Research Article

Risk of Malignancy Index 4 (RMI4) and Risk of Malignancy Index 3 (RMI3) as Diagnostic Tests for Adnexal Tumor

Risk of Malignancy Index 4 (RMI4) dan Risk of Malignancy Index 3 (RMI3) sebagai Alat Diagnostik untuk Tumor Adneksa

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Abstract

Objective: Comparing scoring with RMI3 and RMI4 in establishing the diagnosis of adnexal tumour in RSUD Dr. Saiful Anwar Malang.

Methods: Prospective cohort study with samples of all patients suspected of having an adnexal tumour diagnosed in gynecology policlinic using gynecological oncology policlinic medical records at RSUD Dr. Saiful Anwar in the form of age, demographics, menopause status, Ca125, ultrasound results.

Results: Between the RMI3 results and the results of histopathology, a contingency coefficient of 0.596 was obtained with a p-value of 0.000015 (p <0.05), with a PPV of 83%, an NPV of 91%. Between the RMI4 results and the histopathology results, a contingency coefficient of 0.657 with a p-value of 0.0000004 (p <0.05) was obtained, with a PPV of 92%, NPV of 95%. On the ROC curve, the area of the predicted results using the RMI4 score is higher than the RMI3 score.

Conclusions: Using the RMI4 score results in more accurate predictions than the RMI3 score in detecting adnexal tumour malignancies.

Keywords: adnexal tumours, diagnostic tests, ovarian tumours, risk of malignancy index, ultrasound.

Abstrak

Tujuan: *Membandingkan Skoring RMI3 dan RMI4 dalam menegakkan diagnosis tumor adneksa di RSUD dr. Saiful Anwar Malang.*

Metode: *penelitian kohort prospective dengan sampel semua pasien yang dicurigai menderita tumor adneksa yang didiagnosis di poli Ginekologi menggunakan data rekam medis poli Ginekologi Onkologi RSUD dr. Saiful Anwar berupa usia, demografi, status menopause, Ca125, hasil USG.*

Hasil: *Antara hasil RMI3 dengan hasil hispatologi, didapatkan koefisien kontingensi sebesar 0,596 dengan p-value ,.000015 (p<0,05), dengan PPV 83%, NPV 91%. Antara hasil RMI4 dengan hasil histopatologi, didapatkan koefisien kontingensi sebesar 0,657 dengan p-value 0.0000004 (p<0,05), dengan PPV 92%, NPV 95%. Pada kurva ROC, luas area hasil prediksi dengan menggunakan skor RMI4 lebih tinggi daripada skor RMI3.*

Kesimpulan: *Menggunakan skor RMI4 menghasilkan prediksi yang lebih tepat daripada skor RMI3 dalam mendeteksi keganasan tumor adneksa.*

Kata kunci: *risk of malignancy index, tumor adneksa, tumor ovarium, uji diagnostik, USG.*

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INTRODUCTION

Ovarian tumor is a growth of tissue in the form of a lump originating from the ovary, which can be either solid or liquid / cystic. Like other tumours, ovarian tumours can be malignant or can be benign. Ovarian cancer ranks second among all gynecological cancers in developing countries, and is ranked as the fifth leading cause of mortality due to malignancy in women and is the most common cause of death among gynecological malignant tumours. In the United States, there were approximately 21.290 new cases and 14.180 deaths in 2015 as a result of ovarian cancer. Ovarian cancer accounts for 5% of all cancers among women[1].

The ovary is located inside the abdominal cavity so there is no easy access to obtain tissue samples for malignancy. Therefore, an examination formula is needed for the basis of ovarian malignancy suspicion. Examination of tumour antigen 125 tumour markers (CA-125), ultrasonography, postmenopausal age, and parity can increase suspicion of ovarian malignancy[2].

A number of examination formulas have been developed in various countries carried out in order to establish a suspicious diagnosis of preoperative ovarian cancer. There are many formulas for suspecting pre-malignant malignancy for ovaries such as the Risk of Ovarian Malignancy Algorithm (ROMA), Risk of Ovarian Cancer Algorithm (ROCA), Gatot Purwoto Score and many other examination formulas, made to be implemented in various inspection sites based on the conditions of the facilities available[3].

The Risk of Malignancy Index (RMI), known as RMI 1, in its development has undergone many validations and comparisons of its sensitivity and specificity, with different research designs and results that are not always the same. Until now the International Federation of Gynecology and Obstetrics (FIGO) is still guided by RMI-1 which was first formulated in 1990[4].

A more accurate scoring system is needed in predicting preoperative malignancies to reduce morbidity and mortality due to ovarian malignancies. Risk of Malignancy Index 3 (RMI3) is the result of U x M x CA 125 calculations. Ultrasonography includes multilocularity, solid areas, bilaterality, ascites, and intraabdominal metastases resulting in one point each. A total of 2 or more points are recalculated to U = 3, less than 2 points to U = 1. Menopausal status is defined as more than 1 year of amenorrhea, or age 50 years or more among women who have had previous hysterectomy, and postmenopausal status M score = 3; premenopausal status score M = 1. Serum CA 125 (U / mL) is entered directly into the equation where a cut-off value of 200 indicates discrimination between benign and malignant adnexal masses. In the study l RMI3 with a cut-off rate of 200 has an accuracy of 86%[5].

Risk of Malignancy Index 4 (RMI4) is the result of the calculation of U x M x S x CA 125. The total score of USG 0 or 1 is recalculated to U = 1, and the score 2 becomes U = 4. Premenopausal status score M = 1 and status score postmenopausal M = 4. Tumour size was obtained from ultrasound. Tumour size (largest single diameter) <7 cm was recalculated to S = 1, and ≥7 cm to S = 2, Serum CA 125 (U / mL) was applied directly to calculations where a cut-off value of 450 showed discrimination between benign adnexal masses and ferocious. In the study RMI4 with a cut-off rate of 450 has an accuracy of 90.4%[5].

METHODS

This study uses a prospective cohort study design that compares diagnostic tests using Risk of Malignancy Index 3 (RMI3) and Risk of Malignancy Index 4 (RMI4) in adnexal tumour patients. This research was conducted in October 2018 - April 2019, with samples of all patients suspected of having an adnexal tumour diagnosed in gynecology policlinic using gynecological oncology policlinic medical records at RSUD Dr. Saiful Anwar in the form of age, demographics, menopause status, Ca125, ultrasound results. The exclusion criteria are patients with adnexal masses not from the ovary, patients suffering from other malignancies, patients with infected adnexal masses, and pregnant patient with adnexal tumour.

In this study, the data analysis technique was carried out with several test methods. To test the numerical variables, the T-test was used, while with the categorical variables, the Chi-square test was used. To test the comparison of the accuracy of predictions between scoring RMI3 and RMI4 we used the contingency coefficient test and the ROC curve to determine the cut-off value of RMI3 and RMI4.

RESULTS

Based on the inclusion and exclusion criteria, there were 22 samples in the benign category

and 12 samples in the malignant category. The following are the characteristics of the research sample that have been studied: the average age of 22 patients in the benign category was 42.1 ± 13.6 years and in 12 patients the malignant group was 54.2 ± 10.3 years. Using an independent t-test, a p-value of 0.012 (p <0.05) indicates that there is a statistically significant age difference.

Table 1 shows that in both groups of patients, both benign adnexal tumour patients and malignant categories, most had junior high school education: 11 (32.4%) and 6 (17.6%) patients respectively. Using the Chi-Square test, a p-value of 0.493 (p> 0.05) was obtained which explained that there were no differences in educational characteristics between the two groups of patients.

Table 1. Study Sample Characteristics

Characteristics	Category		*P-value*
	Benign (n = 22)	Malignant (n=12)	
Age (mean ±SD)	42.1 ± 13.6	54.2 ± 10.3	0.012
Education			
Elementary school	0 (0)	1 (2.9)	0.493
Junior high school	11 (32.4)	6 (17.6)	
Senior high school	10 (29.4)	5 (14.7)	
University	1 (2.9)	0 (0)	
Parity			
Nulliparous	5 (14.7)	8 (23.5)	0.012
Primi / Multiparous	17 (50)	4 (11.8)	
Menarche (y.o)			
≤ 11	0 (0)	2 (5.9)	0.048
> 11	22 (64.7)	10 (29.4)	
Menopause			
Not Yet	17 (50)	5 (14.7)	0.038
Already	5 (14.7)	7 (20.6)	
Family history of Gynecologic cancer (Genetic Factor)			
Yes	4 (11.8)	9 (26.5)	0.001
No	18 (52.9)	3 (8.8)	

The data in table 1 also shows that 8 nulliparous patients (23.5%) experienced ovarian malignancy. By using the Chi-Square test, the p-value was 0.012 (p <0.05) which explained that there was a significant difference between parity characteristics and ovarian malignancy.

The benign adnexal tumour patient group has not experienced menopause in 17 (50%) patients, while in the malignant adnexal tumour group mostly have experienced menopause, which is 7 (20.6%) patients. Using the Chi-Square test, a p-value of 0.038 (p <0.05) was obtained which explained that there were differences in the characteristics of menopause between the two groups of patients.

Genetic factors analyzed in this study were family history of the gynecologic tumour. Based on genetic factors (Table 1), a p-value of 0.001 was obtained (p <0.05). From this study it was shown that there were significant differences in genetic factors between benign adnexal tumour patients and malignant category.

Based on the tumour type, it was shown table 2 that in patients in the malignant category, the most common type of serous tumour cell types was found in 6 (17.6%) patients. Whereas in the benign category, the most common type was mucinous cystadenoma in 6 (17.6%) patients.

Table 2. Tumour Type Characteristics

Tumour Type	Benign (%)	Malignant (%)
Mucinous Carcinoma Ovarium		3 (8.8)
Endometrioid Adenocarcinoma		1 (2.9)
High-Grade Serous Ovary Carcinoma		6 (17.6)
Adenocarcinoma		2 (5.9)
Serous Cystadenoma Ovary	3 (8.8)	
Mucinous Cystadenoma Ovary	6 (17.6)	
Hemorrhagic Cyst	3 (8.8)	
Dermoid Cyst	3 (8.8)	
Endometriosis Cyst	3 (8.8)	
Mature Teratoma	1 (2.9)	
Infected Cyst	2 (5.9)	
Fibroma Ovary	1 (2.9)	

Comparison of the accuracy of RMI3 with RMI4 in predicting adnexal tumour malignancy can be done using contingency coefficients, ie comparing the results of RMI3 and RMI4 calculations with the results of histopathological examination. From this study, a contingency coefficient of 0.596 was obtained with a p-value of 0.000015 (p <0.05. It was shown that there was a significant relationship between the results of RMI3 with the results of histopathology. The positive predictive value (PPV) was 83% and negative predictive value was 91%. From 22 patients with benign adnexal tumour category based on histopathology, there were 2 (5.9%) patients who predicted malignant tumours. While from 12 patients with malignant adnexal tumour category based on histopathology, there were 2 (5.9%) patients who were predicted as benign tumours.

In the contingency coefficient test of the relationship between the results of RMI4 with the results of histopathology, the contingency coefficient was 0.657 with a p-value of 0.0000004 (p <0.05). From this test it was shown that there was a significant relationship between the results of RMI4 with the results of histopathology. The positive predictive value (PPV) was 92% and negative predictive value was 95%. From 22 patients with benign adnexal tumour category based on histopathology, there were 1 (2.9%) patients predicted by malignant tumours, while from 12 patients with malignant adnexal tumour categories based on histopathology, 1 patient was predicted as a benign tumour.

Table 3. Comparison of Contingency Coefficient between RMI3 and RMI4

Score	Histopathology		PPV (%)	NPV (%)	Contingency Coefficient	*P-value*
	Malignant	**Benign**				
RMI3						
Malignant	10 (29.4)	2 (5.9)	83	91	0.596	
Benign	2 (5.9)	20 (58.8)				0.000015
RMI4						
Malignant	11 (32.4)	1 (2.9)	92	95	0.657	0.000004
Benign	1 (2.9)	21 (61.8)				

The contingency coefficient on the RMI3 score is 0.596 and the RMI4 score is 0.657. The contingency coefficient of the RMI4 score is higher than the RMI3 score. This proves that the results of the assessment using the RMI4 score produce more accurate predictions than the RMI3 score in detecting adnexal tumour malignancies. The accuracy of the RMI score of 3 with the RMI4 score for predicting adnexal tumour malignancy can be measured using a Receiver Operating Characteristic (ROC) curve.

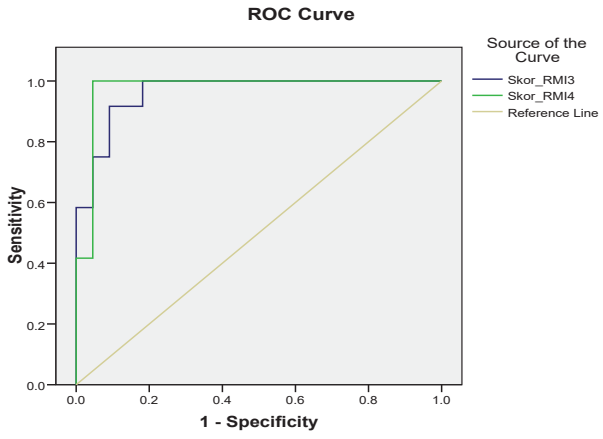

Figure 1. ROC Curves of RMI3 Score and RMI4 Score.

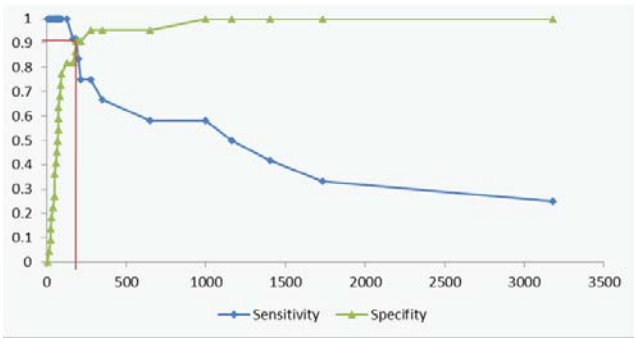

Figure 2. Plot of Sensitivity and Specificity of RMI 3 Score.

The RMI 3 plot sensitivity and specificity curve show the intersection point of the curve located at a score of 183.8. Based on this study, the sensitivity is 0.917 and the specificity is 0.909.

As explained in Figure 2, it is shown that there is an intersection of sensitivity and specificity values. This intersection shows the optimum value that can be used as a cut-off value or limitation in determining the level of malignancy of adnexa tumours. The cut point is obtained from the combination of the highest sensitivity and specificity values. It is shown that the highest combination of sensitivity and specificity values lies at point 183.8 where at that point a sensitivity value of 0.917 and specificity of 0.909

are shown. Thus, the cut-off value of the RMI3 score to determine the level of adnexal tumour malignancy was 183.8.

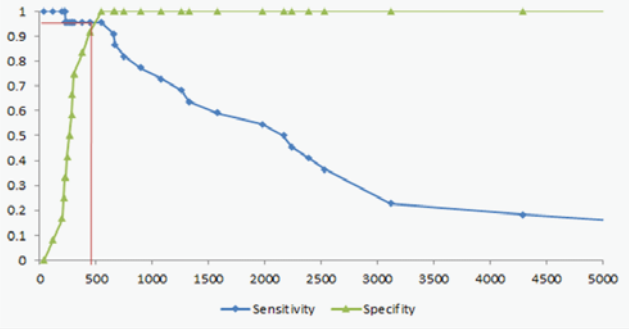

Figure 3. Plot of Sensitivity and Specificity of RMI 4 Score.

The RMI 4 plot sensitivity and specificity curve show the intersection point of the curve located at a score of 463.54. Based on this study, the sensitivity of RMI 4 is 0.954 and the sensitivity of RMI 4 is 463.54.

Based on Figure 3, it is shown that there is an intersection of sensitivity and specificity values. It is shown that the highest combination of sensitivity and specificity values is at point 463.54 where at that point the sensitivity value is 0.917 and specificity is 0.954. Thus, the cut-off value of the RMI4 score to determine the level of adnexal tumour malignancy was 463.54.

DISCUSSION

Ovarian Cancer Risk Factors

This study conducted an evaluation in patients with a diagnosis of adnexal tumour in RSUD dr. Saiful Anwar in October 2018 - April 2019, received a total of 34 samples with a distribution of 22 (68.75%) benign cases and 12 (35.7%) malignant cases. The results obtained in this study are similar to multicenter cohort studies conducted in the United States where the oncology centre shows a higher malignancy rate that is between 22-66% compared to other centres (0-30%)[6].

The mean age of the sample involved in this study in benign and malignant cases was 42.1 ± 13.6 years and 54.2 ± 10.3 years, respectively. The mean age of malignant cases was found to be higher than benign cases and statistically showed significant differences (p = 0.012). The average age of benign ovarian tumours in this study is older than the research conducted in India, which is between 20-40 years. The mean age of malignancy presentation in this study is consistent with studies in India (48 years) and Iran (49 years)[7]. The epidemiological study of meta-analysis of 125 articles published in 1925-2018 stated that the average age of ovarian cancer was detected at 50-79 years old. Detection at an advanced age shows a more severe disease severity and a lower survival rate[8].

Epidemiological studies show an inconsistent association between the age of menarche and the risk of ovarian cancer. A total of 10 (29.4%) patients who experienced menarche at the age above 11 years experienced ovarian malignancy, although it was not statistically significant (p = 0.048). A meta-analysis study revealed that the age of menarche has an inverse relationship with ovarian cancer risk (RR = 0.85; 95% confidence interval (95% CI) 0.75–0.97). The inverse relationship between menarche age and risk of ovarian cancer can be partly explained by the hypothesis of "incessant ovulation" and some hormonal changes in childhood and adolescence. Ovarian carcinogenesis involves several mechanical sequels to ovulation, such as trauma or stimulation of mitosis to the ovarian epithelium. Similar to pregnancy and the use of oral contraceptives, the age of menarche which may then reduce the risk of ovarian cancer is associated with a reduced number of ovulation for a woman's lifetime. On the other hand, early menarche is associated with the onset of a faster ovulation cycle and a tendency to maintain higher levels of luteal phase estradiol and progesterone. Progestins can increase apoptosis in the ovarian epithelium. Women who experience menarche at an older age may experience low levels of extra estrogen (or other hormones) stimulation of their ovarian epithelium without the apoptotic effect of progesterone. Meanwhile, androgens, which are also relatively common in girls with older menarcheal ages, have been shown to stimulate DNA synthesis and reduce cell death in ovarian cell culture lines[9].

Some control cases show that multiparous women have a 30-60% lower risk of ovarian cancer. Increased parity is associated with a reduced risk of ovarian malignancy8. This study revealed that in patients with adnexal tumours who came to RSSA in October 2018 - April 2019, the highest proportion diagnosed with ovarian cancer was in the nullipara group of 8 patients (23.5%). This study showed that there was a significant difference between parity and the incidence of malignancy in adnexal tumours (p = 0.012). Pregnancy decreases the risk of ovarian tumour malignancy by as much as 19%. The effect of

pregnancy on reducing the risk of ovarian cancer is consistent with the hypothesis that anovulation reduces the risk of ovarian cancer in women by reducing the risk of mutation of epithelial cells at risk of becoming malignant. Pregnancy plays a greater role in reducing the risk of ovarian cancer than the anovulation caused by the use of contraception. Hormonal changes that occur in pregnancy are thought to induce apoptosis of premalignant cells.[10]

Tumour malignancy compared to women who do not use or only use it in the short term[10]. This study did not show a significant relationship between the effect of hormones on adnexal tumour malignancy. This can be caused by the distribution of contraceptive users and fertility drugs in small samples.

RMI3 and RMI4 as Diagnostic Test

In the study group stated that there were no statistically significant differences in identifying different risk index for malignancies between RMI 1, RMI 2, RMI 3, and RMI 4, but RMI 2 was a better indicator in distinguishing benign and malignant diseases. In 2001 compares RMI 1, RMI 2, and RMI 3 with each other and also confirms that there are no statistical differences between the three indices in benign malignancy discrimination. In their study, using a cut-off of 120, found that RMI 1 had a sensitivity of 72% and specificity of 87%; RMI 2 has a sensitivity of 76% and a specificity of 81%; RMI 3 has a sensitivity of 74% and a specificity of 84%.

In a study of 34 patients with adnexal tumour in RSUD dr. Saiful Anwar Malang, the obtained accuracy of RMI3 was (P <0.05) at a cut-off level of 183.8, with sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 91%, 90%, 83%, and 91%, respectively, while the accuracy of RMI4 was (p <0.05) at the cut-off level 463 with the value of sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 91%, 95%, 92%, and 95%, respectively. These results do not differ greatly in the study of Yamamoto et al. who developed RMI using tumour size and called it RMI 4. Their study confirmed that, at a cut-off rate of 450, the accuracy of RMI 4 was better than RMI 1 (p = 0.0013), RMI 2 (p = 0.0009) and RMI 3 (p = 0.0013) with a cut-off rate of 200. They observed that at a cut-off level of 450, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 86.8%, 91.0%, 63.5%, 97,5% and 90.4% respectively. In this study, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 85%, 87%, 60%, 95%, and 86%, respectively, which were comparable to the results.

A study of 548 patients, with a mean age of 52 for those with benign lesions and 62 for those with malignant masses. This study involved 415 benign masses (76%), 80 malignant masses (24%), and 53 boundary malignancies (10%). The most common benign and malignant masses are cystadenoma and serous cystadenocarcinoma. They calculated the RMI with a cut-off point of 200, where sensitivity, specificity, PPV, and NPV were 81%, 85%, 48%, and 96%, respectively[4]. Additional research was performed on 152 patients with pelvic mass (mean age for benign masses is 45 and for malignant ones, it is 49). Of this mass, 38.8% (n = 62) was proven to be benign (the most common was cystadenoma) and 61.2% (n = 93) proved to be malignant (the most common was serous cystadenocarcinoma)[11]. Three RMI is checked without sufficient differences in the calculated parameters and at all RMI the best cut-off point is at 200. A study of 100 patients with pelvic mass and the best cut-off point for RMI was 200, where sensitivity, specificity, PPV, and NPV were 90%, 89%, 96%, and 78%, respectively.

The result of this study shows the ROC curve presents the predicted results of the RMI3 score in predicting the level of malignancy of adnexal tumours, with p-value (p <0.05) and an area of 0.962 with 95% CI of 0.907 - 1.017. A p-value of less than 0.05 indicates that the RMI3 score is good for use in predicting the level of malignancy of adnexal tumours. While the results of prediction RMI4 scores in predicting the level of adnexal tumour malignancy, we obtained p-value (p <0.05) with an area of 0.973 and 95% CI of 0.929 - 1.027. A p-value of less than 0.05 indicates that the RMI4 score is better for use in predicting the level of adnexal tumour malignancy.

In our study, the contingency coefficient on the RMI3 score was 0.596 and the RMI4 score was 0.657. The contingency coefficient of the RMI4 score is higher than the RMI3 score. This proves that the results of the assessment using the RMI4 score produce more accurate predictions than the RMI3 score in detecting adnexal tumour malignancies.

CONCLUSION

The results of this study indicate that RMI4 is better when compared with RMI 3 in predicting the level of adnexal tumour malignancy. This is consistent with the results of several studies related to pelvic tumours where RMI4 is more sensitive and specific in predicting tumours in the pelvis, especially adnexal tumours. The RMI 4 is better than RMI3 because there is a tumour size as an indicator. This is in line with the TMN system where the TMN system is used to determine the stage in the tumour.

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