J Nepal Health Res Counc 2020 Apr-Jun;18(47): 253-8

DOI: https://doi.org/10.33314/jnhrc.v18i2.2627

Diagnostic Accuracy of Risk of Malignancy Indices in Ovarian Tumor

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ABSTRACT

Background: Screening test for ovarian cancer has not been developed yet but several tools exist to predict it. The aim is to find out the relative accuracy of commonly practiced versions of Risk of Malignancy Indices to predict ovarian malignancy pre-operatively.

Methods: Intention to treat cross sectional study at Paropakar Maternity and Women's Hospital in Kathmandu during last six months of year 2018. Cases with ovarian mass were taken pre-operatively with serum tumor markers, ultrasound and tumor Doppler study report. Pregnancy and diagnosed malignancy were excluded. Histopathology report traced post-operatively. All five versions of Risk of Malignancy Indices were analyzed by their predictive efficiency and different cut-off value of CA-125.

Results: 116 cases of ovarian tumor from 14 to 76 years (mean=35.2±11.7) were studied. There were 8.6% (n=10) malignant pathology; and isolated high vascular flow and solid component may predict malignancy (p=0.000). Up to 12 multiples of normal CA-125 value could not demonstrate clear predictive value for malignancy (p=0.061). By sensitivity, specificity, diagnostic accuracy and predictive values were similar for Risk of Malignancy Indices-1 and RMI-5 as well as Risk of Malignancy Indices-2 and Risk of Malignancy Indices-3. Cut-off of 250 is efficient by >90% and best at 300. Sensitivity of all Risk of Malignancy Indices versions were similar at cut-off level of 200, 250 and 300.

Conclusions: Isolated value of CA-125 and size of tumor are not useful. All Risk of Malignancy Indices versions are reasonably good. Risk of Malignancy Indices value of 250 or more is the best predictive cut-off. Risk of Malignancy Indices-1 and Risk of Malignancy Indices-5 as well as Risk of Malignancy Indices-2 and Risk of Malignancy Indices-3 have similar predictive accuracy. Doppler study is not mandatory.

Keywords: Cut-off value; diagnostic accuracy; ovarian cancer; RMI

INTRODUCTION

Among all female cancer, ovarian neoplasm contributes 4% only but the morbidity and mortality is high due to the lack of screening tools and advanced disease at presentation. It is the 8th common cancer globally.[1-3] The risk of symptomatic ovarian malignancy increases by age and menopausal status from less than 1% under 35 years up to 2-8% afterwards; so we need to choose a reliable tool out of many to predict cancer prior to intervention.[4-6] Out of them the risk of malignancy index (RMI) is widely studied tool and was established in 1990 to estimate the risk of malignancy preoperatively by taking serum CA-125, USG and menopausal status as parameters to calculate risk.[7] Gradually the subsequent versions of RMI were developed as RMI-2 in 1996,[8] RMI-3 in 1999,[9] RMI-4 in 2009[10] and RMI-5 in 2016.[11,12]

This study was undertaken to find out the relative accuracy of available five versions of RMI in pre-operative diagnosis of ovarian malignancy.

METHODS

It was intention to treat cross sectional study of subsequent 116 cases that underwent surgery for ovarian mass at Paropakar Maternity and Women's Hospital in Kathmandu during six months period from June to December 2018. Sample size was calculated by estimation of proportion at the study site taking 10.3% as its prevalence,[13] 5% α-error and 10% allowable error; then more than three multiples were taken. Research tools used are RMI calculation table and data collection forms (Table 1).

All patients attending at Gynecological clinic with adnexal mass and posted for scheduled surgery were taken; tumor markers, ultrasonography and Doppler vascular study reports recorded. Histopathology report collected from pathology lab after surgery. The cases with proven malignancy but were lacking either USG or CA-125 report or adnexal mass in pregnancy were excluded. Written informed consent was taken after IRC

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approval. There was no additional financial cost to the patient as the whole management process is a routine practice at the study site.

MS Excel was used to generate descriptive value and charts, and SPSS 19 for inferential analysis. Sensitivity, specificity, accuracy, positive and negative predictive values of all five versions of RMIs were calculated at different cut-off values such as 200, 250 and 300. Cutoff of 450 also used as it is the point used by creater of RMI-4. Optimal cut-off value for RMIs was determined by analyzing the greatest point of accuracy in the Receiver operator characteristics (ROC) curve. Likelihood Ratio, Independent-Samples Kruskal-Wallis Test and Pearson Chi-square value were calculated for categorical data.

Table1. Details of Risk of Malignant Indices.[11]

RMI versions	Ultrasound score (U)		Menopausal Status (M)	
	Characteristics	Score	Characteristics	Score
RMI 1 [1990] = U x M x CA125	No features	0	Premenopausal	1
	1 features present	1	Postmenopausal	3
	≥ 2 features present	3		
RMI 2 [1996] = U x M x CA125	≤1 features present	1	Premenopausal	1
	≥ 2 features present	4	Postmenopausal	4
RMI 3 [1999] = U x M x CA125	≤1 features present	1	Premenopausal	1
	≥ 2 features present	3	Postmenopausal	3
RMI 4 [2009] = U x M x CA125 x S	≤1 features present	1	Premenopausal	1
	≥ 2 features present	4	Postmenopausal	4
	A tumor size (single greatest diameter) <7 cm	S=1		
	A tumor size (single greatest diameter) ≥7 cm	S=2		
RMI 5 [2016] =U x M x D x CA125	No features	0	Premenopausal	1
	1 features present	1	Postmenopausal	3
	≥ 2 features present	3		

Cancer Antigen-125 (CA-125) in U/ml.

Ultrasound findings (U) were scored with one point for each of the following: Multi-locular cyst, evidence of solid areas, evidence of metastases, presence of ascites, bilateral lesions.

Doppler blood flow (D) of the ovarian mass was scored as follows: High blood flow is graded D=2. Low blood flow is graded D=1.

Post menopausal status: if the woman had more than one year of amenorrhea or was over 50 years of age if she had undergone hysterectomy.

Interpretation: Minimum score of ≥ 200: cut-off for malignancy

RESULTS

There were 116 cases of ovarian mass who underwent surgery. Age ranges from 14 to 76 years (mean=35.2±11.7) and 80% were in 20-50 years age group (Figure-1).

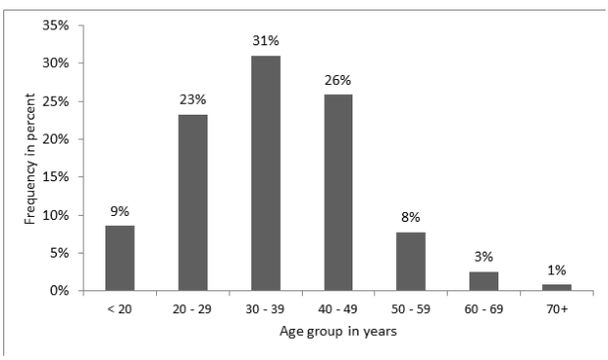

Figure 1. Age group distribution of ovarian mass (N=116).

Ten cases (8.6%) reported as malignant and rests were benign condition with 18 (15.5%) benign ovarian neoplasia. Eight cases had bilateral benign tumors with 26 ovarian pathologies altogether. On benign pathology there were 8 endomtriomas (3 unilateral + 5 bilateral), mucinous cystadenoma (1 unilateral + 3 borderline), Dermoid (1 unilateral + 1 bilateral), Fibroma (1 unilateral + 2 ipsilateral), corpus luteal cyst (2 ipsilateral), serous (1 unilateral). On malignant pathology there were mucinous (4 unilateral, stage IC), serous (1 unilateral, stage IA + 2 bilateral, stage IIIC high grade), granulose cell (1 unilateral, stage IA) and mixed epithelial (2).

7.5% (7/93) of unilateral tumors and 13% (3/23) of bilateral tumors were malignant. Likewise, 41.2% (7/17) of solid and complex tumors are malignant, whereas only 3% (3/99) cystic masses are malignant (likelihood ratio=104, Pearson Chi-square value=152, df=4, P=0.000); 7% (5/71) of unilocular and 12% (5/42) of multilocular cysts were malignant.

Size of tumor ranges from less than 4 cm to over 21cm; 25 (23.6%) were of ≤5cm and 32 (30.2%) were ≥10cm in benign condition; and 5 (50%) were ≤8cm and 5 (50%) were ≥15cm in malignant pathology. Tumor size of benign ovarian conditions appear to be 1/5th (21%) and half (50%) in malignant condition if it exceeds 10cm but a four-fold in number (21 cases against 5 cases) is contributed by benign condition. Independent-Samples Kruskal-Wallis Test is not significant for the size variation in either condition (p=0.146, df=2) (Figure-2).

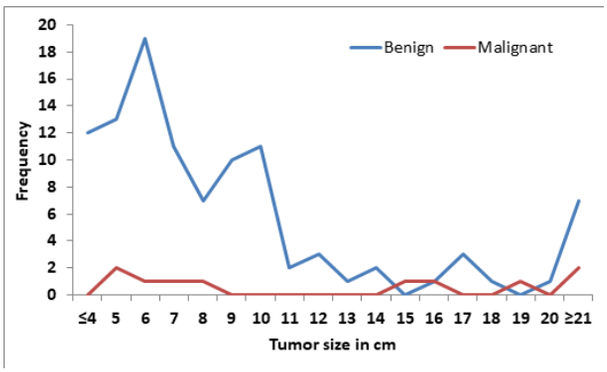

Figure 2. Ovarian tumor size by nature of neoplasm.

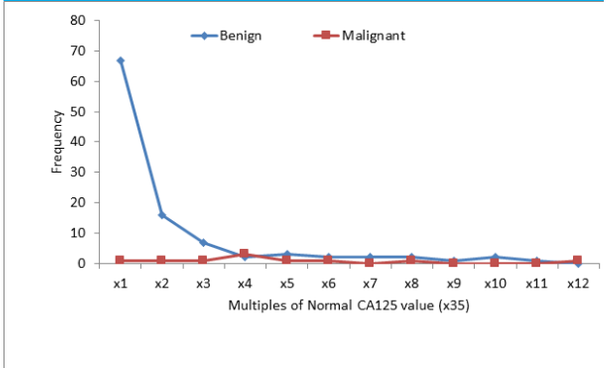

Figure 3. Relation of serum Ca-125 level with nature of ovarian mass.

Up to three multiples of upper limits of normal serum CA-125 (i.e. 35) values were high in benign conditions but from four to 12 multiples were similar in both malignant (p=0.061) and benign (p=0.626) conditions (Figure-3).

High tumor vascular flow was measured in 7% of cases by Doppler ultrasound and it was mainly in malignant tumor (7 in 8 cases, Likelihood ratio=120, Pearson Chi-square value=198, df=4, P=0.000).

RMI cut-off of 300, 250 and 200 were evaluated for all five versions of RMI for their diagnostic parameters. Sensitivity and negative predictive value were perfect in RMI-4 at cut-off of 200 but positive predictive values (PPV) were less than 50% in all versions. RMI-1 and RMI-5 as well as RMI-2 and RMI-3 are also similar at all cut-off level. Positive predictive values are better at higher cut-off values. Diagnostic accuracy appears above 90% in all versions at cut-off of 300 except RMI-4. The unique component in RMI-4 is size of tumor and Doppler vascular flow in RMI-5. Thus without Doppler ultrasound component the RMI-1 appears to be similar to RMI-5. Likewise, without considering size of tumor the RMI-2 and RMI-3 appear to be similar. RMI-1 seems to be better than RMI-3 in cut-off of 250 and 300; 250 cut-off is efficient by >90% efficiency but PPV is better at 300. Sensitivity is found >90% in all versions and all pre-defined cut-off values though the calculated best cutoff points fall on 200-300 in RMI-1 and RMI-4, and 300-400 in RMI-2, RMI-3 and RMI-5 [Table-2,3,4 and Figure-4]. With the cutoff of 450 for RMI-4 thefindings obtained were sensitivity (80%), specificity (92%), accuracy (91%), PPV (47%) and NPV (98%).

Table 2. Diagnostic accuracy of RMI at cut-off of 200.

	RMI1	RMI2	RMI3	RMI4	RMI5
Sensitivity	90%	90%	90%	100%	90%
Specificity	91%	89%	89%	82%	91%
Accuracy	91%	89%	89%	84%	91%
PPV	47%	43%	43%	34%	47%
NPV	99%	99%	99%	100%	99%

Table 3.Diagnostic accuracy of RMI at cut-off of 250.

	RMI1	RMI2	RMI3	RMI4	RMI5
Sensitivity	90%	90%	90%	90%	90%
Specificity	93%	91%	93%	84%	93%
Accuracy	93%	91%	91%	84%	93%
PPV	56%	47%	50%	35%	56%
NPV	99%	99%	99%	99%	99%

Table 4. Diagnostic accuracy of RMI at cut-off of 300.

	RMI1	RMI2	RMI3	RMI4	RMI5
Sensitivity	90%	90%	90%	90%	90%
Specificity	95%	92%	93%	85%	95%
Accuracy	95%	91%	93%	85%	95%
PPV	64%	50%	56%	36%	64%
NPV	99%	99%	99%	99%	99%

False negative rate is around 10% in all versions. Receiver operator characteristics (ROC) curve generated for all five versions of RMI and all have good accuracy of >0.5 but the best one is for RMI-5 that covers maximum area by 0.983. Area under the curve (AUC) difference of RMI-5 is more with RMI-1 and RMI-3; and the total AUC is greatest in RMI-5; RMI-4 has least value in diagnostic accuracy and AUC difference is least with RMI-2 (Figure-4).

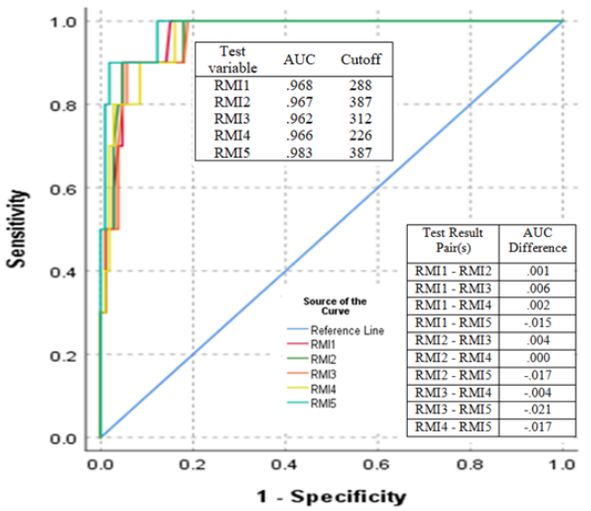

Figure 4. Receiver operator characteristics (ROC) curve of RMI-1 through RMI-5 for diagnostic value in ovarian cancer.

DISCUSSION

The creator of RMI-1 (Jacob I et al[7]) reported mean Ca-125 level as independent significant marker at lower values to differentiate malignant from benign condition from 42 ovarian cancers out of 143 cases but the sensitivity was decreasing for increasing serum values. Combining three criteria as RMI-I attained sensitivity of 85.4%, specificity of 96.9% and likelihood ratio of 42.1at cutoff value of 200. In this current study independent CA-125 values were not significant but other accuracy parameters were comparable.

Tingulstad et al[8] (RMI-2 creater in 1996) found 56 (32%) ovarian cancer out of 173 cases. In comparison to RMI-1, this study found better specificity (96% vs 92%) and positive predictive value (89% vs 83%) but sensitivity was less (71% vs 80%) which increased up to 90% for stage-2 cancer onwards. CA-125 level was not sensitive enough even at three multiples of normal.

TingulstadS et al[9] in 1999 applied RMI-3 in 365 cases with 75 (21%) ovarian cancer and found 68-71% sensitivity and 92-94% specificity from cutoff 200, 255 and 300; thus, the specificity is comparable even to the current study.

Sensitivity, specificity and accuracy in this study are over 90% with cutoff of 250 except RMI-4 and even the 200 cutoff is better than the study done by Dora et al.[14] The isolated value of CA-125 had also less sensitivity than the RMI-3 and solid consistency was significant as in this study. In contrast the comparative study of Hayam et al[15] who reported similar efficiency (p=0.628) of all five RMIs at around 200 cutoff but at 250 cut-off the RMI-5 would have a sensitivity of 90.38% and specificity of 93.88%. This study also calculated efficiency over 90% at all cutoff over 200.Clake et al[16] also found comparable sensitivity of 72-76% at lower cutoff 120 in RMI-1, RMI-2 and RMI-3 with AUC 0.83-0.87 but current study shows better in higher cut-off.

RMI-1 to 3 had sensitivity of 71-74% and specificity of 73-81% as reported by Meys et al.[17] Sensitivity of RMI-1 was very low even in 100-250 cutoff by 54-66% with specificity of 84-93% as reported by Aziz et al[18] but negative predictive value was better as 92-94%.All RMI 1-4 were comparable with lower sensitivity in all ranges of cutoff from 50 to >300 but there was increasing specificity. Specificity reaches over 90% at 250 cutoff but sensitivity is 65-75% only as reported by Akturk et al.[19] Sensitvity of 67-72%, specificity of >90% was referenced by Holsbeke et al[20] for RMI 1, 2 and 3.The findings are comparable to the study done by Yamamoto et al[21] on 296 cases having 25% ovarian cancer taking cutoff of 200 for RMI-1,2,3 and 450 for RMI-4 as the sensitivity was >93% with specificity of around 88%.Report of Insin et al[22] is different than this study, as there was lower level of both sensitivity and specificity with cut off 200 for RMI-1-3 and 450 for RMI-4; the RMI-2 gave highest sensitivity (71%) and RMI-1 gave the highest specificity (80%); AUC was better (0.801) than other lower 3 versions. Shintre et al[23] studied 64 cases for RMI-1 with cutoff 200 and found 70% sensitivity. In contrarary to this study, Ong C et al[24] studied 228 cases with 7.5% cancer rate and found insignificant ROC curve with AUC between 0.42 and 0.55 for RMI-1,2,3 and 4. But median CA-125 level and tumour size ($p = 0.044$ and $p < 0.0005$, respectively) between the benign and malignant cases were significant which are not supported by the current study. Similarly, Moolthiya et al[25] found 74 out of 209 cases of ovarian cancer with comparable RMI-1 and RMI-2 with sensitivity and specificity between 70-80%. Current study is comparable to the first study done by the creater of RMI-4 Yamamoto et al[10] in 2009 with cut-off of 450 as sensitivity (80% vs 86.8%), specificity (92% vs 91%), accuracy (91% vs 90.4%), PPV (47% vs 63.5%) and NPV (98% vs 97.5%).

Thus the predictive values vary in different studies could be because of differential prevalence in different place and time-frame as well as the stages of disease and the number of cases recruited. Isolated parameters have not been used currently as a preoperative tool for predicting malignancy.

CONCLUSIONS

Predictive tool sensitivity is similar by over 90% and false negative rate is around 10% in all RMIs. The RMI-4 is not efficient in prediction, thus tumor size may not be helpful but the cutoff of 450 yields the similar report. RMI cut-off of 250 is efficient by >90% efficiency

but PPV is better at 300. Because of similar predictive accuracies, one index can be chosen from RMI-1 and RMI-5; and same applies to RMI-2 and RMI-3 if we have to choose one. Cut-off of 250 is reasonably efficient by >90% and best at 300. Sensitivity is similar in all RMI versions at all cut-off level. Doppler flow study is not mandatory, and tumor size and isolated value of CA125 do not predict malignancy. Isolated high vascular flow and solid component may predict malignancy but laterality doesn't.

REFERENCES

1. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: the size of the problem. Best Prac Res Clin Obstet Gynaecol. 2006;20(2):207–25. [ScienceDirect][DOI]
2. Bray F, Trabert B. HHS Public Access. Int J Cancer. 2018;140(11):2451–60.[Springer]
3. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014.
4. RCOG/BSGE Joint Guideline. Management of suspected ovarian masses in premenopausal women. Green–top Guideline No. 62; 2011.[FullText]
5. Geomini P, Kruitwagen R, Bremer GL, Cnossen J, Mol BW. The accuracy of risk scores in predicting ovarian malignancy: a systematic review. Obstet Gynecol. 2009;113:384–94.[Link]
6. Poudel KK, Huang ZB, Neupane PR. Age specific incidence of five major cancers in Nepal. 2012. Nepal J Epidemiol. 2016;6(2);565-573.[FullText]
7. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. Risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. BJOG. 1990;97(10):922–9.
8. Tingulstad S, Hagen B, Skjeldestad FE, Onsrud M, Kiserud T, Halvorsen T, et al. Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. BJOG. 1996;103(8):826–1.[DOI]
9. Tingulstad S, Hagen B, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. Therisk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. Obstet Gynecol.1999;93:448–52.[Link]
10. Yamamoto Y, Yamada R, Oguri H, Maeda N, Fukaya T. Comparison of four malignancy risk indices in the preoperative evaluation of patients with pelvic masses. Eur J Obstet Gynecol Reprod Biol. 2009;144(2):163-7. [ScienceDirect][DOI]
11. Hayam FM, Ashraf MQ, Hassan MKH. Assessment of the value of a Modified Risk of Malignancy Index (RMI) in preoperative discrimination between benign and malignant ovarian masses. Gynecol Obstet. 2016;6:417.
12. Valentin L. Prospective cross-validation of Doppler ultrasound examination and gray-scale ultrasound imaging for discrimination of benign and malignant pelvic masses. Ultrasound Obstet Gynecol. 1999;14:273-83.[DOI]
13. Paropakar Maternity and Women's Hospital. Hospital Admission Record 2075. Unpublished.
14. Dora SK, Dandapat AB, Pande B, Hota JP. A prospective study to evaluate the risk malignancy index and its diagnostic implication in patients with suspected ovarian mass. J Ovarian Res. 2017;10:55.[Springer]
15. Hayam FM, Ashraf MQ, Hassan MKH. Assessment of the value of a modified risk of malignancy index (RMI) in preoperative discrimination between benign and malignant ovarian masses. Gynecol Obstet (Sunnyvale). 2016;6:12.
16. Clarke SE, Grimshaw R, Rittenberg P, Kieser K, Bentley J. Risk of malignancy index in the evaluation of patients with adnexal masses. J Obstet Gynaecol Can. 2009;31(5):440-5.[ScienceDirect]
17. Meys EMJ, Jeelof IS, Achten NMJ, Slangen BFM, Lambrechts S, Kruitwagen RFPM, et al. Estimating risk of malignancy in adnexal masses: external validation of the ADNEX model and comparison with other frequently used ultrasound methods. Ultrasound Obstet Gynecol. 2017;49:784–92.[DOI]
18. Aziz AB, Najmi N. Is risk malignancy index a useful tool for predicting malignant ovarian masses in developing countries? Obstet Gynecol Int. 2015:951256.[DOI]
19. Aktürk E, Karaca RE, Alanbay I, Dede M, Karaşahin E, Yenen MC, et al. Comparison of four malignancy risk indices in the detection of malignant ovarian masses. J Gynecol Oncol. 2011;22(3):177-82.[DOI]
20. Holsbeke CV, Calster BV, Bourne T, Ajossa S, Testa AC, Guerriero S, et al. External validation of diagnostic models to estimate the risk of malignancy in adnexal masses. Clin Cancer Res. 2011;18(3):815–25.[Link]
21. Yamamoto Y, Aki Tsuchida, Takashi Ushiwaka, Ryuhei Nagai, Mitsuhiro Matsumoto, Junko Komatsu, et al. Comparison of 4 risk-of-malignancy indexes in the preoperative evaluation of patients with pelvic masses: A prospective study. Clin Ovarian Gynecol Cancer. 2014;7(1/2);8-12.[DOI]

22. Insin P, Prueksaritanond N. Evaluation of four risk of malignancy indices (RMI) in the preoperative diagnosis of ovarian malignancy at Rajavithi Hospital. Thai J Obstet Gynaecol. 2013;21:163-75.[Link]

23. Shintre SA, Survase RM, Patil NA, Sayyed RL. Effectiveness of risk of malignancy index to differentiate benign from malignant ovarian masses- a cross sectional study. Int J Health Sci Res. 2017;7(5):52-9.[FullText]

24. Ong C, Arijit Biswas, Mahesh Choolani, Jeffrey Jen Hui Low. Comparison of risk of malignancy indices in evaluating ovarian masses in a Southeast Asian population. Singapore Med J. 2013;54(3):136-9.[FullText]

25. Moolthiya W, Yuenyao P. The risk of malignancy index (RMI) in diagnosis of ovarian malignancy. Asian Pacific J Cancer Prev. 2009;10:865-8.[FullText]