Research Article

Risk of Malignancy Index is not accurate as a Triage Tool for Ovarian Cancer

Risiko Indeks Keganasan tidak akurat sebagai Alat Triage untuk Kanker Ovarium

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Abstract

Objective: To evaluate Risk of Malignancy Index (RMI) as a triage tool for ovarian cancer in Dr. Cipto Mangunkusumo Hospital.

Method: This is a retrospective study conducted from January 2008-December 2012 in patients diagnosed with ovarian mass. Patients admitted for surgery due to ovarian masses were included to this study. RMI 3 score was calculated based on ultrasonography examination in Dr. Cipto Mangunkusumo Hospital, CA-125 test and menopausal status. Patients without final pathological report and incomplete data were excluded from study. Data were analysed using SPSS 20 to evaluate RMI result and final pathlogical report in benign and malignant case.

Result: From 882 patients identified with ovarian masses from cancer registry, only 99 patients aged 17-70 y.o were included in this study. Most of the patients were nully-parity (28.3%), non-menopausal women (60.6%), normal body mass index (40.4%), and with stage IIIC ovarian cancer (33.3%). Ultrasonography examination showed that most of patients had solid mass and ascites (19.2%). Meanwhile, CA-125 showed that patients with <35 U/ml were 10.1% and ≥ 35 U/ml were 89.9%. Patients with RMI scores <200 (benign cases) were 19 cases (19.2%) and ≥ 200 (malignant cases) were 80 cases (80.8%). Meanwhile, patients with benign final pathological report were 23 cases (23.2%) and malignant cases were 76 cases (76.8%). There was no statistical difference in RMI between benign and malignant cases based on final pathological report.

Conclusion: Our study showed that RMI was not accurate as triage tool for ovarian cancer in our hospital. Further investigation and more patients are needed to confirm this study.

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Keywords: CA-125, menopausal status, ovarian cancer, risk of malignancy index (RMI), ultrasonography.

Abstrak

***Tujuan**: Untuk mengevaluasi Risk of Malignancy Index (RMI) sebagai alat triase kanker ovarium di Rumah Sakit Dr. Cipto Mangunkusumo.*

***Metode**: Penelitian retrospektif ini dilaksanakan dari Januari 2008 sampai Desember 2012 pada pasien yang didiagnosa dengan massa pada ovarium. Nilai RMI 3 dihitung berdasarkan pemeriksaan ultrasonografi di Rumah Sakit Dr. Cipto Mangunkusumo, nilai CA-125 dan status menopause. Data dianalisis dengan menggunakan SPSS 20 untuk mengevaluasi hasil RMI dan penilaian patologi akhir pada kasus jinak dan ganas.*

***Hasil**: Dari 882 pasien yang teridentifikasi dengan massa ovarium dari registrasi kanker, hanya terdapat 99 pasien yang berusia 17-70 tahun yang memenuhi kriteria inklusi. Sebagian besar pasien adalah pasien bukan nuliparitas (28,3%), belum menopause (60,6%), Indeks Massa Tubuh normal (40,4%), dan dengan stadium IIIC (33,3%). Pemeriksaan ultrasonografi menunjukkan sebagian besar pasien mempunyai massa padat dan asites (19,2%). Sementara itu, terdapat 10,1% pasien dengan kadar CA-125 <35 U/ml dan 89,9% dengan CA-125 ≥ 35 U/ml. Terdapat 19 kasus (19,2%) dengan RMI <200 (jinak) dan 80 kasus (80,8%) dengan RMI ≥ 200 (ganas). Pemeriksaan patologi akhir menunjukkan 23 kasus jinak (23,2%) dan 76 kasus ganas (76,8%). Tidak terdapat perbedaan yang bermakna secara statistik pada nilai RMI untuk kasus jinak ataupun ganas berdasarkan pemeriksaan patologi akhir.*

***Kesimpulan**: Penelitian kami menunjukkan bahwa RMI tidak akurat sebagai alat triase untuk kanker ovarium di rumah sakit kami. Investigasi lebih lanjut dan lebih banyak pasien diperlukan untuk mengkonfirmasi penelitian ini.*

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***Kata kunci**: CA-125, Risk of Malignancy Index (RMI), status menopause, kanker ovarium, ultrasonografi.*

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INTRODUCTION

Ovarian cancer is the second most common gynecological cancer in western women and also in Indonesia.[1,2] It varies widely in frequency among different geographic regions and ethnic groups. The majority of cases are sporadic, and only 5% to 10% of ovarian cancers are familial.[3] Ovarian cancer, rare before age 40, increases steeply there after and peaks at ages 65-75. Incidence and mortality rates are higher among white women than among

African-American women. Over the last three decades, ovarian cancer incidence has remained stable in high-risk countries, while an increasing trend has been reported in low-risk countries.[1,4]

Factors associated with an increased risk for invasive epithelial ovarian cancer include age, race, nulliparity, family history of ovarian cancer, and history of endometrial or breast cancer.[4] There is a weak association between ovarian cancer and age at natural menopause and among women with early onset disease. Factors associated with a reduced risk are history of one or more full-term pregnancies, use of oral contraceptives, history of breast feeding, tubal ligation, and hysterectomy.[5] Risk decreased with the number of pregnancies and sterilization. Use of oral contraceptives significantly reduced risk of ovarian cancer and reduced slightly with duration of use.[6-8]

Characterization of adnexal masses to identify patients with malignant ovarian mass preoperatively for referral to a cancer center for treatment has been extensively studied.[9,10] The accuracy of ultrasonography in differentiating between benign and malignant adnexal masses is proportional to the expertise of the operator.[11,12] Findings suggestive of malignancy in an adnexal mass include a solid component, thick septations (greater than 2 to 3 mm), bilaterality, Doppler flow to the solid component of the mass, and presence of ascites.[13]

CA-125 (MUC16) has provided a useful serum tumor marker for monitoring response to chemotherapy, detecting disease recurrence, distinguishing malignant from benign pelvic masses, and potentially improving clinical trial design.[14-16] The normal value for a CA-125 depend on the lab running the test. In general, a level above 35 U/ml are considered abnormal.[17]

The aims of this study were to evaluate the risk of malignancy index (RMI) incorporating menopausal status, serum CA-125 levels, and ultrasound features for discriminating benign from malignant pelvic masses and to evaluate the performance of the three different risk of malignancy indices Dr. Cipto Mangunkusumo Hospital.

METHODS

This is a retrospective study conducted from January 2008-December 2012 in patients diagnosed with ovarian mass. Patients admitted for surgery due to ovarian masses were included to this study. RMI 3 score was calculated based on ultrasonography (U) examination in Dr. Cipto Mangunkusumo hospital, CA-125 (measured in U/ml) test and menopausal status (M). Patients without final pa-thological report and incomplete data were excluded from study. Data were analyzed using SPSS 20 to evaluate RMI result and final pathological report in benign and malignant case.

$$RMI_3 = UxMxCA\text{-}125$$

Ultrasonography is scored based on five attributes suggestive of malignancy. These attributes are the presence of solid parts, multilocular cyst, ascites, bilateral lesions, and intra-abdominal metastases. One point is given for one or no presence of the attributes, and three points for more than one attributes. Menopausal woman is given three points, and non-menopausal woman is given one point. CA-125 is scored equal to the blood level of CA-125 (U/ml). RMI score ≥ 200 is considered to be high is of malignancy, and RMI score <200 is considered to be low risk of malignancy. RMI score was evaluated based on final pathologic report as benign or malignant case. When ovarian mass was malignant, it was staged based on Federation of Gynecology and Obstetrics (FIGO) classification.

RESULT

From 882 patients identified with ovarian masses from cancer registry, only 99 patients aged 17-70 y.o were included in this study. Most of the patients were nullyparity (28.3%), non-menopausal women (60.6%), normal body mass index (40.4%), and with stage IIIC ovarian cancer (33.3%). There were no significant difference between benign and malignant case based on age (p = 0.82), parity (p = 0.09), menopausal status (p = 0.6), and CA-125 mean (p = 0.162). Body Mass Index (BMI) showed significant difference between benign and malignant case (p = 0.011). See Table 1 and 2.

RMI and CA-125 showed good sensitivity (84.2 and 90.8), but Area Under Curve showed low performance (0.57 and 0.51). Our study showed that RMI, ultrasonography score, CA-125, and menopausal status has poor performance as triage tool.

Table 1. Patient's Characteristics.

Variable	Benign (n= 23)	Malignant (n=76)	p
Age			0.82[a]
Median	44	47	
Minimum	18	17	
Maximum	70	68	
Parity			0.09[a]
Mean	3	2	
Minimum	0	0	
Maximum	9	10	
Menopause			0.6[b]
Yes	8 (8.1%)	31 (31.3%)	
No	15 (15.2%)	45 (45.4%)	
BMI			0.011[b]
Underweight	4 (4%)	20 (20.2%)	
Normal	16 (16.2%)	24 (24.2%)	
Overweight	1 (1%)	10 (10.2%)	
Obese I	2 (2%)	19 (19.2%)	
Obese II	0 (0%)	3 (3%)	
CA-125			0.162[a]
Mean	1662.4	775.9	
Minimum	16.6	13.3	
Maximum	23566.0	9537.0	

[a]*Mann-Whitney U test*
[b]*Pearson X2 test*

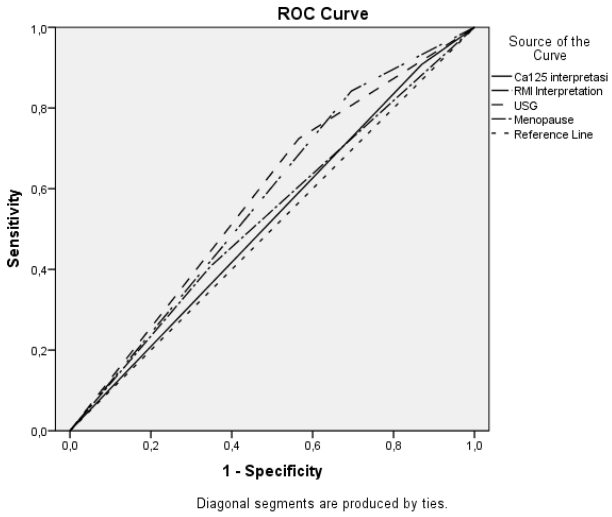

Figure 1. Receiver Operator Characteristic (ROC) Curve Shows the Relationship between Sensitivity and Specificity for RMI, CA 125, Menopausal Status, USG Score.

Table 2. FIGO Stage

FIGO	n = 76
IA	9 (11.8%)
IB	2 (2.7%)
IC	15 (19.8%)
IIA	1 (1.4%)
IIB	5 (6.5%)
IIC	6 (7.9%)
IIIC	33 (43.4%)
IV	5 (6.5%)

Table 3. Area Under Curve, Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value for RMI, CA-125, Menopausal Status, USG Score.

Variable	Histopathological result (n = 99)		AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value
	Malignant	Benign					
RMI ≥ 200	64	16	0.57	84.2	30.4	80.0	36.8
RMI <200	12	7					
CA-125 ≥35 U/ml	69	20	0.51	90.8	13.0	77.5	30.0
CA-125 <35 U/ml	7	3					
Menopause	31	8	0.53	40.8	65.2	79.4	25.0
Non-menopause	45	15					
USG score 3	55	13	0.59	72.4	43.5	80.8	32.2
USG score 1	21	10					

DISCUSSION

Many studies showed that Risk of malignancy index (RMI) is a valuable tool to differ benign from malignant ovarian mass. It has been used widely to help clinician in daily practice encountering adnexal masses.[9,18] RMI is non-invasive and simple to apply in daily clinical practice.[19] RMI has been through 4 times modification since it was first introduced in 1990 by Jacob et al.[20] The last modification (RMI 4) was introduced in 2009 by Yamamoto et al, which is added tumor size in calculation.[21]

In our study, RMI had good sensitivity (84.2) but poor specificity (30.4). RMI showed good performance as screening tool but poor performance as triage tool to differ benign from malignant ovarian mass. Moreover, Area Under Curve of RMI showed low significance level (0.57). Other study conducted by Ong C et al in Singapore showed similar result with our study. Ong C et al concluded that RMI 1, RMI 2, RMI 3, RMI 4 showed no statistical difference to differ benign from malignant cases in Southeast Asian population.[19]

The components of RMI also showed no statistical difference between benign and malignant case. CA-125 showed the higher sensitivity (90.8) with the lowest specificity (13.0). This finding is consistent with other studies. Metaanalysis study showed that CA-125 has good sensitivity for detection malignant ovarian mass, but poor specificity.[22,23] CA-125 level was influenced by several factors, including age, smoking status, ethnicity, and history of breast cancer. Meanwhile, history of previous gynecological operation and obesity lower the CA-125 level.[23]

Evaluation of ovarian mass based on ultrasonography depends on examiner's experience. Experienced ultrasonography examiner can determine benign or malignant adnexal mass accurately.[24] Van Calster et al showed that 93% of tumor were correctly categorized as benign of malignant by pattern recognition.[25] Moreover, pattern recognition was superior than CA-125 to differ benign from malignant ovarian case.[25]

There are several limitation in this study, such as small number of cases. Eventhough, many cases were identified, only few of them could be analyzed. The problems were medical record storage system. Many medical records were not found to be reviewed, and few of them with incomplete data. Others limiting factors in our study included its retrospecitve nature and limited time to do the research.

CONCLUSION

Our study showed that RMI was not accurate as triage tool for ovarian cancer in our hospital. Further investigation and more patients are needed to confirm this study.

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