

ORIGINAL RESEARCH

Medicine Science 2018;7(4):857-60

The role of neutrophil/ lymphocyte ratio (NLR) with ca 125 in preoperative prediction of malignancy in adnexal mass

Meryem Bekmezci, Oguzhan Gunenc

Konya Training and Research Hospital, Clinic of Gynecology and Obstetrics Konya, Turkey

Received 28 March 2018; Accepted 18 July 2018

Available online 08.10.2018 with doi: 10.5455/medscience.2018.07.8893

Copyright © 2018 by authors and Medicine Science Publishing Inc.

Abstract

It is aimed to evaluate the neutrophil / lymphocyte ratio (NLR) and platelet / lymphocyte ratio (PLR) values with CA 125 value in order to distinguish benign / malign / borderline tumors in patients undergoing surgery for adnexal mass. In this retrospective study were included 290 randomized patients having adnexal mass. According to the results of postoperative pathology, 227 patients were benign and 63 were malign. Hematological parameters such as NLR, mean platelet volume (MPV), and PLR were measured in the preoperative period. Multivariate regression analysis was performed statistically to determine the association with CA 125 and hematologic parameters of malignancy in adnexal masses. Women with malignant adnexal mass were older than the ones having benign adnexal mass. CA 125, NLR and PLR levels were statistically higher in patients having malignant adnexal mass than the ones having benign adnexal mass. Age, CA 125 and NLR were associated with malignancy in women with adnexal mass. Multivariable logistic regression analysis depicted that age, CA 125 and NLR were related to increased malignancy risk in adnexal mass (OR=1.047, 95 %CI =1.023-1.071, OR=1.007, 95 %CI = 1.004-1.010 and OR=1.228, 95 %CI = 1.032-1.460, respectively). CA 125, NLR and PLR were positively correlated to malignancy in women with adnexal mass. The CA125 value alone is insufficient for malignancy discrimination. Combination of it with age, and NLR may be useful in distinguishing malignant masses from benign ones in the preoperative period.

Keywords: Adnexal mass, cancer antigen 125, neutrophil lymphocyte ratio, platelet lymphocyte ratio.

Introduction

The etiology of adnexal masses ranges from physiologically normal luteal cysts to ovarian cancer. Ovarian cancer causes mortality than any other cancer of the female reproductive system. Ovarian cancer relative survival rate was 46.5% between 2007-2013 [1].

Evaluation of malignancy related factors are very important in preoperative period for prediction of malignancy risk, the planning of follow-up and treatment in adnexal mass. Despite the study of many markers to determine malignancy risk, the preoperative evaluation of some ovarian masses does not let the clinician to decide the malignancy potential; which includes; sonographic evaluation, computerized tomography and tumor markers [2,3].

It is known that cancer increases the level of inflammation and infection markers. Some markers of systemic inflammation such

as C-reactive protein (CRP) have been correlated to outcomes in ovarian carcinoma and renal cell carcinoma [4].

Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) are easily calculated markers that used as predictive in cancer and premalignant diseases [5,6]. Yıldırım et al., NLR, PLR, CA-125, neutrophil and platelet counts levels were higher in the malignant compared to the benign cases [7] Kokcu et al. Concluded that NLR and PLR increased in advanced stage ovarian cancer. They also stated that PLR is an independent risk factor for advanced stage epithelial ovarian cancer. [8].

CA125 is widely used tumor marker in ovarian cancer; nevertheless, CA125 predictive power is low in ovarian cancer. CA125 is elevated in about 80% of women with epithelial ovarian cancer (EOC) but only in 50% of women with early stage disease [9]. The specificity of CA125 is limited, because of elevated in a range of common benign gynecologic or non-gynecologic conditions [10].

In our study, we aimed to determine the predictive value of CA 125, in combination with simple and rapidly determined inflammation markers such as NLR and PLR for the malignancy potential of the adnexal masses, in the preoperative period.

Materials and Methods

290 patients were admitted to Konya Training and Research Hospital Obstetrics and Gynecology Clinic with adnexal mass between January 1, 2010 and April 10, 2016. The pathology results, laboratory parameters and socio-demographic characteristics of these patients were retrospectively analyzed. Women with all adnexal masses aged 40-65 years were included in the study.

Exclusion criteria for all participants included: masses outside the ovaries, patients having previous operations for ovarian masses, those receiving chemotherapy and / or radiotherapy, women with infectious diseases such as pelvic inflammatory disease, inflammation and abscess that could affect laboratory parameters. The study protocol was approved by the local ethical committee of our hospital. Anthropometric measurements were recorded for all participants included in the study.

All analysis was performed in the hematology and biochemistry laboratory of our hospital with the use of a Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer. Plasma CA 125 levels were determined unit/ milliliter.

The findings of all the cases were noted. Specimen were included in the "frozen section" and postoperative histopathologic examination, and the results were compiled. Histopathological diagnosis was accepted as the gold standard in the interpretation of the results. In the postoperative period; patients were divided into two groups according to the presence of malignancy, by definitions of the World Health Organization (WHO) [11].

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 17 (SPSS Inc., Chicago, IL, United States). The results were expressed as mean $\pm$ SD (95% Confidence Interval). CA125, NLR and PLR receiver operator characteristic (ROC) curve analysis was performed, and the area under the curve (AUC) was calculated. Age, CA125, NLR, PLR and MPV between benign and malignant adnexal mass groups were assessed by independent t test. Multiple logistic regression analysis was performed to calculate the odds ratio (OR) and 95% confidence intervals to demonstrate the association of adnexal masses with malignancy. Correlation analysis was performed to determine correlation with CA 125 and other variables in malignant adnexal masses. A p value less than 0.05 was considered statistically significant.

Results

A total of 290 women with adnexal mass were enrolled in the study. 227 of those had benign adnexal mass, and 63 had malignant adnexal mass. 54 (85.71%) patients were epithelial over ca, 7 (11.11%) patients were germ cell and 2 (3.17%) patients were sex-cord stromal over tumors of the malignant tumors. The baseline anthropometric, clinical and laboratory characteristics of both groups are given in Table 1.

The mean age of the patients was 52.11 ± 15.62 years in malignant adnexal mass, and it was 41.51 ± 14.41 years in benign adnexal mass ($p < 0.001$). Mean age of the patients having malignant adnexal mass were significantly higher than the benign mass ($p < 0.001$). CA 125, NLR and PLR levels were 360.16 ± 84.70 , 4.97 ± 6.62

and 263.43 ± 13.65 in malignant adnexal mass and 35.43 ± 5.58 , 2.47 ± 1.76 and 152.60 ± 8.61 in benign adnexal mass, respectively. CA 125, NLR and PLR levels were significantly higher in malignant adnexal masses than in benign adnexal masses ($p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively) (Table 1). There was no difference in smoking rate, neutrophil count, lymphocyte count and platelet counts between benign and malignant adnexal mass groups ($p = 0.546$, $p = 0.232$, $p = 0.299$ and $p = 0.086$ respectively) (Table 1). ROC curves were performed in patients with malignant adnexal masses. NLR and PLR AUC (95% CI) were calculated. NLR AUC was 0.702 (95%CI: 0.630-0.774) and RPL AUC was AUC: 0.712 (95%CI: 0.635-0.789) (Figure 1).

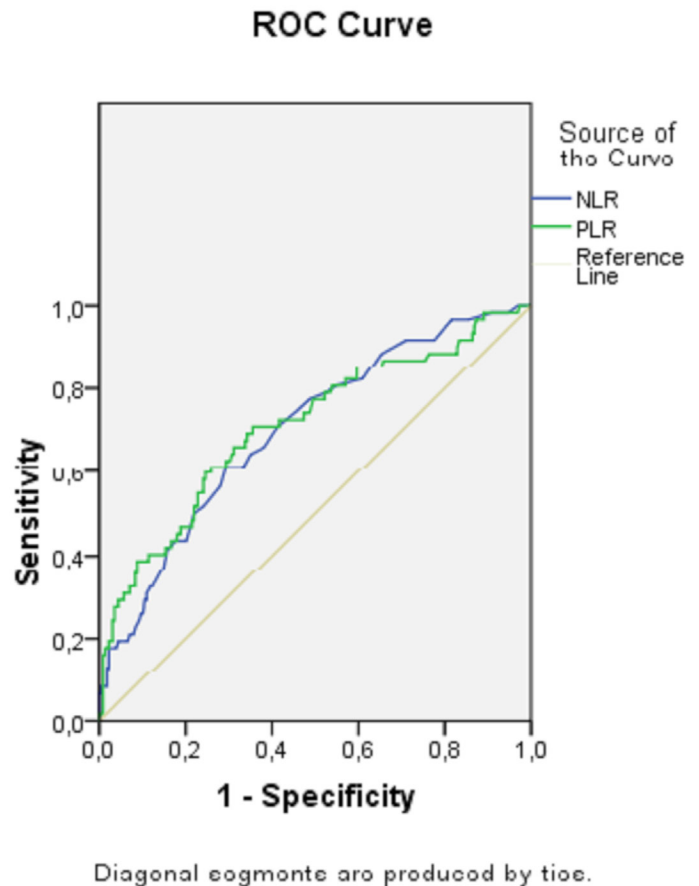


Figure 1. NLR and RLR ROC curve in malignant adnexal mass

Univariate and multivariate logistic regression analysis were applied to determine the best predictors for an increased risk of malignancy in women with adnexal mass. Variables whose univariable test had a significantly was accepted as a candidate for the multivariable model along with all variables of known clinical importance.

Multivariable logistic regression analysis revealed age, CA 125 and NLR were associated with independently increased risk variables of malignancy in women with adnexal mass (OR: 1.047, 95 %CI =1.023-1.07, OR: 1.007, 95 %CI = 1.004-1.010 and OR:1.228, 95 %CI = 1.032-1.460, respectively). In conclusion, age, CA 125 and NLR have high predictive value for malignancy in women with adnexal mass ($p < 0.001$, $p < 0.001$ and $p = 0.002$, respectively) (Table 2).

Correlation analysis was performed to determine whether CA 125 was correlated with NLR and PLR levels in malign adnexal masses. Positive significant correlation was observed between CA 125, NLR and PLR levels ($p=0.003$ and $p=0.001$) (Table 3).

Table 1. Demographic and laboratory features of benign and malign adnexal masses

	Benign n= 227	Malignant n=63	p value
Age	41.51 ± 14.41	52.11 ± 15.62	<0.001
Smoking	84 (%37)	25 (%39,68)	0.546
CA 125(U/mL)	35.43 ± 5.58	360.16 ± 84.70	<0.001
Neutrophil counts	4,44± 0,129	4,69 ± 0,163	0,232
Lymphocyte counts	2,39 ± 0,074	2,27 ± 0,090	0,299
Platelet counts (/mm ³)	247,56 ± 5,62	231,30 ± 7,68	0,086
NLR	2.47 ± 1.76	4.97 ± 6.62	<0.001
PLR	152.60 ± 8.61	263.43 ± 13,65	<0.001
MPV	9.77 ± 1.60	13.62 ± 3.75	0.053

CA 125: Cancer antigen 125; NLR: Neutrophil / Lymphocyte ratio; PLR: Platelet / lymphocyte ratio; MPV: Mean platelet volume; p; statistically significant.

Table 2. Multivariate logistic regression analysis of several factors in the assessment of increased malignancy risk in women with adnexal mass

	Malign adnexal mass			
	Univariate		Multivariate	
	OR (95%CI)	p value	OR (95%CI)	p value
Age	1.052(1.031-1.074)	<0.001	1.047(1.023-1.071)	<0.001
CA 125(U/mL)	1.007(1.005-1.010)	<0.001	1.007(1.004-1.010)	<0.001
NLR	1.269(1.117-1.441)	<0.001	1.228(1.032-1.460)	0.020
PLR	1.004(1.002-1.007)	0.001	0.999(0.996-1.002)	0.581
MPV	1.028(0.933-1.133)	0.575		

CA 125: Cancer antigen 125; NLR: Neutrophil / Lymphocyte ratio; PLR: Platelet / lymphocyte ratio; MPV: Mean platelet volume; OR: odds ratio; p; statistically significant

Table 3. Correlation between variables in malign adnexal masses

	Malign adnexal mass	
	CA 125(U/mL)	
Age	r=0.216	p=0.092
NLR	r=0.372	p=0.003
PLR	r=0.523	p=0.001
MPV	r=0.042	p=0.748

Ca 125: Cancer antigen 125; NLR: Neutrophil / Lymphocyte ratio; PLR: Platelet / lymphocyte ratio; MPV: Mean platelet volume; r: Correlation coefficient; p; Statistically significant

Discussion

In this study; we evaluated the demographic and laboratory characteristics of patients with benign and malignant ovarian masses managed at our clinic. An adnexal mass such as mass of the ovary, fallopian tube, or connective tissue is a common gynecologic problem in reproductive age women. The most important problem in women with adnexal mass is to differentiate malignancy from urgent causes (adnexial torsion, ectopic pregnancy, etc). It is

estimated that there is a 5 to 10 percent lifetime risk for women undergoing surgery for a suspected ovarian neoplasm [12]. In some complex adnexal masses, it is difficult to distinguish if it is benign or malignant, without surgery. It is very important to diagnose malignancy of ovarian tumors at the early stage, because the survival rate is 90% [13]. Ultrasonographic evaluation, menopausal status, and tumor markers such as CA 125 and human epididymis secretory protein 4 (HE4) are important predictors for malignancy [14, 15]. In addition, Romagnolo et al., and Yanaranop et al., reported that risk of malignancy index (RMI) have been introduced to discern benign and malignant cases [14, 17]. Ultrasonography markers, CA125 level and menopausal status were evaluated with the RMI. Although pathological analysis is usually necessary to determine malign adnexal mass, complete blood count (CBC) may help to evaluate an adnexal mass malign or benign. We found statistically significant differences between the groups in terms of age, CA 125 levels, preoperative NLR and PLR. Also, we determined that age, CA 125 and NLR variables can be used to differentiate adnexal masses from preoperative malignancy in multivariate regression analysis.

Preoperative CBC parameters are frequently used in many tumors. Tamussino et al., reported that preoperative thrombocytosis was also in ovarian cancer and other gynecological cancers [17]. Kuyumcuoglu et al. reported that progressively increased platelet number was related with poor prognosis in malign ovarian tumors [18].

NLR and PLR are easily calculated indicators that can be used in the assessment of malignant and benign tumors. Yang et al. reported that NLR and PLR were related to be prognostic indicators for many types of cancer [6, 19]. In our study, we evaluated age and preoperative NLR and PLR with CA 125. We found that preoperative NLR with CA 125 could be a potential marker for predication of malignant adnexal mass in older women. However PLR was found not to be a useful marker. Although PLR does not appear to be a useful marker in prediction of malignancy potential of an adnexal mass, we detected a positive correlation of it with CA 125, and NLR in malign adnexal mass.

The limitation of our study is its retrospective design and relatively small number of patients included.

Conclusion

In conclusion, we suggest that preoperative workshop of an adnexal mass should include CA 125 levels, ultrasound examination and NLR levels. Prospective studies including more participants are needed for absolute results.

Acknowledgements

The authors would like to thank the staff at Konya Training and Research Hospital and to all women who participated in the study.

Competing interests

The authors declare that they have no competing interest

Financial Disclosure

The financial support for this study was provided by the investigators themselves.

Ethical approval

Ethics committee approval was received for this study from the ethics committee of Konya Training and Research Hospital

Reference

- Halazun KJ, Hardy MA, Rana AA, et al. Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. *Ann Surg.* 2009;250:141-51.
- Hafeez S, Sufian S, Beg M, et al. Role of ultrasound in characterization of ovarian masses. *Asian Pac J Cancer Prev.* 2013;14:603-6.
- Arab M, Yaseri M, Ashrafganjoi T, et al. Comparison of two ovarian malignancy prediction models based on age sonographic findings and serum CA125 measurement. *Asian Pac J Cancer Prev.* 2012;13:4199-202.
- Toriola AT, Grankvist K, Agborsangaya CB, et al. Changes in pre-diagnostic serum C-reactive protein concentrations and ovarian cancer risk: a longitudinal study. *Ann Oncol.* 2011;22:1916-21.
- Acmaz G, Aksoy H, Unal D, et al. Are neutrophil/ lymphocyte and platelet/ lymphocyte ratios associated with endometrial precancerous and cancerous lesions in patients with abnormal uterine bleeding? *Asian Pac J Cancer. Prev.* 2014;15:1689-92.
- National Cancer Institute Cancer Stat Facts, Ovarian Cancer Available from URL: <https://seer.cancer.gov/statfacts/html/ovary.html> accessed date 20.09.2017
- Yildirim MA, Seckin KD, Togrul C, et al. Roles of neutrophil/lymphocyte and platelet/lymphocyte ratios in the early diagnosis of malignant ovarian masses. *Asian Pac J Cancer Prev.* 2014;15:6881-5.
- Kokcu A, Kurtoglu E, Celik H, et al. May the platelet to lymphocyte ratio be a prognostic factor for epithelial ovarian cancer? *Asian Pac J Cancer Prev.* 2014;15:9781-4.
- Rosen DG, Wang L, Atkinson JN, et al. Potential markers that complement expression of CA125 in epithelial ovarian cancer. *Gynecol Oncol.* 2005;99:267-77.
- Maggino T, Gadducci A, D'Addario V, et al. Prospective multicenter study on CA125 in postmenopausal pelvic masses. *Gynecol Oncol.* 1994;54:117-23.
- Serov SF, Scully RE, Sobin LH. International histological classification of tumors: No 9, histological typing of ovarian tumors. Geneva, Switzerland: World Health Organization. 1973;
- National Institutes of Health Consensus Development Conference Statement Ovarian cancer: screening, treatment, and follow-up. *Gynecol Oncol.* 1994;55:4-14.
- Myers ER, Bastian LA, Havrilesky LJ, et al. Management of adnexal mass. *Evid Rep Technol Assess (Full Rep).* 2006;130:1-145.
- Romagnolo C, Leon AE, Fabricio ASC, et al. HE4, CA125 and risk of ovarian malignancy algorithm (ROMA) as diagnostic tools for ovarian cancer in patients with a pelvic mass: An Italian multicenter study. *Gynecol Oncol.* 2006;141:303-11.
- Campos C, Sarian LO, Jales RM, et al. Performance of the Risk of malignancy index for discriminating malignant tumors in women with adnexal masses. *J Ultrasound Med.* 2016;35:143-52.
- Yanaranop M, Tiyyon J, Siricharoenchai S, et al. Rajavithi-ovarian cancer predictive score (R-OPS): A new scoring system for predicting ovarian malignancy in women presenting with a pelvic mass. *Gynecol Oncol.* 2016;141:479-84.
- Tamussino KF, Gucer F, Reich O, et al. Pretreatment hemoglobin, platelet count, and prognosis in endometrial carcinoma. *Int J Gynecol Cancer.* 2001;11:236-40.
- Kuyumcuoglu U, Guzel AI, Celik Y, et al. The association of preoperative thrombocytosis with prognostic factors in malign ovarian tumor. *Eur J Gynaecol Oncol.* 2010;31:514-6.
- Yang H, Zhu L, Wang S, et al. Noninvasive diagnosis of moderate to severe endometriosis: the platelet-lymphocyte ratio cannot be a neoadjuvant biomarker for serum cancer antigen 125. *J Minim Invasive Gynecol.* 2013;10:300-2.