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The Role of Systemic Inflammatory Response Markers in Differential Diagnosis of Ovarian Tumors

Over Tümörlerinin Ayırıcı Tanısında Sistemik İnflamatuar Belirteçlerin Rolü

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ÖZ

Amaç: Çalışmamızda preoperatif inflamatuar kan parametrelerinin benign seröz kistadenom, seröz borderline ovarian tümör (BOT) ve high grade over karsinomu (HGSOC) ayırıcı tanısındaki yerini analiz etmek amaçlandı.

Gereçler ve Yöntemler: Ovaryan tümöre sahip 370 hasta retrospektif olarak 3 grup olarak değerlendirildi. Hastalar benign seröz kistadenom, seröz BOT ve HGSOC olarak gruplandırıldı. Preoperatif kan inflamatuar parametreleri: Hemoglobin (Hb), kırmızı hücre dağılım genişliği (RDW), Hb/RDW, Nötrofil / Lenfosit(N/L) ve Platelet/ Lenfosit (P/L) oranları analiz edildi.

Bulgular: P/L and N/L oranlarının benign seröz kist adenomda, seröz BOT'e ve HGSOC 'e göre anlamlı derecede düşük olduğu bulundu (p<0.001 and p<0.001). Benign seröz kistadenom, seröz BOT ve HGSOC ile karşılaştırıldığında daha düşük RDW median değere sahip olduğu saptandı. (p<0.001). Hb/RDW oranı HGSOC'lu hastalarda istatiksel olarak anlamlı olarak en düşük, benign seröz kistadenomlu hastalarda anlamlı olarak en yüksekti (p<0.001).

Sonuç: Preoperatif Hb/RDW, benign seröz kistadenom, seröz BOT ve HGSOC'nin ayırt edilmesinde belirleyici olarak kullanılabilir olduğunu düşünmekteyiz. N/L ve P/L, benign seröz kistadenom ve seröz BOT'ı HGSOC'den ayırt etmek için kullanılabilir .

Anahtar Kelimeler: Over kanseri, inflamatuar kan belirteçleri, kırmızı hücre dağılım genişliği(RDW)

ABSTRACT

Aim: The aim of this study is evaluating the predictive value of preoperative inflammatory blood parameters for differential of serous cystadenoma, serous borderline ovarian tumor (BOT) and high-grade serous ovarian (HGSOC) carcinoma.

Materials and Method: In this single-center study, we retrospectively enrolled 370 patients with ovarian tumors were divided into three groups. The groups were classified as serous cystadenoma, serous BOT and HGSOC. The potential association of preoperative hemoglobin (Hb), red cell distribution width (RDW), Hb/RDW ratio, ratio of neutrophils to lymphocytes (N/L) and ratio of platelets to lymphocytes (P/L) were analyzed.

Results: P/L and N/L were significantly lower in benign serous cystadenoma or serous BOT than HGSOC (p<0.001 and p<0.001). Benign serous cystadenoma was significantly associated with lower median RDW compared to serous BOT and HGSOC (p<0.001). Hb/RDW ratio was significantly lowest in patients with HGSOC and significantly highest in patients with benign serous cystadenoma (p<0.001).

Conclusion: Preoperative Hb/RDW can be used as predictor for discrimination of benign serous cystadenoma, serous BOT and HGSOC. N/L and P/L may be considered to distinguish the benign serous cystadenoma and serous BOT from HGSOC.

Keywords: Ovarian cancer, inflammatory blood markers, red cell distribution width (RDW)

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INTRODUCTION

Epithelial ovarian cancer is one of the most common tumors and has the highest mortality rate among malignancy in the women worldwide (1). Most cases of epithelial ovarian cancer are diagnosed as advanced stage due to the definition of the identifications diagnosis techniques and the absence of obvious clinical symptoms in the early stages (2). Borderline ovarian tumors (BOT) have the good prognosis due to low recurrence and metastasis rates, and surgical cure rates are high in most cases (3). Clinical symptoms, tumoral markers and imaging are still not enough in differential diagnosis among benign cases, BOT and early stage ovarian cancer. Several inflammatory markers have been evaluated by researchers for discrimination of benign, borderline and ovarian cancers (3).

Inflammatory response plays a crucial role in carcinogenesis, tumor progression and metastasis(4). Therefore, preoperative inflammatory ratio and their rates have recently evaluating of many different cancers(5,6). Additionally, blood inflammatory markers seem simple, reproducible and cost-effective for differential diagnosis of ovarian mass. Ratios of neutrophils to lymphocytes (N/L) and platelets to lymphocytes (P/L) can be predictive for diagnosis of ovarian malign tumors(7,8).

Red cell distribution width (RDW) is used to determine red blood volume size variation and the etiology of anemia (9). It has been demonstrated that elevated RDW levels associated with diagnosing ovarian cancer and distinguishing it from benign ovarian tumors. Qin et al. demonstrated that High RDW levels have been shown to be associated with diagnosing ovarian cancer and distinguishing it from benign ovarian tumors(10). Fank et al. reported that hemoglobin-to-red cell distribution width low ratio (Hb/ RDW) ratio poor prognosis hepatocellular cancer. According to our knowledge, value of Hb/ RDW ratio is still not investigated for ovarian masses(11).

The aim of this study was to evaluate the predictive value of preoperative parameters including Hb/RDW, N/L and P/L in discrimination of benign serous cyst adenoma, serous borderline and high-grade serous ovarian cancer.

MATERIALS AND METHODS

This retrospective study enrolled in of 370 adult female patients who underwent primary surgery in the gynecological oncology department between February 2018 and January 2023. Data were collected from the institution's electronic database and patients' file. Having diagnosis of benign serous cystadenoma, serous BOT or high grade serous ovarian cancer (HGSOC) in the final pathologic report, patients older than 18 years old and non-pregnancy were inclusion criteria. The exclusion criteria were the presence history of secondary malignancy, histological types other than serous epithelial tumors such as non-serous epithelial tumors, germ cell tumors, sex-cords cell tumors, patients who received neoadjuvant therapy, having local or systemic infection diseases, receiving preoperative transfusion, history of splenectomy, using anticoagulant drugs, history of comorbidity for renal disease and heart failure. Informed consent was obtained for use of the medical records for research purposes from patients. This study was approved by the Institution Ethics Committee (approval number: E2-23-3188)

The preoperative counts of monocytes, neutrophils, lymphocytes, platelets, Hb, RDW, albumin and CA125 were analyzed within the 9 days before the operation. The cut off value of was CA125:35 U/ml. The International Federation of Gynecology and Obstetrics (FIGO) ovarian cancer staging was revised according to 2021(12). The blood cell ratios were analyzed as follows: Hb/RDW, N/L and P/L.

Statistical Analysis

Continuous variables were evaluated as mean ± standard deviation and median, categorical variables were evaluated frequencies. Statistical analyses were used The Student's t-test or Mann-Whitney U-test for two group comparisons. The differences between more than two groups were evaluated by One-way ANOVA test or Kruskal-Wallis test as appropriate. The differences between three groups were evaluated by Kruskal-Wallis test, and post hoc analysis was performed using Dunn test. P <0.05 was accepted as statistical significance. Data was analyzed using the SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA). Post-hoc test analysis was performed using the "dunn test" package.

RESULTS

All cohort included a total of 320 patients with ovarian tumors. The rate of the groups was benign serous cystadenoma in 104 (28.1%), serous BOT 82 (22.2%) and 184 (49.7%) HGSOC. Age was statistically difference among groups. The median age was 52 years, 43.5 years and 58 years for benign, serous BOT and HGSOC; respectively (p<0.001). The median ve mean values of the cohorts were shown in Table 1.

Table 1: Complete blood counts.

	Mean±SD	Median (Min-Max)
Hb (mg/dl)	12.42±1.62	12.50 (1.60-20.60)
PLT	349.84±127.68	320.00 (2.11-826.00)
RDW (%)	14.20±1.62	13.80 (11.50-24.80)
P/L	222.57±153.18	172.75 (0.98-1376.00)
N/L	3.32±2.48	2.56 (0.86-24.95)
Hb/RDW	0.89±0.16	0.90 (0.12-1.44)
Albumin (g/dL)	43.25±4.60	44.00 (15.10-52.00)
Ca125 (U/ml)	708.06±1565.21	91.50 (2.00-12000.00)

The clinical characteristics and results of the blood cell ratios of cohorts are shown in Table 2. The median Hb and albumin were significantly higher in HGSOC than benign serous cystadenoma or borderline serous ovarian tumors (p<0.001 and p<0.001). PLR and NLR were significantly lower in benign serous cystadenoma or serous BOT than HGSOC (p<0.001 and p<0.001). Benign serous cystadenoma was significantly associated with lower median RDW compared to serous BOT and HGSOC (p<0.001). Median CA125 had statistically significance among groups. Median ca125 was 11 U/ml, 44 U/ml and 457 U/ml for benign serous cystadenoma, serous BOT and HG-

SOC, respectively (p<0.001). Hb/RDW ratio was statistically difference among groups. HB/RDW ratio was significantly lowest in patients with HGSOC and significantly highest in patients with benign cystadenoma (p<0.001).

Table 2: Comparison of clinical characteristics and complete blood count among study groups.

Variables	Benign (n=104)		Borderline (n=82)		Over Ca (n=184)		p value
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
Age (years)	52.74±12.36	52.00[a] (18.00-80.00)	45.17±15.89	43.50[b] (21.00-88.00)	59.26±10.25	58.00[c] (37.00-85.00)	<0.001
Hb (mg/dl)	12.86±1.60	13.10[a] (1.60-15.30)	12.76±1.27	12.95[a] (9.10-15.60)	12.03±1.67	12.10[b] (5.61-20.60)	<0.001
PLT	1.02±0.29	1.00[a] (0.00-3.60)	284.38±64.16	279.00[a] (125.00-474.00)	307.67±70.77	309.50[b] (157.00-481.00)	<0.001
RDW (%)	13.53±0.90	13.40[a] (11.60-15.90)	14.10±1.09	14.00[b] (12.10-19.10)	14.62±1.97	14.00[b] (11.50-24.80)	<0.001
P/L	136.48±44.11	131.35[a] (61.48-245.26)	152.81±46.47	151.18[a] (60.13-302.72)	302.31±180.22	270.45[b] (0.98-1376.00)	<0.001
N/L	1.96±0.58	1.87[a] (1.02-3.82)	2.24±0.77	2.13[a] (0.94-5.20)	4.57±2.96	3.84[b] (0.86-24.95)	<0.001

Malignant ovarian tumors aggressive tumors due to diagnosis advanced stage and the deadliest female genital system cancers (1). Therefore, it is pivotal to establish distinguishing diagnosis among ovarian masses and predicting the prognosis of ovarian cancers (3). In recent years, the differential diagnosis of ovarian tumors has been evaluated by focusing on inflammatory parameters (3). Our study aimed to investigate the predictive value of preoperative blood cell markers and ratios among ovarian benign serous cystadenoma, serous BOT and HGSOC.

Chronic inflammation microenvironment is hallmarks for tumor initiation, development and metastasis (13). Lymphocytes play role in anti-tumoral immune function. Stimulated lymphocytes leads to increase apoptosis and inhibit tumor cell proliferation (14). Kiss et al demonstrated that monocytes increase tumor progression and metastasis (15). Neutrophilia can increase tumor cell proliferation, invasion and vascularization due to an inflammatory microenvironment (16).

Yun et al. showed that N/L and P/L were significantly higher in ovarian cancers compared to benign and borderline tumors (3). In addition to, they reported that N/L and P/L ratio were not significantly difference between benign and borderline ovarian tumors (3). Bakacak et al. reported that N/L and P/L ratio were significantly higher in patients with ovarian cancer than in patients with benign ovarian tumors(17). We found that P/L and N/L significantly higher in HGSOC than in benign serous cystadenoma or serous BOT (p<0.001 and p<0.001).

RDW is a measure of the size heterogenenity of red blood cells. RDW is closely related to patients with non-hemotologic diseases such as endometrial cancer and ovarian cancer (8, 9). Low hemoglobin reflects the body's level of anemia and causes tumor hypoxia (18). Hypoxia in tumor tissue increases angiogenesis and, accelerates tumor aggression and spread (19). Qin et al. reported that there was statistically significant higher RDW in patients with ovarian cancer compared to benign ovarian tumors (p < 0.001)(10). In addition, they reported that high RDW was significantly related to late stage in ovarian cancer(10). We found that the median RDW was significantly higher in HGSOC and BOT than benign serous cystadenoma (p<0.001). Median RDW may be used to distinguish the benign serous cystadenoma from HGSOC and BOT.

Hb/RDW is a novel marker of blood inflammatory markers and reflects the body's systemic inflammatory levels(20). There are scarce studies in the literature on Hb/RDW in oncologic diseases (11,21). Chi at al demonstrated a meta-analysis which reported that low Hb/RDW was predictor of poor prognosis for 2985 cancer patients (21). They reported that low Hb/RDW was associated with two-fold risk for poor disease free survival and overall survival (p < 0.0001). Sun et al reported a study that analyzed Hb/RDW levels in 362 patients with esophageal cancers (22). They demonstrated that low Hb/RDW ratio was significantly associated with metastatic lymph node status and advanced stage. On multivariant analysis, low Hb/RDW was an independent poor prognostic factor for overall survival(22). The median Hb/RDW ratio was reported as 977.68 ± 168.79 and 1121.41 ± 78.68 in patients with nasopharengeal malignancy and benign, retrospectively(20). The Hb/RDW was significantly lower in nasopharengeal cancers groups compared to healthy group (20). In the present study, Hb/RDW ratio was statistically difference among groups. HB/RDW ratio was significantly lowest in patients with HGSOC and significantly highest in patients with benign cystadenoma. Therefore, preoperative Hb/RDW can be useful predictor in differential diagnosis of benign serous cystadenoma, serous BOT and HGSOC.

This study has some limitations, such as its retrospective nature, single center institution and its small sample size. In addition, we did not study other relevant inflammatory markers such as C-reactive protein (CRP), procalcitonin and erythrocyte sedimentation rate (ESR). These indicators may also benefit Hb/RDW to distinguish among ovarian tumors. Despite these limitations, to our knowledge, this is the first study that evaluated the relationship between Hb/RDW and pure serous ovarian masses including benign serous cystadenoma, serous BOT and HGSOC.

CONCLUSION

Because of the importance of early diagnosis in ovarian cancer, preoperative differential diagnosis among ovarian masses is very crucial. Both imaging methods and CA-125 can be insufficient for diagnosis, therefore median RDW, Hb / RDW, N/L and P/L can help to differentiate ovarian masses preoperatively. Preoperative RDW may be used to differential diagnosis the benign serous cystadenoma from HGSOC and BOT. Preoperative Hb/RDW can be useful predictor in differential diagnosis of benign serous cystadenoma, serous BOT and HGSOC. Nevertheless, more prospective clinical trials are necessary to accurate these results.

Conflict of interest

The authors have declared that they have no conflict of interest relevant to this article.

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