Archives of Psychiatry and Psychotherapy, 2017; 3: 16–26

DOI: 10.12740/APP/76508

Comparison of white blood cells parameters in patients with acute schizophrenia, unipolar depression and bipolar disorder

Adam Wysokiński, Aleksandra Margulska

Summary

Objective: We compared white blood cells parameters (total white blood cells (WBC), lymphocytes count (LYMPH#) and percentage (LYMPH%), monocytes count (MONO) and percentage (MONO%), basophils count (BASO#) and percentage (BASO%), eosinophils count (EO#) and percentage (EO%), neutrophils count (NEUT#) and percentage (NEUT%)) in patients with schizophrenia (SHZ), unipolar depression (UD) and bipolar disorder (BIP): bipolar depression (BD) and mania (BM).

Methods: This was a retrospective, cross-sectional, naturalistic study of 2381 patients (SHZ n=1244; UD n=794; BIP n=343, BD n=259, BM n=84). WBC as well as differential leukocytes count were measured using automated hematology analyzer.

Results: There were significant differences between study groups (WBC, p=0.02; LYMPH# p=0.03; LYMPH% p=0.008; EO% p <0.001). Age and sex affected various white blood cells parameters.

Conclusions: There are differences in white blood cells between study groups. Highest WBC was in the schizophrenia and bipolar mania groups, while patients with BM had lowest LYMPH%. Highest frequency of below or above normal WBC was found in patients with BM.

white blood cells, schizophrenia, depression, bipolar disorder

INTRODUCTION

Leukocytes are the cells that circulate in the bloodstream and are divided into following subtypes: neutrophils, lymphocytes, basophils, eosinophils, and monocytes. White blood cell count (WBC) is the number of leukocytes per unit volume in venous blood, while differential leukocytes count represents the relative numbers of their subtypes. WBC helps to detect hematological abnormalities, but mainly it is a part of basic health check-up in patients either admitted to the hospital or presenting to primary care.

A reference range stands for the set of values within which 95 percent of the normal population falls. Therefore, it is interpreted as the range of values for a physiologic measurement in healthy individuals [1]. Normal values may vary depending on the assay used by laboratory. Moreover, among factors influencing WBC are: infections, autoimmunological disorders, splenomegaly and splenectomy, but also age (complex dependence, conflicting results) [2, 3], medications [3, 4], body weight (positive correlation)

Adam Wysokiński, Aleksandra Margulska: Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Poland
Correspondence address: adam.wysokinski@umed.lodz.pl

[3, 5, 6], smoking (positive correlation) [2, 7], alcohol consumption (inverse association) [3, 8], exposure to benzene (leukocytopenia) [2]. Sun et al. concluded that subnormal WBC counts (<3.9 × 10^9 cells/L), which rather exclude even low-grade systemic inflammation, are related to the lower prevalence of metabolic syndrome and the lowest incidence of metabolic syndrome during a 5-year follow-up period among healthy population than WBC counts within reference range [9]. Metabolic alterations are particularly common in patients treated with antipsychotics [10]. In this group around 50% suffer from metabolic disorders, which significantly reduces the lifespan and life quality. So far, studies show that a higher total leukocyte count is a predictor of all-cause mortality and cardiovascular morbidity [11]. Fan et al. suggested that higher white blood cell counts are associated not only with an increased risk for metabolic syndrome, but also more severe psychopathology in patients suffering from schizophrenia [12].

Schizophrenia, unipolar depression and bipolar disorder are severe psychiatric disorders affecting millions of people worldwide. Their complex etiology and pathophysiology are still not satisfactory elucidated, therefore there is a plethora of research examining their psychopathology. Moreover mental illnesses cause great human and economic costs. Alterations in inflammatory system have been suggested as be associated with psychiatric disorders, and white blood cells are important components of it.

The aim of the study is to investigate if there are any differences in white blood cells parameters among patients with schizophrenia, unipolar depression, bipolar depression and bipolar mania.

MATERIAL AND METHODS

This was a retrospective, cross-sectional, naturalistic study. From our psychiatric hospital computer database, we have selected data for Caucasian patients with the diagnosis of schizophrenia, bipolar disorder or unipolar depression, aged 18 or more, both men and women. Only the first entry for each patient was used for analysis. The following data were collected: age, sex, diagnosis and white blood cell parameters.

Patients were grouped under diagnostic criteria as schizophrenia (F20 according to ICD-10, 295 according to DSM-IV), unipolar depression (F31 and F32 according to ICD-10, 296.2 and 296.3 according to DSM-IV), bipolar disorder (F30 and F31 according to ICD-10, 296.[0,4,6] according to DSM-IV), which included: bipolar depression (F31.3-F31.5 according to ICD-10, 296.6 according to DSM-IV) and bipolar mania (F30 and F31.0-F31.2 according to ICD-10, 296.0 and 296.4 according to DSM-IV). In our unit diagnosis is based on the ICD-10 criteria, DSM-IV codes were given as reference. All diagnostic codes are based on discharge diagnosis.

For all patients in our study blood samples were collected into tubes with anticoagulant between 8 and 9 a.m. after 12 hours overnight fast. Usually the first blood test is done next day after admission to our units. Therefore, we have assumed that most patients that we included in the study were in acute phase of their disorder. Immediately after collecting blood samples, complete blood count was determined using Sysmex XS-1000i TM Automated Hematology Analyzer (Sysmex, USA). The following white blood cell parameters were measured: white blood cell count (WBC, expressed in × 10^3/mm^3), lymphocyte count (LYMPH#, expressed in × 10^3/mm^3), lymphocyte percentage (LYMPH%, expressed in %), monocyte count (MONO#, expressed in × 10^3/mm^3), monocyte percentage (MONO%, expressed in %), basophil count (BASO#, expressed in × 10^3/mm^3), basophil percentage (BASO%, expressed in %), eosinophil count (EO#, expressed in × 10^3/mm^3), eosinophil percentage (EO%, expressed in %), neutrophil count (NEUT#, expressed in × 10^3/mm^3) and neutrophil percentage (NEUT%, expressed in %). Table 1 shows our laboratory reference ranges used in the analysis.

Table 1. Total white blood cells – reference ranges

Parameter	Abbreviation	Reference range
White blood cells	WBC	4.0-10.0 × 10^3/mm^3
Lymphocytes, number	LYMPH#	1.32-3.57 × 10^3/mm^3

Lymphocytes, percentage	LYMPH%	21.8-53.1 %
Monocytes, number	MONO#	0.3-0.82 × 10^3/mm^3
Monocytes, percentage	MONO%	5.3-12.2 %
Basophils, number	BASO#	0.01-0.08 × 10^3/mm^3
Basophils, percentage	BASO%	0.2-1.2 %
Eosinophils, number	EO#	0.04-0.54 × 10^3/mm^3
Eosinophils, percentage	EO%	0.8-7.0 %
Neutrophils, number	NEUT#	1.78-5.38 × 10^3/mm^3
Neutrophils, percentage	NEUT%	34.0-67.9 %

Statistical procedures were performed with STATA 13.1 (StataCorp, USA). Simple descriptive statistics (mean±standard deviation) were generated for continuous variables. For discrete variables number of patients and percentages are given. Normality of distribution was tested with Shapiro-Wilk test. While some variables did not follow normal distribution, due to large sample size we used one-way ANOVA with post-hoc Tukey test and t-test. The difference between proportions was analyzed with the chi-square test. Associations were tested by Spearman's correlation coefficient. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using logistic regression adjusted for age. The level of significance was set at $p < 0.05$.

The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

In the study group of 2381 patients included in the analysis there were 60.0% women (n = 1429). The proportion of women in the schizophrenia group (n = 1244) was 46.9% (n = 583), 76.3% (n = 606) in the unipolar depression group (n = 794), 70.0% (n = 240) in the bipolar disorder group (n = 343), 72.2% (n = 187) in the bipolar depression group (n = 259), 63.1% (n = 53) in the bipolar mania (n = 84), see Figure 1. The difference between the groups in the proportion of women was significant ($X^2 = 194.0$, df = 3, $p < 0.001$), with the lowest proportion of women in the schizophrenia group. In the schizophrenia group there were 4 patients with hebephrenic subtype, 5 with residual schizophrenia and 2 with simple-type schizophrenia. These subgroups were too small to include them into separate analysis and therefore we decided to combine all patients with schizophrenia into one group. The age of the study group was 45.6±19.6 years. Mean age in the subgroups was: schizophrenia 40.3±16.2, unipolar depression 51.4±22.3, bipolar depression 52.6±18.2, bipolar mania 46.0±19.2 years. One-way ANOVA showed that there were significant age differences between the groups ($p < 0.001$) with patients in the unipolar depression, bipolar depression and bipolar mania groups being significantly older ($p < 0.001$ for all comparisons; Tukey post-hoc test). Age distribution in the study sample is shown in Figure 1 and Table 2.

Table 2. Age distribution in the study sample.

Diagnosis		Age category				Total, n (%)
		<20	20-40	40-60	>60	
Schizophrenia	Men	28	426	115	92	661 (53.1)
	Women	29	272	164	118	583 (46.9)
	Total	57	698	279	210	1244
Unipolar depression	Men	37	25	54	72	188 (23.7)
	Women	118	45	191	252	606 (76.3)

	Total	155	70	245	324	794
Bipolar disorder	Men	11	35	21	36	103 (30.0)
	Women	10	48	80	102	240 (70.0)
	Total	21	83	101	138	343
Bipolar depression	Men	5	22	15	30	72 (27.8)
	Women	5	40	62	80	187 (72.2)
	Total	10	62	77	110	259
Bipolar mania	Men	6	13	6	6	31 (36.9)
	Women	5	8	18	22	53 (63.1)
	Total	11	21	24	28	84

Mean values of leukocyte parameters are given in Table 3, with significant ($p < 0.05$) intergroup differences for most parameters. Post-hoc analysis using the Tukey test revealed that patients with schizophrenia had higher WBC than patients with unipolar depression ($p = 0.04$), patients with bipolar depression had LYMPH% higher than patients with schizophrenia ($p = 0.001$), bipolar mania ($p = 0.017$) and unipolar depression ($p = 0.003$), while patients with unipolar depression had EO% higher than patients with schizophrenia ($p = 0.008$). For the whole study group there was a significant differences between men and women for WBC (6.93±2.00 vs. 6.73±1.98, $p = 0.01$), LYMPH# (2.27±0.73 vs. 2.21±0.72, $p = 0.02$), MONO# (0.59±0.23 vs. 0.54±0.22, $p < 0.001$), MONO% (8.84±2.71 vs. 8.44±2.68, $p < 0.001$), EO# (0.21±0.15 vs. 0.18±0.14, $p < 0.0001$) and EO% (3.09±2.34 vs. 2.71±1.99, $p < 0.001$).

Table 3. Mean hematological parameters in diagnostic groups.

Parameter	Group					p
	Schizophrenia n = 1244	Unipolar depression n = 794	Bipolar disorder n = 343	Bipolar depression n = 259	Bipolar mania n = 84	
WBC	6.9±1.9 (6.6)	6.7±1.9 (6.4)	6.6±2.0 (6.3)	6.6±2.0 (6.3)	6.9±2.3 (6.7)	0.02
LYMPH#	2.3±0.7 (2.1)	2.2±0.7 (2.0)	2.2±0.7 (2.1)	2.3±0.8 (2.2)	2.1±0.7 (2.0)	0.03
LYMPH%	33.6±8.8 (33.5)	33.7±8.7 (33.8)	35.1±8.9 (34.5)	35.9±8.9 (35.7)	32.7±9.5 (31.9)	<0.001
MONO#	0.57±0.2 (0.57)	0.56±0.2 (0.54)	0.56±0.2 (0.53)	0.55±0.2 (0.53)	0.55±0.2 (0.52)	0.47
MONO%	8.6±2.7 (8.5)	8.7± 2.7 (8.5)	8.8±2.8 (8.7)	8.6±2.7 (8.5)	8.6±3.2 (8.5)	0.88
BASO#	0.03±0.02 (0.03)	0.03±0.02 (0.03)	0.03±0.02 (0.02)	0.03±0.02 (0.02)	0.03±0.01 (0.03)	0.21
BASO%	0.45±0.3 (0.4)	0.46±0.3 (0.04)	0.45±0.3 (0.4)	0.43±0.4 (0.4)	0.41±0.2 (0.4)	0.47
EO#	0.19±0.2 (0.16)	0.20±0.1 (0.17)	0.19±0.2 (0.16)	0.19±.2 (0.16)	0.22±0.1 (0.18)	0.07
EO%	2.6±2.1 (2.4)	3.0±2.1 (2.6)	3.0±2.1 (2.7)	3.0±2.3 (2.5)	3.4±1.8 (3.2)	0.001

NEUT#	3.8±1.6 (3.5)	3.6±1.5 (3.3)	3.5±1.6 (3.2)	3.5±1.7 (3.2)	3.6±1.5 (3.4)	0.09
NEUT%	53.7±10.0 (54.2)	53.3±10.0 (53.3)	51.8±9.9 (52)	51.6±10.5 (52.1)	53.4±10.3 (53.7)	0.05

WBC = white blood cells; LYMPH# = lymphocytes, number; LYMPH% = lymphocytes, percentage; MONO# = monocytes, number; MONO% = monocytes, percentage; BASO# = basophils, number; BASO% = basophils, percentage; EO# = eosinophils, number; EO% = eosinophils, percentage; NEUT# = neutrophils, number; NEUT% = neutrophils, percentage. Results given as mean±standard deviation (median).

Table 4. Distribution of low, normal and high ranges of hematological parameters in diagnostic groups.

	WBC			
	<4.0	4.0-10.0	>10.0	
Schizophrenia	32 (2.6)	1131 (90.9)	81 (6.5)	$\chi^2 = 15.7$ p <0.001
Unipolar depression	33 (4.2)	711 (89.5)	50 (6.3)	
Bipolar disorder	24 (7.0)	300 (87.5)	19 (5.5)	
Bipolar depression	17 (6.6)	229 (88.4)	13 (5.0)	
Bipolar mania	7 (8.3)	71 (84.6)	6 (7.1)	
	LYMPH#			
	<1.32	1.32-3.57	>3.57	
Schizophrenia	89 (7.2)	1094 (88.0)	60 (4.8)	$\chi^2 = 5.07$ p = 0.16
Unipolar depression	57 (7.2)	701 (88.3)	36 (4.5)	
Bipolar disorder	14 (4.1)	312 (90.9)	17 (5.0)	
Bipolar depression	9 (3.5)	235 (90.7)	15 (5.8)	
Bipolar mania	5 (5.9)	77 (91.7)	2 (2.4)	
	LYMPH%			
	<21.8	21.8-53.1	>53.1	
Schizophrenia	113 (9.1)	1108 (89.1)	22 (1.8)	$\chi^2 = 6.04$ p = 0.11
Unipolar depression	62 (7.8)	720 (90.7)	12 (1.5)	
Bipolar disorder	20 (5.8)	316 (92.1)	7 (2.1)	
Bipolar depression	12 (4.6)	240 (92.7)	7 (2.7)	
Bipolar mania	8 (9.5)	76 (90.5)	0	
	MONO#			
	<0.3	0.3-0.82	>0.82	
Schizophrenia	101 (8.1)	984 (79.2)	158 (12.7)	$\chi^2 = 0.65$ p = 0.88
Unipolar depression	67 (8.4)	642 (80.9)	85 (10.7)	
Bipolar disorder	32 (9.3)	272 (79.3)	39 (11.4)	
Bipolar depression	25 (9.7)	201 (77.6)	33 (12.7)	
Bipolar mania	7 (8.3)	71 (84.5)	6 (7.2)	
	MONO%			
	<5.3	5.3-12.2	>12.2	

Schizophrenia	133 (10.7)	1017 (81.8)	93 (7.5)	$\chi^2 = 7.8$ p = 0.05
Unipolar depression	69 (8.7)	658 (82.9)	67 (8.4)	
Bipolar disorder	40 (11.7)	272 (79.3)	31 (9.0)	
Bipolar depression	25 (9.6)	210 (81.1)	24 (9.3)	
Bipolar mania	15 (17.9)	62 (73.8)	7 (8.3)	
	BASO#			
	≤0.08	>0.08		
Schizophrenia	1019 (97.2)	29 (2.8)		$X^2 = 2.0$ p = 0.57
Unipolar depression	639 (97)	20 (3)		
Bipolar disorder	266 (97.8)	6 (2.2)		
Bipolar depression	201 (197.1)	6 (2.9)		
Bipolar mania	65 (100)	0		
	BASO%			
	≤1.2	>1.2		
Schizophrenia	1029 (98.2)	19 (1.8)		$\chi^2 = 2.4$ p = 0.49
Unipolar depression	640 (197.1)	19 (2.9)		
Bipolar disorder	267 (98.2)	5 (1.8)		
Bipolar depression	203 (98.1)	4 (1.9)		
Bipolar mania	64 (98.5)	1 (1.5)		
	EO#			
	≤0.54	>0.54		
Schizophrenia	1025 (97.7)	24 (2.3)		$\chi^2 = 2.7$ p = 0.44
Unipolar depression	639 (96.7)	22 (3.3)		
Bipolar disorder	262 (96.3)	10 (3.7)		
Bipolar depression	200 (96.6)	7 (3.4)		
Bipolar mania	62 (95.4)	3 (4.6)		
	EO%			
	≤7.0	>7.0		
Schizophrenia	1016 (96.9)	33 (3.1)		$\chi^2 = 5.2$ p = 0.16
Unipolar depression	626 (94.7)	35 (5.3)		
Bipolar disorder	259 (95.2)	13 (4.8)		
Bipolar depression	197 (95.2)	10 (4.8)		
Bipolar mania	62 (95.4)	3 (4.6)		
	NEUT#			
	<1.78	1.78-5.38	>1.78	
Schizophrenia	38 (3.6)	877 (83.7)	133 (12.7)	$\chi^2 = 15.7$ p = 0.001
Unipolar depression	27 (4.1)	553 (83.8)	80 (12.1)	
Bipolar disorder	25 (9.2)	220 (80.6)	28 (10.2)	
Bipolar depression	19 (9.1)	167 (80.3)	22 (10.6)	
Bipolar mania	6 (9.2)	53 (81.6)	6 (9.2)	
	NEUT%			
	<34.0	34.0-67.9	>67.9	

Schizophrenia	27 (2.6)	938 (89.5)	83 (7.9)	$\chi^2 = 6.9$ p = 0.07
Unipolar depression	18 (2.7)	592 (89.7)	50 (7.6)	
Bipolar disorder	13 (4.8)	245 (89.7)	15 (5.5)	
Bipolar depression	12 (5.8)	187 (89.9)	9 (4.3)	
Bipolar mania	1 (1.6)	58 (89.2)	6 (9.2)	

WBC = white blood cells; LYMPH# = lymphocytes, number; LYMPH% = lymphocytes, percentage; MONO# = monocytes, number; MONO% = monocytes, percentage; BASO# = basophils, number; BASO% = basophils, percentage; EO# = eosinophils, number; EO% = eosinophils, percentage; NEUT# = neutrophils, number; NEUT% = neutrophils, percentage. Results given as n (%).

Table 4 shows distribution of low, normal and high ranges of blood cells parameters in the study groups. Patients with bipolar mania had the highest percentage of abnormal results for WBC (both below and above normal range – 8.3% and 7.1%, respectively), MONO% below normal range (17.9%) and NEUT# below normal range (9.2%). Patients with schizophrenia had the highest percentage of NEUT# above normal range (12.7%). There were no significant inter-group differences for other hematological parameters. Apart from neutrophils and eosinophils, patients with WBC, LYMPH#, LYMPH%, MONO#, MONO% below normal range were significantly older ($p < 0.01$ for all variables). Patients with BASO# and BASO% above normal range were significantly older ($p < 0.001$ for both variables), no differences were found for the remaining white blood cells parameters being above normal range.

Table 5. Correlations between white blood cells parameters and age in diagnostic groups.

Parameter	Group				
	Schizophrenia n = 1244	Unipolar depression n = 794	Bipolar disorder n = 343	Bipolar depression n = 259	Bipolar mania n = 84
WBC	-0.06*	-0.004	-0.16***	-0.12*	0.09
LYMPH#	-0.13***	-0.11**	-0.09*	-0.03	0.07
LYMPH%	-0.11***	-0.11**	0.09*	0.08	0.07
MONO#	0.007	0.008	-0.11*	-0.08	-0.05
MONO%	0.07**	0.03	0.03	-0.003	-0.08
BASO#	0.06*	0.09*	0.09	0.13*	-0.12
BASO%	0.09**	0.09*	0.16**	0.16*	-0.09
EO#	0.09**	-0.09*	-0.08	-0.13	0.02
EO%	0.13***	-0.08*	0.005	-0.09	0.07
NEUT#	-0.02	0.05	-0.13**	-0.05	-0.04
NEUT%	0.05	0.08*	-0.05	-0.01	-0.08

WBC = white blood cell count; LYMPH# = lymphocytes, number; LYMPH% = lymphocytes, percentage; MONO# = monocytes, number; MONO% = monocytes, percentage; BASO# = basophils, number; BASO% = basophils, percentage; EO# = eosinophils, number; EO% = eosinophils, percentage; NEUT# = neutrophils, number; NEUT% = neutrophils, percentage. Results given as Spearman's correlation coefficient; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 5 shows correlations between hematological parameters and age in diagnostic groups. Also, we tested several regression models for red blood cells parameters and calculated odds ratios for hematological parameters being below or above normal values. All models were adjusted for sex and age, with the schizophrenia group as the reference. For WBC no variables were statistically significant in the model. For LYMPH# age was statistically significant in the model ($p < 0.001$, $R^2 = 0.015$) and was associated with decreased (regression coefficients $\beta = -0.12$) value. For LYMPH% age and diagnosis of bipolar depression were statistically significant in the

model ($p < 0.001$, $R^2 = 0.01$), with age associated with decreased ($\beta = -0.09$) and bipolar depression associated with increased ($\beta = 0.1$) value. For MONO# and MONO% sex was statistically significant in the model ($p < 0.001$, respectively; $R^2 = 0.01$), with male sex associated with increased value ($\beta = 0.01$ and 0.09). For BASO# age and diagnosis of bipolar depression were statistically significant in the model ($p < 0.05$, $R^2 = 0.01$), with age associated with increased ($\beta = 0.09$) and bipolar depression associated with increased ($\beta = 0.05$) value. For BASO% age was statistically significant in the model ($p < 0.001$, $R^2 = 0.01$) and was associated with increased ($\beta = -0.1$) value. For EO# and EO% sex and diagnosis of bipolar mania and unipolar depression were statistically significant in the model ($p < 0.05$, $R^2 = 0.02$), with male sex and bipolar mania or unipolar depression associated with increased value (for EO# $\beta = 0.12$, 0.05 and 0.08, respectively; for EO% $\beta = 0.12$, 0.06 and 0.12, respectively). For NEUT# diagnosis of bipolar depression was statistically significant in the model ($p = 0.04$, $R^2 < 0.01$) and was associated with decreased ($\beta = -0.05$) value. Finally, for NEUT% age and diagnosis of bipolar depression were statistically significant in the model ($p = 0.03$ and 0.001, respectively; $R^2 = 0.01$), with age associated with increased value ($\beta = 0.05$) and bipolar depression associated with decreased value ($\beta = -0.08$). Note that all R^2 and beta values are very low, indicating little effect of these variables.

For WBC below normal value male sex was associated with decreased risk (OR = 0.55 [95% CI: 0.34-0.91], p = 0.02) and age was associated with increased risk (OR = 1.02 [95% CI: 1.00-1.03], p = 0.005). For LYMPH# and LYMPH% below normal value age was associated with increased risk (OR = 1.02 [95% CI: 1.01-1.03], p <0.001 and OR = 1.01 [95% CI: 1.01-1.02], p = 0.001, respectively). For MONO# below normal value male sex and age were associated with decreased risk (OR = 0.70 [95% CI: 0.51-0.96], p = 0.02 and OR = 0.99 [95% CI: 0.98-0.99], p = 0.002, respectively). For MONO# above normal value male sex was associated with increased risk (OR = 1.69 [95% CI: 1.31-2.19], p <0.001). For MONO% below normal value age was associated with decreased risk (OR = 0.98 [95% CI: 0.98-0.99], p <0.001). For BASO# and BASO% below normal value age was associated with decreased risk (OR = 0.97 [95% CI: 0.96-0.99], p <0.001 and OR = 0.97 [95% CI: 0.95-0.98], p <0.001, respectively), while for BASO# and BASO% above normal value age was associated with increased risk (OR = 1.03 [95% CI: 1.01-1.04], p <0.001 and OR = 1.03 [95% CI: 1.02-1.05], p <0.001, respectively). No variables analyzed were associated with WBC, LYMPH#, LYMPH% and MONO% above normal range. For EO#, EO%, NEUT a# and NEUT% no variables were associated with values above or below normal range.

DISCUSSION

The objective of this study was to investigate if there are any differences in white blood cells parameters in a large sample (n = 2381) of patients with acute phase of schizophrenia, unipolar depression, bipolar depression and bipolar mania. We have confirmed that there were differences for several analyzed parameters.

As reported by previous studies, higher total leukocyte count may predict increased risk of metabolic syndrome and cardiovascular mortality and morbidity [11]. Highest total number of white blood cells was found in the schizophrenia and bipolar mania groups. This observation would indicate that these two groups of patients should be particularly carefully observed for metabolic alterations. Patients with schizophrenia had highest (although non-significant) mean value of absolute neutrophil count. Also, the percentage of patients with below norm value of absolute neutrophil count was lowest in the schizophrenia group and highest in the bipolar disorder group (both mania and depression). Patients with bipolar mania had lowest number of lymphocytes (both absolute and percentage) and highest number of eosinophils (both absolute and percentage). Highest frequency of below or above normal value of white blood cells was found in patients with bipolar mania. In our study, higher neutrophil/lymphocyte ratios (NLR) were found in SHZ (1.75) and bipolar mania (1.71) groups and lower in bipolar depression (1.52) group. In patients with schizophrenia elevated neutrophil/lymphocyte ratio was observed (SHZ vs. healthy controls: 2.6 vs. 1.9; p <0.001) [13]. Other authors observed high-

er NLR in patients with bipolar disorder [14]. As there is no healthy controls in our study it is difficult to compare those study findings. There were also numerous age – and gender-related differences for the majority of parameters.

Inflammatory process has been suggested as a risk factor as well as underlying cause of psychiatric disorders, hence inflammation has become a putative pharmacological target. Inflammatory parameters (e.g., C-reactive protein – CRP and white blood count as easily available and routinely collected in patients) have been examined in psychiatric patients. Recent population-based study by Horsdal et al. has shown that CRP differed across mental disorders, while WBC did not differ. Moreover elevated values of CRP were associated with increased mortality in psychiatric population, while values of WBC were not associated with mortality [15].

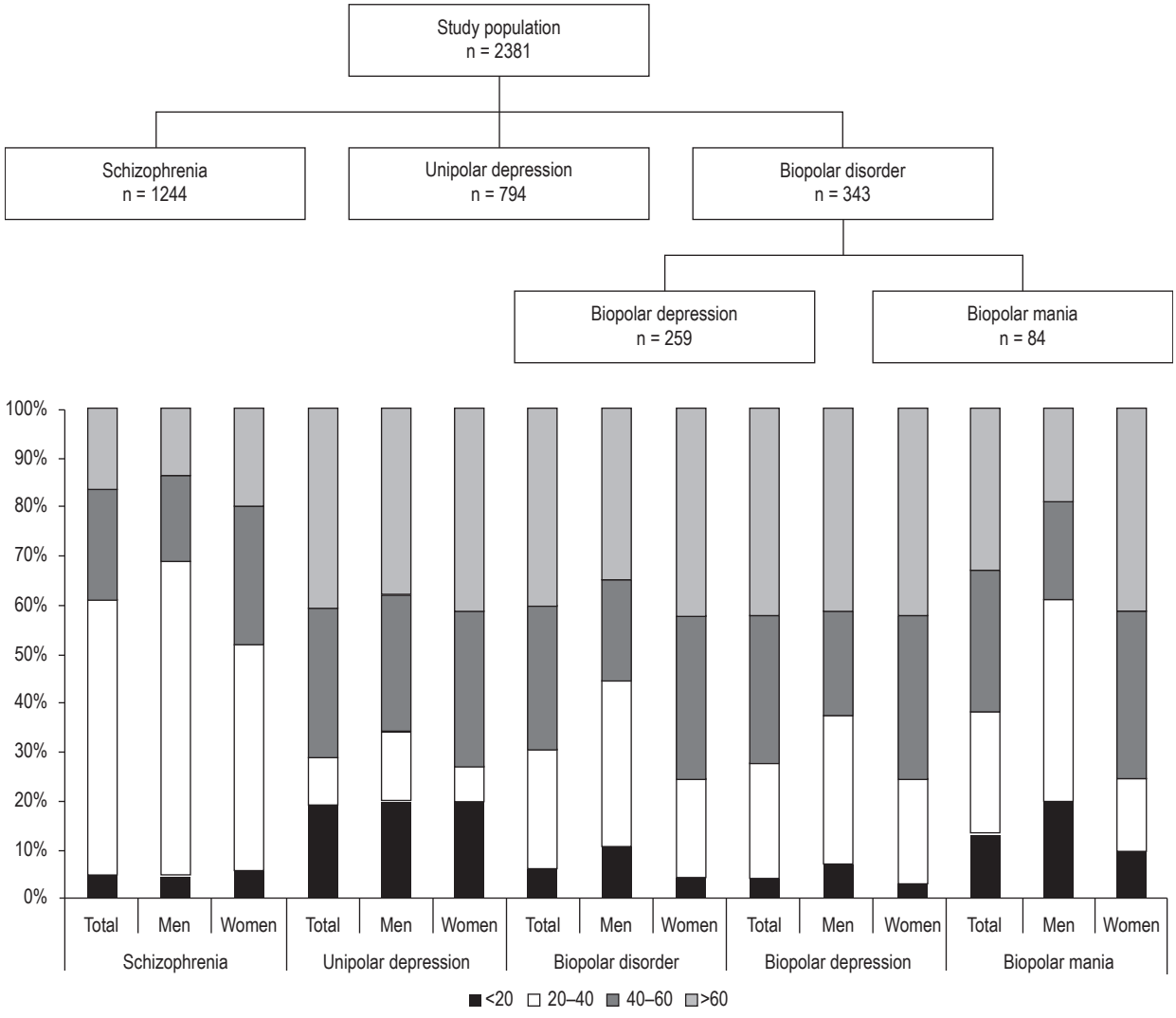
Moreover, effectiveness and tolerance of anti-inflammatory agents (e.g., omega 3 polyunsaturated fatty acids (PUFA), celecoxib, minocycline, N-acetylcysteine, pioglitazone, TNF-alpha antagonists) have been widely investigated in psychiatric population [16-20]. Recent meta-analyses indicated moderate antidepressant effect of adjunctive anti-inflammatory agents (N-acetyl cysteine, PUFA, celecoxib) in the treatment of bipolar depression [16, 20]. So far studies have demonstrated some effectiveness of PUFAs, Anti-TNF-alpha and celecoxib in treatment of unipolar depression, and minocycline in treatment of schizophrenia [21].

Furthermore, it has been suggested that patients with high (>5 mg/l) concentration of C-reactive protein (CRP) may be particularly responsive to anti-inflammatory drugs [22]. No cut-off values for white blood count that could determinate patients who could benefit from anti-inflammatory treatment have been proposed. There are study findings indicating significant change in CRP and WBC during treatment with traditional antidepressants [23, 24]. Further research could evaluate potential change of WBC values during anti-inflammatory treatment of mental illnesses. Study by Miller et. al. indicated that WBC may be a predictor of an elevated 10-year estimated risk of myocardial infarction, which underlines significance of WBC in assessment of cardiovascular risk in schizophrenia patients [25].

Our study has some limitations, which result from its cross-sectional and naturalistic design, as well as lack of control group. We only have data representing current white blood cells parameters and have no information regarding presence of past hematological abnormalities. White blood cells parameters may also result from other factors, which could not be included in the analysis, such as detailed inflammatory status of individuals (e.g., levels of other inflammatory biomarkers, subtypes of lymphocytes), exposure to ionizing radiation [26], nutritional status [27, 28], lifestyle [29], duration of disease [13, 30-32], etc. which also may have a significant impact on white blood cells parameters. Comorbidities (such as hypertension or extrapyramidal syndrome) were not an exclusion criterion. Participants of the study presented a number of comorbidities, but detailed and reliable data on co-occurring disorders were not available and therefore were not included into the analysis. Moreover, due to large study samples we believe that the distribution of major comorbidities and other factors that affect white blood cells parameters became comparable across the study groups and therefore should not affect observed differences. Results of rating scales for psychiatric conditions were not analyzed as we focused mainly on clinical diagnoses. Diagnostic groups were not homogenous, there were fewer women in the schizophrenia group comparing to other groups, while patients with unipolar and bipolar depression were significantly older comparing to other groups. Also, the bipolar disorder group was smaller comparing to schizophrenia and unipolar disorder (this is particularly true for bipolar mania group). These factors may affect results of intra – and inter-group comparisons. On the other hand, the large sample size and ability to compare tree major clinical groups (schizophrenia, unipolar disorder and bipolar disorder) are strengths of the study. Also, there are no studies comparing differences in white blood cells parameters between these diagnostic groups.

In conclusion, our study showed that there are differences in white blood cells parameters between schizophrenia, unipolar depression and bipolar disorder (both in manic and depressive episode). Total and differential white blood cell count are laboratory tests performed routinely,

that is why their thoughtful interpretation is crucial. Since many psychiatric patients are at increased risk of white blood cells parameters alterations due to treatment (such as neutropenia during clozapine treatment), monitoring for abnormal white cells status is recommended.



Figures 1a, 1b: Distribution of subjects and distribution of age (in years) in study groups.

REFERENCES

1. Wakeman L, Al-Ismail S, Benton A, Beddall A, Gibbs A, Hartnell S, et al. Robust, routine haematology reference ranges for healthy adults. Int J Lab Hematol. 2007;29(4):279-83.
2. Sakuragi S, Moriguchi J, Ohashi F, Ikeda M. Reference value and annual trend of white blood cell counts among adult Japanese population. Environ Health Prev Med. 2013;18(2):143-50.
3. Nakanishi N, Suzuki K, Tatara K. Age-related change in relationship between white blood cell count and some features of the metabolic syndrome. Ind Health. 2004;42(3):359-68.
4. Zhang M, Owen RR, Pope SK, Smith GR. Cost-effectiveness of clozapine monitoring after the first 6 months. Arch Gen Psychiatry. 1996;53(10):954-8.
5. Nanji AA, Freeman JB. Relationship between body weight and total leukocyte count in morbid obesity. Am J Clin Pathol. 1985;84(3):346-7.
6. Chae JS, Paik JK, Kang R, Kim M, Choi Y, Lee SH, et al. Mild weight loss reduces inflammatory cytokines, leukocyte count, and oxidative stress in overweight and moderately obese participants treated for 3 years with dietary modification. Nutr Res. 2013;33(3):195-203.
7. Otsuka R, Tamakoshi K, Wada K, Matsushita K, Ouyang P, Hotta Y, et al. Having more healthy practice was associat-

ed with low white blood cell counts in middle-aged Japanese male and female workers. Ind Health. 2008;46(4):341-7.

8. Nakanishi N, Yoshida H, Okamoto M, Matsuo Y, Suzuki K, Tatara K. Association of alcohol consumption with white blood cell count: a study of Japanese male office workers. J Intern Med. 2003;253(3):367-74.
9. Sun S, Wu H, Zhang Q, Wang C, Guo Y, Du H, et al. Subnormal peripheral blood leukocyte counts are related to the lowest prevalence and incidence of metabolic syndrome: Tianjin chronic low-grade systemic inflammation and health cohort study. Mediators Inflamm. 2014;2014:412386.
10. Hasnain M, Vieweg WV, Fredrickson SK, Beatty-Brooks M, Fernandez A, Pandurangi AK. Clinical monitoring and management of the metabolic syndrome in patients receiving atypical antipsychotic medications. Prim Care Diabetes. 2009;3(1):5-15.
11. Huang ZS, Lo SC, Tsay W, Hsu KL, Chiang FT. Revision in reference ranges of peripheral total leukocyte count and differential leukocyte percentages based on a normal serum C-reactive protein level. J Formos Med Assoc. 2007;106(8):608-16.
12. Fan X, Liu EY, Freudenreich O, Park JH, Liu D, Wang J, et al. Higher white blood cell counts are associated with an increased risk for metabolic syndrome and more severe psychopathology in non-diabetic patients with schizophrenia. Schizophr Res. 2010;118(1-3):211-7.
13. Semiz M, Yildirim O, Canan F, Demir S, Hasbek E, Tuman TC, et al. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatr Danub. 2014;26(3):220-5.
14. Cakir U, Tuman TC, Yildirim O. Increased neutrophil/lymphoctye ratio in patients with bipolar disorder: a preliminary study. Psychiatr Danub. 2015;27(2):180-4.
15. Horsdal HT, Kohler-Forsberg O, Benros ME, Gasse C. C-reactive protein and white blood cell levels in schizophrenia, bipolar disorders and depression – associations with mortality and psychiatric outcomes: a population-based study. Eur Psychiatry. 2017;44:164-72.
16. Rosenblat JD, Kakar R, Berk M, Kessing LV, Vinberg M, Baune BT, et al. Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis. Bipolar Disord. 2016;18(2):89-101.
17. Husain MI, Chaudhry IB, Hamirani MM, Minhas FA, Kazmi A, Hodsoll J, et al. Minocycline and celecoxib as adjunctive treatments for bipolar depression: a study protocol for a multicenter factorial design randomized controlled trial. Neuropsychiatr Dis Treat. 2017;13:1-8.
18. Faridhosseini F, Sadeghi R, Farid L, Pourgholami M. Celecoxib: a new augmentation strategy for depressive mood episodes. A systematic review and meta-analysis of randomized placebo-controlled trials. Hum Psychopharmacol. 2014;29(3):216-23.
19. Cohen IV, Makunts T, Atayee R, Abagyan R. Population scale data reveals the antidepressant effects of ketamine and other therapeutics approved for non-psychiatric indications. Sci Rep. 2017;7(1):1450.
20. Ayorech Z, Tracy DK, Baumeister D, Giaroli G. Taking the fuel out of the fire: evidence for the use of anti-inflammatory agents in the treatment of bipolar disorders. J Affect Disord. 2015;174:467-78.
21. Fond G, Hamdani N, Kapczinski F, Boukouaci W, Drancourt N, Dargel A, et al. Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review. Acta Psychiatr Scand. 2014;129(3):163-79.
22. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013;70(1):31-41.
23. Chavda N, Kantharia ND, Jaykaran. Effects of fluoxetine and escitalopram on C-reactive protein in patients of depression. J Pharmacol Pharmacother. 2011;2(1):11-6.
24. Canan F, Ataoglu A. Effect of escitalopram on white blood cells in patients with major depression. J Clin Med Res. 2009;1(5):290-1.
25. Miller BJ, Kandhal P, Rapaport MH, Mellor A, Buckley P. Total and differential white blood cell counts, high-sensitivity C-reactive protein, and cardiovascular risk in non-affective psychoses. Brain Behav Immun. 2015;45:28-35.
26. Rybkina VL, Azizova TV, Scherthan H, Meineke V, Doerr H, Adamova GV, et al. Expression of blood serum proteins and lymphocyte differentiation clusters after chronic occupational exposure to ionizing radiation. Radiat Environ Biophys. 2014;53(4):659-70.
27. Hsu WY, Wu CH, Hsieh CT, Lo HC, Lin JS, Kao MD. Low body weight gain, low white blood cell count and high serum ferritin as markers of poor nutrition and increased risk for preterm delivery. Asia Pac J Clin Nutr. 2013;22(1):90-9.
28. Dias JA, Wirfalt E, Drake I, Gullberg B, Hedblad B, Persson M, et al. A high quality diet is associated with reduced systemic inflammation in middle-aged individuals. Atherosclerosis. 2015;238(1):38-44.
29. Scott HA, Latham JR, Callister R, Pretto JJ, Baines K, Saltos N, et al. Acute exercise is associated with reduced exhaled nitric oxide in physically inactive adults with asthma. Ann Allergy Asthma Immunol. 2015;114(6):470-9.
30. Nolen SL, Dimmick WF. EPA's control technology approach to assisting states and regions with air toxics problems: five case studies. Toxicol Ind Health. 1990;6(5):257-67.
31. Di Nicola M, Cattaneo A, Hepgul N, Di Forti M, Aitchison KJ, Janiri L, et al. Serum and gene expression profile of cytokines in first-episode psychosis. Brain Behav Immun. 2013;31:90-5.
32. Baskak SC, Ozsan H, Baskak B, Devrimci Ozguven H, Kinikli G. [Peripheral blood T-lymphocyte and T-lymphocyte subset ratios before and after treatment in schizophrenia patients not taking antipsychotic medication]. Turk Psikiyatri Derg. 2008;19(1):5-12.