Predictive factors of malignancy in patients with adnexal masses

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Summary

Introduction: Good preoperative tumor triage is essential for choosing the appropriate approach. *Objective:* The study aim was to identify factors from standard preoperatively collected data, which could predict the nature of adnexal masses prior surgery. *Material and Methods:* The study involved all women treated in the Clinic for Gynecology and Obstetrics Clinical Center of Serbia for adnexal tumors throughout a period of 18 months. On admission, detailed anamnestical and laboratory data were obtained and ultrasound scans were performed. Obtained data were compared with hystopathological findings of tumors. Methods of correlation and logistic regression were applied to create association models. *Results:* Three new models for predicting tumor nature were achieved from anamnestical data, characteristics of women and tumors, and laboratory analyses. Two statistically significant (p = 0.000) equations were obtained for anamnestical data and characteristics of women and tumors, while three were made for laboratory analyses. Sensitivity of anamnestical malignancy index (AMI) was 73.33%, specificity 72.87%, positive predictive value (PPV) 39.49% and negative predictive value (NPV) 91.88%. Sensitivity of characteristic malignancy index (CMI) was 92.38%, specificity 67.36%, PPV 40.59% and NPV 97.34%. Sensitivity of laboratory malignancy index (LMI) was 56.45%, specificity 90.24%, PPV 68.63%, and NPV 84.57%. *Conclusions:* The best predictors of malignancy are menopausal status, body mass index (BMI), age, metastases, ascites, tumor marker CEA level, and erythrocyte sedimentation rate (ESR). Along with the risk of malignancy index (RMI), for more reliable triage and preoperative tumor evaluation the authors propose introduction of another three indexes (AMI, CMI, LMI) in clinical practice.

Key words: Adnexal masses; Preoperative triage; Predictors; Models.

Introduction

Although ovarian cancer, in the form of a malignant epithelial tumor, represents only the seventh most common malignant tumor in women, it is the fourth most common cause of death [1]. Good preoperative discrimination between benign and malignant ovarian tumors results in more women being appropriately referred for gynecologic oncology care and more women with benign conditions undergoing conservative surgical treatment [2]. The risk of malignancy index (RMI) is so far the best and most widely used tool for preoperative identification of patients with ovarian cancer [3]. However, currently there is no effective tool available to reliably predict the nature of adnexal masses and there are still significant false results [4]. Therefore, further research on recognition of new and trustworthy parameters that can preoperatively assess tumor nature is needed. The aim of this study was to identify factors from standard preoperatively collected data which could predict the nature of the adnexal masses prior to surgery.

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Materials and Methods

The study included all consecutive patients operated for adnexal tumors at the Clinic of Gynecology and Obstetrics, Clinical Center of Serbia throughout the period of 18 months (January 1, 2010 to June 30, 2011). All variables used in the protocol of the Clinic upon admission for adnexal tumor operation were prospectively collected for every patient and considered for association with the histopathological (HP) finding. Clinical and ultrasound informations were collected in a standardized manner. Clinical information obtained anamnestically regarded patient demographics (age, educational level, occupation, and residency) and gynecological data (family and personal history of gynecological and other diseases, menarche age, parity, last menstrual cycle, symptoms). Standard laboratory analysis included erythrocyte sedimentation rate (ESR), tumor marker levels (CA-125, CEA, Ca 19.9, Ca 15.3). Furthermore, body mass index (BMI) was calculated using the regular formula BMI = body weight (kg)/height^2 (m^2). Aside from clinical examinations of pelvic organs, a detailed/expert ultrasonographic scan was performed. The authors used HDI 5000, Sono CT, and Xres, with endovaginal-V8-4MHz (V) probe and its associated software. Ultrasound scan was performed by two experienced doctors. Risk of malignancy index (RMI) was calculated using the proposed formula: RMI = U x M x CA-125 [5]. In the formula, U represents the ultrasonographic index. In multilocular and bilateral tumors, the presence of solid areas in tumor, metastasis and ascites are marked with one point each. The sum of these points, are scored so that U 0 = 0 points, U 1 = 1 point, U 2-5 = 3 points. In the formula, M represents

menopausal status (1 for premenopausal and 3 for postmenopausal women). Levels of CA-125 are calculated directly to the equation. RMI < 25 shows low risk, 25-250 intermediate risk, while RMI > 250 shows high risk for malignancy. When different masses were present, only information from the most complex one was used for analysis. Standard operative procedures appropriate for the staging of the tumor were undertaken and all tumors were extracted and sent for HP analysis. Postoperatively, final HP enabled to classify each mass as benign, borderline, or malignant. First simple correlations of examined parameters and HP findings, as well as RMI were done. Then, all examined variables were divided into three groups and evaluated their correlation with tumor type, for the whole group. The first group regarded anamnestical data (personal and family illness history, employment status, menopausal status menarche time, number of births, miscarriages, and abortions), the second one included characteristics of women (age, presence of symptoms, and BMI) and tumors (dimensions, multilocularity, and bilateralism, solid parts, metastases, and ascites), and the third consisted of laboratory analyses (tumor marker levels, RMI, and ESR). Having all the necessary information, models for preoperative malignancy predictions were made. The authors calculated numerical values in the examined population of these newly-constructed overall models: anamnestical malignancy index (AMI), characteristic malignancy index (CMI), and laboratory malignancy index (LMI). The parametrical factors were calculated directly into the equations. Non-parametrical factors were categorized and scored. Having positive family history of gynecological diseases or being in menopause received one point while the opposite situation was scored with two points. Ascites presence received one point and absence zero points. Tumors < five cm were scored with one point, from five to ten cm with two points, while > ten cm with three points. The cut-off point for each index was determined. Finally, sensitivity [(true positive/true positive + false negative) x 100], specificity [(true negative/true negative + false positive) x 100], positive [(true positive/true positive + false positive) x 100], and negative [(true negative/true negative + false negative) x 100] predictive values were calculated for AMI, CMI, and LMI.

In the statistical analysis, for the general description percentages (%) were mostly used. Spearman correlation was used to determine associations between tumor types or RMI and individual investigated parameters as well as for model values and HP findings. At the end, multivariate binary logistic regression was applied to investigate the relationships of groups of investigated parameters together and the tumor type (benignant/malignant) in order to form equations that could be of use in preoperative patient assessment. The level of significance was $p < 0.05$. Obtained data were analyzed using the SPSS software (Advanced Statistics, version 17.0, Chicago, IL).

Results

This study involved 520 women. HP revealed that 85 (15.74%) women had malignant while 435 (80.56%) had benignant tumors.

HP findings significantly correlated with patients' age ($p = 0.257$; $p = 0.000$), employment status ($p = 0.100$; $p = 0.020$), menopausal status ($p = 0.252$; $p = 0.000$), number of births women had ($p = 0.904$; $p = 0.029$), number of abortions ($p = 0.159$; $p = 0.000$), women's BMI ($p = 0.108$; $p = 0.000$), presence or absence of metastases ($p = 0.576$; $p = 0.000$), ascites ($p = 0.455$; $p = 0.000$), Ca 125 level ($p = 0.272$; $p = 0.000$), Ca 15.3 level ($p = 0.468$; $p = 0.000$), RMI ($p = 0.296$; $p = 0.000$) and ESR ($p = 0.279$; $p = 0.000$).

RMI significantly correlated with HP findings ($p = 0.296$; $p = 0.000$), menopausal status ($p = 0.364$; $p = 0.000$), number of miscarriages ($p = 0.142$; $p = 0.001$), BMI ($p = 0.137$; $p = 0.000$), symptoms ($p = 0.117$; $p = 0.007$), Ca 19.9 level ($p = 0.178$; $p = 0.004$), Ca 15.3 level ($p = 0.305$; $p = 0.001$), ESR ($p = 0.284$; $p = 0.000$) and patients age ($p = 0.246$; $p = 0.000$). As expected, the characteristics that are assessed in order to calculate RMI are all highly and significantly correlated with RMI values: multilocularity ($p = 0.217$; $p = 0.000$), solid parts ($p = 0.142$; $p = 0.001$), metastases ($p = 0.341$; $p = 0.000$), ascites ($p = 0.307$; $p = 0.000$), bilaterality ($p = 0.138$; $p = 0.001$) and Ca 125 level ($p = 0.801$; $p = 0.000$).

As numerous simple correlations were established and almost all examined parameters were associated either with tumor type HP or with the RMI, all variables were divided into three groups and evaluated their correlation with tumor type, for the whole group.

When anamnestical characteristics of examined women were assessed all together, a significant model - anamnestical malignancy index (AMI), was achieved in Enter method ($\chi^2 = 102.959$; $p = 0.000$). The model's total calcification success was 82.4% and R^2 Nagelkerke 0.277. Menopausal status and family history of gynecological illnesses were significant parameters. Therefore, using Forward Wald method, two equations were constructed ($\chi^2 = 73.466$; $p = 0.000$; R^2 Nagelkerke = 0.203 and $\chi^2 = 92.686$; $p = 0.000$; R^2 Nagelkerke = 0.252) (Table 1).

When characteristics of women and tumors were assessed together, a significant model - characteristic malignancy index (CMI), was achieved in Enter method ($\chi^2 = 273.425$; $p = 0.000$). The model's total calcification success was 91.3% and R^2 Nagelkerke 0.635. Patients' BMI and age, ultrasound scan estimated diameters, and presence of ascites were significant parameters (Table 1). Using the Forward Wald method, one more parameter – metastases, proved to be significant ($\chi^2 = 149.561$; $p = 0.000$; R^2 Nagelkerke = 0.386) (Table 1).

When findings of laboratory analyses were assessed together, a significant model - laboratory malignancy index (LMI) was achieved in Enter method ($\chi^2 = 48.868$; $p = 0.000$). The model's total classification success was 85.9% and R^2 Nagelkerke 0.671. No specific parameters were pointed out. However, using Forward Wald method, three equations were created ($\chi^2 = 31.913$; $p = 0.000$; R^2 Nagelkerke = 0.488; 2 = 37.439; $p = 0.000$; R^2 Nagelkerke = 0.533; 2 = 49.729; $p = 0.000$; R^2 Nagelkerke = 0.624) (Table 1).

Numerical values for the overall models achieved for three investigated factor groups (AMI, CMI, LMI) were calculated. Mean ± SD of AMI was 1.73 ± 1.06 (min = -1.55; max = 2.51). Mean ± SD of CMI was 2.85 ± 1.73 (min = -2.31; max = 5.82). Mean ± SD of LMI was 4.75 ± 12.18 (min = -9.52; max = 124.52). Obtained indices were correlated with HP findings and RMI as the most

Table 1. — *Logistic regression equations for preoperative malignancy calculation.*

Parameters	Models
Anamnestical data - AMI	Malignancy = 4.303 – 1.953 x menopausal status
	AMI: Malignancy = 0.352 + 2.069 x gynecological ilnesses in family – 1.984 x menopausal status
Characteristics of women and tumors - CMI	Malignancy = 1.914 + 23.117 x metastases
	CMI: Malignancy = 10.269 – 0.130 x BMI – 0.559 x US tumor dimensions – 2.669 x ascites – 0.057 x age
Laboratory analyses - LMI	Malignancy = 1.395 + 0.002 x RMI
	Malignancy = 2.633 + 0.002 x RMI – 0.025 x ESR
	LMI: malignancy = 3.168 - 0.259 x CEA + 0.002 x RMI – 0.031 x ESR

reliable parameter for prediction of tumor nature so far. All three indices were significantly correlated with HP (AMI $p = 0.280$; $p = 0.000$; CMI $p = 0.380$; $p = 0.000$; LMI $p = -0.195$; $p = 0.003$). AMI was HP significantly correlated ($p = 0.593$; $p = 0.000$) with CMI. AMI and LMI ($p = -0.044$; $p = 0.510$), as well as CMI and LMI were not significantly correlated ($p = -0.097$; $p = 0.145$). Moreover, all three new indices were also significantly correlated with RMI: AMI $p = -0.333$; $p = 0.000$; CMI $p = -0.311$; $p = 0.510$; LMI $p = -0.460$; $p = 0.510$.

Cut of values were set. AMI < 1 showed possible malignancy and ≥ 1 benignancy. CMI < 3 showed possible malignancy while ≥ 3 benignancy. LMI ≥ 3 showed possible malignancy and < 3 benignancy. Sensitivity of AMI was 73.33%, specificity 72.87%, positive pradictive value (PPV) 39.49%, and negative predictive value (NPV) 91.88%. Sensitivity of CMI was 92.38%, specificity 67.36%, PPV 40.59%, and NPV 97.34%. Sensitivity of LMI was 56.45%, specificity 90.24%, PPV 68.63%, and NPV 84.57%.

Discussion

Ovarian cancer has the worst prognosis among all forms of gynecological malignancies, mainly due to the lack of an effective screening method for the detection of early-stage disease [6]. An accurate preoperative diagnosis of adnexal masses is essential to provide optimal treatment [2]. Therefore, a number of strategies have been proposed to triage women with suspicious adnexal tumors [7]. Recently made multivariate logistic regression models have been introduced using a variable set of demographic, clinical, tumor marker, and ultrasound characteristics [8-11]. Over the past years, various screening methods and challenging biostatistical algorithms have been developed and validated in order to estimate the absolute risk of having ovarian cancer in women with and without symptoms [12]. Thus, it is becoming possible to analyze the relevance of combinations of markers for identification of tumor type [13]. Nevertheless, most logistic regression models were developed to discriminate benign from malignant tumors, using small sample sizes [2]. This study provides new insights into preoperative evaluation of adnexal masses using statistical modeling in a larger group of patients.

Some investigators state that in order to identify ovarian cancer with reasonable accuracy, the age of patients, their family history, serum level of CA-125, and ultrasound findings should always be taken into consideration simultaneously [11, 14]. Other studies found that the most useful independent prognostic variables for the logistic regression model were: personal history of ovarian cancer, hormonal therapy, age, maximum diameter of lesion, pain, ascites, blood flow within a solid papillary projection, presence of an entirely solid tumor, maximal diameter of solid component, irregular internal cyst walls, acoustic shadows, and a color score of intratumoral blood flow. Sensitivity of this model was 93% and specificity was 76% [15]. When researchers placed as risk factors age, family history of ovarian cancer, previous cancers other than ovarian, BMI, smoking, alcohol, deprivation, loss of appetite, weight loss, abdominal pain, abdominal distension, rectal bleeding, postmenopausal bleeding, urinary frequency, diarrhea, constipation, tiredness, and anaemia, a model explained 56% of variance [12]. The authors attempted to take into consideration all available parameters used in daily practice. The models involved similar parameters as the ones from literature and had comparable and satisfactory sensitivity and specificity.

Well-known risk factors for malignancy include: nulliparity, low parity, delayed childbearing, early onset of menses, late menopause, postmenopausal estrogen use for ten or more years, and a family history of ovarian or breast cancer [7, 14]. Furthermore, higher BMI was associated with an increased ovarian cancer risk [16-18]. Substantial literature data showed a link between adnexal mass and menopausal status [7]. Moreover, the incidence and mortality rate of ovarian cancer increases with patient age [14]. All these risk factors were also found to be significant for tumor triage in the patients studied. Achieved models showed that the most important for predicting malignancy out of all anamnestical data was menopausal status, from characteristics of women, tumors metastases, and from laboratory analyses RMI and ESR.

Serum CA-125 has been investigated for ovarian cancer screening with conflicting results [19]. CA-125 determination is useful for the detection of the persistence and recurrence and monitoring of the therapeutic effects in patients with epithelial ovarian carcinomas.

CA-125 is the most reliable serum marker in use for serial measurements to calculate the risk of cancer, which appears to have greater utility than evaluation of a single value [20]. However, elevated levels of CA-125 can also be detected in many non-malignant gynecological diseases and some physiological conditions. Numerous researchers have confirmed that CA-125 has limitations when used to distinguish between benign and malignant ovarian masses, but have concluded that by using likelihood reference tables, clinicians will be able to better interpret preoperative serum CA-125 results in patients with adnexal masses [5, 18, 20-22]. Regarding the results in this study, it can be concluded that, CA-125 is significantly correlated with HP findings, but some other tumor markers, like CEA and Ca 15.3, should also be taken into consideration.

Some studies suggest that transvaginal ultrasound (TVUS) can discriminate between benign and malignant ovarian tumors, better than all other radiological methods [4]. However, imaging techniques including TVUS evaluation alone have not fulfilled this goal [13]. This study showed that simple ultrasound findings - larger tumor dimensions, as well as the presence of metastases and ascites - can determine the malignancy of the tumor. In addition, multilocularity, bilaterality, and solid parts can implicate that the tumor is either malignant or borderline.

RMI is the most often used method for predicting the likelihood of malignancy of adnexal mass. It is derived from multivariate logistic regression analysis, incorporating menopausal status, ultrasonic score, and serum CA-125 levels. Each of these parameters has been shown to be significantly and independently related to the likelihood of malignancy [7]. Moreover, it comprises the majority of significant parameters and takes into consideration their relationships. Its effectiveness has been validated in a number of retrospective and prospective studies in which RMI had sensitivity of 85% and a specificity of 97% in differentiating malignant from benign diseases [7]. Although, some other more complex models available in literature also outperform the current reference test RMI - for discriminating between benign and malignant adnexal masses [23], RMI represents a low-cost, simple but highly-effective tool for triage in the management of women with adnexal masses [5, 7]. This study also showed that RMI can discriminate malignant and benignant as well as borderline tumors. Furthermore, Forward Wald method has proven to have the most importance for prediction of malignancy. The higher the RMI, the more probable is that the tumor is malignant. Moreover, the authors found that RMI can be considered simultaneously with the levels of ESR and CEA for more precise triage.

The established models in this study for AMI, CMI, and LMI were calculated, and proved to be linked with HP findings. Therefore, they can be introduced in preoperative evaluation of patients with adnexal tumors. Further studies can prove the validity of these new models by testing and retesting them in different populations, as well as to assess how to best implement these indices.

Conclusions

The achieved models showed that the most important for predicting malignancy out of all anamnestical data was menopausal status, from characteristics of women and tumors metastases, and from laboratory analyses RMI and ESR. Moreover, previous gynecological illnesses, patient age, and BMI have proved to be of great significance. RMI can be combined with ESR and CEA levels for better discrimination of malignant from other tumor types. Sensitivity of AMI was 73.33%, specificity 72.87%, PPV 39.49%, and NPV 91.88%. Sensitivity of CMI was 92.38%, specificity 67.36%, PPV 40.59%, and NPV 97.34%. Sensitivity of LMI was 56.45%, specificity 90.24%, PPV 68.63%, and NPV 84.57%. According to these results, the authors can advise introduction of these three indices (AMI, CMI, LMI) in clinical practice for more reliable differentiation of adnexal masses nature.

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