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The ovarian cancers in geriatric population: the validity of inflammatory markers, malignancy risk indices 1, 2, 3, 4, and CA-125 levels in malignancy discrimination of adnexal masses

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Summary

Purpose: To investigate the predictive value of the Risk of Malignancy Index (RMI), CA-125, and inflammatory markers in discriminating ovarian cancers (OCs). *Materials and Methods:* The postmenopausal (PM) women (n=139) with adnexal masses who underwent surgery were included. The predictive value of CA-125, RMI (1, 2, 3, and 4) and inflammatory markers [neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR)] were calculated in geriatric (G) and non-geriatric women. *Results:* OCs had significantly increased NLR and PLR. RMI models were highly reliable in PM (Kappa: 0.642-0.715; AUC: 0.907-0.934). CA-125 measurement alone had good accuracy and moderate reliability in PM (kappa: 0.507-0.587), excellent accuracy and moderate reliability in G, NLR, and PLR predicting OCs, showed fair agreement in the PM, while PLR had a moderate agreement with G. *Conclusion:* RMI algorithms were the best models for malignancy prediction. However, the rise of PLR and CA-125 levels in a G population may be used as referring adnexal masses to gynecologic oncologists.

Key words: Ovarian cancers; Risk of malignancy risk index; Adnexal masses; CA-125; cancer screening; Neutrophil lymphocyte ratio; Platelet lymphocyte ratio; Geriatric; Menopause.

Introduction

The advances in medicine and health care that extend life expectancy and the world's elderly population is expected to rise to two billion by 2050. The trends of population dynamics have been shown that the aging world will be a major public health concern in the future. Cancer is one of the health problems that most of the cases encountered in the elderly population. It is expected that there will be 2.3 million cancer cases in 2030, with the greatest increase in the geriatric (G) population [1].

Ovarian cancers (OCs) occur at advanced ages and they are the fifth most common cancer among women [2]. In the premenopausal period, only 7-13% adnexal masses are malignant, but unfortunately in the postmenopausal (PM) period, 30-45% are malignant [2] Due to non-specific signs and symptoms, the majority of the cases diagnosed at advanced stages. Early diagnosis of OCs decreases the mortality rate in half and has an 80% cure rate [3]. Therefore, early and accurate diagnosis before surgery is an important issue, but there is no ideal screening tool for OCs.

CA-125 levels and ultrasonography are the most widely used tools for malignant adnexal masses. Approximately 80% of patients with advanced OC have elevated concentrations of CA-125. A maximum of only 50% of patients with clinical Stage I disease have elevated CA-125 levels [4]. However, many other benign and malignant conditions may raise CA-125 level, including physiologic conditions such as ovulation and menstruation, make this test ineffective for screening premenopausal women. Therefore, increased false positivity of CA-125 test and operator-dependent subjective nature of ultrasonography precludes the reliable use of these methods. To improve the diagnostic accuracy of ultrasonography and CA-125 levels, the Risk of Malignancy Index (RMI) was developed by Jacobs *et al.* [5]. The RMI is a scoring system of the combination of ultrasonographic findings, CA-125 levels, and menopausal status. Then, RMI was modified by Tingulstad *et al.* (RMI 2 and RMI 3)[6, 7]. Finally, Yamamoto *et al.* in 2009 modified RMI and added the parameter of tumor size to calculations (RMI 4) [8]. After that many studies have been done, but there is still no ideal way of screening OCs due to the heterogeneity of the population and OCs. The sensitivity of any test is affected by the prevalence of the diseases. The majority of the prior studies investigated the RMI values of the general population. Few studies have explored these formulas in premenopausal and PM women [9-12]. There is no prior study in G population comparing to non-geriatric PM women.

Recently, certain blood cells or inflammatory markers were studied in the diagnosis and prognosis of different malignancies. The main response of the human body to cancer is inflammation [13-18]. Neutrophils are the most common white

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blood cell in the body and new findings suggest the role of neutrophils in cancer survival [13]. Thrombocytosis is also associated with poor prognosis due to growth factors released from platelets contribute to tumor growth [13]. Neutrophil lymphocyte ratio (NLR) and a platelet lymphocyte ratio (PLR) are markers of inflammation and oxidative stress. It is well-defined for many cancer types that NLR and PLR reflect advanced stage and aggressive tumor behavior [19, 20]. However, the data are limited in OCs and recent studies suggest the relationship between OC stage and survival with NLR and PLR [21-26].

Most of the studies searched RMI and inflammatory markers in the general population [12, 21-26]. Although OC is the disease of older patients and G population in previous studies were neglected. In this study, the authors aimed to explore the validity of CA-125, RMI (1, 2, 3, 4) models, and inflammatory markers in a preoperative diagnosis of OCs in PM and G population.

Materials and Methods

A total of 139 PM women with adnexal masses underwent surgery in the Haydarpaşa Numune Teaching Hospital, Obstetrics and Gynecology Department, between November 2009 and March 2015 and were recruited in the study. The data were obtained from hospital records and computer files retrospectively. Women who were lacking data or laboratory or ultrasonographic evaluation were excluded from the study. Out of 170 PM adnexal masses, 139 women included in the study. This study was planned in accordance with local ethics regulations and the Helsinki Declaration.

Baseline characteristics:

Menopause (M) was defined as one year or more period of amenorrhea. The G group was accepted as women more than 65 years of age. All patients had serum CA-125 levels, complete blood counts, and detailed gray scale ultrasonographic evaluations preoperatively. Ultrasound imaging of the cases was performed by an expert radiologist via ultrasound device with five MHz convex abdominal and eight MHz vaginal probes. The ultrasonographic findings of the masses such as metastatic foci in the abdomen, the nature of the masses as bilaterally, multilocularity, solid areas, papillary projections, and presence of septate were carefully recorded . The main outcome measures were CA125 and RMI 1, 2, 3, and 4 calculations with a histopathologic diagnosis end point.

RMI Models

RMI calculations use ultrasonographic scoring, CA-125 level, and menopausal status. Ultrasonographic scoring was done via using characteristic appearances of the masses such as: multilocularity, solid areas, bilateral tumor, and presence of ascites and metastases. Each was scored 1 point. RMI 1, 2, and 3 use the same formula with different scores. RMI 4 adds tumor size into the formula.

RMI 1 (5): U x M x serum CA-125 level. If the ultrasonographic is score 0, U is 0. If the score is 1, U is 1. If the score is more than 2, U is 3. M is the menopausal status. (M=3; PM).

RMI 2 (6): U x M x CA-125 level. If the ultrasonographic is score 0, U is 0. If the score is 1, U is 1. If the score is more than 2, U is 4. M is the menopausal status. (M=4; PM women).

RMI 3 (7): U x M x CA-125 level. If a total ultrasound score is 0 or 1 U is 1 and if ultrasonography score is more than 2, U is 3. M is the menopausal status.

(M=4; PM women).

RMI 4 (8): Ux Mx S (size of a mass) x CA-125. U is one if the total ultrasound score of 0 or 1. U is 4 if ultrasonographic score more than 2. M is the menopausal status. (M=4; PM women). S= 1, if the mass size was less than seven cm. S=2, if a mass size was above seven cm.

Table 1. — *The comparison of characteristic findings of adnexal masses in non-geriatric and geriatric group.*

	Non-geriatric masses (n=89)	Geriatric masses (n=50)	*p* value
General characteristics*			
Age	56.0±5.5	71.3±5.7	0.000
Gravidity	5.2±2.8	6.5±3.1	0.020
Parity	3.9±2.4	5.3±3.0	0.005
Abortion	0.5±1.0	1.0±1.7	0.058
Postmenopusal years	7.3±5.4	23.0±7.5	0.000
Tumor size (cm)	9.6±5.5	11.6±6.7	0.081
Stage at diagnosis**			
Malignancy prevalence	34.8% (31)	42% (21)	0.255
Borderline tumors	5.6% (5)	6% (3)	0.926
Stage I	7.9% (7)	6% (3)	0.374
Stage II	3.3% (3)	4% (2)	0.629
Stage III	9.0% (8)	16% (8)	0.213
Stage IV	9.0% (8)	10% (5)	0.844
Presenting complaints**			
Pelvic pain	59.6% (53)	60% (30)	0.958
Abdominal mass/distention	13.5% (12)	14% (7)	0.932
Weight loss	1.1% (1)	4% (2)	0.262
Vaginal bleeding	5.6% (5)	8% (4)	0.583
Urinary symptoms	11.2% (10)	2% (1)	0.052
Routine controls	9.0 % (9)	12% (6)	0.730

**mean±standard deviation*; **% (n).

Inflammatory markers

The inflammatory markers were NLR, PLR, and mean platelet volume (MPV). Blood analyzer was used for the determination of the complete blood cell counts. The authors recorded the neutrophils, the lymphocytes, the platelet counts, MPV and calculated the NLR and PLR).

Data analysis

Statistical Package for Social Sciences for Windows 18.0 program was used. The authors evaluated the data in 95% confidence interval and accepted p-value < 0.05 as statistically significant. Descriptive variables were expressed as mean values and standard deviations. The groups were compared using an independent t-test for normally distributed variables and χ^2-test for categorical variables. For qualitative data, McNemar test and Kappa analysis were used. ROC analysis was used for accuracy and cutoff values of tests.

Results

Among 139 PM women included in the study, 50 women were in G ages (36%) and 89 patients were non-geriatric PM women (64%). The age of all patients ranged from 42 years to 87 years (mean ± standard deviation: 61.1±8.9). Fifty-two

Table 2. — *The comparison of benign and malign masses relative to inflammatory markers.*

	Benign masses	Malign masses	*p* value
WCC (µl)	7.6 ±2.1	7.9±2.6	0.436
Neutrophil (µl)	5.4±6.4	5.4±2.4	0.963
Lymphocyte (µl)	2.3±2.4	1.8±0.6	0.110
Platelet (x103, µl)	259±69	312±87	0.000
NLR	2.5±1.9	3.6±3.3	0.030
PLR	132±45	216±133	0.000
MPV (fl)	8.8±1.3	8.6±1.5	0.461

women had malignant masses, including borderline tumors and 87 women had benign pathology. The malignancy prevalence was 37.4% in PM women (42% in G age women, 34.8% in non-geriatric women, $p > 0.05$). The majority of the OCs were epithelial (n=38, 73.1%), sex-cord stromal tumors (n=3, 5.8%), and metastatic tumors (n= 11, 21,1%). The G group had significantly increased age, gravidity, and parity ($p < 0.05$). The 43.8% of PM OCs were detected at Stage III or IV and pelvic pain was the most common symptom. The comparison of the groups was relative to the stage at diagnosis and presenting symptoms were similar. The details are given in Table 1.

The comparison of inflammatory markers of benign and malignant adnexal masses is shown in Table 2. White cell count (WCC), neutrophil, lymphocyte counts, and MPV were similar in malignant and benign masses. Platelet counts, NLR, and PLR were significantly increased in malignant tumors ($p < 0.05$).

Table 3 presents the comparison of inflammation and tumor markers in G and non-geriatric adnexal masses relative to pathology. The inflammatory markers of G and non-geriatric women were similar in both benign and malignant adnexal masses. CA-125 levels were significantly higher in G malign cases than non-geriatric masses. Table 4 shows the ROC analysis results of RMI indices, inflammatory markers, and CA-125.

In PM women: the diagnostic performance of RMI 1, 2, and 3 were similar with regard to AUC and Kappa statistics. RMI 2 (cutoff: 200) was the most sensitive test in both G and non-geriatric PM women. In G women, CA-125 yielded cutoff 35 with 80% sensitivity and 83.3% specificity. However, the sensitivity of CA-125 decreased to 62.5% in a non-geriatric group and 66.0% in PM women. The PPV) and NPV of each test calculated separately for each group.

PM women: RMI 1 showed PPV 80.7% and NPV 87.5%. RMI 2 showed PPV 75%, NPV 93.3%. RMI 3 for cutoff 200 showed PPV 80.7% and NPV 87.3%. RMI 4 for cutoff 450 yielded PPV 88.5% and NPV 78.8%. CA-125 (for cutoff 35 U/ml) had PPV 77.7% and NPV 80.8%.

G population: RMI 1 showed PPV 81.8% and NPV 89.2%. RMI 2 showed PPV 73% and NPV 91.6%. RMI 3 for cutoff 200 showed PPV 78.2% and NPV 88.8%. RMI 4 for cutoff 450 yielded PPV 88.2% and NPV 81.8%. CA-125 (35) had PPV 71.4% and NPV 79.3%.

Table 3. — *The comparison of tumor and inflammatory in non-geriatric and geriatric population with benign and malignant adnexal masses.*

	Benign masses (n=89)			Malign masses (n=50)		
	Non-geriatric	Geriatric	*p* value	Non-geriatric	Geriatric	*p* value
CA-125 (U/ml)	21.3±43.6	21.8±19.5	0.956	2.9±446	1.5±3902	0.002
Hematocrit %	8.2±2.9	36.7±8	0.380	36.8±4.3	37.0±4.5	0.903
WBC (µl)	7.3±1.9	8.2±2.3	0.070	7.6±2.5	8.4+2.8	0.319
Neutrophil (µl)	5.5±7.8	5.4±1.9	0.927	5.1±2.2	5.8±2.7	0.329
Lymphocyte (µl)	2.5±2.9	2.0±0.6	0.430	1.8±0.6	1.7±0.7	0.576
Platelet (x103, µl)	256±62	265±83	0.558	314±92	309±82	0.854
NLR	2.4±2.2	2.8±1.1	0.465	3.1±1.7	4.4±4.6	0.154
PLR	131±48	134±40	0.762	204±123	232±149	0.463
MPV (fl)	8.9±1.3	8.7±1.3	0.601	8.6±1.6	8.7±1.5	0.722

Table 4. — *The ROC analysis results of RMI (1, 2, 3, 4), CA-125, and inflammatory markers.*

Markers	Postmenopausal				Non-geriatric				Geriatric women			
(cutoff)	Sen	Spp	AUC	Kappa	Sen	Spp	AUC	Kappa	Sen	Spp	AUC	Kappa
RMI 1 (200)	79.2	89.5	0,934	0.693	71.9	91.2	0.935	0.676	85.2	86.2	0.936	0.715
RMI 2 (200)	90.6	82.6	0.929	0.692	90.3	82.5	0.935	0.719	90.0	75.9	0.929	0.642
RMI 3 (200)	79.2	88.4	0.928	0.673	71.9	91.2	0.933	0.676	85.7	82.8	0.928	0.676
RMI 4 (450)	76.0	86.0	0.907	0.576	70.0	87.7	0.899	0.514	85.7	82.0	0.926	0.663
CA125 (35)	66.0	88.4	0.863	0.560	62.5	93.0	0.825	0.587	80.0	83.3	0.956	0.507
NLR (3.0)	50.0	77.5	0.650	0.273	43.3	84.9	0.656	0.302	57.0	66.7	0.642	0.200
PLR (190)	43.0	90.0	0.713	0.358	33.3	90.6	0.725	0.268	57.0	88.9	0.683	0.475

Non-geriatric population: RMI 1 showed PPV 82.7% and NPV 94.1%. RMI 2 showed PPV 76.3 % and NPV 94.1%. RMI 3 for cutoff 200 showed PPV 82.7% and NPV 86.6%. RMI 4 for cutoff 450 yielded PPV 88.8% and NPV 77.4%. CA-125 had PPV 71.4% and NPV 79.3%. CA-125 had PPV 83.3% and NPV 81.5%.

The reliability of RMI models was assessed by Kappa statistics. According to these results: RMI 1, 2, and 3 had a substantial agreement in all PM women (Kappa: 0.642 - 0.715). The accuracy of the models (1, 2, 3, 4) were excellent (AUC: 0.907 - 0.934). CA-125 measurement alone had good accuracy and moderate reliability (Kappa: 0.507 - 0.587) in PM women. In G women, CA-125 > 35 U/ml had excellent accuracy and moderate reliability. ROC analysis of NLR (cutoff: 3 and PLR (cutoff: 190) predicting OCs showed fair agreement in PM and non-geriatric women. PLR showed moderate agreement in G women.

Discussion

Screening of OCs and developing accurate diagnostic tools with high sensitivity and specificity is an important issue. This paper investigated the predictive role of CA-125 levels, RMI indices, and inflammatory markers in OCs . In brief, this study showed the high accuracy of RMI algorithms. Despite decreased sensitivity in non-geriatric ages, CA-125 test was both sensitive and specific tests in G women. Both NLR and PLR significantly increased in OCs, but the diagnostic performance of inflammatory markers were not superior to RMI models.

The G population has been increasing in the world [1]. Aside from the prior studies that investigated usually general population, the present studied PM women and G population. Prior studies with diagnostic performance of inflammatory markers in OCs are limited in number and there is no prior study comparing diagnostic performance of inflammatory factors, CA-125 and RMI (1, 2, 3, 4) in the G population. The CA-125, ultrasonography, and recently inflammatory markers have been studied in the literature. However, as a screening test CA-125 in premenopausal women has some limitations since test results may increase in the variety of conditions other than epithelial OCs [2]. The American College of Obstetrics and Gynecology (ACOG) determined the referring criteria of adnexal masses [27]. However, ACOG standards have 47% sensitivity at 77% specificity. Women with a family history of ovarian and breast cancer, evidence of metastasis, associates, and a rise in CA-125 level are the referring criteria [27]. In the present study when CA-125 levels used cutoff 35 U/ml, yielded 80% sensitivity, 83.3% specificity, and AUC: 0.956. However, the sensitivity of test decreased in non-geriatric ages. The present results suggest that increased CA-125 levels above normal ranges may be used as referring criteria in a G population to gynecologic oncologists, but further studies with larger populations on this issue are needed.

After the first description of Jacobs *et al.* [5], RMI algorithms have been developed and studied to increase the diagnostic performance of CA-125 and ultrasonography [5-9]. In a systematic review of 109 studies, including 21,750 women with adnexal masses consisted of 83 different prediction models. RMI was the best predictor, and when 200 were used as the cutoff level (sensitivity: 78%, specificity: 87%) [12]. The RMI algorithms have been used throughout the United Kingdom, and various studies have confirmed its value [11,12,28]. However, there is still need for good performance tests in premenopausal women, early stage cancers, and borderline tumors [11]. In this study, RMI 1, 2, and 3 had a substantial agreement (Kappa: 0.642 - 0.715) and excellent accuracy (AUC: 0.907 - 0.934) in all PM women. The present study confirms the prior studies that RMI calculations in PM women were highly reliable.

Tumor growth depends on the interaction of tumor and host microenvironment. The angiogenesis and inflammation are the two main cascades in tumor progression [13-16]. Systemic inflammation produces proinflammatory mediators induce megakaryocyte proliferation leading to increased platelet count and reduced lymphocyte count [14-17]. Recently, hematologic indices have been incorporated into many studies to investigate the prognostic value in various cancer types [19, 20]. Firstly, prior studies searched platelet counts and relation of thrombocytosis with advanced disease [17]. Then studies with NLR and recently with PLR have been done [19, 20]. Prior studies in gynecologic cancers have been demonstrated association NLR with prognosis and survey in epithelial OCs [21-23], lymph node metastasis of endometrial cancers [29], and recurrences of cervical cancers [30]. Literature has been shown that PLR is an independent prognostic factor in ovarian [24, 25] colorectal [31], and pancreatic cancers [32]. Despite the bulk of studies in the literature about solid tumors [19, 20], studies about OCs and PLR are limited in number. After the study of Asher *et al.* that found PLR as an independent prognostic factor [24], Raungkaewmanee *et al.* found PLR was a better prognostic indicator for OC compared to thrombocytosis or NLR [25]. PLR might reflect a novel inflammatory marker incorporating both proinflammatory and procoagulatory pathways, however, the role of PLR as a prognostic biomarker in OCs needs to be clarified. Moreover, literature about the diagnostic performance of these markers in OC is limited.

Cho *et al.* investigated the diagnostic value of NLR in epithelial OC cases and found that preoperative NLR in OC patients was significantly higher compared to that in benign ovarian tumor patients [21]. Furthermore, they found the sensitivity and specificity of NLR in detecting OC were 66.1% and 82.7%, respectively (cutoff value, 2.60). Another study by Yıldırım *et al.* found the sensitivity of 55% and specificity of 81% [23]. Similar to prior studies, malignant cases had significantly increased platelet count, NLR, and PLR in the present study. NLR had a sensitivity

of 50% and specificity of 77.5% in PM women while 57% sensitivity and 66.7% specificity in G patients (cutoff value 3). PLR > 190 had a sensitivity of 57% and specificity of 88.9% in G women. This paper showed that the test performance of PLR was better than NLR. NLR and PLR predicting OCs showed fair agreement in PM and non-geriatric women. PLR showed moderate agreement in geriatric women.

This study found that RMI models (1, 2, 3) had a substantial agreement and excellent accuracy in all PM women. CA-125 measurement alone had good accuracy, moderate reliability, decreased sensitivity in PM women, while test accuracy and sensitivity increased in geriatric women. These results showed that RMI models best for malignancy discrimination. However, the predictive performance of PLR and/or CA-125 test in G women need further studies with larger populations.

This study is unique that this is the first search combined RMI models with inflammatory markers in the G population. However, retrospective design of the study was a major limitation. For this reason, prospectively designed studies with RMI algorithms on G women and the use of CA125 and/or PLR in primary healthcare centers for screening need further studies with a larger sample size.

In conclusion, RMI calculations are reliable tests for malignancy discrimination in PM women. The diagnostic performance of inflammatory factors and CA-125 test were not as good as RMI models. This study suggests that, if an ultrasonography is an unavailable, the rise of PLR (> 190) and CA-125 levels (>35 U/ml) in a G population may be used as referring the point of adnexal masses to gynecologic oncologists. These results should be verified with further studies in the G population.

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