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PDW and RDW are new parameters for bipolar episodes and unipolar depression

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ABSTRACT

INTRODUCTION: Bipolar disorder (BD) and unipolar depression (UD) are complex and multifactorial mental disorders characterized by mood swings, disability, and impaired quality of life. In the present study, we researched the roles of inflammatory cells and their value as inflammation markers in BD and UD.

OBJECTIVE: Sixty-nine manic, 60 euthymic, and 70 UD patients and 60 sex-matched healthy volunteers (control group) were retrospectively analysed. Platelet (PLT), platelet distribution width (PDW), and red cell distribution width (RDW) levels were measured in four groups. The aim of this study was to evaluate PLT, PDW, and RDW levels patient with UD and two different phases of BD: euthymic and manic.

RESULTS: In our study, 199 patients and 60 controls were included. There were no differences between the patients and the healthy control group participants in terms of age and sex. The bipolar episodes and the UD patient group were statistically significantly different from the healthy controls in terms of PLT, PDW, and RDW.

CONCLUSION: Our study is the first in the literature to compare blood PLT, PDW, and RDW levels in bipolar episodes, UD patients, and healthy control groups. We believe that the levels of PLT, PDW, and RDW can be used as novel markers of bipolar episodes and UD. More detailed and larger prospective clinical studies are required to confirm these findings.

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KEYWORDS

Bipolar disorder; depression; inflammation; red cell distribution width; platelet number; platelet distribution width

Introduction

Bipolar disorder (BD) and unipolar depression (UD) are complex and multifactorial mental disorders characterized by mood swings, disability, and impaired quality of life. According to the World Health Organization, it is estimated that 60 million people suffer from BD globally and that 300 million suffer from UD globally [1,2]. Although these disorders are estimated to be common in worldwide, their pathophysiology are not fully understood. Several factors, such as genetics, oxidative and psychological stress, infections, changes in synaptic plasticity and neuronal survival, abnormalities in morphology, and diet, including inflammatory processes, have been suggested in the etiopathology of both diseases [3–5].

In recent years, to contribute to the etiological understanding and early diagnosis of these disorders, increasing efforts have been made to classify mental disorders on the basis of objective and repeatable biomarkers and to apply this during the standard diagnostic process [6]. Biomarker searches have excited many researchers. However, until now, no biomarkers for psychiatric disorders have been found, except hypocretin [7]. Furthermore, an ideal biomarker should be

cheap, easy, and fast to implement. For these reasons, researchers have focused on the blood parameters and haemogram components.

Platelets (PLT) that are one of the main elements of haemostasis and may reflect biochemical changes in the brain in various psychiatric conditions including neuroinflammation and effect of psychotropics [8–10]. Platelet distribution width (PDW) is a platelet parameter that directly measures the variability in platelet size and has been used to identify platelet disorders [11]. Hence, high PDW values may suggest the increased production of larger reticulated platelets [12]. Therefore, PDW can be an interesting model for studying BD's and UD's pathogenic mechanisms. The red cell distribution width (RDW) is a parameter that measures the heterogeneity in the size of the circulating red blood cells [13]. Recent studies have suggested a relationship between RDW and several diseases and inflammatory processes [14,15].

Inflammation, which is a complex response to foreign stimulant, is characteristic of a number of mental disorders, including BD and UD. In the literature, circulating peripheral cells, such as platelets, lymphocytes, and neutrophils, are often used as markers of

systemic inflammation. Considering the previous findings, we carefully selected PLT, PDW, and RDW because it was important to determine whether these were biomarkers for mood disorders.

Our main aim was to evaluate PLT, PDW, and RDW levels patient with UD and two different phases of BD: euthymic and manic. Furthermore, our secondary aim was to explore whether a combination between PLT, PDW, and RDW could be used as a biomarker for BD and UD.

Materials and methods

Participants

The data were derived from the clinical records of the inpatient unit and outpatient unit for affective disorders in the Psychiatry Department of Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey, between January 2016 and January 2017. After performing an *a priori* power analysis to ensure significant findings (according to our power analysis, 259 subjects were planned to study with alpha of 0.05 about 90% power), records were gathered from patients who were followed for at least two years by the Affective Disorders Clinic of our hospital. Patients who had been diagnosed with type 1 BD (manic and euthymic) or UD according to the DSM-5 were selected for this cross-sectional, naturalistic study. Euthymic criteria were set as a Montgomery-Asberg Depression Rating Scale (MADRS) score of <9 and a Young Mania Rating Scale (YMRS) score <5 and patients' euthymic stage period was at least six months. Mania criteria were set as a YMRS score ≥ 20 and UD criteria were set as a MADRS score of ≥ 10 . A sociodemographic form and information on the clinical course of the disease (such as duration of illness, number of hospitalizations, and suicide attempts), other clinical factors (height and weight for body mass index), and haematological components such as PLT, PDW, and RDW were recorded. Additionally, the same data were gathered from age- and gender-matched healthy controls. Patients with any other psychiatric disorders, pregnancy, alcohol, and/or substance abuse/dependence, or other medical diseases (e.g. hypertension, diabetes mellitus, hepatic and renal failure, obesity, acute or chronic endocrinological disease, neurological deficits, and inflammatory or autoimmune diseases) were not included in the study. Patients between the ages of 18 and 65 were included in the study. Sixty-nine manic patients, 60 euthymic patients with BD, 70 patients with UD, and 60 healthy controls were included in the study. This study was approved by the Clinical Trials Ethics Committee of Haydarpaşa Numune Training and Research Hospital (IRB:2017/369) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Healthy controls

The healthy control group ($n = 60$) proved their well-being via being examined in nine clinics (neurology, cardiology, internal medicine, ophthalmology, orthopedics, physical therapy and rehabilitation, psychiatry, otolaryngology, urology, general surgery, and dermatology). The healthy control group was age- and sex-matched with the patients. None of the healthy control subjects were taking any form of prescribed or other medication and had no history of psychiatric disorders, dementia, or mental retardation in themselves or their first-degree relatives. None of the healthy control subjects met the exclusion criteria listed above.

Haematologic examinations

Blood samples were drawn in the outpatient and inpatient clinics of the hospital at the end of overnight fasting, in the morning around 7–9 a.m., from the antecubital vein of each subject by applying minimal tourniquet force. For inpatients, the blood samples were drawn within the first two days after night-fasting for at least 8 hours. During the blood draw, blood pressure, pulse, and temperature remained within normal limits. The blood samples were collected into tubes containing EDTA and processed within 30 minutes of blood collection. The assays were performed using a fully automated blood cell counter (Cell-Dyn Sapphire hematology analyzer, Abbott Diagnostics Division Inc, CA, USA) at the laboratory in Sultan Abdulhamid Han Training and Research Hospital. The devices were calibrated automatically before the study of the samples, and the coefficients of variation for the laboratory evaluations were found to be within normal limits ($< 3\%$). Platelet, PDW, and RDW levels were measured in all of the groups using the same devices and kits.

Statistics

Statistical procedures were performed with SPSS for windows Version 20.0 (SPSS Inc. Chicago, IL, USA). Descriptive statistics were used to summarize all the variables. The data were presented as the mean \pm SD values or percentages as appropriate. The normality of the distribution was tested with a Kolmogorov-Smirnov test. One-way ANOVA or student's *T*-tests were used when the data had a normal distribution. Data were log-transformed when a normal distribution was not found. If the data were not still normally distributed after transformation, a Kruskal-Wallis test or Mann-Whitney two-sample rank-sum test was used. The relationships between variables were tested using Spearman correlation analysis, and a Chi-square test was used for the categorical variables. Receiver operating characteristic (ROC) curve analysis was used to show the utility of PDW and RDW in

differentiating between patients experiencing manic episodes of BD and the healthy control group. $p \leq .05$ was regarded as being statistically significant.

Results

In our study, 199 patients and 60 controls were included. The mean ages of the manic and euthymic BD patients, UD patients, and control group were 36.81 ± 12.67 , 38 ± 12.27 , 40.86 ± 12.77 , and 35.57 ± 9.26 , respectively. There were no differences between the patients and healthy control group participants in terms of age and sex ($p = .108$ and $p = .708$, respectively). The mean duration of the disease (9.07 ± 7.78 years for manic BD, 15.63 ± 9.20 years for euthymic BD, and 3.20 ± 2.59 years for UD patients) and total number of hospitalization (3.18 ± 2.88 for manic BD, 2.13 ± 1.56 for euthymic BD, and 0.34 ± 0.73 for UD patients) were significantly different from those in the control group ($p < .001$ and $p = .007$, respectively) (Table 1).

The average PLT, PDW, and RDW levels of the manic BD, euthymic BD, and UD patients and the control group were 278.42 ± 78.53 , 266.81 ± 65.48 , 252.28 ± 65.00 , and 231.86 ± 13.22 for PLT; 16.57 ± 0.61 , 16.69 ± 0.49 , 16.70 ± 0.55 , and 17.97 ± 0.97 for PDW; and 13.99 ± 1.46 , 13.88 ± 1.00 , 14.12 ± 1.81 , and 13.16 ± 0.99 for RDW, respectively. All patients group was statistically significantly different from the healthy controls regarding RDW, PLT and PDW (Table 2).

The RDW levels in the manic and euthymic BD and UD patient groups were significantly higher than those in the healthy control group ($p = .001$, $p = .001$, and $p = .006$, respectively). In contrast, there were no significant differences between manic and euthymic BD patients, euthymic BD, and UD patients, or manic BD and UD patients in terms of RDW levels ($p = .688$, $p = .542$, $p = .693$, respectively) (Table 2).

The PLT levels of manic and euthymic BD patients were significantly higher than those of controls ($p < .001$, $p = .001$ for either of them). In contrast, there were no significant differences in PLT levels between the other groups ($p = .29$, $p = .29$, $p = .191$, and $p = .151$, respectively) (Table 2).

The PDW levels of manic BD, euthymic BD, and UD patients were significantly lower than those of the healthy control group ($p < .001$, $p < .001$, and

$p < .001$, respectively). However, the PDW levels of the euthymic patients were significantly higher than those of the manic patients ($p = .025$). In contrast, there were no significant differences in PDW between manic BD and UD patients or between euthymic BD and UD patients ($p = .059$ and $p = .822$, respectively) (Table 2).

Platelet counts were associated with PDW levels in both BD episodes and UD (manic episodes of BD: $r = -0.620$, $p = .000$; euthymic episodes of BD: $r = -0.519$, $p = .000$; UD: $r = -0.403$, $p = .001$; the healthy control group: $r = 0.136$, $p = .300$).

The ROC analysis revealed that a PDW measurement lower than 95% differentiated healthy controls from the manic BD group with a sensitivity of 92% and a specificity of 83% (area under the curve of 0.904, $p = .000$). The cutoff value for PDW for the diagnosis of manic BD in the study population was 17.15 (Figure 3). The ROC also analysis revealed that an RDW measurement lower than 95% differentiated manic BD from the healthy control group with a sensitivity of 62% and a specificity of 68% (area under the curve of 0.665, $p = .001$). The cutoff value for RDW for the diagnosis of manic BD in the study population was 13.55 (Figure 2). In addition, the correlation of platelet count with PDW is presented in BD episodes and UD (Figure 1).

Discussion

The major finding of the present study is that there is a statistically significant difference in PDW and RDW levels in UD patients and two both euthymic and manic BD patients as compared to controls. Furthermore, platelet counts were also increased in euthymic and manic BD patients as compared to controls. Another important finding is that there is a negative correlation between platelet counts and PDW in the patient groups. As far as we know, these findings are the first in the literature regarding RDW and PDW in UD and euthymic and manic BD patients.

Because the central nervous system is difficult to reach, investigators search for biological markers will provide information about the central nervous system in those suffering from psychiatric conditions [16]. The similar functional and structural features of neurons and platelets have suggested the use of platelets as

Table 1. Clinical characteristics of all participants.

	Manic BD patient (n: 69) Mean \pm SD	Euthymic BD patient (n: 60) Mean \pm SD	UD patient (n: 70) Mean \pm SD	Controls (n: 60) Mean \pm SD	p Values
Age (years) ^a	36.81 \pm 12.67	38 \pm 12.27	40.86 \pm 12.77	35.57 \pm 9.26	0.108
Sex (female/male) ^b	27/42	23/37	32/38	28/32	0.708
Duration of disease (years) ^c	9.07 \pm 7.78	15.63 \pm 9.20	3.20 \pm 2.59	–	0.000**
Number of hospitalization ^c	3.18 \pm 2.88	2.13 \pm 1.56	0.34 \pm 0.73	–	0.007**

Notes: The data are presented as the mean \pm standard deviation. The data were compared using the one-way ANOVA^a, chi-square^b and Kruskal–Wallis test^c.

* $p < .05$ (statistically significant).

** $p < .01$ (statistically significant).

Table 2. Laboratory finding of groups.

	Manic vs. control ^a		Manic vs. depression ^a		Manic vs. euthymic ^a		Euthymic vs. depression ^a		Euthymic vs. control ^a		Depression vs. control ^a		<i>p</i> Value ^b
RDW (%)	<i>z</i> = −3.232	<i>p</i> = .001**	<i>z</i> = −0.394	<i>p</i> = .693	<i>z</i> = −0.402	<i>p</i> = .688	<i>z</i> = 0.610	<i>p</i> = .542	<i>z</i> = −3.274	<i>p</i> = .001**	<i>z</i> = −2.733	<i>p</i> = .006**	<i>p</i> = .003**
PLT (10 ³ /μL)	<i>z</i> = −3.900	<i>p</i> < .001**	<i>z</i> = −2.184	<i>p</i> = .29	<i>z</i> = −1.055	<i>p</i> = .291	<i>z</i> = −1.308	<i>p</i> = .191	<i>z</i> = −3.348	<i>p</i> = .001**	<i>z</i> = −1.435	<i>p</i> = .151	<i>p</i> = .001**
PDW (FL)	<i>z</i> = −7.908	<i>p</i> < .001**	<i>z</i> = −1.890	<i>p</i> = .059	<i>z</i> = −2.244	<i>p</i> = .025*	<i>z</i> = −0.225	<i>p</i> = .822	<i>z</i> = −7.645	<i>p</i> < .001**	<i>z</i> = −7.911	<i>p</i> < .001**	<i>p</i> < .001**

Notes: The data are presented as the mean ± standard deviation. The data were compared using the Mann–Whitney two-sample rank-sum test^a and Kruskal–Wallis test^b. PDW, platelet distribution width; PLT, platelets; RDW, red cell distribution width.

**p* < .05 (statistically significant).

***p* < .01 (statistically significant).

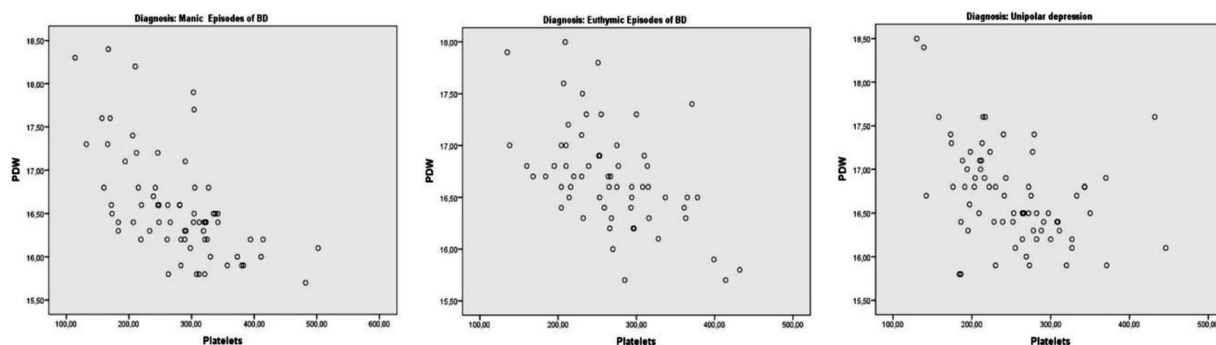


Figure 1. The correlation coefficients of platelet count with PDW are presented in BD episodes and UD. Note: The data are presented as Spearman's RHO.

peripheral models of neural activity [17,18]. Platelets are often utilized as peripheral indicators of the central 5-HT metabolism; furthermore, they are known to reflect certain biochemical changes that occur in the brain under different mental conditions [8,19]. Because of the importance attributed to disorders of platelet function in the etiology of psychiatric disorders, effort has been devoted to the study of platelets and platelet markers, such as MPV and PLR [8,20,21]. According to previous studies, some authors have suggested an association between the inflammatory process and PLT [8,9,22]. Many researchers have investigated the PLT levels in psychiatric disorders. In many studies, the differences between BD and UD patients and control groups were not statistically significant [5,8,20,22,23]. Kalelioğlu et al. found higher PLT counts in the control group than among BD patients [21]. However, similar to Özdin et al., the results of our study showed PLT counts to be higher in BD and

UD patients than in the control group [24]. The reasons for these contradictory results could be multifactorial and are certainly unclear. Firstly, the conflicting data may be due to the failure to rule out confounding factors, such as drug use, hypertension, coronary artery disease, diabetes mellitus, malignancy, dyslipidemia, stroke, smoking, and alcohol abuse [25,26]. On the other hand, inflammatory processes known to be effective in the etiopathogenesis of BD and UD may cause abnormal platelet induction and inconsistent outcomes [3,4,21,23]. Therefore, an abnormal PLT count can be used as a marker of the inflammatory process in BD and UD patients.

In the literature, there are no comparative studies of mean PDW as a specific marker of platelet activation in BD and UD patients. However, studies conducted by Liang et al. and Wang et al. found lower PDW levels in Alzheimer's patients than in control groups. In our results, PDW levels were found lower in BD and UD

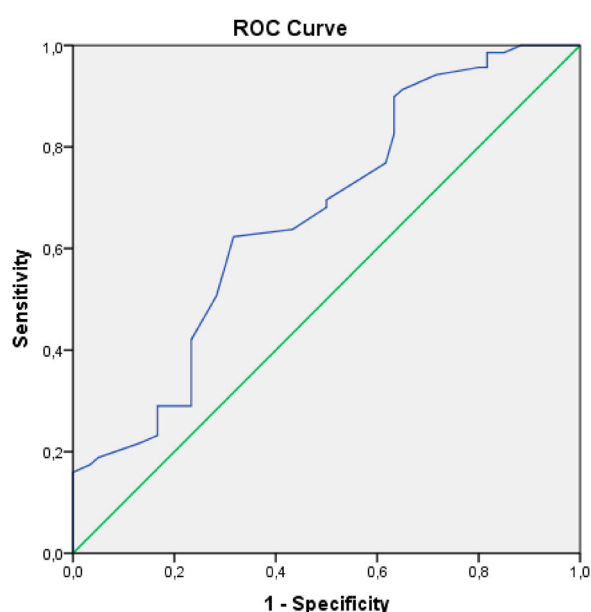


Figure 2. Curve of RDW levels in patients with manic episodes of BD versus healthy control.

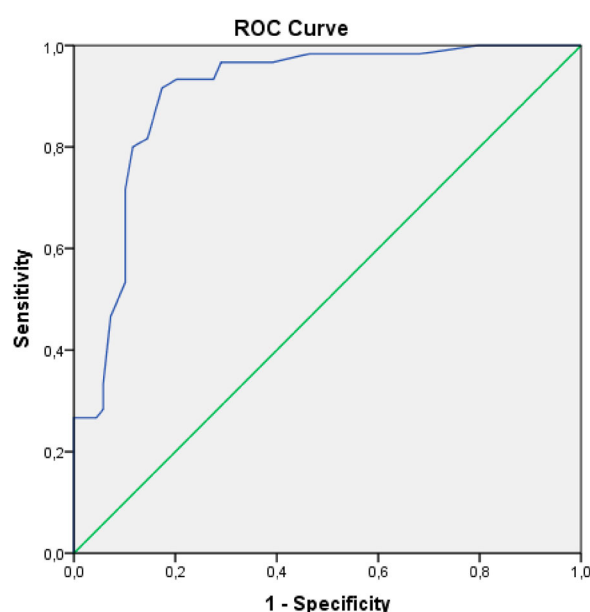


Figure 3. Curve of PDW levels in healthy control versus patients with manic episodes of BD.

patients than in the control group. These decreased PDW levels may be explained by the dysregulation of platelet activity in the bone marrow or the consumption of large platelets via inflammatory processes [27]. Some studies have suggested that PDW is a more specific marker of platelet activation and is associated with inflammatory vascular damage [28]. Sağlam Aykut et al., who studied cognitive function and NLR, an inflammation marker like PDW, found a negative correlation between inflammatory processes and cognitive functions in BD patients [29]. These studies may suggest that PDW is a predictor of cognitive decline in BD and UD patients due to neuroinflammation. In the light of above-mentioned studies and our findings, we believe that PLT and PDW can predict inflammation in BD and UD patients.

RDW levels, which are thought to be association with chronic inflammation, have been studied before [30]. Similar to studies by Mert et al. and Yıldız et al., we found a statistically significant difference in RDW levels between BD and UD patients and the control group in our study. The inflammatory process plays a powerful role in the etiopathogenesis of BD and UD and suppresses erythropoiesis [31]. This process may be caused by increased RDW levels.

According to the ROC analysis of manic BD patients and the healthy control group, PDW seems to be a biological indicator that can be used in distinguishing healthy controls from those diagnosed with manic BD. In complex cases, PDW measurements may aid in diagnosis.

The results of present study should be considered in the context of the following limitations. Firstly, because this study had a cross-sectional, retrospective design, there were limitations regarding the evaluated data. Secondly, we could not control for the effects of antipsychotics, mood stabilizers, or combinations of these on the inflammatory system. Medications used in the treatment of BD and UD have been reported to exert anti-inflammatory effects. Lastly, the lack of data regarding other inflammation markers, such as C-reactive protein (CRP) and inflammatory cytokines, is another limitation of this study.

Conclusion

In conclusion, our study showed that there are differences in PLT, RDW, and PDW values between UD and BD episodes. This study is the first to demonstrate that the PDW, RDW, and PLT levels significantly differ in patients with UD and both phases of BD. In the light of above-mentioned studies and our findings, RDW, PDW, and PLT may be involved in the inflammatory processes of UD and both BD episodes. We believe that PDW, RDW, and PLT levels can be used as novel markers for UD and BD episodes. Given the statistical analyses, PDW seems to be especially promising

in this regard. More controlled, advanced, detailed, and larger prospective clinical studies are required to confirm the value of our findings regarding the pathophysiology of affective disorders, including depressive episodes of BD.

Disclosure statement

No potential conflict of interest was reported by the authors.

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