

Original Research Article

Comparison of the international ovarian tumor analysis simple rules scoring system and risk of malignancy index-4 as predictors of ovarian malignancy

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ABSTRACT

Background: Ovarian cancer is one of the top three most common cancers in women. Most are detected at an advanced stage, so early detection is essential. A scoring system can easily predict an ovarian malignancy. IOTA Simple Rules and RMI-4 are easy-to-implement scoring systems. This study aimed to evaluate the comparison between the accuracy of the IOTA simple rules scoring system and RMI-4 as a predictor of malignancy in ovarian tumor cases at Prof. Dr. IGNG Ngoerah general hospital.

Methods: This study used a diagnostic trial design involving 120 ovarian tumor patients undergoing surgery at Prof. Dr. IGNG Ngoerah general hospital, with 100 patients meeting the inclusion criteria. The collected data were tabulated and analyzed using SPSS for Windows ver. 22. Results were considered significant if $p \leq 0.05$.

Results: From 100 patient samples who met the inclusion criteria, 60 subjects (60%) were ovarian tumors with benign histopathologic results, and 40 (40%) subjects were tumors with malignant histopathology. The majority of ovarian tumors with malignant histopathology were found in the age group >50 years (52.5%), the menopausal group (57.5%), and multiparity (70%). CA-125 levels above 35 U/ml are found in 90% of the population, with details of 92.5% found in populations with malignant histopathological tumors. The AUC values for RMI-4 and IOTA simple rules are 0.846 and 0.925, with the p value for each scoring system being <0.001 .

Conclusions: This study found that the IOTA simple rules scoring method has a better diagnostic value than RMI-4 scoring.

Keywords: Diagnostic, IOTA simple rules, Ovarian cancer, RMI-4, Scoring

INTRODUCTION

Ovarian cancer is one of the most common gynecology malignancies and is one of the causes of death with a high number of cases. According to Ferlay et al there are 250,000 new instances of ovarian cancer worldwide each year.¹ Two hundred seven thousand two hundred fifty-two mortalities from ovarian cancer occurred in 2020,

accounting for approximately 2.1% of all cancer-related deaths in women, while 313,959 new instances of ovarian cancer were identified globally, according to GLOBOCCAN statistics.² Out of all gynecological cancers, ovarian cancer has the lowest 5-year survival rate (43%) globally.³ 13,310 new ovarian cancer cases were reported in Indonesia in 2016, accounting for 7.1% of all new female cancer cases.⁴

The mortality rate due to ovarian cancer in Indonesia ranks at the top in Asia (6.1 per 100,000 people).⁴ In 2017, it was shown that, with a 5-year life expectancy of just 15%, ovarian cancer accounted for 35% of all gynecological malignancies.⁵ Ninety-four incidences of ovarian cancer, or 19.4% of all gynecological cancer cases at Prof. Dr. IGNG Ngoerah general hospital, were discovered through a descriptive study that was undertaken between January 2018 and December 2019. Forty-two cases (44.7%) of the 94 cases were stage IIIC ovarian cancer, which was followed by stage IIB 13 cases (13.8%), stage IA 11 cases (11.7%), and stage IVB 7 cases (7.4%) of the total number of cases.⁶ An accurate preoperative diagnosis of a benign or malignant tumor can influence adequate care. Encouraging patients to seek a referral and treatment from a gynaecological oncologist expedites establishing a histological diagnosis and subsequent postoperative therapy. The most accurate way to evaluate ovarian mass pathology using ultrasonography is by subjective assessment by a qualified practitioner. Since examiners' subjectivity and competence vary greatly, many ultrasound-based prediction models have been developed to aid operators in accurately distinguishing between benign and malignant tumors. Timmerman, who participated in the international ovarian tumor analysis (IOTA) in 2000, released the most recent grading system, which underwent several revisions till 2013.⁷ This system is more widely applicable than other scoring systems due to its multicentre testing involving over 1000 patients and internal and external validation across Europe. Additionally, it has been validated on the European continent and has a higher ROC curve (0.936 vs. 0.87) than the risk of malignancy index-4 (RMI-4) scoring system. IOTA has created a basic rules model based on five characteristics predictive of malignancy (feature M) and five indicated benignity (feature B).⁸ The use of pre-operative IOTA simple rules and RMI-4 scoring and its link to a mass's post-operative histological malignant/benign outcome need to be evaluated in light of the previous discussion. There is still little data comparing the IOTA simple rules scoring system's diagnostic performance with RMI-4 and its use in Indonesia. Therefore, this study aimed to evaluate the comparison between the accuracy of the IOTA simple rules scoring system and RMI-4 as a predictor of malignancy in ovarian tumor cases at Prof. Dr. IGNG Ngoerah general hospital.

METHODS

This study was an analytical study using diagnostic tests. Data was collected in the obstetrics and gynecology polyclinic and anatomical pathology laboratory of Prof. Dr. IGNG Ngoerah general hospital from May to December 2022. Women with ovarian tumors who visited the obstetrics and gynecology polyclinic at Prof. Dr. IGNG Ngoerah general hospital, Denpasar, and underwent a laparotomy or laparoscopy procedure were included in the sample. These women were chosen by

consecutive sampling from the accessible population after meeting the inclusion and exclusion criteria. The women were 18 years of age or older. Real study participants are samples of people who have given informed permission and are genuinely willing to participate.

Inclusion and exclusion criteria were applied during the sample selection procedure. Women who were diagnosed with ovarian tumors and who underwent laparotomy or laparoscopy at RSUP Prof. Dr. IGNG Ngoerah, Denpasar, with anatomical pathology results showing benign tumors and ovarian cancer, were eligible for participation in this study provided they signed a written informed consent form. Women with ovarian tumors and primary malignancy in other organs, a history of therapy for ovarian cancer, and ovarian tumors with indeterminate histology results were excluded. A minimum of 100 samples are required, depending on the measurement of the minimum sample size. The following information was gathered: age, parity, menopausal state, oral contraceptive history, family history of ovarian cancer, level of CA-125, IOTA simple rules scoring, RMI-4, and histology of ovarian neoplasm (benign or malignant). With SPSS for Windows version 22, the gathered data were tabulated and examined. A p value of less than 0.05 indicated that the results were significant.

RESULTS

Study sample characteristics

The study revealed that out of the 100 patients who fulfilled the eligibility requirements, 60 individuals (or 60%) had ovarian tumors with benign histology, and 40 individuals (or 40%) had tumors with malignant histopathology. A significant proportion of ovarian tumors with malignant histology (52.5%) are observed in the age group over 50. The (Table 1) indicates no malignant tumors were discovered in the age range below 19. In the premenopausal age range, benign histopathological tumors accounted for 75% of the population. Of the forty tumor cases with malignant histology in total, the majority belonged to the categories of menopause (57.5%) and multiparity (70%). Out of 40 individuals with ovarian cancer, the majority (87.5%) did not take oral contraceptives. Ninety percent of the population had CA-125 levels of more than 35 U/ml, of which ninety-two percent had malignant histopathological lesions. Forty instances were identified as potentially malignant based on the IOTA simple-rules score technique computation. About 34 (85%) of the 40 cases were true positives, while 7 (15%) were false positives.

Accuracy of IOTA simple rules and RMI-4 in diagnosing ovarian cancer

Based on the calculation of the RMI-4 scoring method, 40 cases were diagnosed with suspicion of malignancy.

Of the 40 cases, around 32 (80%) were true positives and 8 were false positives.

Table 1: Study sample characteristics.

Variables	Histopathology	
	Malignant N (%)	Benign N (%)
Age (years)		
≤19	0 (0)	4 (6.7)
20-49	19 (47.5)	43 (71.7)
≥50	21 (52.5)	13 (21.6)
Menopause status		
Pre-menopause	17 (42.5)	45 (75)
Post-menopause	23 (57.5)	15 (25)
Parity		
Nullipara	2 (5)	18 (30.3)
Primipara	10 (25)	4 (6.7)
Multiparitas	28 (70)	38 (63)
Contraception history		
Yes	5 (12.5)	5 (8.3)
No	35 (87.5)	55 (91.7)
CA-125 levels		
<35	3 (7.5)	7 (11.7)
≥35	37 (92.5)	53 (88.2)
IOTA simple rule		
Malignant	34 (85.0)	7 (11.7)
Benign	6 (15.0)	53 (88.3)
RMI-4		
Malignant	32 (80.0)	8 (13.3)
Benign	8 (20.0)	52 (86.7)
Total	40 (40)	60 (60.0)

RMI-4 diagnosed suspected benignity in 60 cases, with details of 52 cases being true negatives and 8 cases being false negatives. From the calculation of the IOTA simple-

rules scoring method, 41 cases were diagnosed with suspicion of malignancy.

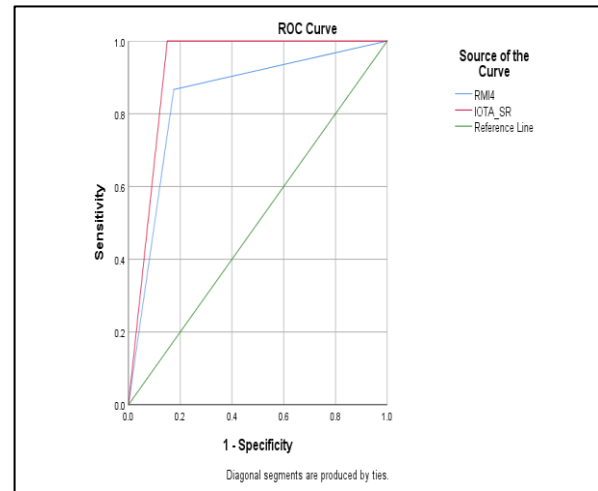


Figure 1: ROC curve for each scoring method.

Of the 41 cases, around 34 (85%) were true positives and 7 were false positives. IOTA simple rules diagnosed suspected benignity in 59 cases, with details of 53 cases as true negatives and 6 as false negatives. The calculation results can be seen in (Table 2). Because the curve in (Figure 1) ROC curve picture advances away from the 50% line and toward 100%, it is more indicative of the IOTA simple rules' superior diagnostic value. When predicting the malignancy of an adnexal tumor that has been preoperatively categorized, ROC curves evaluate the precision of both scoring systems. IOTA Simple Rules has a higher AUC value than RMI-4, with values of 0.846 and 0.925, respectively. There is a statistically significant difference when the p value for each scoring system is less than 0.001.

Table 2: Accuracy of IOTA simple rules and RMI-4 in diagnosing ovarian cancer.

Scoring methods	Sensitivity	Specificity	PPV	NPV	AUC	P value
IOTA simple rules	85	88	83	90	0.925 (0.761-0.931)	<0.001*
RMI-4	80	86	80	86	0.846 (0.859-0.991)	<0.001*

*Results were considered significant if $p \leq 0.05$. Analysis was carried out using the receiving operating characteristic curve. PPV; positive predictive value, NPV; negative predictive value, AUC; area under the curve.

DISCUSSION

According to this study, the age group over 50 had the highest incidence of ovarian cancer (52.5%), followed by the age group between 20 and 49 (47.5%). The chance of developing ovarian cancer rises with age, peaking between 50 and 80 years of age.^{9,10}

The study that compares the incidence of ovarian cancer with age reveals notable variations in ovarian cancer incidence rates among different age groups. The research highlights that ovarian cancer is more frequent in older women, with around 75% of cases occurring after

menopause. According to the report, the median age of diagnosis is around 63 years old in most industrialized nations.¹¹ Ovarian cancer that occurs in women under 40 years of age is mostly germ cell tumors. In the case of ovarian cancer over the age of 40 years, most of it is an epithelial-type tumor, and the risk increases with age.^{9,10} Out of all forty tumor cases with malignant histopathological results, the majority (70%) were multiparous.

Meanwhile, the multiparity group dominated the benign histopathology group at 63%. This illustrates that there is no significant difference in the parity of women in the

group with ovarian cancer compared to the group with benign ovarian tumors. These results are not by previous research, which found that women who had given birth had a reduced risk of ovarian cancer, and each increase in parity was associated with a further 10-20% risk reduction.⁹ This applies especially to epithelial-type ovarian cancer but is most influential for clear cell type and endometrioid-type ovarian cancer. Higher parity was also associated with a reduced risk in BRCA1 gene mutation carriers.

Higher parity decreases the number of ovulatory cycles, reducing ovarian cancer risk. Factors that prolong exposure to ovulation, such as low parity, early menarche, and late menopause, increase the risk of ovarian cancer.^{9,10} A study conducted by Ali et al showed that ovarian cancer is more common in older women, with the majority of cases (around 75%) diagnosed after menopause. In terms of the median age of diagnosis, the study indicates that it is around 63 years in most developed countries.¹¹

The proportion of epithelial type was significantly higher in the ovarian cancer group. More than 80% of ovarian cancers in this study were epithelial type. The majority of epithelial types in subjects with ovarian cancer in this study were serous type (27.5%), followed by clear cell type (22.5%), endometrioid type (20%), and mucinous type (12.5%). This is in accordance with the global epidemiology of ovarian cancer, where up to 85-90% of ovarian cancer is the epithelial type, and the remainder is non-epithelial type.¹²

The results of this study show that the sensitivity of the IOTA simple rules is 85%, with a specificity of 88%, a positive predictive value of 83%, a negative predictive value of 90%, and an accuracy of 87%. This means that the IOTA simple rules method can predict the diagnosis of malignancy in the population with malignant ovarian tumors at as much as 85% and predicts no malignancy in the population that does not have malignant ovarian tumors at 88%.

Suppose examination results suggest malignancy using the IOTA simple rules method in individuals who have ovarian neoplasms with suspicion of malignancy. In that case, around 83% of these results are accurate of malignancy (positive predictive value). Meanwhile, suppose you get negative results in a population with ovarian neoplasms with suspicion of being benign. In that case, around 90% of the results are correct and not malignant (negative predictive value).

The results of this study found high sensitivity and specificity of the IOTA simple rules in determining ovarian malignancy. This study's results align with previous research conducted by Timmerman et al., who were part of the IOTA phase-2 study, finding that this simple-rules method had a sensitivity of 95% and a specificity of 91%.¹³

Timmerman et al validated this system, which showed a sensitivity of 90% and a specificity of 93%.¹⁴ A meta-analysis indicated that the rules' pooled sensitivity was 93% (95% CI, 90-96%).¹⁵ Based on the results of this study, the RMI-4 scoring method has a sensitivity of 80% with a specificity of 86%, a positive predictive value of 80%, a negative predictive value of 86%, and an accuracy of 84%. This means that the RMI-4 method can predict a diagnosis of malignancy in a population with a malignant ovarian tumor 80% of the time and predict that there is no malignancy in a population that doesn't have a malignant ovarian tumor 86%.

If examination results suggest malignancy using the RMI-4 method in individuals who have ovarian neoplasms with suspicion of malignancy, then around 80% of these results are indeed malignant. Meanwhile, if you get negative results in a population with ovarian neoplasms with suspicion of being benign, then around 86% of the results obtained are accurate and not malignant. RMI-4 can have an accuracy of both positive and negative results of 84%. The results of this study are consistent with previous research by Yamamoto et al obtaining sensitivity and specificity of 86.8% and 91%.

The significant difference in specificity between this study and Yamamoto's study could be due to the parameters of tumor size and menopausal status.¹⁶ This specificity is in line with previous research findings. For instance, a meta-analysis published in the European journal of obstetrics, gynaecology, and reproductive biology revealed that the rules' pooled specificity was 90% (95% CI, 85-95%).¹⁵

This study found that the IOTA simple rules scoring method had better sensitivity, specificity, positive predictive value, negative predictive value, and accuracy than RMI-4 scoring. These results are in line with research conducted by Feharsal et al which found that the IOTA simple rules scoring system had a sensitivity of 98%, a negative predictive value of 86%, and an accuracy of 86%, better than the RMI-4 method and the Sassone morphology index in diagnosing ovarian tumors.¹⁷ Apart from that, research findings by Sayasneh et al also obtained an RMI sensitivity of only 72% compared to IOTA Simple Rules, with a sensitivity of 91%.¹⁸

The IOTA simple rules scoring system has high sensitivity and specificity in diagnosing ovarian malignancy and can be applied very well in a broad population. The low-cost factor in diagnosing a malignancy is essential; this scoring can also reduce the number of unwarranted operations. IOTA simple rules do not require examination of the tumor marker CA-125, making it easier and cheaper to use in health facilities at the regional level. In the RMI-4 scoring method, one of the variables is checking CA-125 levels.

The tumor marker CA-125 is considered to have low sensitivity because CA-125 levels have also been found

to be elevated in several benign gynaecological cases, such as fibroids, adenomyosis, endometriosis, and pelvic infections. By using scoring predictors of ovarian malignancy, a clinician can fulfil an essential aspect in the management of ovarian malignancy, namely diagnosing the incidence of ovarian cancer as early as possible so that appropriate management of ovarian malignancy can be provided and can be referred to a service center that specializes in gynaecological oncology. This research still has limitations. This study has not controlled for confounding variables that may affect the patient's clinical outcomes.

CONCLUSION

Based on this study, IOTA simple rules have a better diagnostic value than RMI-4. Further studies are needed to validate these findings regarding the confounding variables that have not been controlled in this research so that they can produce diagnostic values that are more representative of the population. Further studies need to be carried out on cases with inconclusive results in the IOTA simple rules categorization system. Apart from that, additional research can be carried out to test the accuracy of the IOTA simple rules model in diagnosing ovarian cancer. A multivariate model can be formed using a combination of tumor markers or other morphological indices.

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