RESEARCH ARTICLE

Modified Risk of Ovarian Malignancy Algorithm and Risk of Malignancy Index in Predicting Epithelial Ovarian Cancer in Indonesian Population: A Single-centered Validation Study

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Abstract

Background: Risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) are two scoring systems that are commonly used to predict ovarian tumor malignancy. Literature shows different cutoff points for a different population.

Objective: This study aims to validate and compare the performance of ROMA and RMI and also validate the cutoff points for Indonesian population.

Methods: This is a retrospective study conducted at Dr Cipto Mangunkusumo Hospital (CMH). Medical records of patients with epithelial ovarian cancer who underwent surgery in our institution during 2010–2014 were collected. The diagnostic values of ROMA and RMI were calculated.

Results: From the analysis of 213 subjects included in this study, ROMA was statistically better than RMI [AUC (area under the curve) in all groups: 87.00% > 81.30%, $p \leq 0.001$; postmenopausal group: AUC 91.47% > 88.97%, $p \leq 0.001$]. RMI had values of sensitivity: 85.3%, specificity: 66.3%, positive predictive value (PPV): 79.7%, negative predictive value (NPV): 74.3%, positive likelihood ratio (LR): 2.53, negative LR: 0.22, and accuracy: 0.77. ROMA had values of sensitivity: 95.4%, specificity: 32.5%, PPV: 68.9%, NPV: 81.8%, positive LR: 1.41, negative LR: 0.14, and accuracy: 0.71. At the ideal cutoff point (RMI 330, premenopausal ROMA 30.4, and postmenopausal ROMA 53.1), ROMA showed better sensitivity and specificity than RMI (sensitivity of 82.31 vs 74.62%; specificity of 78.31 vs 75.9%).

Conclusion: ROMA is better than RMI in predicting epithelial ovarian cancer in Indonesian population. Using the modified cutoff, the specificities of both ROMA and RMI were better than the standard cutoff points.

Keywords: Epithelial ovarian cancer, Risk of malignancy index, Risk of ovarian malignancy algorithm.

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Introduction

Ovarian cancer is the second most common gynecological malignancy, especially in lower to middle-income countries.[1] Ninety percent of ovarian cancer cases are epithelial type.[2] Annually, an estimated 192,000 new cases of ovarian cancer are diagnosed worldwide.[3] In Indonesia, ovarian cancer is the third most common malignancy in women and 10,238 cases were diagnosed in 2014.[4] The higher the stage of ovarian cancer, the lower the survival rate.[5]

Various methods have been developed to predict malignancy in ovarian tumors. Jacob et al. developed the RMI, an algorithm based on ultrasound examination, cancer antigen 125 (CA-125) level, and menopausal status. Based on RMI, ovarian tumor is differentiated into high risk and low risk for epithelial-type ovarian malignancy.[5,6] RMI is limited in that it can only improve the diagnosis in invasive malignancy and only in menopausal women, because the diagnostic accuracy of CA-125 is low in premenopausal women.[7]

Human epididymis protein 4 (HE4) is a whey acidic protein, and a tumor marker found in high concentrations in serous-type ovarian carcinoma.[2] A study by Holcomb et al. shows that HE4 has better sensitivity than CA-125 (88.9 vs 83.3%) and that combining the two markers increases the sensitivity.[7,8]

Moore et al. demonstrated that utilization of HE4, CA-125, and menopausal status in the ROMA demonstrates higher sensitivity in predicting ovarian cancer in women presenting with a pelvic mass, when compared to RMI.[9,10] At 75% specificity, the sensitivity of ROMA was 94.3%, whereas the sensitivity of RMI was 84.6%. In the early stages, the sensitivity of ROMA is better than RMI (85.3 vs 64.7%).[11]

In our institution, RMI has been used as a scoring system to predict ovarian tumor malignancy. However, controversies still exist

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in the superiority of the ROMA scoring system in predicting ovarian cancer. From several studies in different ethnicities, modification of ROMA and RMI cutoff points resulted in better sensitivity and specificity.[12–14] In a previous study by Winarto et al., in Indonesian population, a different cutoff for RMI and ROMA might be able to predict ovarian tumors better than the standard cutoff.[14] Therefore, this study aims to compare ROMA with RMI to ascertain which method is better in predicting malignancy in ovarian tumors in Indonesia, especially in our institution, Dr Cipto Mangunkusumo Hospital (CMH).

Methods

This is a retrospective study aimed to compare the diagnostic values of the original ROMA and RMI with the same scoring systems with a modified cutoff in diagnosing epithelial ovarian cancer in Indonesian population. We collected medical records of the patients with ovarian malignancy in CMH during 2010–2014, because HE4 is no longer available in our institution since 2015. Of all the ovarian cancer patients in that time period, 213 patients fulfilled the inclusion and exclusion criteria. The inclusion criteria for this study were women aged >30 years with an operable ovarian mass, who underwent surgery, had recorded preoperative CA-125 and HE4 data, and had histopathology of the mass. Patients who had chemotherapy or radiation, nonovarian malignancy, ovarian mass originating from metastasis of other organs, or nonepithelial ovarian tumor were excluded from the study. We scored the patients using ROMA and RMI and compared them to the histopathology results.

The RMI scoring is based on a multiplication formula of ultrasound score, menopausal status, and CA-125 level. The ultrasonographic component was given a score of 0, 1, 2, or 3. The parameters for scoring were the presence of multilocular cysts, presence of solid components, evidence of metastasis, ascites, and presence of bilateral lesions. If none of the parameters was fulfilled, the U score was 0. If only one parameter was fulfilled, the U score was 1. Subsequently (fulfilling 2–5 criteria), the U score was 3. An M score was given based on menopausal status. Premenopausal women were given score 1, whereas postmenopausal women were given score 3.

The ROMA scoring is based on the natural log (LN) coefficient for HE4 and CA-125 as follows:

Premenopausal: Predictive index (PI) = –12.0 + 2.38 × LN (H. E4) + 0.0626 × LN (CA-125)

Postmenopausal: Predictive index (PI) = –8.09 + 1.04 × LN (H. E4) + 0.732 × LN (CA-125)

Predictive probability (PP) = exp(PI)/(1 + exp(PI)).[9,11]

Results

In this study, two groups were defined based on the histopathology, namely the benign ovarian tumor group and the borderline and malignant epithelial tumor group. In Table 1, it can be seen that there were 83 benign ovarian tumor cases and 130 borderline and malignant tumor cases. The medians for CA-125 and HE4 were higher in the borderline and malignant epithelial tumor group and were 198.6 (8–9872.3) U/mL, and 296.05 (26.1–13719.2) pM.

As shown in Table 2 and (Figs 1A to C), RMI shows a sensitivity of 85.3%, specificity of 66.3%, PPV 79.7%, NPV 74.3%, positive likelihood ratio (LR) 2.53, negative LR 0.22, and accuracy of 0.77.

Table 1: Comparison of age, menopausal status, CA-125, and HE4 in the study groups

Variables	*Benign ovarian tumor (n = 83)*	*Borderline and malignant epithelial-type ovarian tumor (n = 130)*
Age (years)	46.82 ± 12.1	46.64 ± 9.92
Menopausal status		
Premenopausal	51 (61.4%)	80 (61.5%)
Postmenopausal	32 (38.6%)	50 (38.5%)
CA-125 (U/mL)	55.5 (8.1–2416.3)	198.6 (8–9872.3)
HE4 (pM)	70.2 (29.5–485.6)	296.05 (26.1–13719.2)
Ultrasound score		
1	34 (41%)	42 (32.3%)
3	49 (59%)	88 (67.7%)
Total ultrasound score	83	130

CA-125, cancer antigen 125; HE4, human epididymis protein 4

Table 2: Diagnostic values for CA-125, HE4, RMI, and ROMA based on standard cutoff vs modified cutoff points* to predict epithelial-type ovarian carcinoma

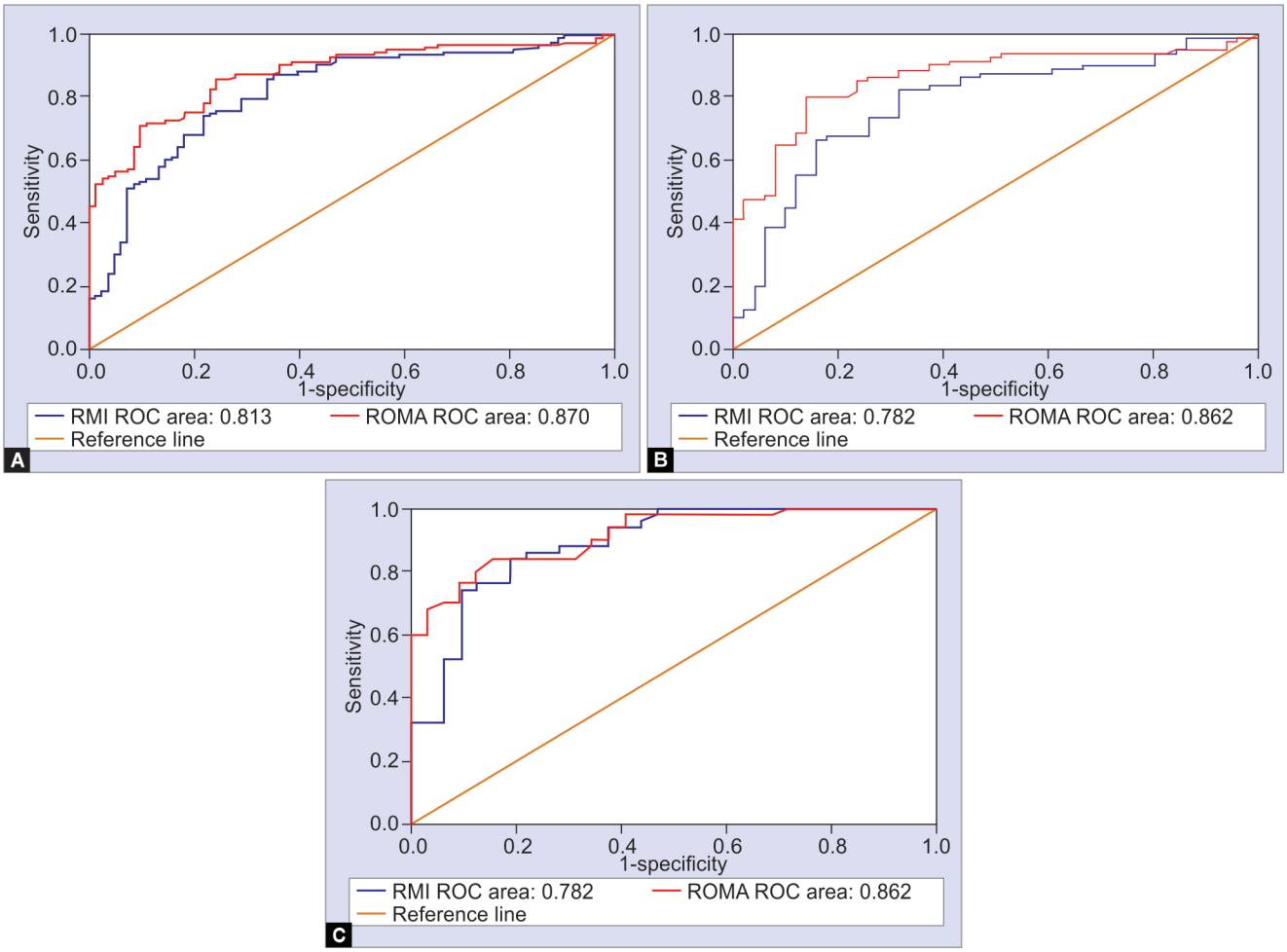
	RMI		*ROMA*	
Diagnostic values	*Standard*	*Modified*	*Standard*	*Modified*
Sensitivity	85.30%	74.62%	95.40%	82.31%
Specificity	66.30%	75.90%	32.50%	78.31%
Positive predictive value	79.70%	82.91%	68.90%	85.60%
Negative predictive value	74.30%	65.63%	81.80%	73.86%
Positive likelihood ratio	2.53	3.09	1.41	3.79
Negative likelihood ratio	0.22	0.33	0.14	0.23
Accuracy	0.77	0.75	0.71	0.81

CA-125, cancer antigen 125; HE4, human epididymis protein 4; RMI, risk of malignancy index; ROMA, risk of ovarian malignancy algorithm. Standard cutoff value, CA-125 = 35 U/mL; HE4 = 70 pM; RMI = 200; premenopausal ROMA = 7.4, and postmenopausal ROMA = 25.3. Ideal cutoff point: CA-125 = 108.3 U/mL; HE4 = 104.5 pM; RMI = 330; premenopausal ROMA = 30.4, and postmenopausal ROMA = 53.1;[14] *Means the ideal cut off point

ROMA shows a sensitivity of 95.4%, specificity of 32.5%, PPV 68.9%, NPV of 81.8%, positive LR 1.41, negative LR 0.14, and accuracy of 0.71. The ideal cutoff point (RMI 330, premenopausal ROMA 30.4, and postmenopausal ROMA 53.1) ROMA showed better sensitivity and specificity compared with RMI (sensitivity 82.31 vs 74.62%; specificity 78.31 vs 75.9%).

Discussion

In Indonesia, ovarian cancer is the second most common gynecological malignancy after cervical cancer. Various methods have been developed to detect ovarian malignancy, but no prediction method has been found to have a good diagnostic value. Currently, there are two risk calculators that are currently used widely in Indonesia, namely ROMA and RMI. As they were found to be widely accessible and affordable, many researches have been conducted in Indonesia to assess the efficacy and efficiency of



Figs 1A to C: (A) AUC comparison of RMI and ROMA in predicting epithelial-type ovarian carcinoma in all groups (AUC ROMA is better than RMI 86.96 vs 81.33%; 95% CI 82.21–91.70 vs 75.40–87.27; AUC difference 0.057; $p \leq 0.001$); (B) AUC comparison of ROMA and RMI in predicting epithelial-type ovarian carcinoma in the premenopausal group (AUC ROMA > RMI: 86.20 vs 78.16%; 95% CI 79.75–92.65 vs 69.98–86.34; AUC difference 0.0804, $p \leq 0.001$); (C) AUC comparison of ROMA and RMI in predicting epithelial-type ovarian carcinoma in the postmenopausal group (AUC ROMA >RMI: 91.50 vs 88.97%; 95% CI 85.75–97.25 vs 81.61–96.33 AUC difference 0.0250, $p \leq 0.001$). AUC, area under the curve; RMI, risk of malignancy index; ROMA, risk of ovarian malignancy algorithm; CI, confidence interval

these risk calculators.[14,15] There is a need to revaluate the methods as diagnostic tools based on the ideal cutoff point.[16]

Subject characteristics in CMH were analyzed. As expected, most patients in this tertiary referral hospital presented with borderline and malignant epithelial ovarian tumor. The levels of CA-125 and HE4, which were the parameters assessed, were found to be four times higher than in a benign tumor. This finding might indicate that the population in CMH is appropriate to be used as a sample for this study.

In the present study, we found that the AUCs of ROMA and RMI are better in the postmenopausal group than those in the premenopausal group and all groups. This result was in accordance with the study of Van Gorp et al.[16] and Montagnana et al.[2] This might be caused by the increase in epithelial-type ovarian malignancy incidence up to the age of 70.[17] Disaia concurred that the incidence of epithelial-type ovarian malignancy mostly occurs in women above the age of 50 (81%).[18]

Furthermore, in this study, we analyzed the sensitivity, specificity, PPV, NPV, positive LR, negative LR, and accuracy of ROMA and RMI as diagnostic tools. From Table 2, we know that at a standard cutoff point, ROMA shows a better sensitivity as compared to RMI (95.4 vs 85.3%), but the specificity is lower than RMI (32.5 vs 66.3%). The sensitivity in this study is better than that was found by Moore et al., which was 89% in the first study and 94% in their second study.[9,11] At the ideal cutoff point, ROMA has a better sensitivity than RMI (82.31 vs 74.62%) and better specificity (78.31 vs 75.9%). This was in accordance with the study by Moore et al. of 457 women, in which they found that at the specificity of 75%, ROMA had a better sensitivity as compared to RMI, 94.3 vs 84.6%.[11] In our present study, we found that the diagnostic value is better at the ideal cutoff point possibly because the study is conducted on a different population than the studies of Moore and Van Gorp.[11,16] Zheng et al. found that the ideal cutoff point for ROMA differs from that proposed by Moore, and this is possibly caused by the study population being a different ancestry.[18] The ideal cutoff point in postmenopausal group in this study is higher than the premenopausal group. This might be the result of an increase in HE4 along with the increase in age, as hypothesized by Li et al. and Simmons et al.[19,20]

The present study is limited by its small sample size, and so the result of this study may not yet be generally applicable to every clinical situation. A strength of this study is the ability to identify a

better cutoff point for RMI and ROMA scores. By determining a more ideal cutoff point, we can obtain a better specificity. This more ideal cutoff point warrants further study to predict epithelial-type ovarian cancer. A reason why the previously used standard cutoff point is different from our more ideal cutoff point may be that it originated from a different population. A larger sample is needed to achieve a more optimal result, allowing its general applicability in Indonesia.

Conclusion

Based on this study, it can be concluded that using ROMA is better than RMI in terms of predicting epithelial-type ovarian malignancy, using either standard or ideal cutoff value. Using standard cutoff, the sensitivity of ROMA is better than RMI, but the specificity of RMI is better than ROMA. Using the modified cutoff point, the sensitivity and specificity of ROMA are better than RMI. Nevertheless, the sensitivity and specificity of ROMA are better. Using either scoring method is still acceptable according to the clinical setting, but it is recommended to use ROMA whenever it is practicable.

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