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Research Article

Enhancing Diagnostic Accuracy in Ovarian Tumour Assessment: A Combined Approach of IOTA Simple Rules and CA125

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Abstract

Objectives: Ovarian cancer is a significant contributor to gynecological cancer mortality, often diagnosed at advanced stages, leading to poor survival rates. Effective screening and diagnostic tools are crucial for improving outcomes for affected individuals.

Methods: This retrospective study, examined 210 patients with adnexal masses diagnosed via ultrasound who subsequently underwent surgery from March 2018 to February 2022. Patients over 18 years old with complete pre-operative CA125 levels, ultrasound data, operative findings, and histopathology reports were included in the study. Non-ovarian adnexal masses were excluded from the analysis.

Results: Of the initially identified 210 ovarian cancer patients, 19 were excluded and 191 included for analysis. Among them, 70.2% were benign and 29.8% were malignant. Significant differences were observed between benign and malignant groups in age, menopausal status, family history of ovarian cancer and all components of the IOTA Simple Rules, including M and B-features. The mean CA125 level was significantly higher in malignant tumours.

IOTA Simple Rules exhibited 91.2% sensitivity and a 73.2% positive predictive value. CA125 had 68.4% sensitivity and a 65.2% PPV. Combining IOTA and CA125 increased sensitivity to 96.6% with an 83.3% PPV, outperforming individual tools. The area under the receiver operating characteristic curve (AuROC) with a combined approach was 0.94 (95% CI 0.89-0.97), compared to 0.748 for CA125 and 0.884 for IOTA Simple Rules.

Conclusion: In this study, the combination of IOTA Simple Rules and CA125 demonstrated superior diagnostic performance in discriminating between benign and malignant ovarian tumours compared to using CA125 or IOTA Simple Rules alone.

Keywords: CA125, diagnostic performance, ovarian cancer, international ovarian tumor analysis (IOTA) Simple rules

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Ovarian cancer is a prevalent gynaecological cancer with a high mortality rate, often detected at an advanced stage, leading to a 5-year survival rate of less than 30%.[1] The standard treatment for these tumours primarily involves debulking surgery followed by chemotherapy. The crucial factor influencing survival is the stage of the disease at diagnosis. Consequently, significant efforts have been made to develop effective screening and early diagnosis methods, though an accurate screening tool for ovarian malignancy remains elusive.

Ultrasonography is the primary imaging modality for evaluating ovarian masses, and it is also recommended by ACOG.[2] The IOTA guidelines, established in 2005, provide a user-friendly approach, relying on ultrasound features

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of ovarian masses, making them accessible even to less experienced clinicians.[3] However, the drawback of the IOTA Simple Rules is the potential for inconclusive results in cases where they do not apply. Previous reports suggest that up to 20% of cases may yield inconclusive results.[4] To address this issue, a two-step strategy has been proposed, involving subjective assessment by experts.[5] Nevertheless, the limited availability of experts can pose challenges to implementing this approach.

CA125 levels remain elevated in malignant ovarian tumors, but their discriminatory ability from benign tumors is limited because CA125 can also be elevated in other benign conditions. Another biomarker in use for screening and diagnosing epithelial ovarian cancer (EOC) is serum Human Epididymis Secretory Protein 4 (HE4).[6] HE4 is believed to offer higher specificity than CA125 in diagnosing EOC, but it can increase with age, smoking, and renal diseases. Various algorithms have been proposed, such as the Risk of Malignancy Index (RMI), Risk of Ovarian Malignancy Algorithm (ROMA), and Assessment of Different NEoplasias in the adneXa (ADNEX) model.[7-11] However, HE4 testing is not widely available, leading to limited popularity of the ROMA approach. The IOTA ADNEX model, developed in 2014, involves a more comprehensive assessment of patients with ovarian masses. IOTA SR has demonstrated superior performance compared to other scoring systems. Additionally, CA125 is considered the best single protein biomarker for diagnosing ovarian tumours. Combining CA125 with the IOTA rules is expected to enhance diagnostic accuracy. Therefore, our study aims to compare the diagnostic performance of IOTA, CA125, and a combined tool in distinguishing between benign and malignant ovarian tumours.

Methods

This was a retrospective study conducted in a tertiary care hospital of east India. We consecutively enrolled 191 patients diagnosed with adnexal mass via ultrasound and underwent surgery at our centre from March 2018- February 2022. The inclusion criteria were: Age >18 years, pre-operative CA125, ultrasound details, operative findings and histopathology report were complete. Exclusion criteria included were women with adnexal mass not derived from ovarian tissue. All data were collected from patient's medical record sheet. Demographical details included were age, BMI, parity, menstrual cycle details, age at menarche, menopausal status, prior medical and surgical history, use of hormonal contraceptives, family history of breast and ovarian cancer. Clinical details included serum CA 125 level, details of ultrasound features of ovarian masses as per IOTA simple rule and histopathology report. Serum CA125 measurements was performed by solid phase chemiluminescence using Siemens Medical Solutions. Ultrasound (transvaginal & trans abdominal) was performed by skilled personnel using either Samsung RS80 or Ge Logiq E9; available in the Radiodiagnosis department of the institute. The B-features encompassed the following: single-locular cyst, existence of solid components with a maximum diameter of <7 mm, presence of acoustic shadowing, even-structured multi-locular growth with a largest diameter of <100 mm, and absence of blood flow indicated by colour Doppler. Conversely, the five M-features consisted of an uneven solid growth, presence of ascites, four or more papillary projections, an irregular multi-locular solid growth with a maximum diameter exceeding 100 mm, and notably intense blood flow detected via colour Doppler. The SR criteria were applicable in situations where at least one of the B-features was evident, while no M-feature was observed, signifying a benign mass or when at least one M-feature was present without any B-feature (malignant mass). Histopathological (HPE) diagnosis was reported by Pathology department based on College of American Pathologists were considered as the gold standard post operatively.

Statistical Analysis

Quantitative data was shown as the mean±standard deviation (SD). Qualitative variables were expressed as absolute and relative frequency. ROC curve plotted. Using AUC, sensitivity and specificity computed. Data was given 95% confidence interval. P-value of <0.05 was considered statistically significant. Data analysis was done by MedCalc Statisitical software version 19.2.6 (medcalc.org; 2021).

Results

Total 210 patients were diagnosed with ovarian cancer, 19 were excluded and final analysis were done for 191 cases, out of which 134 (70.2%) were benign and 57(29.8%) were malignant (Fig. 1).

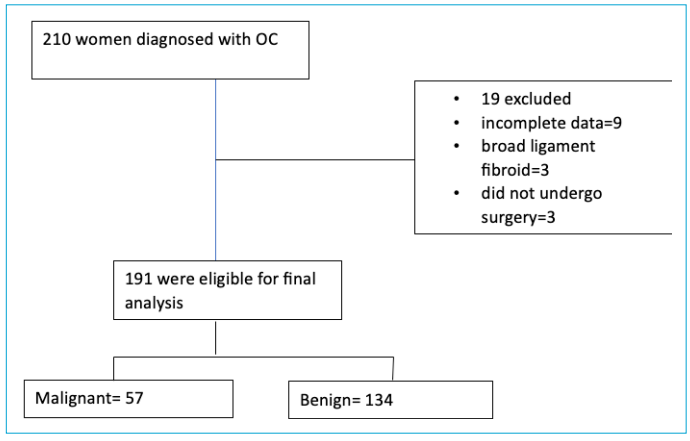

Figure 1. Showing enrolment of studied population.

Table 1 compares the clinical characteristics of the patients with benign and malignant tumour. The mean age among malignant group was 49.3±15.1 years compared to 32.5±12.8 in benign group. The proportion of menopause (16.4% vs 80.7%) and family history of ovarian cancer (1.4% vs 8.7%) were significantly higher among the malignant group. Significant distinctions were observed between women diagnosed with malignant and benign ovarian tumours across all components of the IOTA Simple Rules, including both the M features and the B-features. The mean CA125 level was significantly higher (79.7±91.7 vs 340.5±559.7 p-value <0.0001) in women with malignant tumour.

Table 2 demonstrates the diagnostic performances of the included tools. IOTA simple rules showed 91.2% sensitivity at PPV of 73.2%, CA125 had 68.4% sensitivity at PPV of 65.2% and combined IOTA and CA125 exhibited sensitivity of 96.6% at PPV of 83.3%. Combined IOTA and CA125 was superior in differentiating benign from malignant tumours than CA125 and IOTA simple rules alone.

The discriminating ability of CA125, IOTA SR and combined tool (IOTA+CA125) between malignant ovarian tumours and benign ovarian tumours via AuROC were 0.748 (95% CI 0.680 to 0.808), 0.884(95% CI 0.83-0.926), and 0.94(95% CI 0.89-0.97) respectively (Fig. 2a-c). Figure 3 compares the AUC of all three variables and ROC analysis showed that a combination of IOTA SR and CA125 had a larger AUC than a simple IOTA rules and Ca125 alone.

Discussion

Ultrasonography is the most frequently used method for diagnosing ovarian lesions, and in recent times, the IOTA simple rules have gained widespread recognition for assessing ovarian tumors.[3] It is simple to be used and has been validated and implemented in many multicentric trials.[12] Present study has demonstrated that IOTA simple

Table 1. Clinical profile of studied population

Characteristics	Histopathology (n=191)		p
	Benign (n=134)	Malignant (n=57)	
Age(years)			
Mean±SD	32.5±12.8	49.3±15.1	0.04
Parity			
Nullipara	31	21	0.08
Multipara	103 (76.8%)	36 (63.1%)	
Current or prior hormonal contraception			
Yes	29	14	0.07
No	105	43	
Menopausal			
No	112 (83.5%)	11 (19.2%)	
Yes	22 (16.4%)	46 (80.7%)	<0.0001
Family history of Breast & Ovarian Cancer			
Yes	2	5	0.02
No	132	52	
CA125 (IU/ml)			
Mean±SD	79.7±91.7	340.5±559.7	<0.0001
Malignant feature			
M1	6 (4.5%)	39 (68.4%)	<0.0001
M2	4 (2.9%)	15 (26.3%)	<0.0001
M3	7 (5.4%)	13 (22.8%)	0.0003
M4	7 (5.4%)	29 (50.8%)	<0.0001
M5	14 (11%)	34 (59.6%)	<0.0001
Benign features			
B1	84 (62.6%)	3 (5.2%)	<.0001
B2	10 (7.8%)	1 (1.7%)	0.122
B3	35 (26.1%)	2 (3.5%)	0.0003
B4	38 (28.3%)	5 (8.7%)	0.0031
B5	120 (89.5%)	19 (33.3%)	<0.0001

Table 2. Performance of Diagnostic Indices

	Histology		Performance			
	Benign	**Malignant**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
IOTA						
Benign (n=111)	108	3	91.23%	85.1%	73.2%	95.8%
Malignant (n=71)	19	52				
Inconclusive (9)	7	2				
CA125						
Benign (n=122)	110	12	68.4%	73.9%	65.2%	90.2%
Malignant (n=69)	24	45				
IOTA+ CA125						
Benign (n=125)	123	2	96.6%	91.8%	83.3%	98.4%
Malignant (n=66)	11	55				

PPV-Positive predictive value; NPV-Negative Predictive value; IOTA- International Ovarian Tumor Analysis; CA125-Cancer Antigen 125.

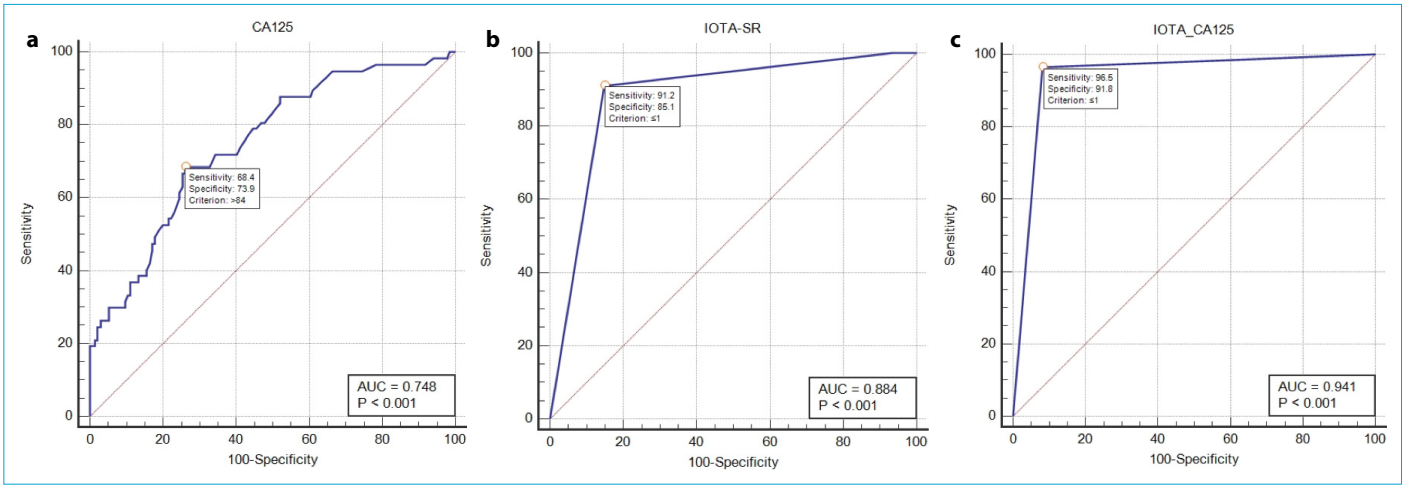

Figure 2. Diagnostic efficacy of CA125, IOTA-SR and combined IOTA-SR & CA125. **(a)** ROC analysis of CA125. **(b)** ROC analysis of IOTA SR. **(c)** ROC analysis of IOTA SR + CA125.

ROC: Receiver Operating Characteristic; IOTA SR: International Ovarian Tumor Analysis Simple Rules: CA125= Cancer Antigen 125; AUC: Area Under Curve.

rules perform better than CA125 in discriminating benign from malignant ovarian tumours. However, ultrasound all alone is not sufficient in diagnosing malignant tumours.

CA 125 continues to be the most commonly employed marker for distinguishing benign from malignant ovarian tumours, but its role is contentious due to its decent level of sensitivity paired with low specificity.[13] Furthermore, CA125 may remain high in benign conditions too. So, to overcome this problem, we investigated the efficacy of combined ultrasound and biochemical marker in differentiating the malignant from the benign ovarian lesion. This study has proven the improved accuracy of combined tool of CA125 and IOTA simple rules in discriminating benign from malignant ovarian tumours.

In a study conducted by Wen et al. in 2022, it was found that CA125 exhibited a sensitivity of 80.30% and a specificity of 82.07% for distinguishing between benign and malignant ovarian masses.[14] This result aligns closely with our own study, wherein we identified a sensitivity of 68.2% and a specificity of 73.9%. The ROC curve assesses the discriminatory power of a test, indicating its capacity to differentiate between individuals with the disease and those without it. In our study, we observed a relatively modest Area under the ROC curve (AuROC) value of 0.78 for CA125 at cut-off value of 84 IU/ml. Similarly, in 2015, Dikmen et al. reported a weak AuROC of 0.78 for CA125, implying that it may not be the suitable marker for the diagnosis of ovarian malignancy.[15]

IOTA SR is a widely accepted tool for assessing ovarian tumours. External validation of IOTA simple rules had demonstrated sensitivity and specificity of 94.3 and 94.9% re-

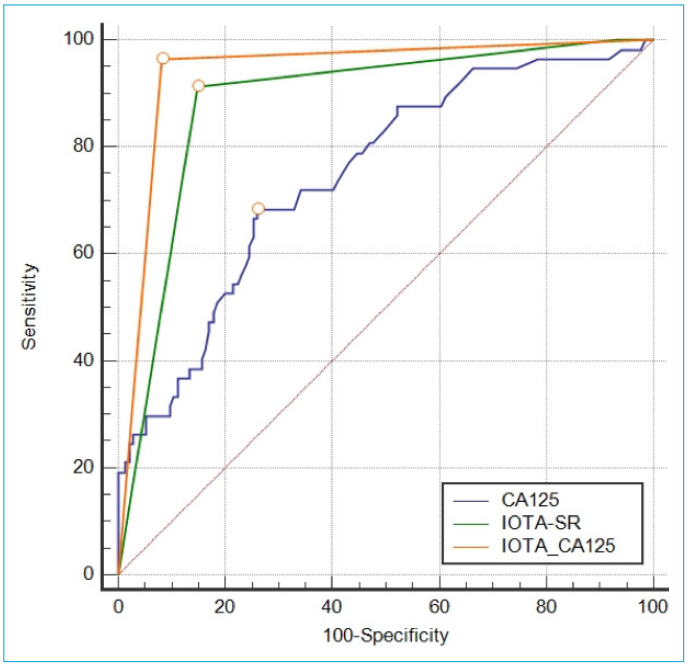

Figure 3. Comparative ROC analysis of CA125, IOTA-SR and combined IOTA-SR & CA125.

ROC: Receiver Operating Characteristic; IOTA SR: International Ovarian Tumor Analysis Simple Rules: CA125: Cancer Antigen 125; AUC: Area Under Curve.

spectively.[16] These findings are consistent with our results, which also demonstrated a sensitivity and specificity of 91.2% and 85.1% respectively. A recent meta-analysis including 19,674 adnexal tumours indicated that the pooled sensitivity and specificity of IOTA SR were 93.0 and 80.0%, respectively.[5] However the simple rules could be used in 76–89% of tumours and proportion of inconclusive results remains high up to 20%.[4] Recently few reports have revealed better detectability of malignant ovarian lesion by combined biochemical and ultrasound markers.[17] A recent study on 479 pre and postmenopausal women had reported that a combination of CA-125 and IOTA SR model had a better diagnostic value in differentiating between malignant and benign ovarian tumour with AUC of 0.94 and 0.98 respectively.[18] We also demonstrated overall AUC of 0.94 for combined tool (IOTA-SR+ CA125).

A recent systematic review and meta-analysis of 47 studies have proposed the adoption of a two-step approach for patients with inconclusive results from the IOTA Simple Rules. This strategy suggest that in situations where an expert is unavailable, the IOTA logistic regression model 2 (LR2) can serve as a viable alternative to the IOTA Simple Rule.[5] However, it's worth noting that the IOTA logistic models requires a more comprehensive set of data for each predictor, making them less straightforward to apply in practice. So we propose, combined IOTA-SR along with CA125 should be used for prediction of ovarian malignancy.

Recently, European and North American gynecologists and radiologists have developed a management system for adnexal masses. This system relies on specific ultrasound features to categorize masses into various risk groups for malignancy and is referred to as the Ovarian-Adnexal Reporting and Data System (O-RADS). A study investigating the effectiveness of the IOTA Simple Rules, O-RADS, and CA125 in distinguishing between benign and malignant adnexal masses had concluded that there was no significant difference in diagnostic accuracy when utilizing a combination of two methods, namely IOTA SR & CA125 and O-RADS & CA125. Consequently, the authors recommend the use of either IOTA SR or O-RADS in conjunction with CA125 for preoperative differentiation between benign and malignant lesions.[14]

Some authors have proposed incorporating HE4 (Human Epididymis protein 4) into the diagnostic process alongside IOTA and CA125 to enhance accuracy.[19] However, the widespread acceptance and adoption of this model might be limited because HE4 testing is not routinely conducted.

There are few limitation of the study. The first is the retrospective nature of the study, ultrasound was performed by examiners with varied experience, second, we included only those patients who underwent surgery at our centre that might have affected the final result.

Conclusion

In summary, our study emphasizes the importance of employing a combined approach involving IOTA Simple Rules and CA125 for the more accurate pre-operative differentiation of benign and malignant ovarian tumours. While CA125 alone has its limitations, our findings suggest that when used in conjunction with IOTA Simple Rules, it significantly enhances diagnostic accuracy. This approach offers a practical and accessible means of improving the pre-operative diagnostic accuracy of ovarian lesion, particularly in situations where specialized expertise may be lacking.

Disclosures

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