Diagnostic value of risk of malignancy index in the clinical evaluation of ovarian mass

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Received September 5, 2021; Accepted December 15, 2021

DOI: 10.3892/mco.2022.2551

Abstract. In the present study, the Risk Malignancy Index (RMI) was calculated based on menopausal status, ultrasound (US) findings and serum biological cancer antigen 125 (CA-125) levels as a scoring system in Libyan females with ovarian masses (OMs) to differentiate between benign and malignant tumors. A total of 51 females with OMs referred to the Gynaecology Department of the National Cancer Institute in Misurata (Libya) between January 2019 and December 2020 were retrospectively reviewed for diagnostic testing. Clinicopathological and demographic data were obtained from patient records. A cut-off point of RMI=200 was used to differentiate between benign and malignant tumors. The mean age of the patients was 47 years (range, 19-90 years) and 60% of the patients were premenopausal. Examination of the four RMI indices and disease status indicated that the association with the US score (P<0.0001) and with CA-125 (P=0.017) was highly significant. However, the age at diagnosis and menopausal status did not have any significant association with the disease status. The RMI with a cut-off point of 200 had a sensitivity and specificity of 87.5 and 90.7%, respectively, and a positive and negative predictive value of 63.6 and 97.5%, respectively. The association between the RMI and disease status was highly significant (P<0.0001). In conclusion, the RMI appears to be a reliable, simple and cost-effective tool for clinical differentiation between benign and malignant OMs. This may help to improve the optimal diagnosis and planning of an individualized treatment strategy. However, given the small sample size of the cohort, further validation using larger cohorts in other settings is recommended.

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Abbreviations: CA-125, cancer antigen 125; OM, ovarian mass; RMI, Risk of Malignancy Index; ROC, receiver operating characteristic

Key words: ovarian mass, risk of malignancy index, diagnosis

Introduction

Ovarian cancer has a high mortality rate compared to other cancer types of the female reproductive organs (1). In 2015, ~1.2 million females developed ovarian cancer, resulting in 160,000 deaths worldwide (2-4). It is called a 'silent killer', as the disease usually does not produce any obvious symptoms in early stages and there is no effective screening program to date. Therefore, the majority of patients are diagnosed only at advanced stages and have a poor survival rate (5). The diagnosis of ovarian cancer includes careful review of patients' medical history, physical examination, serum cancer antigen 125 (CA-125) levels, radiologic findings and histopathologic confirmation (6). This also helps with the study of the behaviour of ovarian masses (OMs), whether they are benign or malignant. Therefore, OM is an important radiological finding that may indicate ovarian cancer if it is associated with specific criteria such as fixation, irregularity and nodularity (7). Approximately 12-20% of OMs are malignant; however, OMs may also be benign, such as leiomyomas, ovarian follicular cysts and endometriosis (7). OMs are the main reason for referral and hospitalization of patients to assess the risk of malignancy. Accurate initial diagnosis in females with ovarian cancer is important to obtain an early and correct diagnosis of ovarian cancer and to avoid the risk of overtreatment. In the clinical context, there are several methods for assessing the risk of ovarian malignancy, such as the Risk Malignancy Index (RMI) and the Risk Algorithm for Ovarian Cancer (6,7). The RMI is a widely known method for malignancy risk assessment. However, the primary evaluation of OMs is mainly based on the initial diagnostic workup, which includes ultrasound findings, menopausal status and serum CA-125 levels (7,8). An RMI score of >200 is associated with a high risk of ovarian cancer in females with OMs (6,7). The aim of the present study was to investigate the diagnostic value of the RMI in Libyan females with OMs by using the indices of RMI in combination with ultrasound (US) findings, menopausal status and CA-125 levels to distinguish between benign and malignant tumors.

Patients and methods

With the approval of the Institutional Review Board of the National Cancer Institute (Misurata, Libya), the present retrospective study was performed on 51 patients with OMs who were admitted and underwent surgery at the Gynaecology Department of the National Cancer Institute (Misurata, Libya) between January 2019 and December 2020. Demographic characteristics, US findings, menopausal status, serum CA-125 levels and histopathology reports were collected. OMs were evaluated based on the US findings by determining the following items: Solid area, irregularity, nodularity, bilaterality, multilocularity, ascites and intra-abdominal metastases. The US score was assigned as follows: 1, no abnormality or one abnormality was detected; or 3, two or more abnormalities were detected.

Serum CA-125 levels were also determined for all patients and CA-125 >35 U/ml was defined as abnormal (9).

The menopausal status was determined for all patients and the status was defined as postmenopausal when the patient presented with amenorrhea for one year or more, or underwent surgical ablation. The menopausal score was assigned as follows: 1 patient was premenopausal; or 3, the patient was postmenopausal.

The RMI was calculated as follows: RMI=US score x menopausal score x CA-125 level in U/ml (7). The cut-off point for the RMI at 200 was used to distinguish between benign and malignant tumors, as it provided the best diagnostic accuracy value results in the present study and others (10-12).

Furthermore, the histopathology reports were collected and analyzed for the correlation with the RMI.

Statistical analysis. The variables of the collected data were arranged into logical classes and descriptive statistics were used for the continuous variables using SPSS 19.0 for Windows (IBM Corporation). Frequency tables were analyzed using the χ^2 test, with the likelihood ratio (LR) regarding the probability of malignant disease vs. benign, or Fisher's exact test to assess the significance of the association between the categorical variables and to compare demographic, radiological and biological variables between patients with benign or malignant OMs. The sensitivity, specificity and positive/negative predictive values of the RMI based on benign or malignant OMs as a reference test that is able to indicate the malignancy of a tumor were estimated for all patients. Different cut-offs points (range from 25 to 1,000) in the receiver operating characteristic (ROC) curve were used to estimate the predictive significance of the RMI. P<0.05 was considered to indicate statistical significance.

Results

Patient characteristics. The mean age of the patients was 47 years (range, 14-90 years) (Fig. 1) and 60% of the patients were premenopausal (Fig. 2). A total of 51 patients with OMs were enrolled in the present study; malignant tumors were confirmed in 8 (15.6%) patients and 43 (84.4%) patients had benign tumors.

Patient characteristics and disease status. The patient characteristics according to disease status, including age, menopausal status, ultrasound findings and serum CA-125 levels are presented in Table I. A significant association was noted between US score and disease status (P<0.0001). The mean CA-125 expression was 41 U/ml in females with benign tumors and 635 U/ml in females with malignant tumors (P=0.017). The age at diagnosis and menopausal status were not significantly associated with disease status (P=0.095 and 0.237, respectively). In the present study, it was also observed that 90.7% of females with benign disease had an RMI score <200, while an RMI score ≥200 was observed in 87.5% of females with malignant tumors.

Diagnostic value of the RMI. As presented in Fig. 3, an ROC curve was plotted and different cut-off points of RMI were used. The RMI at a cut-off point of 200 had high sensitivity and specificity of (87.5 and 90.7%, respectively) with positive and negative predictive values of 63.6 and 97.5%, respectively, for distinguishing between benign and malignant OMs (Table II). The results also suggested that the area under the curve (AUC) was large (0.94, 95% CI, 0.798-1.000) and the RMI at a cut-off point of 200 was the best criterion to identify ovarian malignant tumor in females with OMs (Table III). Furthermore, as presented in Table IV, 11 of 51 patients had an RMI ≥200, of which 7 (87.5%) patients had histopathological malignancy and 4 (9.3%) patients had benign tumors. In addition, 40 patients had an RMI <200, of which 39 (90.7%) had a benign tumor and 1 (12.5%) had a malignant tumor (P<0.0001).

Discussion

Cancer-related deaths continue to be a major problem worldwide. Ovarian cancer (OC) in particular is among the deadliest malignancies in females. The reasons for this high mortality rate are mainly the advanced stage at diagnosis and the frequent recurrence after surgical resection and adjuvant therapy (13). However, the major challenges in treating OC include early diagnosis, prognosis, prediction, development of resistance to anticancer drugs and recurrence. With no effective treatment for OC, early diagnosis remains an important step to support current clinical approaches and improve patient outcomes (14,15).

The present study was tailored to investigate the diagnostic value of the RMI in evaluating and differentiating between benign and malignant OMs in Libyan females for effective early diagnosis. For this purpose, the RMI was used as an index calculated from the US features, menopausal status and serum CA-125 levels.

In the present study, numerous important and valuable observations have been made, all suggesting that the assessment of the RMI in Libyan subjects provides important useful information. However, comparisons with other studies are difficult, as the present study is somewhat limited by the small size of the cohort. The mean age of all patients was 47 years and that of patients with malignant and benign disease was 59.5 and 44.8 years, respectively. A high percentage of patients aged >50 years presented with OC, as reported in other studies (16,17). Females with advanced age had an elevated

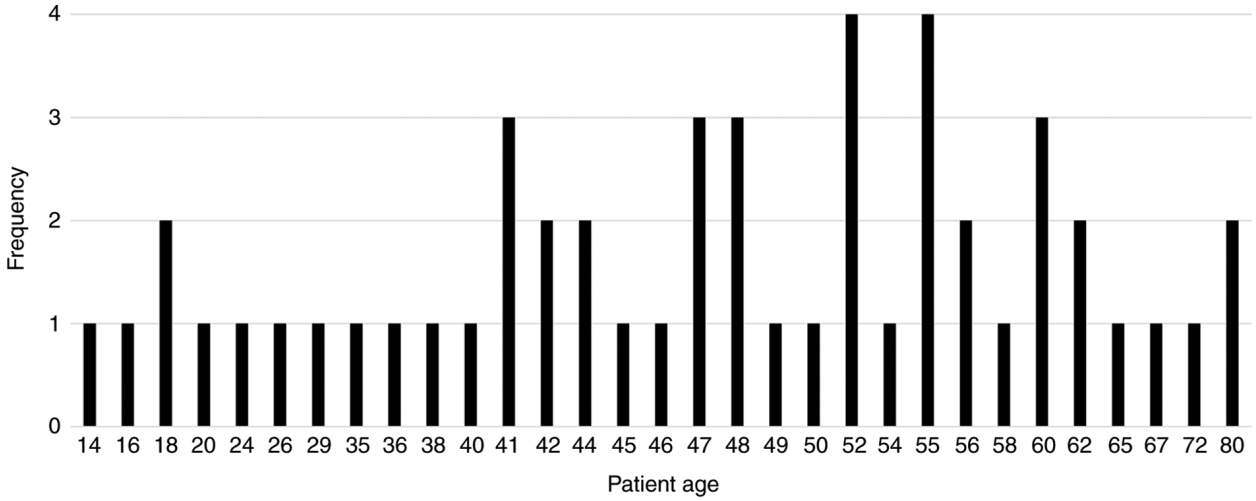

Figure 1. Age distribution of 51 females with ovarian mass in Libya (2019-2020).

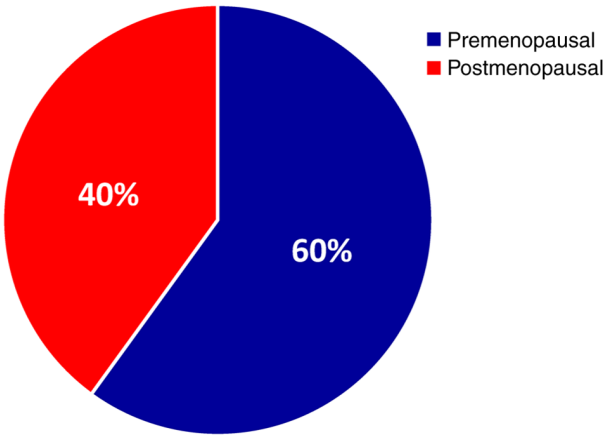

Figure 2. Menopausal status of 51 females with ovarian mass in Libya (2019-2020).

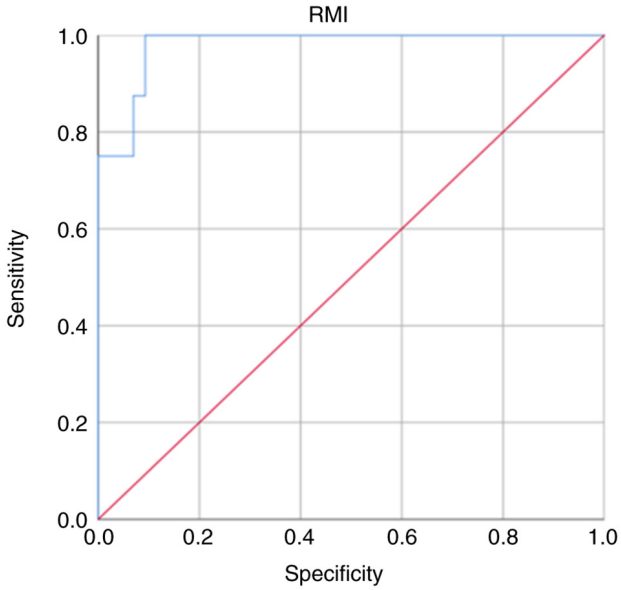

Figure 3. Receiver operating characteristic curve for the RMI to differentiate between benign and malignant ovarian masses. RMI, Risk of Malignancy Index.

risk of OC, as more mutations and accumulations in cells may cause cancer (6).

In the present study, 84% of OMs were observed to be benign. This result is consistent with those of studies on OMs, which reported that 70-90% of OMs were benign and 12-20% were malignant (16-19). Benign OMs were observed to be more common than malignant OMs. US has been widely used as the primary imaging modality to define and characterize OMs (20-22). Vaginal US examination was frequently the best and first imaging method when OMs were detected. However, numerous features of OMs indicated malignant features, such as solid area, multilocularity, papillary features and irregularity of internal septations. Extensive experience from numerous centers around the world suggested that the accuracy of assessment of OMs was 90% based on US findings (23). The significant value of US in evaluating OMs to assess the risk of malignancy was investigated in several studies and the results suggested that sensitivity, specificity and positive predictive value were high (24). High sensitivity of the US method was observed in the early stages of ovarian cancer. Therefore, the method was encouraged as the first test for malignancy risk assessment in patients with OMs (24). Of note, in the present study, it was determined that all malignant cases had a US score of 3 ($P<0.0001$). Furthermore, US has higher sensitivity (100% vs. 87.5%) than the RMI and a lower specificity (69.8% vs. 90.7%) than the RMI. These results are consistent with the findings of other studies (20-22).

Furthermore, CA-125 is useful as a biological marker for differential diagnosis and follow-up of patients with OMs. Numerous studies have investigated the value of CA-125 in assessing malignancy risk in females with OMs. The results suggested that CA-125 values were inaccurate in early-stage ovarian cancer and almost 50% of stage I patients had normal CA-125 values (6,19). The CA-125 level may also be elevated in benign disease (25). Furthermore, due to its low sensitivity and specificity, CA-125 is ineffective for screening early ovarian cancer when the test is used alone (7,19). Be that as it may, to this day, CA-125 is widely used as a biological

Table I. Distribution of subjects by age, menopausal status, ultrasound features, serum CA-125 levels and RMI risk.

Variable	Benign (n=43)	Malignant (n=8)	P-value
Age/years (mean, 47 years; range, 14-90)			0.095
>30	8	0	
30-44	9	2	
45-54	14	1	
≥55	12	5	
Menopausal status			0.237
Pre	26	3	
Post	17	5	
US score			<0.0001
1	30	0	
3	13	8	
CA-125, U/ml			0.017
Mean	41	635	
Median	25	662	
Minimum	2.5	22	
Maximum	212	1,125	
RMI			<0.0001
<200	39	1	
≥200	4	7	

RMI, Risk of Malignancy Index; CA-125, cancer antigen 125; US, ultrasound.

Table II. Predictive value of RMI, menopausal status, serum CA-125 levels and ultrasound score for benign and malignant ovarian masses.

Variable	Benign, %	Malignant, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC (95%, CI)
RMI			87.5	90.7	63.6	97.5	0.94 (0.798-1.000)
<200	90.7	12.5					
≥200	9.3	87.5					
Menopausal status			62.5	60.5	22.7	89.7	0.61 (0.401-0.828)
Pre	60.5	37.5					
Post	39.5	62.5					
US score			100	69.8	38.1		0.849 (0.743-0.954)
1	69.8	0.00					
3	30.2	100.0					
CA-125, U/ml			87.5	58.1	28.0	96.2	0.728 (0.566-0.900)
<35	58.1	12.5					
≥35	41.9	87.5					

Values are expressed as n (%). PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; AUC, area under curve; RMI, Risk of Malignancy Index; CA-125, cancer antigen 125; US, ultrasound.

tumor marker for the detection of ovarian cancer. However, while CA-125 used separately may have poor specificity, when coupled with the RMI, the specificity is markedly enhanced (18). The present study indicated that CA-125 was

Table III. Sensitivity, specificity and LR for malignant ovarian masses given a positive or negative result for different cut-off points of the RMIs.

RMI	Sensitivity, %	Specificity, %	Positive LR	Negative LR
25	98.6	34.9	1.51	0.04
50	98.6	53.5	2.12	0.02
75	98.6	58.1	2.35	0.02
100	97.7	69.8	3.23	0.03
125	97.7	81.4	5.30	0.02
150	97.7	81.4	5.30	0.02
175	96.8	83.7	5.93	0.03
200	87.5	97.7	38.04	0.12
225	87.5	90.7	9.40	0.13
250	87.5	90.7	9.40	0.13
500	87.5	93.0	12.5	0.13
1000	75.5	93.0	10.78	0.16

LR, likelihood ratio; RMI, Risk of Malignancy Index.

Table IV. Distribution of subjects by the RMI above/below the cut-off of 200.

RMI	Benign (n=43)	Malignant (n=8)	P-value
<200	39 (90.7)	1 (12.5)	<0.0001
≥200	4 (9.3)	7 (87.5)	

Values are expressed as n (%). RMI, Risk of Malignancy Index.

highly expressed (≥35 U/ml) in 87.5% of patients with malignant ovarian tumors and in 41.9% of patients with benign ovarian tumors. In comparison, it was noted that CA-125 had the same sensitivity (87.5 vs. 87.5%) as the RMI, but lower specificity (58.1 vs. 90.7%) than the RMI. This was consistent with the results of previous studies (15,18,26).

The RMI and estimation scores based on initial diagnostic workups, including CA-125 levels, US and patient age, are widely used for estimating the risk of malignancy in patients with Oms (7,8). In patients with OMs, an RMI score of >200 is associated with an increased risk of malignancy (7).

In the present study, different cut-off points of the RMI (25-1,000) were assessed to determine the best predictive value for malignancy risk. The cut-off point of 200 provided the highest sensitivity, specificity and positive predictive value (87.5, 97.7 and 38.4% respectively).

In addition, the ROC curve analysis indicated that at a cut-off value of 200 for the RMI, the likelihood of having malignant disease was 38.4%, while the likelihood of having benign disease was only 0.12% in females with OMs. The RMI with a cut-off value of 200 had the highest significance in discriminating OMs (<25, 25-250 and >250, respectively) (27). The present observations were in agreement with numerous studies, which also noted that RMI at a cut-off point of 200 may serve as a quantitative criterion for splitting Libyan patients with OM into two groups (benign vs. malignant) depending on malignancy risk (28,29). While certain unexpected but minor fluctuations of the negative LR below the threshold were observed, in general, the RMI of OMs was strongly discriminated by the 200 cut-off value. However, further confirmation of the present findings may only be provided by more intensive studies with a large sample size in Libya. In addition, a randomized controlled trial (RCT) is the most effective scientific method to evaluate the effectiveness of such clinical research. RCTs are undoubtedly of high value in Libya and will be considered and planned for patients with cancer in the future.

In conclusion, calculating the RMI is the best method and the most reliable tool for defining subsequent diagnostic, management and therapeutic strategies for benign and malignant OMs. However, due to the limitation of the small sample size in the present study, further research is warranted.

Acknowledgements

The authors would like to thank Professor Mohamed Ahmed Elfagieh, Director of the National Cancer Institute (Misurata, Libya), for his continuous support of the medical research.

Funding

No funding was received.

Availability of data and materials

All relevant raw data from the study are freely available to any researcher upon request.

Authors' contributions

AH: Study design and demographical and clinicopathological data collection; AA: Data collection; MA: Analysis and interpretation of the results, and writing and proofreading of the manuscript; AB: Statistical analysis of the data, preparation of figures, and writing and proofreading of the manuscript. AB: preparation of the figures, review the study manuscript and proofreading; EE: Statistical analysis, study design and manuscript drafting. Both AH and EE reviewed and approved the authenticity of the raw data, and all authors reviewed and approved the final version of the manuscript.

Ethics approval and consent to participate

This study is part of the medical research studies approved by the Institutional Review Board of the National Cancer Institute (Misurata, Libya; ethical approval no. 7-20121).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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