Diagnostic accuracy of inflammatory markers for distinguishing malignant and benign ovarian masses

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Abstract

Objective: To evaluate the role of inflammatory markers for distinguishing malignant and benign ovarian masses.

Methods: Preoperative demographic, clinicopathologic, and laboratory variables were reviewed in patients with an ovarian mass that was subsequently diagnosed as either epithelial ovarian cancer (EOC) or a benign ovarian mass on histologic analysis. The differences between variables of the two groups were further evaluated. Logistic regression analysis was applied to evaluate variables to predict the presence of EOC.

Results: According to the analysis of 229 patients with EOC, 120 (52.4%) patients had serous adenocarcinoma. Of the 229 patients, 110 (48.1%) patients had stage I or II disease and 119 (52.0%) had stage III or IV disease. There was a significant difference between EOC and benign ovarian mass in median values of variables such as age, white blood cell (WBC) count, hemoglobin concentration, platelet count, cancer antigen 125 (CA125) levels, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) (all \( P < 0.001 \), except for WBC count \( P = 0.009 \)). In addition, there was significant difference in median values of these continuous variables among early-stage EOC, advanced-stage EOC, and benign ovarian mass (\( P < 0.001 \) for all variables). On multivariate logistic regression analysis, age (odds ratio \( OR = 4.14, P < 0.001 \)), CA125 levels (\( OR = 9.87, P < 0.001 \)), NLR (\( OR = 1.76, P = 0.049 \)), PLR (\( OR = 2.41, P = 0.004 \)), and LMR (\( OR = 0.51, P = 0.024 \)) were found to significantly predict the presence of EOC.

Conclusion: The three LMR, NLR, and PLR markers were found to be predictors for the presence of EOC. Further prospective studies to assess these markers as screening tools for the presence of EOC are required.

Key words: Inflammation, Biomarkers, Ovarian neoplasms, Early detection of cancer

Introduction

Although the incidence of ovarian cancer is low, ovarian cancer remains one of the leading causes of cancer death worldwide among women in both economically developed and developing countries [1]. In 2012, reported deaths due to ovarian cancer included an estimated 65,900 and 86,000 in developed and developing countries, respectively [2]. One of the reasons for the poor prognosis of ovarian cancer is
that most cases are diagnosed late in the course of disease progression [3]. Reasons for this delayed diagnosis include silent growth of the tumor and the challenges associated with preoperative evaluation of an ovarian mass.

Clinical diagnosis of ovarian cancer is primarily carried out with the help of radiologic findings, clinical symptoms, physical examination, and detection of tumor markers [4-6]. The most important radiologic modality is transvaginal ultrasonography, an important component of the risk of malignancy indices (RMIs) [6, 7]. In addition, magnetic resonance imaging, computed tomography, and positron emission tomography-computed tomography are also useful in the detection of ovarian cancer [8, 9].

Women commonly report symptoms prior to the diagnosis of ovarian cancer including bloating, increased abdominal size, pelvic pain, and urinary symptoms that may be more indicative of ovarian cancer rather than benign causes. However, it is difficult to distinguish the symptoms of cancer from those associated with benign masses [10]. The sensitivity and specificity of pelvic examinations for the detection of asymptomatic ovarian cancer are poor and do not support physical examination as a screening method [11].

Cancer antigen 125 (CA125) is one of the most extensively validated tumor markers in ovarian cancers [5, 6, 9, 12], and is a part of the multivariate index assay (OVA1) [13], risk of ovarian malignancy algorithm (ROMA) [14], and RMIs [6, 7]. An increase in the level of CA125 may not be observed in early-stage ovarian cancer and so its role as a screening tool appears to be limited [6]. Recently, the predictive value of other markers such as human epididymis protein 4 has been reported [5]; however, these results are still debatable. Lastly, screening tools for ovarian cancer may include multi-marker panels and bioinformatic analysis [15]. However, the performance of these tests for screening when used alone or in combination has been poor. The U.S. Preventive Services Task Force (USPSTF) recommended against screening for ovarian cancer [16]. Currently, no organization recommends screening in asymptomatic, average-risk women for ovarian cancer [15].

Although there are few sensitive and specific tests for preoperative screening of ovarian cancer, a recent promising approach released by the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) suggests a more favorable outcome for ovarian cancer patients undergoing annual multimodal screening using a risk of ovarian cancer algorithm [17].

Tumor-associated inflammation has long been accepted as a key factor in tumorigenesis and tumor growth. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are considered predictive factors for survival in ovarian cancer. In addition, preoperative NLR and PLR may help distinguish malignant from benign ovarian masses [18-20]; however, there is lack of consensus regarding their value as a screening tool for ovarian cancer [21]. Recently, the LMR, the ratio of absolute neutrophil count (ANC) to the absolute monocyte count (AMC), has been reported to be a predictive factor for survival in early- and advanced-stage epithelial ovarian cancer (EOC) [22, 23]. However, to the best of our knowledge, there are no published reports on the cut-off LMR value distinguishing malignant from benign ovarian masses. Hence, the aim of present study was to evaluate preoperative LMR as a potential screening tool for EOC.

Methods

We retrospectively reviewed medical records of patients who had undergone surgical exploration for an ovarian mass by highly trained gynecologic oncologists at university hospitals between July 2003 and September 2016. Patients with either EOC or benign ovarian masses were eligible for inclusion in the study. Patients with the presence of concurrent primary cancers or those having a history of cancer within 5 years of the ovarian mass exploration were excluded from the study. Those patients who had undergone any type of radiation therapy or chemotherapy before surgical exploration were also excluded. Moreover, patients with coexisting autoimmune diseases or with evidence of active infection were excluded.

For consistency, a single, expert pathologist reviewed the histology-based type classification of the ovarian masses. The stage of disease according to the International Federation of Gynecologists and Obstetricians (FIGO) was acquired for analysis. The age of the patients at the time of surgical exploration was obtained from the medical records. Laboratory variables including CA125 levels, white blood cell (WBC) count, hemoglobin (Hb) concentration, platelet count, ANC, absolute lymphocyte count (ALC), and AMC were obtained from the patient medical records. Variables such as NLR, PLR, and LMR were calculated by dividing ANC by ALC, platelet count by AMC, respectively. Data were collected for only those laboratory measurements that were measured prior to surgical resection. If numerous measurements prior to surgery were available, the one that was performed on the date closest to the surgical resection was selected for...
analysis. Quality control criteria and reference ranges adopted at each institution were taken into consideration while collecting the laboratory results. The Mann-Whitney-U test was used to compare the medians between two groups, while comparison of medians between three or more groups of subjects were performed using the Kruskal-Wallis test. A $P$-value of less than 0.05 was regarded as statistically significant.

The initial set of variables in the logistic regression consisted of age, WBC count, Hb concentration, platelet count, CA125 level, NLR, PLR, and LMR. Variables such as age, WBC count, Hb concentration, platelet count, and CA125 level were dichotomized based on the predefined cut-off values. However, the optimum cut-off points of NLR, PLR, and LMR for predicting the presence of EOC were determined using receiver operating characteristic (ROC) curve analysis. Subsequently, logistic regression analyses were used to evaluate variables predictive of the presence of EOC. Multivariate analysis was carried out incorporating variables that reached significance in univariate analysis. In addition, all continuous variables were tested using the Pearson’s correlation. The SPSS, version 18.0 (SPSS Inc., Chicago, IL, USA), and R-packages were used for data analysis.

Results

Based on data collected from 229 patients with EOC, the most frequent histology noted was serous adenocarcinoma (52.4%), followed by mucinous (22.3%), clear cell (12.7%), and endometrioid (10.5%) types. The most frequent histologic grade in our cohort was grade 3 (45.4%), followed by grade 2 (31.0%), and grade 1 (23.6%). In total, 92 (40.2%) patients had stage I, 18 (7.9%) had stage II, 103 (45.9%) had stage III, and 16 (7.0%) had stage IV disease.

There was a significant difference between EOC and benign ovarian masses in terms of the median values of age, WBC count, Hb concentration, platelet count, CA125 level, NLR, PLR, and LMR (all $P<0.001$, except for WBC count [$P=0.009$]) (Table 1). A significant difference was also noted among the three groups, early-stage EOC (stage I or II), advanced-stage (stage III or IV) EOC, and benign ovarian masses, in relation to the aforementioned variables (all $P<0.001$). On applying Bonferroni correction, there was a significant difference in medians between advanced-stage EOC and benign ovarian masses in terms of age, WBC count, Hb concentration, platelet count, CA125 level, NLR, PLR, and LMR. However, a significant difference between early stage EOC and benign ovarian masses was noted in terms of age, Hb concentration, CA125 level, NLR, PLR, and LMR. Finally, there was a significant difference in medians between early- and advanced-stage EOC in terms of age, WBC count, platelet count, CA125 level, NLR, PLR, and LMR (Table 2).

### Table 1. The difference in median values between benign ovarian mass and EOC according to laboratory values

|                      | Benign ovarian mass, median (IQR) $(n=261)$ | EOC, median (IQR) $(n=229)$ | $P$ value |
|----------------------|-------------------------------------------|----------------------------|----------|
| Age (years)          | 35.0 (21.0)                               | 54.0 (16.0)                | $<0.001$ |
| WBC (per µL)         | 6220.0 (2350.0)                           | 6650.0 (2750.0)            | 0.009    |
| Hemoglobin (g/dL)    | 13.0 (1.4)                                | 12.5 (1.8)                 | $<0.001$ |
| Platelets $(×10^9)/µL$ | 253.0 (75.0)                             | 285.0 (124.0)              | $<0.001$ |
| CA125 (unit/mL)      | 19.0 (21.0)                               | 194.2 (541.5)              | $<0.001$ |
| NLR                   | 1.9 (1.1)                                 | 2.8 (2.5)                  | $<0.001$ |
| PLR                   | 136.1 (64.2)                              | 190.1 (138.5)              | $<0.001$ |
| LMR                   | 5.4 (2.9)                                 | 4.0 (3.1)                  | $<0.001$ |

Medians with the same letter (superscript) are not significantly different. $P$-values for comparisons of medians were obtained using the Mann-Whitney-U test.

EOC, epithelial ovarian cancer; IQR, interquartile range; WBC, white blood cell; CA125, cancer antigen 125; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio

### Table 2. The difference in median values between benign ovarian masses and early- or advanced-stage EOC according to laboratory variables

|                      | Benign ovarian mass, median (IQR) $(n=261)$ | EOC, median (IQR) $(n=229)$ | $P$ value |
|----------------------|-------------------------------------------|----------------------------|----------|
| Age (years)          | 35.0 (21.0)                               | 51.0 (14.0)                | $<0.001$ |
| WBC (per µL)         | 6220.0 (2350.0)                           | 6215.0 (2600.0)            | $<0.001$ |
| Hemoglobin (g/dL)    | 13.0 (1.4)                                | 12.6 (1.5)                 | $<0.001$ |
| Platelets $(×10^9)/µL$ | 253.0 (75.0)                             | 271.5 (95.0)               | $<0.001$ |
| CA125 (unit/mL)      | 19.0 (21.0)                               | 52.7 (227.9)               | $<0.001$ |
| NLR                   | 1.9 (1.1)                                 | 2.4 (1.7)                  | $<0.001$ |
| PLR                   | 136.1 (64.2)                              | 163.4 (93.1)               | $<0.001$ |
| LMR                   | 5.4 (2.9)                                 | 4.8 (3.1)                  | $<0.001$ |

Medians with the same letter (superscript) are not significantly different. $P$-values for comparisons of medians were obtained using the Kruskal-Wallis test. A post-hoc test (Bonferroni) was applied with pairwise comparison between medians.

EOC, epithelial ovarian cancer; IQR, interquartile range; WBC, white blood cell; CA125, cancer antigen 125; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio

Using data from all eligible patients, the best cut-off points based on ROC curve analyses for NLR, PLR, and LMR were found to be 2.64 (AUC=0.709; sensitivity 0.568, specificity 0.774; $P<0.001$), 191.71 (AUC=0.718; sensitivity 0.498, specificity 0.843; $P<0.001$) and 3.52 (AUC = 0.683; sensitivity 0.437, specificity 0.862; $P<0.001$), respectively (Figure 1). Univariate logistic regression analyses identified the following significant variables for EOC: age, WBC count, Hb concentration, CA125 level, NLR, PLR, and LMR (all $P<0.001$, except for WBC count [$P=0.015$]). On multivariate logistic regression analyses, age
(odds ratio [OR]=4.14, 95% confidence interval [CI]=2.00–8.90, \(P<0.001\)), CA125 levels (OR=9.87, 95% CI=6.27–15.84, \(P<0.001\)), NLR (OR=1.76, 95% CI=1.00–3.09, \(P=0.049\)), PLR (OR=2.41, 95% CI=1.34–4.38, \(P=0.004\)) and LMR (OR=0.51, 95% CI=0.28–0.91, \(P=0.024\)) were found to predict the presence of EOC (Table 3 and Figure 2).

The correlation between variables is shown in Figure 3. There was a moderate negative correlation between LMR and NLR \((r=-0.43, P<0.001)\) or PLR \((r=-0.31, P<0.001)\), weak negative correlation between LMR and CA125 level \((r=-0.26, P<0.001)\), very weak negative correlation between LMR and age \((r=-0.16, P<0.001)\) or WBC count \((r=-0.19, P<0.001)\), and very weak positive correlation between LMR and Hb concentration \((r=0.19, P<0.001)\).

![Figure 1](http://www.jcancer.org)

**Figure 1.** Receiver operating characteristic (ROC) curves for (A) neutrophil-lymphocyte ratio (NLR), (B) platelet-lymphocyte ratio (PLR), and (C) lymphocyte-monocyte ratio (LMR). The numbers before the parentheses depict cut-off values, and the numbers in the parentheses show specificity and sensitivity in order.
Table 3. Univariate and multivariate analyses for the evaluation of variables that predict the presence of EOC

| Variable                  | Univariate                      | Multivariate                     |
|---------------------------|---------------------------------|----------------------------------|
|                           | OR (95% CI)                      | P value                         | OR (95% CI)                      | P value |
| Age (years) (<65 vs. ≥65) | 4.39 (2.47, 8.18)                | <0.001                          | 4.14 (2.00, 8.90)                | <0.001  |
| WBC (per µL) (≤11000 vs. >11000) | 2.86 (1.27, 7.06)            | 0.015                           |                                  |         |
| Hemoglobin (g/dL) (≤12.0 vs. >12.0) | 0.42 (0.28, 0.64)            | <0.001                          |                                  |         |
| Platelets (×10^3 per µL) (≤4000 vs. >4000) | 7.93 (3.52, 21.26) | <0.001                          |                                  |         |
| CA125 (unit/mL) (≤35 vs. >35) | 12.58 (8.26, 21.26)            | <0.001                          | 9.87 (6.27, 15.84)               | <0.001  |
| NLR (≤2.64 vs. >2.64)     | 4.50 (3.06, 6.68)               | <0.001                          | 1.76 (1.00, 3.09)                | 0.049   |
| PLR (≤191.71 vs. >191.71) | 5.68 (3.70, 8.88)               | <0.001                          | 2.41 (1.34, 4.38)                | 0.004   |
| LMR (≤3.52 vs. >3.52)     | 0.21 (0.14, 0.33)               | <0.001                          | 0.51 (0.28, 0.91)                | 0.024   |

Results of multiple logistic regression with variables show a P-value less than 0.05 in univariate regression.

EOC, epithelial ovarian cancer; OR, odds ratio; CI, confidence interval; WBC, white blood cell; CA125, cancer antigen 125; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio

Discussion

Although previous studies have reported various potential tools to predict the presence of ovarian cancer, the results are debatable, with no evidence in support of tools that can distinguish ovarian cancer from benign ovarian masses [15, 16]. In the present study, we specifically evaluated inflammatory markers and found that LMR, along with NLR and PLR, could predict the presence of EOC.

Monocytes from patients with advanced cancer are considered to display immunosuppressive properties [24]. In addition, the monocyte count of the peripheral blood has an association with the density of the tumor-associated macrophages, which creates a favorable microenvironment for the development of...
cancer [25]. An elevated monocyte count in peripheral blood has been associated with detrimental outcomes for cancer patients. LMR is calculated as the ratio of ALC and AMC, and it has been proposed as a prognostic or predictive factor associated with survival in various malignancies including ovarian cancers [22, 23, 26, 27]. In EOC with stage I to IV disease, a low LMR is an independent predictor for overall survival (OS) [22]. In addition, a low LMR is a significant prognostic factor associated with adverse progression-free survival (PFS) and OS in advanced EOC (stage III and IV) [23]; the cut-off values of the previous studies range from 2.07 to 3.45. Furthermore, preoperative LMR, with a cut-off value of 3.75, is reported to be an independent predictor associated with suboptimal cytoreduction in stage III and IV EOC [27]. However, there are no studies describing the LMR cut-off value as a screening tool for EOC. In our study, the LMR with a cut-off value of 3.52 predicted the presence of EOC, along with NLR and PLR.

The NLR has been recognized as a potent prognosticator for PFS [28, 29] and OS [19, 29, 30] in ovarian cancer. In addition, NLR has been suggested to predict the presence of ovarian cancer. In previous studies, the cut-off values based on ROC curve analysis have ranged from 3.45 to 3.47 [18, 20]. In our study the cut-off value by ROC curve analysis was 2.64; we also demonstrated that NLR predicts the presence of EOC. However, the value of NLR that can predict the presence of EOC needs further evaluation, as a significant conclusion could not be reached at the end of the present study.

The peripheral blood platelet count is reportedly increased in 31% to 56% of adnexal tumors [31]. Although the underlying mechanism of increased platelet counts is not well understood, increased hepatic thrombopoietin has been suggested as one of the contributors [32]. Platelets are actively involved in the growth of ovarian cancer cells [33], and the change in the platelet count itself may control tumor growth in ovarian cancers. Decreasing platelet count using anti-platelet antibodies prevents the growth of ovarian cancer [32], and increasing the platelet count via platelet transfusion increases the size of the tumor [34]. In addition, elevated platelet count in the peripheral blood is associated with aggressive behavior and advanced stages of ovarian cancer [32, 35]. Furthermore, the peripheral blood platelet count is suggested to predict the presence of ovarian cancer [31, 36, 37]. In our study, however, platelet count did not predict the presence of EOC. A possible explanation for this anomaly could be the analysis of the platelet count with PLR, a more potent systemic inflammatory response marker derived from the platelet count and ALC. The PLR has been associated with the prognosis of ovarian cancer [38, 39]. In addition, use of the PLR as a screening tool for the diagnosis of ovarian cancer has been reported; however, the number of patients enrolled in those studies was too small for clinical translation [18, 20], and one of those studies included only advanced stage disease (stage IIIc or IV) [18]. On ROC curve analysis, the cut-off values in the previous studies ranged from 161.13 to 572.9 [18, 20]. In our study, the PLR with a cut-off value of 191.71, by ROC curve analysis, predicted the presence of EOC.

In this study, age also predicted the presence of EOC. Several researchers have suggested age to be an independent demographic variable to distinguish malignant from benign ovarian masses [20, 31, 40, 41], and our finding was compatible with these reports. In addition to age, menopausal status has been adopted to form the ROMA that classifies an adnexal mass into high- or low-risk EOC groups [14]. In our study, however, we could not analyze the role of menopausal status due to missing values.

CA125 is one of the most extensively validated biomarkers in ovarian cancers [5, 6, 9, 12, 31, 41]. Approximately 80% of women with EOC have CA125 levels exceeding the cut-off value of 35 kU/L, with elevations of 50-60%, 80-90%, and >90% in clinical stage I, II, and III-IV disease, respectively [6]. The frequency of elevated concentrations is the highest in patients with serous EOC followed by endometrioid, clear cell, and mucinous types [6]. In the clinic, CA125 has been used as a laboratory tool for monitoring response to first-line chemotherapy [6]. In addition, CA125 is a part of OVA1 [13], ROMA [14], and RMI [6, 7]. Furthermore, preoperative CA125 levels can be used to predict the presence of ovarian cancer [6, 7, 13, 14, 20, 31, 40-45], and the result of our study is compatible with these studies. However, CA125 is not currently recommended as a screening tool for ovarian cancer in asymptomatic patients because of its low sensitivity and limited specificity, and due to the fact that increased CA125 levels may not observed in early-stage ovarian or mucinous type cancer [6]. In the present study, analysis of CA125 levels in serous and non-serous types revealed no significant differences in CA125 level according to histologic type in advanced-stage EOC (median, 492.6 unit/mL with an interquartile range [IQR] of 725.2 unit/mL in the serous type and median, 444.6 unit/mL with IQR of 795.1 unit/mL in the non-serous type; P=0.768). However, there was a significant difference in CA125 levels in early-stage EOC according to histologic type (median, 240.6 unit/mL with IQR of 403.4 unit/mL in the serous type and median, 32.6 unit/mL with IQR of 91.9 unit/mL in the
non-serous type; *P*<0.001). When considering the pre-defined CA125 cut-off value of 35 unit/mL in ovarian cancer, our results may limit the clinical application to patients with non-serous histology and early-stage EOC. In addition, drawbacks of the CA125 biomarker include its elevation in various benign gynecologic diseases such as uterine myoma, adenomyosis, endometriosis, salpingitis, and ovarian cysts and in several non-gynecological diseases such as pelvic inflammatory disease, liver cirrhosis, acute hepatitis, and pancreatitis, and in peritoneal, pleural, and musculoskeletal diseases. Additionally, elevated concentrations can also occur in other malignancies such as hepatocellular carcinoma and advanced adenocarcinomas of the pancreas, biliary tract, lungs, and ovarian masses of the endometrium, stomach, cervix, breasts, and colorectal areas [6, 46].

To the best of our knowledge, this is the first study to identify LMR as a predictor of the presence of both early- and advanced-stage EOC in patients with an ovarian mass. Specifically, in the present study, the value of LMR as an independent predictive factor associated with the presence of EOC was demonstrated by analyzing it together with other inflammatory markers, such as NLR and PLR, using multivariate analysis. However, the main limitation of the study is the fact that it is a retrospective cohort study. In addition, although we excluded patients with the coexistence of autoimmune diseases or evidence of active infection, the diverse systemic diseases or various inflammatory conditions may have affected the LMR values [47].

In conclusion, LMR along with NLR, PLR, age, and CA125 levels could predict the presence of EOC in our study. The results of our study indicate that in addition to the previously validated biomarkers, there exists a potential role of LMR as a predictor of the presence of EOC. However, it is too early to apply LMR as a screening tool in the general population at present and additional large-scale prospective investigations to determine the utility of such predictive biomarkers are clearly warranted.

**Competing Interests**

The authors have declared that no competing interest exists.

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