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INTERRELATION OF RISK INDICATORS OF MALIGNANCY INDEX AND MORPHOLOGICAL DETERMINANTS OF OVARIAN TUMOR

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Abstract

Introduction. Despite the favorable outcomes of benign ovarian neoplasms, there are still certain risks of their malignancy. At the same time, the prognosis is mediated by the morphological type of benign neoplasms detected at the early stages of maturation. An important starting point for a better prognosis and survival is the preoperative study of malignancy rates and the choice of optimal treatment tactics.

Objective: To present the morphological features of ovarian neoplasms in close relationship with the risk index of malignant neoplasms.

Materials and methods. The prospective study was conducted in the gynecology department of Aktobe hospital (Kazakhstan) and Ahmadi hospital (Kuwait). Informed consent was obtained from patients to participate in the study. There were included 264 women with ovarian tumors, that are divided into three age groups (reproductive, premenopausal, and postmenopausal). RMI calculation and subsequent morphological examination of ovarian cyst samples with histopathological (HP) confirmation were performed.

Statistically numeric variables are presented as mean ± standard deviation, categorical as numbers and percent (%). For the analysis of quantitative and qualitative data, Student's t and chi-square (x2) tests were used, respectively. A receiver operating characteristic (ROC) curve was used to determine the RMI value with sensitivity, specificity, PPV, and NPV and to analyze the correlation coefficient between the RMI and the variables.

Results. There were identified about 26.5% of malignant and 73.48% of benign ovarian lesions were. The average age of women with newly diagnosed ovarian neoplasms was 52.3 ± 9.1 and 41.5 ± 11.7 years, respectively (P = 0.9). The incidence of malignant tumors was significantly higher in the premenopausal and postmenopausal groups compared with the reproductive age group (P = 0.0008 and 0.0008, respectively). HP malignancy showed a higher RMI> 200, except for 12 false negatives. The ROC curve at a cut-off value > 247.5 in the three study groups had high sensitivity and specificity (82.9% and 100%, respectively), PPV 100%, and NPV 98.1%. The area under the ROC curve (AUC) is 0.955.

Conclusion: In the study population, 96.7% of women with malignant ovarian cancer were correctly identified by the RMI 2 method with a threshold value of 200. The correspondence between the risk of malignancy according to RMI and postoperative HP data is statistically significant. The area under the curves (AUC) ROC is 0.955 for RMI (P = <0.001).

Keywords: *ovarian tumors, histopathology, malignant neoplasms, risk assessment.*

Резюме

ВЗАИМОСВЯЗЬ ПОКАЗАТЕЛЕЙ РИСКА ИНДЕКСА МАЛИГНИЗАЦИИ И МОРФОЛОГИЧЕСКИХ ДЕТЕРМИНАНТ ОПУХОЛИ ЯИЧНИКА

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Актуальность. Несмотря на благоприятные исходы доброкачественных новообразовании яичников, все же существуют определенные риски их озлокачествления. При этом прогноз опосредован морфологическим типом доброкачественного новообразования, выявляемого на ранних этапах созревания. Важной отправной точкой для

лучшего прогноза и выживания является дооперационное исследование показателей малигнизации и выбор оптимальной тактики лечения.

Цель: Представить морфологические особенности новообразований яичников в тесной взаимосвязи с индексом риска злокачественных новообразований.

Материалы и методы. Проспективное исследование проводилось в отделении гинекологии больницы г. Актобе (Казахстан) и госпиталя Ахмади (Кувейт). Получено информированное согласие пациентов на участие в исследовании. Были включены 264 женщины с опухолями яичников, разделенных на три возрастные группы (репродуктивная, пременопаузальная и постменопаузальная). Выполнены расчет RMI и последующее морфологическое исследование образцов кисты яичника с гистопатологическим (HP) подтверждением.

Статистически числовые переменные представлены как среднее ± стандартное отклонение, категориальные в виде числа и процента (%). Для анализа количественных и качественных данных использовались критерии Стьюдента и хи-квадрат (x^2) соответственно. Кривую рабочей характеристики приемника (ROC), использовали для определения значения RMI с чувствительностью, специфичностью, PPV и NPV и анализ коэффициента корреляции между RMI и переменными.

Результаты. Было выявлено 26,5% злокачественных и 73,48% доброкачественных образований яичников. Средний возраст женщин с впервые диагностированными новообразованиями яичников составил 52,3 ± 9,1 и 41,5 ± 11,7 лет соответственно (P = 0,9). Частота злокачественных опухолей была значительно выше в группах пременопаузы и постменопаузы по сравнению с группой репродуктивного возраста (P = 0,0008 и 0,0008 соответственно). Злокачественность HP показала более высокий RMI> 200, за исключением 12 ложноотрицательных результатов. Кривая ROC при пороговом значении >247,5 в трех исследуемых группах имела высокую чувствительность и специфичность (82,9% и 100% соответственно), PPV 100% и NPV 98,1%. Площадь под ROC-кривой (AUC) - 0,955.

Выводы: В исследуемой популяции методом RMI 2 при пороговом значении 200 правильно идентифицировано 96,7% женщин со злокачественным раком яичников. Соответствие риска злокачественности по RMI и послеоперационными данными HP статистически значимо. Кривая ROC площади под кривыми (AUC) составляет 0,955 для RMI (P = < 0,001).

Ключевые слова: *опухоли яичников, гистопатология, злокачественные новообразования, оценка риска.*

Түйіндеме

ҚАТЕРЛІЛІК ИНДЕКСІНІҢ ҚАУІП КӨРСЕТКІШТЕРІНІҢ ЖӘНЕ АНАЛЫҚ БЕЗ ІСІКТЕРІНІҢ МОРФОЛОГИЯЛЫҚ ДЕТЕРМИНАНТТАРЫНЫҢ ӨЗАРА БАЙЛАНЫСЫ

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Кіріспе. Аналық бездердің қатерсіз ісіктерінің қолайлы ақырына қарамастан, олардың қатерлі ісіктерге ауысу қаупі әлі де бар. Бұл жағдайда болжам ерте сатысында анықталуы қатерсіз ісіктің морфологиялық түрлеріне тәуелді. қатерлі ісіктердің отаға дейінгі зерттеу көрсеткіштері және оңтайлы емдеу тактикасын таңдау қолайлы болжам мен өмір сүрудің бастапқы нүктесі болып табылады.

Мақсаты: аналық без ісіктерінің морфологиялық ерекшеліктерін қатерлі ісіктердің қауіп индексімен тығыз байланыста көрсету.

Материалдар мен әдістері. Проспективті зерттеу Ақтөбе (Қазақстан) ауруханасының және Ахмади ауруханасының (Кувейт) гинекология бөлімшесінде жүргізілді. Зерттеуге қатысу үшін пациенттерден ақпараттандырылған келісім алынды. Аналық без ісігі бар 264 әйелдер үш жас тобына (репродуктивті, пременопауза және постменопауза) бөлінді. Қатерлі ісік қауіпі индексін (RMI) есептеу және аналық без кистасының үлгілеріне морфологиялық зерттеу гистопатологиялық (HP) растауымен жүргізілді.

Статистикалық сандық айнымалылар орташа ± стандартты ауытқу, категориялық сандар және пайыз (%) ретінде ұсынылады. Сандық және сапалық деректерді талдау үшін тиісінше Стьюденттің t және хи-квадрат (x^2) тесттері қолданылды. Сезімталдық, ерекшелік, PPV және NPV бар RMI мәнін анықтау және RMI мен айнымалылар арасындағы корреляция коэффициентін талдау үшін қабылдағыштың жұмыс сипаттамасы (ROC) қисығы пайдаланылды.

Нәтижелері. Аналық бездердің 26,5% қатерлі және 73,48% қатерсіз зақымданулар анықталды. Жаңадан анықталған аналық безінің ісіктері бар әйелдердің орташа жасы сәйкесінше 52,3 ± 9,1 және 41,5 ± 11,7 жасты

құрады (P = 0,9). Қатерлі ісіктердің жиілігі репродуктивті жас тобымен салыстырғанда пременопауза және постменопауза жасындағы топтарда айтарлықтай жоғары болды (тиісінше P = 0,0008 және 0,0008).

HP қатерлі ісігі 12 жалған теріс нәтижені қоспағанда, жоғары RMI> 200 нәтижелерін көрсетті. Үш зерттеу тобында шекті мән > 247,5 кезінде ROC қисығы жоғары сезімталдық пен ерекшелікке ие (тиісінше 82,9% және 100%), PPV 100% және NPV 98,1% болды. ROC-қисық астындағы ауданы (AUC) - 0,955.

Тұжырымдар: Зерттелетін популяцияда аналық бездің қатерлі ісігі бар 96,7% әйелдердің 200 шекті мәні бар RMI2 әдісімен дұрыс анықталды. RMI және операциядан кейінгі HP деректері бойынша қатерлі ісік қаупінің сәйкестігі статистикалық маңызды. Қисықтар астындағы аудан (AUC) ROC RMI үшін 0,955 (P = <0,001).

Түйінді сөздер: *аналық без ісіктері, гистопатология, қатерлі ісіктер, тәуекелді бағалау.*

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Introduction

In recent years, the prevalence of benign ovarian tumors in women of fertile age is close to 70-80% [7]. Despite the favorable outcomes provided timely diagnosis, there are still certain risks of their malignancy [5].

A holistic prognosis is determined by the morphological type of a benign neoplasm but is still detected at the early stages of maturation [10]. Therefore, in this regard, the clinician is faced with difficulties associated with the lack of a screening test, methods of early diagnosis of malignancy, and determination of their predictors [1].

Preoperative study of indicators of malignancy and the choice of the best treatment tactics increase the chances of a successful prognosis [6]. One of the studied indicators at present is the calculation of the risk of malignancy index, which is disclosed in detail in our work.

Aim: To present the morphological features of ovarian neoplasms in close relationship with the risk index of malignant neoplasms.

Material and methods. Study design: a prospective comparative study. The research protocol was approved by the Local Ethics Committee West Kazakhstan Marat Ospanov Medical University No. 3 dated 09.04.2019. The informed consent of women to participate in the study and the consent of the management of the clinics for the study were obtained. The work was carried out in the departments of gynecology in Aktobe (Kazakhstan) and Ahmadi hospital (Kuwait) in the period from 2019 to 2021. A total of 264 patients were divided: I group of reproductive age (≥18-40 years), II group of premenopause (> 41-50 years), and III groups of postmenopause (> 50 years). Inclusion criteria are <18 years, ultrasound confirmation of ovarian neoplasm, subject to surgical treatment. Exclusion criteria are pregnant women, endometriosis, adenomyosis, ovarian cancer, pelvic formations arising from the urinary tract and/or gastrointestinal tract.

The risk index for malignancy (RMI) was calculated using the formula of Tingulstad et al. [14] based on ultrasound scores (U), menopausal status (M), and CA levels of 125. The cut-off level is 200. An overall ultrasound score of 0 or 1 gave U = 1 and a score of ≥2 gave U = 3. Premenopausal status gave M = 1 and postmenopausal status gave M = 3. Postmenopausal status was defined as amenorrhea more than one-year-old or previous hysterectomy and age ≥50 years.

The morphological study was carried out in the laboratory of the West Kazakhstan Marat Ospanov Medical University. The material was fixed in a 10% solution of buffered formaldehyde. Then, after the stage of paraffinization, a series of histological sections with a thickness of 4-5 μm were made from paraffin blocks and stained with hematoxylin-eosin according to the standard technique. Microscopic studies of the histotructures were performed using an Axio Lab A1 light microscope (Germany) with a digital camera AxioCam Erc s (Germany) using lenses × 10, × 40. For quantitative microscopic analysis (volume of epithelium, epithelial cells, nuclei, vessels), an eyepiece micrometer and an object micrometer were used (G.G. Avtandilov, 1990).

Statistical analysis was performed using the SSAS - 25.0 application program. Numerical variables (M ± SD) are presented as mean ± standard deviation. Categorical variables are presented as numbers and percentages (%). For the analysis of quantitative and qualitative data, Student's t and chi-square (x^2) tests were used, respectively. The receiver operating characteristic (ROC) curve was used to determine the RMI value with the highest sensitivity, specificity, PPV, and NPV when distinguishing between benign and malignant ovarian lesions in the study groups. Correlation coefficient analysis was also used to find the relationship between RMI and participant variables. P <0.05 was considered significant.

Result

In the reproductive group, the incidence of benign ovarian tumors prevailed (90.9%) compared with the premenopausal and postmenopausal groups (64.8%) and (64.8%). Whereas malignant ovarian tumors are significantly higher in the premenopausal (35.2%) and postmenopausal (35.2%) groups compared with the reproductive group 9.1% (P = 0.0008).

Comparative characteristics of variable malignant and benign tumors in the study groups (reproductive, premenopausal, and postmenopausal) are presented in table 1,2,3.

Table 1.

Comparison between malignant and benign ovarian tumors in reproductive age group

Variables	Malignant tumors (N=8)	Benign tumors (N=80)	P-value (Student t test) (95% Confidence interval)
Age (Years)	36.5 ± 4.4	29.4 ± 5.4	0.7 (3.3, 7.1, 10.9)
Weight (Kg)	82.5 ± 8.7	64.2 ± 10.3	0.6 (10.9, 18.3, 25.6)
BMI (Kg/m2)	30.2 ± 2.8	24.2 ± 3.6	0.7 (3.7, 6, 8.3)
Parity	1.25 ± 1.4	3.2 ± 0.8	0.006* (-3.2, -1.9, -0.75)
CA-125 (IU/ml)	92.8 ± 49.2	18.8 ± 10.8	0.0 (32.8, 74, 115.2)
Ultrasound score	3.0 ± 0.0	1.4 ± 1.1	1.0 (-1.5, -1,1 -0.67)
Risk malignancy index	278.6 ± 147.7	33.9 ± 34.8	0.0 (120.8, 244.7, 368.6)

*: Significant difference. BMI: Body mass index. CA-125: Cancer antigen-125. Data presented as mean ± SD (Standard deviation). N: Number. Student t test used for statistical analysis.

Table 2.

Comparison between malignant and benign ovarian tumors in premenopausal group.

Variables	Malignant tumors (N=31)	Benign tumors (N=57)	P-value (Student t test) (95% Confidence interval)
Age (Years)	47.4 ± 1.3	44.2 ± 2.5	0.9 (2.4, 3.2, 4.0)
Weight (Kg)	80.7 ± 7.9	69.04 ± 7.6	0.3 (8.2, 11.7, 15.1)
BMI (Kg/m2)	31.1 ± 2.9	26.3 ± 2.7	0.3 (3.5, 4.8, 6.1)
Parity	0.68 ± 0.47	3.37 ± 1.24	1.0 (-3.1, -2.7, -2.3)
CA-125 (IU/ml)	110.4 ± 68.3	23.5 ± 22.1	0 (60.9, 86.9, 112.8)
Ultrasound score	3.0 ± 0.0	2.1 ± 1.07	1.0 (-2.3, -2.0, -1.74)
Risk malignancy index (RMI)	331.1 ± 204.8	54.7 ± 64.7	0.0 (198.8, 276.4, 353.9)

BMI: Body mass index. CA-125: Cancer antigen-125. Data presented as mean ± SD (Standard deviation). N: Number.

Table 3.

Comparison between malignant and benign ovarian tumors in postmenopausal group.

Variables	Malignant tumors (N=31)	Benign tumors (N=57)	P-value (Student t test) (95% Confidence interval)
Age (Years)	61.4 ± 2.9	55.5 ± 3.5	0.8 (4.5, 5.9, 7.2)
Weight (Kg)	85.8 ± 7.9	66.5 ± 6.2	0.05 (15.9, 19.3, 22.6)
BMI (Kg/m2)	32.8 ± 2.9	25.7 ± 2.2	0.03* (5.9, 7.1, 8.3)
Parity	0.77 ± 0.75	3.03 ± 0.86	0.7 (-2.6, -2.3, -1.9)
CA-125 (IU/ml)	87.8 ± 168.8	14.2 ± 7.1	0.0 (11.7, 73.6, 135)
Ultrasound score	3.0 ± 0.0	2.6 ± 0.8	1.0 (-2.7, -2.5, -2.27)
Risk malignancy index (RMI)	497.1 ± 240.7	94.7 ± 58.5	0.0 (312.5, 402.4, 492.3)

*: Significant difference. BMI: Body mass index. CA-125: Cancer antigen-125. Data presented as mean ± SD (Standard deviation). N: Number.

The age of those examined between malignant and benign ovarian tumors was not significant, but there was a relationship between age and RMI. The average weight was significantly higher in the case of a malignant process than in the case of a benign one in the study groups (P = 0.6, P = 0.3, P = 0.05). Between malignant and benign tumors, BMI readings were not significant in the reproductive (P = 0.7) and premenopausal (P = 0.3) groups. Although there was a significant difference between malignant and benign ovarian tumors in the postmenopausal group in terms of BMI (32.8 ± 2.9 and 25.7 ± 2.2 kg / m2, respectively, P = 0.03).

In malignant ovarian tumors, the parity was significantly lower than in benign tumors (in the reproductive group (P = 0.006), in the premenopausal and postmenopausal groups.

It should be noted that significant differences in Ca125 levels were detected between malignant and benign ovarian tumors in the study groups. At the same time, there was a significant positive correlation between the CA-125 examined and RMI (r = 0.55, P <0.0001) in the group of ovarian malignant neoplasms.

Although the USG score in this study was significantly higher in the premenopausal and postmenopausal compared with the reproductive group (P = 0.01), the analysis showed no significant correlation between the USG score and RMI in the ovarian malignancy group (P = 0.1). The group of malignant tumors is characterized by 2 or more morphological changes (the presence of multilocularity, hard nodules, ascites), which tend to

increase with age. A group of benign tumors is characterized by no more than one morphological sign (multilocularity).

RMI at a cut-off> 200 reproductive age group on HP 6 showed true positive ((TP) = 6), 1 was false positive ((FP) = 1). At <200, 2 cases were confirmed as false negative ((FN) = 2) and 79 were confirmed as true negative ((TN) = 79). At the same time, RMI with a threshold value of> 200 had a sensitivity of 75%, a specificity of 98.75%, PPV and NPV of 85.7% and 97.5%, respectively, in distinguishing benign and malignant ovarian tumors in the reproductive group. While ROC showed that RMI at a value> 231.6 at reproductive age had a sensitivity and specificity of 75% and 100%, PPV and NPV 100% and 97.3%, respectively (area under the ROC curve (AUC) 0.950, 95 % CI: 0.88-0.98, P = <0.001). Figure 1a.

In the premenopausal group, RMI at a cut-off value of> 200 on HP in 25 were confirmed as true positive ((TP) = 25), in 5 were confirmed as false positive ((FP) = 5). At <200, 6 were confirmed as false negative ((FN) = 6), and 52 were confirmed as true negative ((TN) = 52). RMI with a cut-off value> 200 had 80.6% sensitivity, 91.2% specificity, 83% PPV and 89.7% NPV in differentiating malignant and benign ovarian tumors in the premenopausal group. At the same time, ROC showed that RMI with a value> 247.5 had a sensitivity of 80.65%, a specificity of 100%, a PPV of 100% and 97.9% of NPV (AUC 0.96, 95% CI: 0.89-0.99 , P = <0.001). Figure 1b.

In the postmenopausal RMI group, at cut-off value> 200, 27 were confirmed as true positive (TP) = 27), and 6 were confirmed as false positives ((FP) = 6) by HP. With RMI <200, 4 was confirmed as false negative ((FN) = 4), and 51 was true negative ((TN) = 51). RMI with a cut-off value> 200 had a sensitivity of 87.1%, a specificity of 89.5%, PPV of 81.8%, and NPV of 92.7% when distinguishing benign and malignant ovarian tumors in the postmenopausal group. ROC showed that RMI at cut-off value> 245.7 in the postmenopausal group had 87.1% sensitivity, 100% specificity, 100% PPV and 98.6% NPV (AUC 0.960, 95% CI: 0.89-0.99 , P = <0.001). Figure 1c.

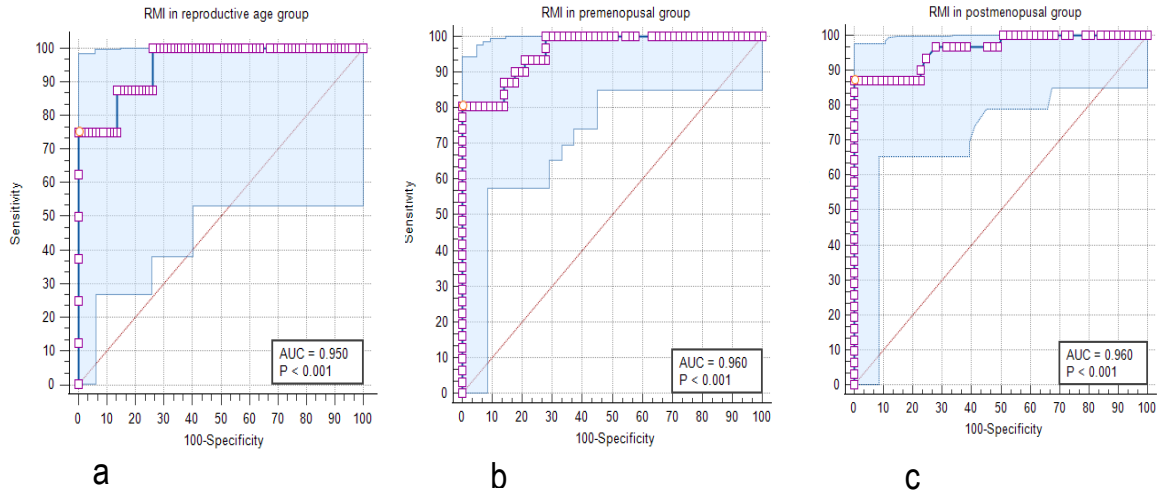


Figure 1. ROC curve in the studied groups a-reproductive, b-premenopausal, c-postmenopausal.

The prevalence of histological structures of ovarian tumors is shown in Fig. 2. In the reproductive group, among benign neoplasms, the majority of cases were serous (simple) cysts (38.75% (31/88)), followed by follicular cysts in 23.75% (19/88). Fig. 2a. Ovarian malignancies were squamous cell carcinoma in 87.5% (7/8) and endometrioid carcinoma in 12.5% (1/8).

The inner surface of the serous cyst wall is lined with a flattened epithelium (in some observations, cubic), 16.5 ± 0.73 microns. Dystrophic changes and necrosis of epithelial cells or desquamation are observed in places. The connective tissue base directly under the epithelium is represented by parallel bundles of collagen fibers, in which loosening and cellular infiltration take place in the deep layers, especially at the border with the intact ovarian tissue. Fig. 3a.

In second place were follicular cysts, the wall of which is represented by small cubic cells, and occasionally there was slight luteinization of the epithelium. The basis of the epithelium is loose connective tissue, there is a plethora and stasis of the vessels of the microvasculature with diapedesis of erythrocytes into the surrounding tissues. Fig. 3b.

In the premenopausal and postmenopausal groups, there is a predominance of cystadenoma of 31.6% (18/57) and 29.8% (17/57) over serous cysts - in 24.6% (14/57), and 14.0% (8 / 57) observations, respectively. A relationship was found between the increase in the frequency of dermoid cysts with the age of patients in these groups - 19.3% (11/57) and 21.0% (12/57), respectively. Fig. 2 b, c.

Among malignant tumors, the most common malignant variant in premenopausal women was cystadenocarcinoma in 32.2% (10/31) and squamous cell carcinomas in postmenopausal women in 35.5% (11/31), squamous cell carcinoma in second place in 25.8% (8 / 31) and endometrioid carcinoma in 22.6% (7/31), respectively.

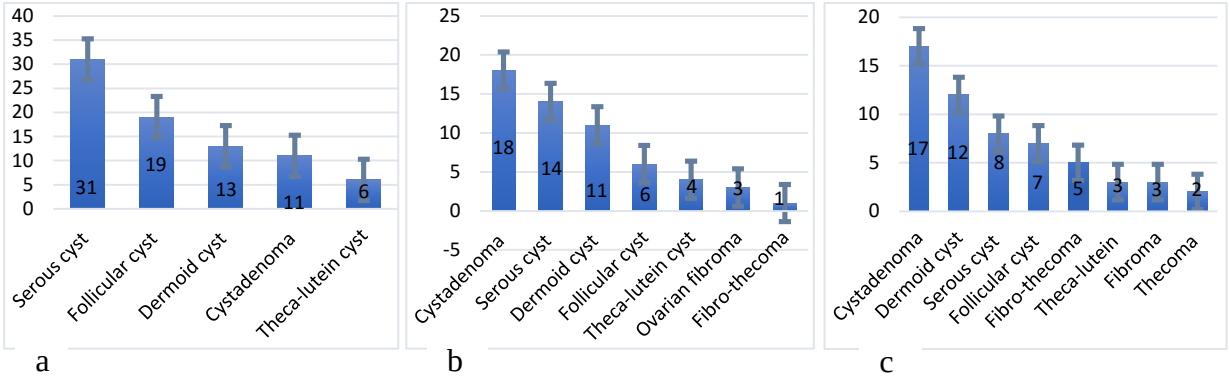
Various variants of cystadenomas (serous, papillary, mucinous) were revealed histologically. The lining of the inner surface of serous cystadenoma is represented by ciliated prismatic epithelium with the presence of separate secretory cells, 18.4 ± 0.22 μm thick. To the outside is a layer of angiomatous tissue, which is represented by a

heterogeneous structure of vessels of a different caliber. In places, a sharp venous plethora of large vessels and pronounced edema of the stroma with perivascular sclerosis. Fig. 3c.

On the inner surface of papillary serous cystadenoma, multiple papillary growths of the epithelium with signs of dysplasia with stratification, without atypical changes were revealed. The focal proliferation of epithelial tissue in the form of budding with different cell populations is expressed. Bubble large cells with an oval nucleus alternate with ciliated intercalated and tall cylindrical cells with a light cytoplasm with a hyperchromic nucleus. The thickness of the epithelium in the places of stratification with a diameter ranging from 25.4 ± 0.13 to 29.3 ± 0.11 microns. Fig. 3 d

The inner wall of the mucinous cystadenoma is lined with a single-row high columnar epithelium, 23.7 ± 0.38 microns thick. The cytoplasm is eosinophilic with a basal arrangement of the nuclei. In the central and apical part of the cytoplasm of epithelial cells, there are whitish vacuoles (mucus). Under the epithelium, the stroma is edematous, represented by parallel thick bundles of collagen fibers and deserted vessels, followed by a layer of loose dense connective tissue. Fig. 3e.

The dermoid cyst is histologically represented by tissues of ectodermal origin; The inner surface of the cyst wall was lined with multilayer squamous epithelium with the presence of skin appendages in the thickness of the wall - hair follicles, sebaceous glands. Fig. 3f.



a – Reproductive; b – Premenopausal; c - Postmenopausal;

Figure 2: The histological structure of benign ovarian tumors in the study groups

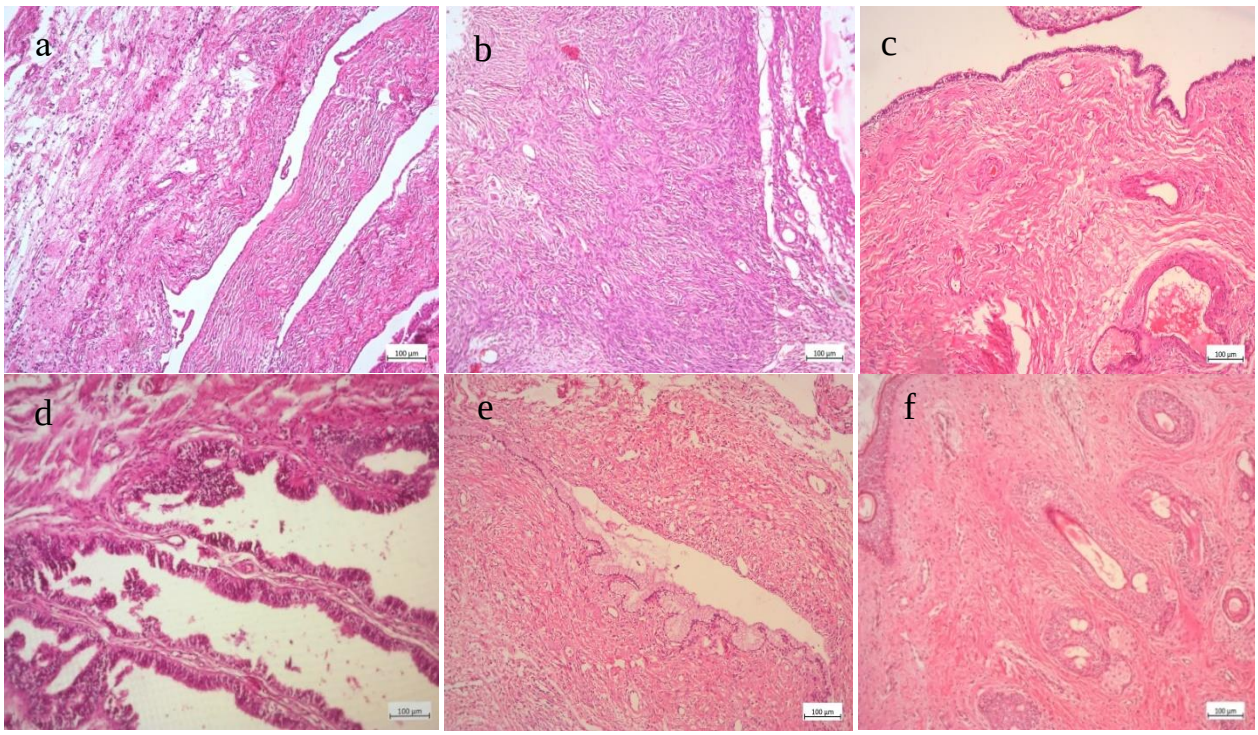


Figure 3. a - Simple serous cyst; b - Follicular cyst; c - Serous cystoadenoma; d - The wall of serous papillary cystadenoma; e - Wall of mucinous cystadenoma; f - Dermoid cyst. Staining with hematoxylin and eosin, ×100

Comparative characteristics of malignant and benign ovarian tumors in the three study groups are presented in Table 4.

Table 4.

Comparison between studied malignant and benign ovarian tumors.

Variables	Malignant ovarian tumors (N=70 women)	Benign ovarian tumors (N=194 women)	P-value (Student t test) (95%Confidence Interval)
Age (Years)	52.3 ± 9.1	41.5 ± 11.7	0.9 (8.1, 10.8, 13.5)
Weight (Kg)	83.2 ± 8.4	66.3 ± 8.7	0.6 (14.6, 16.9, 19.3)
BMI (Kg/m2)	31.8 ± 3.1	25.3 ± 3.1	0.4 (5.6, 6.5, 7.3)
Parity	0.78 ± 0.8	3.2 ± 0.9	0.8 (-2.6, -2.4, -2.2)
CA-125 (IU/ml)	85.5 ± 57.1	18.8 ± 14.8	0.0 (53, 66.7, 80.4)
Ultrasound score	3.0 ± 0.0	1.9 ± 1.1	1.0 (-2.0, -1.85, -1.7)
RMI	392.7 ± 235.9	57.9 ± 58.04	0.0 (277.8, 334.8, 391.7)
Post-operative histological examination	Malignant ovarian tumors Squamous carcinoma 37.1% (26/70) Cystadenocarcinoma 28.6% (20/70) Endometrioid carcinoma 18.6% (13/70) Granulosa-cell tumors 14.3% (10/70) Malignant Brenner tumor 1.4% (1/70)	Benign ovarian tumors Serous cyst: 27.3% (53/194) Cystadenoma: 23.7% (46/194) Dermoid cyst: 18.6% (36/194) Follicular cyst: 16.5% 32/194 Thecal lutein cyst: 6.7 (13/194) Ovarian Fibroma: 3.1% (6/194) Fibro-thecoma: 3.1% (6/194) Thecoma: 1.0% (2/194)	

BMI: Body mass index. CA-125: Cancer antigen-125. Data presented as mean ± SD Standard deviation and number and percentage (%). N: Number. RMI: Risk malignancy index. Student t test used for statistical analysis.

RMI with a cut-off value> 200 in the three study groups had a sensitivity of 82.9%, a specificity of 93.8%, a PPV of 82.9%, and an NPV of 93.8% when distinguishing between benign and malignant ovarian lesions. The ROC showed, at an RMI cut-off of> 247.5 in the three study groups, it had a sensitivity of 82.9%, a specificity of 100%, a PPV of 100%, and an NPV of 98.1%. A ROC curve was constructed for all obtained RMI estimates from the study, the area under the curves (AUC) is 0.955 for RMI (P = <0.001). Figure 4.

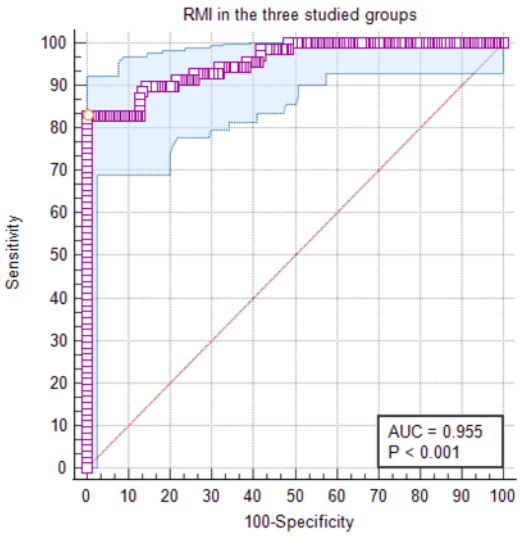


Figure 4. ROC Curve for RMI at > 247.5 in Three Study Groups

The analysis of the correlation coefficient showed a significant positive correlation depending on the age of the surveyed and RMI (P = 0.001) and a significant positive correlation between CA-125 participants and RMI (P <0.0001) in the group with a high risk of ovarian malignancy.

Discussion

In our study, 26.5% of malignant and 73.48% of benign ovarian lesions were found. Of these, 90.9% of benign ovarian tumors were present in the reproductive age group, while 35.2% of premenopausal and postmenopausal ovarian tumors were malignant. The average age of women with newly diagnosed ovarian neoplasms was 52.3 ± 9.1 and 41.5 ± 11.7 years, respectively, (P = 0.9).

Similar results were obtained by the researchers Malli M et al. [8], where the percentage of malignant tumors was 27%, and the most common was a benign process - 73%. Concerning the age characteristics of the detection of neoplasms, we had differences, the authors had benign tumors up to 40 years old, while germ cell tumors were detected at an early age - up to 30 years, while malignant tumors were over 40 years old. Terzić M, et al. [15], report that a benign tumor was 62.96%, and a malignant one - 37.04%. Of these, in the premenopausal age group, malignant (25.5%) were lower and benign tumors (74.51%), higher, while in postmenopausal women, higher rates of malignant (56.67%) and low (43.33%) were observed. benign neoplasms compared to our work. Mallika B et al. [9] in their studies claim a lower rate of ovarian neoplasms (40-60 years) of borderline (3%) and malignant origin (10%), while the incidence of benign ovarian tumors is insignificant, but higher and amounted to 87%. 55% of them were of reproductive age (20-39 years), which was significantly lower than in our studies (90.9%). The age range was 15-70 years old. A study Boujoual M., et al. [2] showed that malignant neoplasms of the ovaries are more common in premenopausal and postmenopausal women.This observation is consistent with previous studies, which showed that the disease is more common in the 41-60 age group (average 50 years).

Thus, if we talk about the age priorities of detecting ovarian formations, then the studies carried out show such a tendency that malignancy is gaining its pace of development closer to the postmenopausal age. Moreover, the difference in age data and indicators, in our opinion, can be mediated by the sample size, lifestyle, and region of residence, which affect the physiological processes of the body.

Further analysis according to the type of tumors showed that among benign tumors in the reproductive group, the most common histological types were serous ovarian cysts in 38.75%, followed by follicular cysts in 23.75%, and teratomas in 16.25%, cystadenomas 13, 75%. At the same time, the frequency of serious cysts was higher in the reproductive group compared with the postmenopausal group (14.0%), p = 0.001. In the premenopausal and postmenopausal groups, cystadenomas are in the lead. The most common benign tumor is serous cystadenoma, while the most common malignant tumor is serous cystadenocarcinoma [8]. In other studies, mucinous cystadenoma and dermoid cysts are considered the most common benign ovarian tumors (11.9% and 10.32%, respectively) [3]. Although frequent histological variants of benign tumors were serous cystadenoma (59%), followed by cystic teratoma (12%) [9]. However, Hakansson F, Høgdall ˚ et al. Presented endometriotic cysts (272) and serous cystadenomas (107) as frequent benign conditions [4]. Thus, the difference in our study is that one of the exclusion criteria was suspicion of endometriosis, since endometriosis, benign disease of reproductive age, is associated with an increase in CA-125 levels [11]. In the reproductive group, the serous cyst was in the lead (38.75%), followed by follicular (23.75%), dermoid (16.25%), cystadenoma (13.75%). In the premenopausal and postmenopausal groups, there is a predominance of cystadenomas (31.6% and 29.8%, respectively), which is comparable with the data of many authors. There is a close relationship between the growth of dermoid cysts with age (19.3% and 21.0%, respectively), but the follicular type is adherent to a younger age (10.5% and 12.3%, respectively).

During the RMI study, we focused on a cut-off rate> 200 - false positive in 1 case (dermoid cyst), and <200 false negative which was in 2 cases (squamous cell carcinoma - 2) reproductive age group. RMI at a cut-off value> 200 had a sensitivity of 75%, a specificity of 98.75%, a PPV of 85.7% and an NPV of 97.5% in distinguishing between benign and malignant ovarian tumors. ROC showed, at cut-off> 231.6, sensitivity 75%, specificity 100%, PPV 100% and NPV 97.3% (area under the ROC curve (AUC) 0.950, 95% CI: 0.88-0.98, P = <0.001).

RMI at cut-off value> 200 resulted in 5 false positive cases (fibroma, tecoluteic cyst, 2-dermoid cyst and cystoadenoma), with <200 false negative cases in 6 cases (granulosa cell malignancies - 6) premenopausal age group. RMI with a cut-off value> 200 had 80.6% sensitivity, 91.2% specificity, 83% PPV and 89.7% NPV in differentiating malignant and benign ovarian tumors in the premenopausal group. ROC showed that RMI at a cut-off value> 247.5 in the premenopausal group had a sensitivity of 80.65%, a specificity of 100%, a PPV of 100% and an NPV of 97.9% (AUC 0.96, 95% CI: 0.89-0 , 99, P = <0.001).

RMI at a threshold value of> 200 was false-positive in 6 cases (serous cyst-1, cystoadenoma-5), at <200, false-negative were in 5 cases (malignant granulosa cell tumors) postmenopausal age group. RMI with a cut-off value >200 had a sensitivity of 87.1%, a specificity of 89.5%, PPV of 81.8% and NPV of 92.7% when distinguishing benign and malignant ovarian tumors in the postmenopausal group. ROC showed that RMI at cut-off value> 245.7 in the postmenopausal group had 87.1% sensitivity, 100% specificity, 100% PPV and 98.6% NPV (AUC 0.960, 95% CI: 0.89-0.99 , P = <0.001). RMI at a cut-off value >200 in the three study groups had a sensitivity of 82.9%, a specificity of 93.8%, a PPV of 82.9% and an NPV of 93.8% when distinguishing between benign and malignant ovarian lesions. The ROC showed that the RMI at a cut-off value> 247.5 in the three study groups had a sensitivity of 82.9%, a specificity of 100%, a PPV of 100% and an NPV of 98.1% (AUC 0.955, 95% CI: 0.92-0, 97, P = <0.001).

In another work showed that RMI with a cutoff >200 between the HP and RMI categories showed a positive correlation. Moreover, the HP malignant result gave a higher RMI. The sensitivity-specificity of the RMI was 83.33% and 94.12%, the positive predictive value and the negative predictive value were 89.29% and 90.57%, respectively [15]. The 3 methods included in the RMI score were also compared with each other (RMI, CA-125, ultrasound) to find the best diagnostic test. RMI is considered to be more effective than CA-125 for individual ultrasound, which had good sensitivity but poor specificity. According to their data, when RMI>150 was used, they had 17 false-negative (non-epithelial) and 12 false-positive cases (dermoid and endometrioid cysts). At the same time, RMI had poor sensitivity in the tumor of germ cells and genital cord stroma. Moreover, RMI had the fewest false-positive cases with a threshold value >150 than RMI>200. [16]. Simsek H.S. et al. [13] report that RMI at cut-off> 168 gives an optimal result that the analysis of the ROC curve showed a sensitivity of 74.7%, specificity of 96.2%, PPV 94%, NPV 82.6%, respectively, than the individual parameters of the ultrasound assessment and the level of CA125. Although RMIs show lower sensitivity and specificity 70.5% and 87.8%, PPV and NPV 70.5% and 87.8%, respectively, it is associated with small sample size and a significant number of benign tumors. At the same time, the relationship was significant (p 0.0003) between RMI and the histological type of serous tumors, except for mucinous tumors [12].

Thus, the RMI values in the groups of malignant neoplasms prevailed >200 than in the group of benign ones. RMI had a sensitivity of 82.9%, a specificity of 93.8%, a PPV of 82.9%, and an NPV of 93.8% when distinguishing between benign and malignant ovarian lesions. At the same time, RMI had a low sensitivity to tumors of germ cells and genital cord stroma, which manifested itself as a false-negative result.

Conclusion.

In this work, we evaluated RMI 2 in the study population and found that at a cut-off value of 200, this method was able to correctly identify 96.7% of women with malignant ovarian cancer. This may be due to the very high level of CA-125. You can see that high levels of CA-125 directly and significantly affect RMI 2.

The incidence of cancer detection was significantly higher in the premenopausal and postmenopausal groups compared to the reproductive group (P = 0.0008). The malignancy index allows one to suspect the malignancy of the ovarian formations, which corresponds to the results of HP in 26.5% of cases (malignant tumors). The correspondence of the risk of malignancy according to RMI and postoperative HP data is statistically significant. The area under the curves (AUC) ROC is 0.955 for RMI (P = <0.001).

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Author contribution statement:

All authors were equally involved.

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