessment	Final group
IOTA simple rules				
	Benign	-	-	Benign
	Malignancy	-	-	Malignancy
IOTA simple rules with subjective assessment				
	Benign	-	-	Benign
	Inconclusive	-	Benign	Benign
	Inconclusive	-	Malignancy	Malignancy
	Malignancy	-	-	Malignancy
IOTA simple rules with CA125				
	Benign	Negative	-	Benign
	Benign	Positive	-	Malignancy
	Inconclusive	Negative	-	Benign
	Inconclusive	Positive	-	Malignancy
	Malignancy	Negative	-	Malignancy
	Malignancy	Positive	-	Malignancy
IOTA simple rules' inconclusive group with CA125				
	Benign	-	-	Benign
	Inconclusive	Negative	-	Benign
	Inconclusive	Positive	-	Malignancy
	Malignancy	-	-	Malignancy

IOTA: international ovarian tumor analysis, CA125: cancer antigen 125

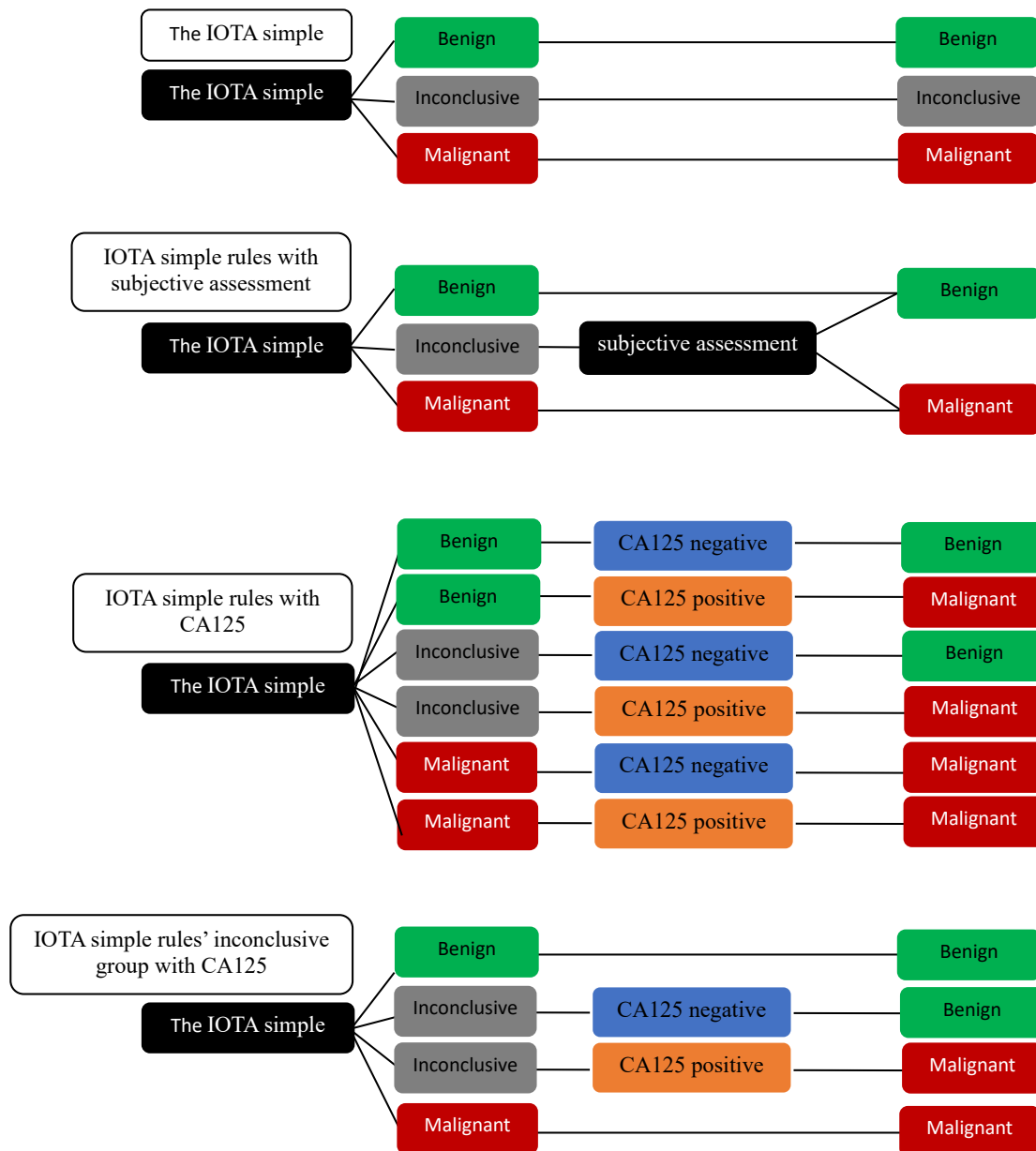


Fig. 2. Interpretation of each diagnostic approach.

Serum CA125 were measured using an electrochemiluminescence immunoassay on the Cobas e601 platform (Roche Diagnostics). The assay demonstrated a lower limit of detection of 0.6 U/mL, with inter-assay and intra-assay coefficients of variation (CV) of 2.5% and 1.6%, respectively.

Histopathological diagnoses served as the gold standard. All excised tissues were examined in the Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, following World Health Organization guidelines⁽²⁰⁾. Malignant tumors were staged according to the International Federation of Gynaecology and Obstetrics

(FIGO)⁽²¹⁾. All borderline ovarian tumors were classified as malignant.

Data were analyzed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY) and MedCalc, version 23.2.0 (MedCalc Software, Ostend, Belgium). Descriptive variables were reported as medians, frequencies, or percentages. The diagnostic performance of IOTA SR was evaluated by sensitivity, specificity, positive predictive value, and negative predictive value, along with their 95% confidence intervals (95% CI). Statistical significance was defined as a p value < 0.05. Additionally, the receiver operating characteristic (ROC) curves for each model were plotted, and the area under the ROC curve (AUC)

was calculated to reveal the diagnostic ability and optimal threshold for the CA125 cutoff value. The new optimal CA125 threshold was defined as the cutoff value yielding the highest Youden index. The Hanley and McNeil method was applied for pairwise comparisons between diagnostic methods.

Results

All 357 patients from the previous study were included without exclusion. The median age of the participants was 43 years. The majority were postmenopausal (71.4%), while premenopausal women accounted for 28.6%. Baseline characteristics and CA125 levels are presented in Table 3.

Table 3. Baseline characteristics of the patients according to type of tumor in 357 patients.

	Total (n = 357)	Benign (n = 296)	Malignant (n = 61)
Age, years	43 (35-53)	41 (34-50)	52 (43-62)
Menopausal status			
Premenopause	102 (28.6)	71 (24)	26 (42.6)
Postmenopause	255 (71.4)	225 (76)	35 (57.4)
Parity			
0	190 (53.2)	161 (54.4)	29 (47.5)
1	60 (16.8)	50 (16.9)	10 (16.4)
2	78 (21.8)	63 (21.3)	15 (24.6)
3 or more	29 (8.2)	22 (7.4)	7 (11.5)
Family history of ovarian cancer			
Yes	8 (2.2)	7 (2.4)	1 (1.6)
No	349 (97.8)	289 (97.6)	60 (98.4)
Underlying disease			
None	263 (73.7)	227 (76.7)	36 (59)
Other cancer	8 (2.2)	6 (2)	2 (3.3)
Others	86 (24.1)	63 (21.3)	23 (37.7)
CA125 level	28.5 (14.5-67.5)	24.4 (13.2-50.2)	155.8 (43.1-566)

Data are presented as median (interquartile range) and n (%) unless otherwise specified.

CA125: cancer antigen 125

Histopathological assessment showed that most adnexal masses in the study were benign (296 cases, 83%) Malignant tumors accounted for 61 cases (17%), including 11 borderline tumors (3%). Among the malignant tumors, 32.8% were stage I, 41.0% were stages II-IV, and five cases (8.2%) were metastatic. Endometrioma was the most prevalent benign adnexal lesion, accounting for 41.6% of cases. In the inconclusive group (41/357), 12.2% (5/41) were malignant: two high-grade serous carcinomas, two clear cell carcinomas, and one borderline mucinous tumor. The most common benign lesion found in the inconclusive group was mature cystic teratoma (13/36). Overall, the IOTA SR could be applied to 316 cases (88.5%). The most common benign feature was unilocular cyst (B1), while the most frequently observed malignant feature in this study was an

irregular multilocular-solid tumor with the largest diameter equal to or greater than 100 mm (M4), observed in 52 cases. The ultrasonographic features of benign and malignant tumors are summarized in Table 4.

The IOTA SR demonstrated the highest diagnostic performance, with an AUC of 0.938 (95% CI, 0.897-0.979), sensitivity of 93.6% (95% CI, 83.3-98.1), and specificity of 94.6% (95% CI, 91.1-97). The IOTA simple rules combined with CA125 showed an AUC of 0.825 (95% CI, 0.776–0.875), which was significantly lower compared with the IOTA simple rules and the IOTA simple rules with subjective assessment. The sensitivity, specificity, negative predictive value, positive predictive value, accuracy, and AUC of each model are presented in Table 5, with corresponding ROC curves in Fig. 3.

Table 4. Features of the international ovarian tumor analysis simple rules (IOTA SR)

Characteristics	Histopathology (n = 357)		
	Total (n = 357)	Benign (n = 296)	Malignant (n = 61)
Benign features			
B1	187	186	1
B2	1	1	0
B3	13	11	2
B4	54	52	2
B5	93	90	3
Malignant features			
M1	6	1	5
M2	30	5	25
M3	32	6	26
M4	52	11	41
M5	33	5	28

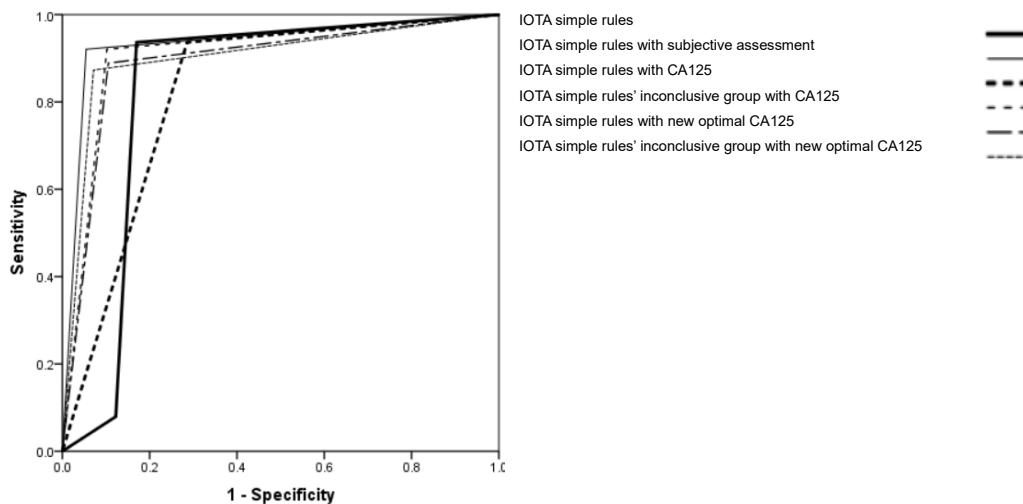
Data are presented as n.

Table 5. Diagnostic performance of each diagnostic approach.

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC (95% CI)
IOTA simple rules	93.1 (83.3-98.1)	94.6 (91.1-97)	79.4 (69.8-86.6)	98.4 (95.9-99.4)	0.938 (0.897-0.979)
IOTA simple rules with subjective assessment	92.1 (82.4-97.4)	94.6 (91.3-96.9)	78.4 (69.1-85.4)	98.2 (96-99.2)	0.933 (0.892-0.975)
IOTA simple rules with CA125	93.6 (84.5-98.2)	71.4 (65.9-76.5)	41.3 (36.7-46)	98.1 (95.3-99.2)	0.825 (0.776-0.875)
IOTA simple rules' inconclusive group with CA125	92.1 (82.4-97.4)	89.8 (85.7-93)	65.9 (57.7-73.2)	98.1 (95.8-99.2)	0.909 (0.866-0.953)
IOTA simple rules with new optimal CA125	64.4 (53.4-74.3)	97.4 (94.7-98.9)	88.9 (79.1-94.4)	89.5 (86.5-91.8)	0.892 (0.842-0.941)
IOTA simple rules' inconclusive group with new optimal CA125	72.4 (60.9-82)	97.1 (94.5-98.8)	87.3 (77.4-93.2)	92.9 (90-94.9)	0.901 (0.850-0.951)

Data are presented as presented as percentage.

CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, IOTA: international ovarian tumor analysis, CA125: cancer antigen 125

**Fig. 3.** Receiver operating characteristic curves for differentiating between benign and malignant adnexal masses using each diagnostic approach.

Using our dataset, the new optimal CA125 cutoff was determined to be 115 U/mL, which yielded the highest Youden index (0.535). Applying this threshold, the IOTA simple rules' inconclusive group with CA125, the IOTA simple rules with the new optimal CA125, and the IOTA simple rules' inconclusive group achieved AUCs of 0.909 (95% CI, 0.866–0.953),

0.892 (95% CI, 0.842–0.941), and 0.901 (95% CI, 0.850–0.951) respectively. None of these models showed statistically significant differences compared with either the original IOTA simple rules or the IOTA simple rules with subjective assessment. Pairwise comparisons of the diagnostic approaches with p-values are provided in Table 6.

Table 6. Pairwise comparison of area under the curves between diagnostic approaches.

	IOTA simple rules	IOTA simple rules with subjective assessment	IOTA simple rules with CA125	IOTA simple rules' inconclusive group with CA125	IOTA simple rules with new optimal CA125	IOTA simple rules' inconclusive group with new optimal CA125
IOTA simple rules		0.8663	0.0005*	0.3403	0.1589	0.2571
IOTA simple rules with subjective assessment	0.8663		0.0009*	0.4300	0.2092	0.2571
IOTA simple rules with CA125	0.0005*	0.0009*		0.0117*	0.0581	0.3270
IOTA simple rules' inconclusive group with CA125	0.3403	0.4300	0.0117*		0.6097	0.0351*
IOTA simple rules with new optimal CA125	0.1589	0.2092	0.0581	0.6097		0.8143
IOTA simple rules' inconclusive group with new optimal CA125	0.2571	0.3270	0.0351*	0.8143	0.8030	

Data was presented in p value.

* Statistically significant different $p < 0.05$

AUC: area under the curve, IOTA: international ovarian tumor analysis, CA125: cancer antigen 125

Discussion

Preoperative diagnosis of adnexal mass is critical for optimal patient management. Ovarian cancer remains a leading cause of cancer-related mortality in women worldwide, largely due to the lack of effective early detection and screening strategies. Multiple diagnostic tools have been developed to differentiate benign from malignant adnexal lesions, including RMI, ADNEX model, O-RADS, and the IOTA SR. According to the 2021 consensus from the European Society of Gynecological Oncology (ESGO), the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), the IOTA, and the European Society for Gynecological Endoscopy (ESGE), subjective assessment by expert ultrasonographers provides the highest diagnostic accuracy in differentiating benign from malignant tumors. However, in settings without expert ultrasonographers, validated ultrasound-based, such as the IOTA SR or the IOTA ADNEX model are valuable alternatives⁽¹⁰⁾. Although the ADNEX model is robust, it requires software support for risk calculation⁽¹⁷⁾, while the IOTA SR are straightforward and do not require additional tools. The IOTA group has consistently been recognized for developing reliable algorithms for ovarian cancer diagnosis, and the simplicity of the simple rules makes them particularly useful for both non-expert and experienced sonographers⁽²²⁾.

In this study, the IOTA SR was applicable in 88.5% of cases, consistent with the findings of a recent systematic review by Awadia et al, who reported an applicability rate of 85.7% across 27 studies involving 7,841 adnexal masses⁽²³⁾. When applicable, the IOTA SR demonstrated high diagnostic performance, with a sensitivity of 93.0% (95% CI 83.0%–98.1%) and specificity of 94.6% (95% CI 91.0%–97.1%), consistent with the pooled estimates reported by Awadia et al (sensitivity and specificity both at 92%)⁽²³⁾ and closely match a prospective study

conducted at two tertiary-care hospitals in Spain, which reported sensitivity and specificity of 94.3% and 94.9%, respectively⁽²⁴⁾.

Secondary analysis enabled application of the IOTA SR model to all patients. The highest accuracy and AUC of 0.933 were achieved when subjective assessment was used as the secondary analysis. To optimize the efficacy of CA125, subgroup analysis was conducted, where CA125 was applied exclusively to the inconclusive results, which were presumed to have a more malignant tendency. The diagnostic accuracy of the IOTA SR is significantly augmented by the addition of serum CA125 for the classification of adnexal masses, according to findings by Phinyo et al⁽²⁵⁾. The combination of CA125 with the inconclusive group of the IOTA simple rules provided an AUC of 0.909 (95% CI 0.866–0.953).

Ultrasonography is inherently operator-dependent, with outcomes influenced by clinical experience, interpersonal variability, and ultrasonographic machine performance. Although ultrasonography is an operator-dependent tool, the IOTA SR reduces this variability by standardizing assessment and providing a practical tool for preoperative identification of malignant ovarian tumors. Prior studies have reported varying levels of agreement between expert and non-expert ultrasonographers. For example, Alba et al reported only moderate agreement (Cohen's Kappa coefficient 0.50; 95% CI 0.300–0.704) when non-experts applied the IOTA SR⁽²⁶⁾, while Tinnangwattana et al demonstrated substantial agreement (Cohen's Kappa 0.713–0.884) in a prospective study⁽²⁷⁾. A recent study in Thailand showed that the IOTA simple rules demonstrated high diagnostic accuracy, even when performed by non-expert examiners⁽²²⁾.

The use of tumor markers may further improve diagnostic performance of the IOTA SR. In our study, combining the IOTA SR with CA125 increased sensitivity but reduced specificity and AUC. We

attempted to optimize the cutoff value of CA125; however, this did not yield any further improvement in test performance. The established cutoff values — greater than 35 U/mL for postmenopausal women and greater than 50 U/mL for premenopausal women. CA125 provides limited benefit except in inconclusive cases. This suggests that the tumor marker could be useful in settings without an expert sonographer, though the small size of our inconclusive group limits the strength of this finding.

The main strength of this study was the use of prospectively collected data, providing comprehensive information. However, limitations included its single-center design, inclusion of only patients who underwent surgery, lack of data on clinical decision-making in non-surgical cases and the variability in ultrasound expertise. Additionally, the small sample size of inconclusive cases may limit the statistical power of this assessment. Future prospective research with a dedicated design is required to further investigate the efficacy of combining CA125 with the IOTA simple rules.

Conclusion

In summary, an accurate pre-operative diagnosis of ovarian malignancy is crucial to enhance patient outcomes. The IOTA SR was an effective ultrasound-based model for detecting ovarian malignancy. The selective combination of CA125 with the inconclusive group of the IOTA SR demonstrated diagnostic performance comparable to that of subjective assessment. This model is simple, effective, and could be useful in settings where an expert ultrasonographer is unavailable.

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Authors contribution

K.L.: design, planning, data analysis, and manuscript drafting. P.T.: design, planning, data analysis, and manuscript drafting with critical revisions and supervision. V.P.: design, acquisition of data, data analysis and manuscript drafting with critical revisions.

Potential conflicts of interest

The authors declare no conflicts of interest.

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