

Research Report

## Risk of Malignancy Index of Ovarian Cancer Patients in Dr. Sardjito Hospital, Yogyakarta

*Indeks Risiko Keganasan Kanker Ovarium di Rumah Sakit Dr. Sardjito, Yogyakarta*

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### Abstract

**Objective:** To analyse retrospectively the score of the risk of malignancy index (RMI) in determining malignancy in the patients with ovarian mass in Dr. Sardjito Hospital Yogyakarta.

**Method:** Retrospective analysis.

**Results:** Ninety patients with complete medical record and adnexal mass were enrolled in the study from January 2007 to March 2009. Subjects consisted of 70 patients (77.78%) diagnosed with malignant ovarian mass and 20 patients with benign mass (22.22%). More than half of the malignant ovarian mass were serous carcinomas and at advanced stages (51.43% and 51.43% subsequently). Univariate analysis presented significant difference for ultrasound score and serum Ca-125 level in identification of ovarian malignancy, but not with the age or the menopausal status. The performance of RMI ( $\geq 200$  for malignancy) had a sensitivity of 70%, a specificity of 75%, a positive predictive value of 90.74%, and negative predictive value of 41.67%. The serum Ca-125 level had a sensitivity of 81.43%, a specificity of 60%, a positive predictive value of 87.69%, and a negative predictive value of 48%. The ultrasound score had a sensitivity of 65.71%, a specificity of 65%, a positive predictive value of 86.79%, and a negative predictive value of 35.14%.

**Conclusion:** Due to the nature of retrospective study, RMI is reliable for identification of malignant and benign ovarian mass improve the management of ovarian mass including referral system and the decision regarding the approach used during surgery.

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**Keywords:** risk of malignancy index, RMI, ovarian cancer, ovarian malignancies, ovarian carcinomas

### Abstrak

**Tujuan:** Menganalisis indeks risiko keganasan untuk menentukan keganasan ovarium di RS Dr. Sardjito, Yogyakarta.

**Metode:** Analisis retrospektif.

**Hasil:** Sembilan puluh pasien dengan massa adneksa dan data rekam medik yang lengkap dikumpulkan sejak Januari 2007 sampai Maret 2009 terdiri atas 70 pasien (77,78%) dengan keganasan ovarium dan 20 pasien dengan massa jinak (22,22%). Lebih dari setengah seluruh subyek penelitian menunjukkan histopatologi serous carcinoma (51,43%) dan berada pada stadium lanjut (51,43%). Analisis univariat menunjukkan bahwa perbedaan yang signifikan pada pasien dengan kanker ovarium dan massa jinak ovarium diperlihatkan oleh penilaian pemeriksaan ultrasonografi dan pemeriksaan Ca-125 serum, tetapi tidak pada umur dan status menopause. Pada penelitian ini, RMI menunjukkan sensitivitas 70%, spesifisitas 75%, prediksi positif 90,74%, dan prediksi negatif 41,67%. Pemeriksaan tumor marker Ca-125 pada serum menunjukkan sensitivitas 81,43%, spesifisitas 60%, prediksi positif 87,69%, dan prediksi negatif 48%. Penilaian hasil pemeriksaan ultrasonografi menunjukkan sensitivitas 65,71%, spesifisitas 65%, prediksi positif 86,79%, dan prediksi negatif 35,14%.

**Kesimpulan:** Pada penelitian yang bersifat retrospektif ini, RMI dapat membedakan massa ovarium ganas dan jinak dengan baik. Hal ini dibutuhkan untuk meningkatkan penanganan massa adneksa termasuk keputusan merujuk dan keputusan menggunakan pendekatan onkologi saat dilakukan operasi.

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**Kata kunci:** indeks risiko keganasan, RMI, kanker ovarium, karsinoma ovarium, malignansi ovarium

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## INTRODUCTION

Ovarian cancer still has a high mortality rate in developed and developing countries. There are no exact data on ovarian cancer incidence and mortality in Indonesia. A study in 2002 revealed that ovarian cancer was the third most frequent female cancer in Indonesia (829 new cases and 7.77% of all female cancers).<sup>1</sup> Another study in 2001 reported that based on pathological reports in 12 cancer registries in Indonesia, the number of ovarian cancer new cases was 1200 in 1994.<sup>2</sup> Surveillance Epidemiology and End Result

(SEER) United States reported that the incidence of ovarian cancer on 1975 - 2005 was 7.3 per 100,000 and the death rate was 5.0 per 100,000. A total of 21,650 new ovarian cancer cases and 15,520 deaths were reported in the United States in 2008.<sup>3</sup> In the Netherlands, approximately 1,100 patients were newly diagnosed with ovarian cancer in 2005 and 946 women died as a result of this disease in the same year.<sup>4</sup> Having the high number of mortality and morbidity, it is well established that ovarian cancer cases which were treated by gynecologic oncologists had

marginally better outcome. A large number of patients (3,067 patients) were enrolled in a study to compare the surgery outcomes on ovarian cancer patients managed by gynecologic oncologists to general gynecologist or general surgeon.<sup>5</sup> Beside less morbidities, surgeries done by gynecologic oncologists also have better survivals.<sup>5,6</sup> Repeated surgery was reported to be associated not only with younger patients, germinal tumors, well-differentiated tumors and early stages but also with the surgeon's discipline.<sup>7</sup>

Approach to pelvic mass should be done through pelvic examination including radiologic examination and tumor marker in order to differentiate the mass from benign to malignant tumors. That is necessary to adequately assess the adnexal mass because the presumed diagnosis determines the management. Moreover, pelvic mass is the most frequent indicator to refer the patient to a cancer center or a tertiary center with gynecologic oncologist attendance. For such reasons improved both specificity and sensitivity diagnostic methods are needed.

The risk of malignancy index (RMI) is a simple scoring system that can be used to assess the adnexal mass. The RMI scoring system is based on menopausal status, ultrasound and serum concentration of Ca-125. The scoring provides a better method to assess the adnexal mass especially in the less specialized centers compared to single parameter.<sup>8-12</sup> Jacobs *et al* has developed risk of malignancy index RMI 1 followed by RMI 2 and RMI 3 by Tingulstad *et al* and RMI 4 by Yamamoto *et al*. Except RMI 4 which uses the tumor size score, all RMIs use the parameter of the ultrasound findings (U), the menopausal score (M), and the serum of Ca-125 level (Ca-125).

1. RMI 1 = U x M x Ca-125; a total ultrasound score of 0 gave U = 0, a score of 1 gave U = 1, and a score of  $\geq 2$  gave U = 3. Premenopausal status gave M = 1 and postmenopausal status gave M = 3. The serum level of Ca-125 was applied directly to the calculation.<sup>8</sup>
2. RMI 2 = U x M x Ca-125; a total ultrasound score of 0 or 1 gave U = 1, and a score of  $\geq 2$  yielded U = 4. Premenopausal status gave M = 1 and postmenopausal status gave M = 4. The serum level of Ca-125 was applied directly to the calculation.<sup>10</sup>
3. RMI 3 = U x M x Ca-125; a total ultrasound score of 0 or 1 gave U = 1, and a score of  $\geq 2$  gave U = 3. Premenopausal status gave M = 1 and postmenopausal status gave M = 3. The serum Ca-125 level was applied directly to the calculation.<sup>11</sup>
4. RMI 4 = U x M x S x Ca-125, where a total ultrasound score of 0 or 1 gave U = 1, and a score of  $\geq 2$  gave U = 4. Premenopausal status gave M = 1 and postmenopausal status gave M = 4. A tumor size (single greatest diameter) of  $< 7$  cm yielded S = 1, and  $\geq 7$  cm gave S = 2. The serum level of Ca-125 was applied directly to the calculation.<sup>12</sup>

Although the results still differ in many studies, RMI 3 is generally considered to have the best sensitivity and specificity.<sup>12,13</sup> Validation of RMI 3 usage

has been done in several studies.<sup>14-16</sup> In this study, we will further use only RMI 3 to be compared with the singular parameters; the serum Ca-125 level, menopausal status, and ultrasound score.

## METHOD

This study is a retrospective analysis taken from medical record. The clinical data of 90 women with pelvic mass were taken from January 1, 2009 to March 1, 2010 at the Obstetrics and Gynecology Department of Dr. Sardjito Hospital, Yogyakarta. The incomplete data was excluded. The clinical data include age, the detail result of ultrasound, preoperative serum Ca-125 level, and the final pathology result of the mass.

The ultrasound was performed abdominally or vaginally and the ultrasound score was assigned for the following features multiloculations, the presence of solid elements, bilaterality, the presence of ascites, or the evidence of metastases. An ultrasound score (U) of 1 was given if none or one of the features was found, and a score of 3 was given if two or more of these features were shown. A menopausal score (M) of 1 or 3 was given to pre- and postmenopausal women. The level of Ca-125 in serum was calculated directly to the formula below:

$$\text{RMI} = \text{U} \times \text{M} \times \text{Ca-125}$$

The histopathological result determined the final diagnosis of benign or malignant mass. When a gynecological cancer was found, it was staged according to the International Federation of Gynecology and Obstetrics classification.<sup>17</sup> All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc.), Version 15. Mann Whitney U test was performed for the continuous data and Pearson chi-square test was used for the dichotomous data. The sensitivity was defined as the percentage of patients with malignant ovarian mass having a positive test result. The specificity was defined as the percentage with benign ovarian mass showing negative results. The positive predictive value was defined as the percentage of patients with a positive test result having malignant ovarian mass and the negative predictive value was defined as the percentage of patients with a negative test result having benign ovarian mass. A receiver operating characteristic (ROC) curve was created to show the relation between sensitivity and specificity of the RMI, serum Ca-125 level, and ultrasound score in the discrimination between benign and malignant ovarian mass.

## RESULTS

A total of 90 patients were enrolled in the study, 70 of them (77.78%) were diagnosed with malignant ovarian mass whereas 20 of them (22.22%) were benign. The distribution of age, menopausal status, ultrasound score, and serum Ca-125 level were shown in Table 1 for the two groups (the groups with benign and malignant ovarian mass). Univariate analysis was

**Table 1.** Distribution of age, menopausal status, ultrasound score and serum Ca-125 levels in patients with benign ovarian mass (n=20) and malignant ovarian mass (n=70).

	Malignant ovarian mass (n = 70)	Benign ovarian mass (n = 20)	Significance level (p)
Age (years)			
Median (range)	47.50 (15 - 76)	44.00 (19 - 72)	0.191 <sup>a</sup>
Menopausal status			
Menopause n (%)	38 (73.1)	14 (26.9)	0.210 <sup>b</sup>
Not-menopause n (%)	32 (84.2)	6 (15.8)	
Ultrasound score			
Score 3 n (%)	46 (64.9)	7 (35.1)	0.014 <sup>b</sup>
Score 1 n (%)	24 (86.8)	13 (13.2)	
Serum Ca-125 level (U/ml)			
Mean	545.57	116.3	0.001 <sup>a</sup>
Median (range)	195.73	31.31	
Minimum	6.87	3.59	
Maximum	15258	600	

<sup>a</sup>Mann-Whitney U test  
<sup>b</sup>Pearson X<sup>2</sup> test

done on the two groups. The differences on ultrasound score and serum Ca-125 level were significant between the two groups, but not with the age or the menopausal status as described in Table 1. Ultrasound score of 3 were mostly found in malignant patients as well as higher level of serum Ca-125.

Among patients with malignant ovarian mass, 34 patients (48.57%) were considered to be at early stages and 36 patients (51.43%) were at advanced stages. The majority of histopathological result for malignant mass shown serous adenocarcinoma (51.43%) followed by mucinous adenocarcinoma (32.29%). The different histology results are listed in Table 2.

The performance of menopausal status, serum Ca-125 level, ultrasound score and RMI in predicting malignancy in this study are presented in Table 3. The cut-off point of RMI ( $\geq 200$ ) was determined from previous studies.<sup>12-14</sup> In our study, the RMI had a sensitivity of 70%, a specificity of 75%, a positive predictive value of 90.74%, and negative predictive value of 41.67%. The serum Ca-125 level had a sensitivity of 81.43%, a specificity of 60%, a positive predictive value of 87.69%, and a negative predictive value of 48%. The ultrasound score had a sensitivity of 65.71%, a specificity of 65%, a positive predictive value of 86.79%, and a negative predictive value of 35.14%. The performances of RMI, serum Ca-125 level, age and ultrasound score are presented individually in receiver operator characteristic curves (Figure 1).

## DISCUSSION

The probability of malignancy should always be taken into consideration in approach to adnexal mass. Modalities to differentiate malignancy in ovarian mass include ultrasound examination and serum Ca-125 level examination. Since the first time introduced by Jacobs *et al*<sup>8</sup>, RMI has continuously shown to have the ability in improving malignancy identification of ovarian mass.<sup>10,11,18</sup> Although this study shows lower sensitivity and specificity compared to previous stu-

dies<sup>12-14,19</sup>, it still confirmed that the combination of RMI's sensitivity, specificity, positive predictive value and negative predictive value were better than the same combination parameters for serum Ca-125 level and ultrasound score to discriminate malignant and benign adnexal mass in Dr. Sardjito Hospital. This might due to lesser subjects with benign ovarian mass compared to the previous studies.

**Table 2.** Distribution of Diagnosis and Stages in 90 Patients with Ovarian Masses.

Diagnosis	n (%)
Ovarian cancer	
Stage I	22 (31.43)
Stage II	12 (17.14)
Stage III	32 (45.71)
Stage IV	4 ( 5.72)
Histopathology results of malignant ovarian mass	
Serous cystadenocarcinoma	32 (51.43)
Mucinous cystadenocarcinoma	24 (34.29)
Endometrioid carcinoma	5 ( 7.14)
Clear cell carcinoma	3 ( 4.29)
Undifferentiated carcinoma	2 ( 2.86)
Total malignant ovarian mass	70 (77.78)
Total benign ovarian mass	20 (22.22)

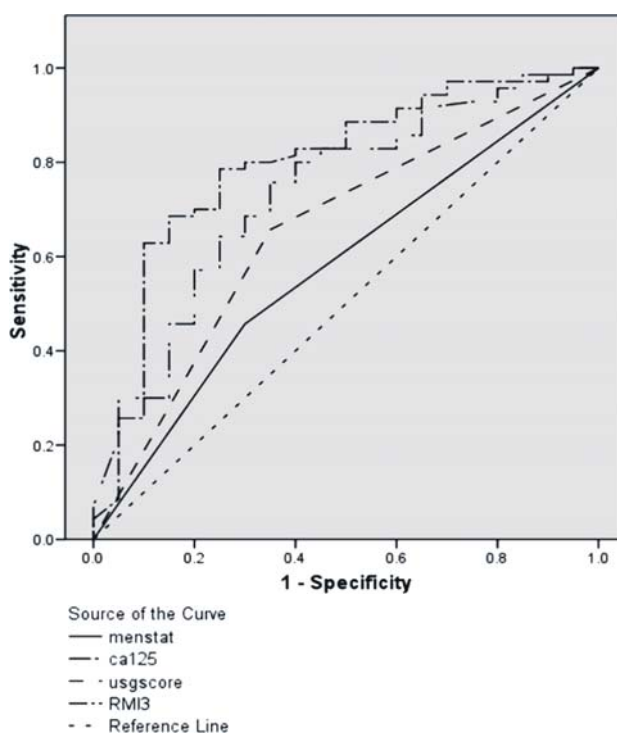
A high sensitivity was detected in serum Ca-125 level, yet it was not accompanied by better specificity just like previous studies.<sup>12-14</sup> Ca-125 level could increase not only in ovarian malignancy but also in endometriosis, pelvic inflammatory diseases, other benign ovarian cysts, and other malignancies such as colon cancer.

In Indonesian setting of health care, laboratories are often not equipped with an adequate tumor marker panel. The ultrasonographer and the ultrasound machine are also not available in smaller or rural hospi-

tals. Therefore, RMI can only be performed at tertiary hospitals. RMI can help determining whether the patient should be operated by a gynecologic oncologist or a general gynecologist.

### CONCLUSION

Risk of malignancy index is a scoring system using menopausal status, ultrasound, and serum Ca-125 level to discriminate malignant adnexal mass from benign ones. In this study, RMI is reliable to identify malignant and benign ovarian mass in Dr. Sardjito Hospital. This scoring system can be used to improve the management of ovarian mass including the urgency to refer and the decision regarding the approach used during surgery. Since it is well established that the management of this malignancy was conducted better in the cancer center with oncologists.



**Figure 1.** Receiver operator characteristic curve showing the performance of menopausal status, ultrasound score, serum Ca-125 level, and Risk of Malignancy Index (RMI 3).

**Table 3.** Sensitivity, Specificity, and Positive (PPV) and Negative (NPV) Predictive Values of Risk of Malignancy Index, Menopausal Status, Serum Ca-125 Levels, and Ultrasound Score of Malignant Ovarian Masses.

	Result of histopathology		Sensitivity	Specificity	PPV	NPV
	malignant (n)	benign (n)				
RMI $\geq$ 200	38	14	70.00	75.00	90.74	41.67
RMI $<$ 200	32	6				
Menopause	38	14	54.29	30.00	73.08	15.79
Non-menopause	32	6				
Ca-125 $\geq$ 35	56	8	81.43	60.00	87.69	48.00
Ca-125 $<$ 35	14	12				
USG score 3	46	7	65.71	65.00	86.79	35.14
USG score 1	24	13				

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