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Original Research

Is there a relationship between systemic inflammatory markers and abnormal uterine bleeding in unclassifiable cases according to the PALM-COEIN system?

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Summary

Objective: The aim of this study is to assess the possibility of subclinical inflammation and the difference of SIR markers in cases with abnormal uterine bleeding (AUB). *Materials and Methods:* A total of 529 women were enrolled in the study. Patients were classified according to diagnostic categories of PALM-COEIN. The comparisons between the groups were analyzed by one way variant analysis and Kruskal-Wallis analysis. Relations between numerical variables were assessed by Spearman Correlation analysis. *Results:* No significant difference was found between the groups for SIR markers. When SIR markers were compared between the groups Neutrophil / lymphocyte ratio (NLR) was negatively correlated with lymphocyte/platelet ratio (LPR) in all the groups. Although a strong negative correlation was detected between NLR and lymphocyte/monocyte ratio (LMR) in Groups 2, 3, and 4, no significant relation was detected in Group 1. *Conclusions:* In this study, no significant difference of SIR markers was observed between AUB cases with functional or structural abnormalities and unclassifiable AUB cases according to PALM-COEIN classification.

Key words: Abnormal uterine bleeding; Systemic inflammatory response markers; PALM-COEIN System.

Introduction

Abnormal uterine bleeding (AUB) is a common health problem that affects 20% of all reproductive aged women and causes almost two-thirds of all hysterectomies. The upcoming prevalence of AUB has been associated with obesity due to new life standards [1-3]. AUB deteriorates quality of life by causing anemia and requiring blood transfusion, as well as negative effects on business life and sexual activity, besides increasing hospitalizations [4].

In 2011, the PALM-COEIN classification was created by FIGO because of the absence of a standard regulation in terms of both terminology and classification, although AUB is such an important health problem. According to this classification, the PALM group (polyp, adenomyosis, leiomyoma, malignancy, and hyperplasia) contains structural abnormalities and the COEIN group (coagulopathy, ovulatory dysfunction, endometrial dysfunction, iatrogenic reasons and unclassifiable) contains non-structural abnormalities [5, 6]. The PALM-COEIN-N, category which was first defined as "unclassified" is now being used for "pathology not otherwise classifiable" pathologies. Nevertheless, the menstrual disorders committee named EMDC of the FIGO has recently reported a requirement subclasification systems similar to the leiomyomas in the categories of some PALM-COEIN subclasses, which are to be used in clinical researches [7, 8].

Inflammation and hemostasis are pathophysiological processes that affect each other [9]. Platelets affect the period of inflammation when they are in coaction with leucocytes and vascular endothelia. Neuthrophils, lymphocytes, and platelets play important roles in immune response and inflammation by serving antigens, activating other cells, and producing mediators such as interleukins [10-13].

Mean platelet volume (MPV) is equivalent to the mean corpuscular volume (MCV) of the erythrocytes which gives the mean volume of peripheral platelets [14]. Normally, there is a negative correlation between the volume of the platelets and the number of the platelets. MPV, platelet distribution width (PDW), and erythrocyte distribution width (RDW) are simple markers of chronic inflammation. The ratio of platelet/lymphocyte reflects the balance of inflammation and thrombosis [15].

In recent years many studies have explored the relation between the diagnosis of several diseases and the markers of systemic inflammatory response (SIR). Neutrophil/lymphocyte ratio (NLR) is closely related to the presence of inflammation and oxidative stress and is a good marker of systemic inflammation. Many studies have shown the importance of monitorization with respect to cardiovascular

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Table 1. — *Patient characteristics.*

	Group 1 (n=174) $M(Q_1\text{-}Q_3)$	Group 2 (n=42) $M(Q_1\text{-}Q_3)$	Group 3 (n=114) $M(Q_1\text{-}Q_3)$	Group 4 (n=55) $M(Q_1\text{-}Q_3)$	Group 5 (n=43) $M(Q_1\text{-}Q_3)$	Group 6 (n=99) $M(Q_1\text{-}Q_3)$	*p*
Age (years)	46.4±7.4	40.1±4.6	52.1±9.9	50.4±9.9	48.9±7.8	31.7±7.9	<0.001
Gravity	2(2 -3)	2.5(2-3)	2(2-3.3)	3(2-3)	2(2-4)	2 (1-3)	0.961
Parity	2(2-3)	2 (2-3)	2 (2-3)	2 (2-3)	2 (1-3)	1.7 (1-2)	0.991
BMI (kg/cm^2)	27.7±4.1	28.6±3.1	27.2±4.2	29.1±4.3	27.7±.37	27.5 ±3.2	0.108
Postmenauposal patients (%)	31	11.9	20.2	43.6	11.6	0	<0.001
Endometrial thickness (mm)	8.4±3.7	9.8±3.1	8.4±3.7	10.6±4.4	9.5±3.8	9.7±4.1	<0.001

and, autoimmune rheumatological diseases, as well as the prognostic effect on urinary, lung, esophageal, and gynecological cancers [15-17].

In this study, the authors aimed to discover whether there is any difference between the patients in the category of AUB-N and the ones with structural or functional pathologies in terms of SIR markers, and to investigate whether subclinical inflammation could be a cause of AUB.

Material and Methods

This retrospective cross-sectional study was held between January 2015 and September 2017 in the Obstetrics and Gynecology Clinic of Izmir Katip Celebi University Ataturk Research and Training Hospital. A total of 430 cases of ages between 23 to 85 years who suffered from AUB, in addition 99 healthy women that received family planning advice, were involved in the study. The study protocol was approved by the Ethics Board of the Izmir Katip Celebi University (2016-144). Cases with chronic inflammatory diseases such as inflammatory bowel disease, systemic lupus erythematosus or hematological diseases, patients using hormone replacement therapy, corticosteroids or similar antiinflammatory drugs, patients with acute genital infections, and patients who had a blood transfusion in the last three months before the application were excluded. A written informed consent was completed by all patients.

All of the patients were examined by transvaginal ultrasonography, and routine laboratory tests including serum human chorionic gonadotropin (hCG) and thyroid stimulating hormone (TSH), complete blood count, C-reactive protein, prothrombin and active partial thromboplastin time were done. Hemoglobin (Hb), number of platelet, neutrophil, leucocyte, lymphocyte, monocyte, platocrite (PCT), and MPV levels were noted. NLR, lymphocyte/monocyte (LMR), lymphocyte/platelet (LPR) ratios were calculated. For the detection of etiology, imaging methods such as saline infusion sonography, pelvic magnetic resonance imaging, and computerized tomography were used. After a first step evaluation, endometrial samples were taken from all cases by pipelle canula, using dilatation and curettage or hysteroscopic biopsy. During the period of treatment, the final pathology results were used in pathological assessment in patients for whom hysterectomy was applied to. Two cases who did not follow up after their first step evaluation were excluded from the study.

Patients were classified according to the diagnostic categories of PALM-COEIN as AUB-P (polyp), AUB-A (adenomyosis), AUB-L (leiomyoma), AUB-M (malignancy or hyperplasia), AUB-C (coagulopathy), AUB-O (ovulatory dysfunction), AUB-E (endometrial reasons) or AUB-I (iatrogenic). The analyses were performed in 527 cases. Cases were subclassified into six groups; AUB-N (PALM-COEIN-N Group) as Group 1, AUB-O and AUB-C as Group 2 (functional reasons), AUB-L, AUB-A, and AUB-P as Group 3 (structural pathologies), AUB-M as Group 4, AUB-E and AUB-I as Group 5 (endometrial reasons), and healthy women as Group 6 (control group).

Because of the significant differences of age between the groups, serum inflammatory markers, which are the main outcome measures of the study were assessed by adjusting for age.

The data were analyzed via SPSS Statistics 22.0. Definitive statistics were given as number (n), percentage (%), mean ± standard deviation (x ± ss) and median (Q_1-Q_3). The distribution of normality of the numerical variables were calculated using a Shapiro Wilks normality test and *Q*-*Q* graphics. The comparisons between the groups were analyzed using a one way variant analysis in normally distributed variables and Kruskal-Wallis analysis in abnormally distributed variables. For differences detected by the one-way variant analysis, Dunnett and Tukey tests were done for multi-comparison test. Relations between numerical variables were assessed by Spearman's correlation analysis. The comparison of the categorical variables of the groups for r x c tables was done using Fisher's exact test and a chi-square test. A *p* value <0.05 was accepted as significant.

Results

The groups showed similar results for demographical data such as body mass index (BMI), gravity, and parity. The average age was significantly lower in Group 2 (AUB-C, AUB-O) when compared with the other groups. Seventy-nine percent of the cases were premenopausal, while 21% were postmenopausal. The number of postmenopausal cases was significantly higher in Group 4 (AUB-M) (Table 1).

Among the study groups, 55.1% of the cases were sampled for heavy menstrual bleeding (HMB), 16.4% for postmenopausal bleeding (PMB), and 6.5% for intermenstrual bleeding (IMB), while 2.3% of the cases were sampled with endometrial biopsy for evaluating the effect of treatment given for endometrial hyperplasia. The ratio of endometrial samples for postmenopausal bleeding was similar in Group 1 (AUB-N) and Group 4 (AUB-M). In Group 3 (AUB-L, AUB-A, AUB-P), 19.3% of the cases were evaluated for HMB but IMB and other biopsy results were similar between the groups ($p = 0.292$).

According to the biopsy results, 29.3% showed a proliferative endometrium, 25.9% showed a secretory endometrium, 24.7% had disorganized tissue fragments, and inadequate sampling was detected in 11.4% of Group 1 cases. Among Group 2, 76.2% showed proliferative en-

Table 2. — *SIR markers differences between groups.*

	Group 1 (n=174) *mean±sd*	Group 2 (n=42) *mean±sd*	Group 3 (n=114) *mean±sd*	Group 4 (n=55) *mean±sd*	Group 5 (n=43) *mean±sd*	Group 6 (n=99) *mean±sd*	*p**
NLR	2.1±0.2	2.8±0.3	2.6±0.2	2.2±1.3	2.6±0.3	2.05±0.7	0.114
LMR	10.5±3.0	6.7±6.3	4.6±3.8	4.8±5.3	6.2±6.0	5.6±2.0	0.859
LPR	0.1±14.0	0.6±29.5	0.3±17.7	69.0±24.9	0.5±28.0	0.8±24.0	0.676
PCT (%)	0.3±0.8	0.3±0.7	0.4±0.8	0.3±0.6	0.3±0.9	0.28±0.6	0.544
MPV (Fl)	10.0±1.01	9.8±1.01	9.9±1.6	10.2±1.8	10.1±0.9	10.32±1.08	0.126
Hb (g/dL)	12.0±1.6	11.7±1.7	11.7±1.9	12.1±1.3	11.9±1.7	12.5±1.3	0.323

*NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte to monocyte ratio; LPR: lymphocyte- platelet ratio; PCT: platocrit; MPV: mean platelet volume; Hb: haemoglobin. *Adjusted for age.*

Table 3. — *Comparison of SIR markers between AUB groups.*

	NLR-LPR		LMR-LPR		NLR-PCT		NLR-LMR		LMR-MPV		**LMR-PCT**	
	*p**	*rho*	*p**	*rho*	*p**	*rho*	*p**	*rho*	*p**	*rho*	***p****	***rho***
Group I	0.048	- 0.151	0.001	+0.993	0.001	+0.259	0.103		0.750		**0.793**	
Group II	.001	- 0.521	0.067		0.674		0.011	-0.394	0.006	-0.420	**0.006**	**-0.466**
Group III	0.001	-0.374	0.001	+0.417	0.815		0.001	-0.350	0.787		**0.959**	
Group IV	0.023	-0.310	0.147		0.835		0.001	-0.501	0.666		**0.031**	**+0.293**
Group V	**0.003**	**-0.445**	**0.001**	**-0.445**	**0.946**		**0.003**	**-0.452**	**0.638**		**0.918**	

Rho: correlation coefficient. p: adjusted for age.*

dometrium. In Group 3, polyps were detected in 19.3% of the cases, while 55.3% showed proliferative or secretory endometrium. In Group 5, 30.2% of the cases showed proliferative endometrium, 28.9% showed hormone-related changes, and 7% showed endometritis.

The main outcome were evaluated after the serum inflammation markers were adjusted according to the age. No significant difference were found between the groups for SIR markers such NLR, LMR, LPR, MPV, and PCT values ($p > 0.05$). Among the comparisons of the variables between the groups, age showed a negative correlation with endometrial thickness ($p < 0.01$; r^2- 0,252) (Table 2).

When SIR markers were compared among the groups, NLR was negatively correlated with LPR in all of them. This correlation was strong in Groups 2, 3, and 5 and weak in Groups 1 and 4. In Group I, NLR had a positive correlation with PCT, which was distinct from the other groups. Although a strong negative correlation was detected between NLR and LMR in Groups 2, 3, and 4, no significant relation was detected in Group 1 (Table 3).

Discussion

In the present study, no significant differences were detected for SIR markers between the PALM-COEIN-N group and other groups of PALM-COEIN, as well as healthy controls.

Diseases that are not yet clearly definable (e.g. chronic endometritis, arteriovenous malformations, myometrial hypertrophia) or pathologies that have not clearly proven as associated with AUB have been advised to be classified as AUB-N, in the original PALM-COEIN classification of FIGO [6]. As far as the present authors are aware, from the first classification, no further developments were achieved in defining specific pathologies in this category. Many studies have reported the diagnostic and prognostic importance of SIR markers, such as the number of leukocytes, platelets, NLR and PLR in various diseases in recent years [12-19]. In the present study, the authors tested whether subclinical inflammation could be an etiological factor in AUB cases with no clearly defined structural or functional abnormalities. The study groups were compared according to the ultrasonographic findings of the uterus and the endometrium, the presence of additional systemic factors and biopsy indications in addition to the SIR markers. The high number of postmenopausal patients in Group 4 (AUB-M) is thought to depend on the sight of the most of endometrial neoplasias (3/4) in the postmenopausal period. When compared according to the biopsy indications, most of the biopsies performed for postmenopausal bleeding were detected in Groups 1 (AUB-N) and 4 (AUB-M).

Various studies have focused on the relationship between endometrial pathologies and SIR markers. The predictivity of SIR markers were assessed in the foresight of dissemination and prognosis in endometrial malignancies and the differential diagnosis of endometrial hyperplasia with atypia and benign-malignant endometrial diseases [20-22]. To the knowledge of the authors, the present study is the first study to investigate the predictive value of SIR markers in AUB cases with unknown etiologies. Although no significant differences for SIR markers were detected between AUB cases with unknown etiologies and healthy control groups in our study, when study groups were compared for SIR markers, a negative correlation with NLR and LPR was detected. When SIR markers were evaluated within the same group (i.e, Group I), a different relation

was detected for NLR and platocrite in addition to NLR and the LMR. A positive correlation was found in Group 1 for NLR and platocrite in contrast to the insignificant relation among the other groups. There are studies in the literature that investigated the efficacy of SIR markers in predicting the prognosis of proinflammatory processes that play a role in the pathophysiology of myocardial ischemic dysfunction and preeclampsia [23, 24]. The mechanism leading to the change in SIR markers is reported to be the development of lymphocytopenia and thrombocytosis as a result of proinflammatory response and stress due to leukocyte activation. Lymphocytes contribute to healing through the modulation of mononuclear cell subtypes and the inhibition of metalloproteinase-1 expression. Increased NLR in patients with heart failure, as well as increased platelets, decreased lymphocyte levels have been shown to be associated with myocardial dysfunction and poor prognosis [25, 26]. Based on this information, it could be speculated that the proinflammatory response to endomyometrial tissue in AUB-N cases may be the cause of AUB. In the present study, it was stated that a positive correlation between NLR-platocrite and NLR-LPR in the AUB-N group, unlike other groups, may be indicative of the current proinflammatory response to endomyometrial inflammation.

The strength of the present study is the high number of patients examined by the same obstetrician and pathologist. As the authors did not perform hysterectomy in all cases, the major weakness of this study is the loss of the possibility of some diagnoses (e.g. adenomyosis), which can only be diagnosed after hysterectomy.

Conclusion

In this study, it has been concluded that there is no significant difference between SIR markers for AUB cases with functional or structural abnormalities and unclassifiable AUB cases according to the PALM-COEIN classification system. However, further studies are required at the molecular level for detecting subclinical endometrial inflammation can which contribute to the identification of the etiology in unknown AUB-N cases in order to better understand the relation between AUB and subclinical endometrial inflammation.

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