•Original research article•

Relationship of mean platelet volume to MDD: a retrospective study

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Background: Results of numerous studies show that major depressive disorder (MDD) is associated with a chronic low-grade inflammation, but the underlying mechanism remains unclear.

Aim: To compare the results of blood cell analysis of MDD patients with healthy controls, and explore the potential value of it as an indicator of immune-inflammation in MDD, especially the mean platelet volume.

Methods: 103 MDD patients and 106 healthy controls with matched age and gender were recruited.

We collected peripheral blood samples from both groups and gathered basic data. For comparison of normally distributed data (age, body mass index, lymphocyte count, white blood cell count, red blood cell count, hematocrit, platelet count and mean corpuscular volume) between groups, single t-test were used; and for comparison of non-normally distributed data (Neutrophil count, neutrophil count, platelet/lymphocyte ratio, hemoglobin, red blood cell distribution width, mean platelet volume, mean hemoglobin concentration, mean hemoglobin and platelet distribution width), we used Mann-Whitney U-test.

Results: Compared with healthy controls, the MDD groups showed significantly higher white blood cell count (F=0.443, p=0.004), plateletcrit (F=8.3, p<0.001), neutrophil and lymphocyte ratio (Z=-6.063, p<0.001), neutrophil count (Z=-5.062, p<0.001), platelet/lymphocyte ratio (Z=-2.469, p=0.014), red blood cell distribution width (Z=-2.481, p=0.013) and mean platelet volume (Z=-2.668, p=0.008). In addition they had significantly lower hemoglobin (Z=-3.876, p<0.001), mean hemoglobin amount (Z=-3.005, p=0.003), red blood cell count (F=0.248, p<0.001), lymphocyte count (F=3.826, p=0.004) and hematocrit (F=0.000, p>0.001).

Conclusions: The results suggest that serum inflammatory response probably exists in people with MDD, and indicators of blood analysis especially mean platelet volume have a potential value as biomarker for inflammation.

Key words: major depressive disorder; mean platelet volume; inflammation; China

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1. Introduction

Major Depressive Disorder (MDD) is one of the most common mood disorders seen in clinical practice. Although various approaches to treatment have been explored, for patients treated with antidepressants there are still about 40% of patients who have almost no response to a first administration. [1,2,3] In addition, residual symptoms and functional damage were left on about one third of patients after treatment, for whom the opportunity to achieve total remission gets

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smaller and smaller with the extension of time. [4,5] A five-year follow-up study observed 102 patients with a diagnosis of MDD in a general hospital setting and found that patients spent 33.4% of the follow-up time in major depressive episodes (MDE), 24.2% in partial remission and 42.4% in full remission. [6,7] There are many factors that lead to poor curative efficacy of depression, including racial differences, incorrect diagnosis, genetic inheritance and comorbidity with physical health conditions.[8,9] Another study found that the incidence of MDD was highly correlated with the disturbance of neuro-immunological function, and that inflammation also was involved in its pathogenesis. [10] When an episode (MDE) arose, a series of abnormal changes occur in the concentration level of inflammatory factors and C-reactive protein (CRP), with an aberrant of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio as well as the red cell distribution width. [11,12,13] A recent study suggests the concentration level of CRP has potential to be applied as a predictive factor for the curative efficacy of antidepressants. It showed that in patients with MDD with lower CRP (<1mg), the score of Montgomerie Scale for Depression (MADRS) for patients with 6-weeks intervention of escitalopram were 3 points higher on average than the group receiving 6-weeks treatment with nortriptyline. In contrast, in the patients with relatively higher CRP, the MADRS score of the nortriptyline group was higher than escitalopram by 3 points on average after 6-week administration.[14] Our previous work indicated that the serum level of inflammatory factors such as interleukin-8 (IL-8), macrophageinflammatoryprotein-1α(MIP-1α), monocyte chemoattractant protein 1(MCP-1) and stromal cell derived factor-1(SDF-1) are significantly greater in MDD patients and remain greater than normal controls even after an 8-week drug therapy program. These results suggest that MDD is strongly related to inflammation. [15]

Inflammatory markers could be used for monitoring the inflammation level of the body. First, clinical trials have proven that mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and red blood cell distribution width have the value to be used as biomarkers of inflammation in various diseases.[16,17,18] Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were already used for consequently evaluating inflammation in clinical practice.[19] But there is still a lack of studies on mean platelet volume. Research already demonstrated that mean platelet volume, neutrophil/ lymphocyte ratio, platelet/lymphocyte ratio and red blood cell distribution width are correlated with inflammation in chronic diseases (such as cardiovascular diseases, chronic nephropathies, neoplasms, cerebrovascular diseases and autoimmune diseases), and that they may have valuable potential to evaluate the inflammation in these diseases.[16,18,19,20] Moreover, researchers also found that mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and red blood cell distribution width in people with MDD are significantly higher than in individuals who are mentally healthy.[21,22] Platelets are fractions produced by megakaryocytes, and the volume of platelets is inversely proportional to the amount.[23,24] Despite a previous study reporting the change of serum mean platelet volume also could be used in evaluation of inflammation in diseases,[20] the relationship between it and MDD is still unclear. Our study compared the inflammation biomarkers in MDD patients with healthy controls, and explored whether the level of serum mean platelet volume has the potential of being applied in inflammation detection in MDD.

2. Methods

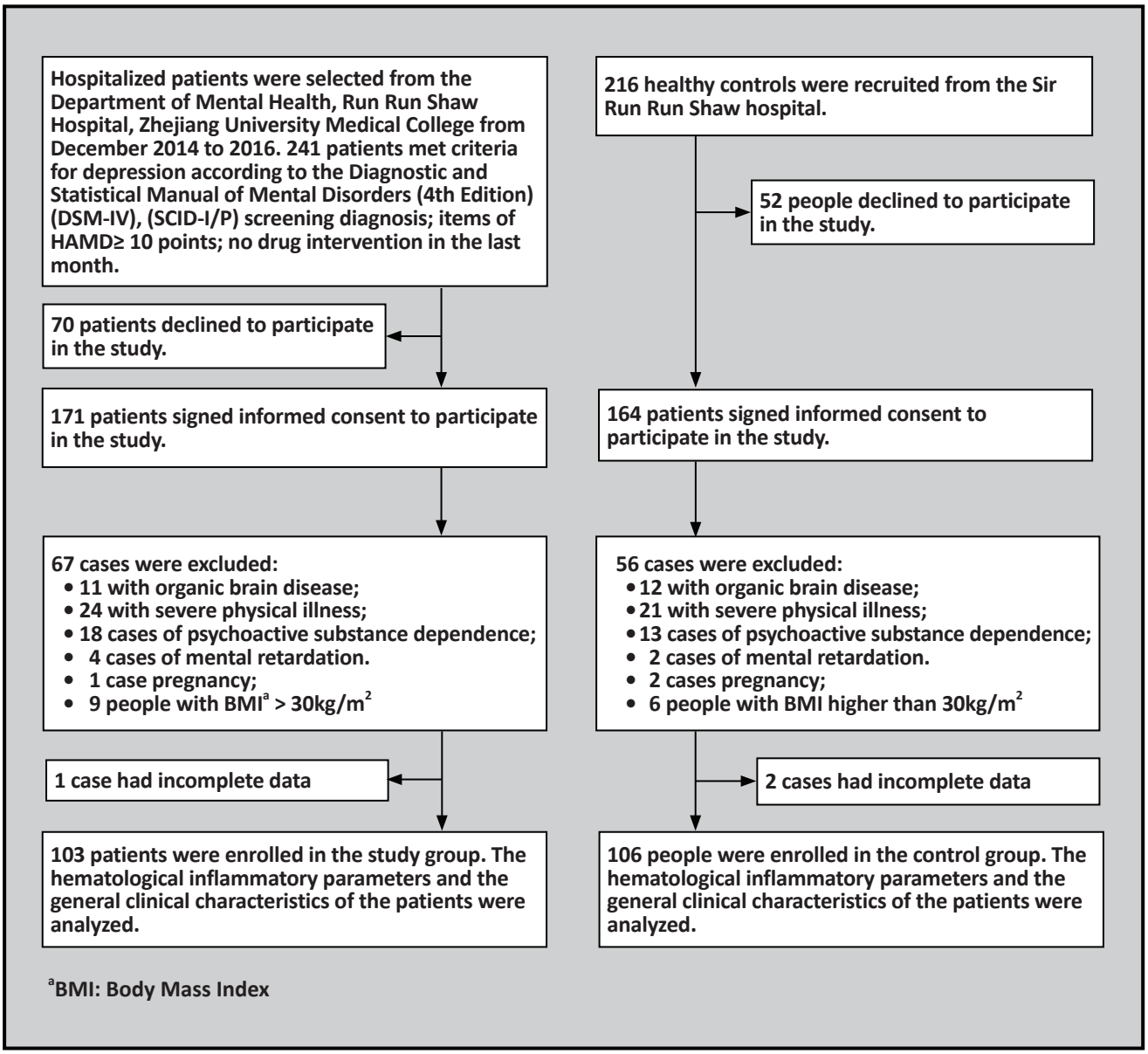
2.1 Sample

The flow chart in figure 1 shows the inclusion procedure for the study. All participants enrolled into the MDD group were registered inpatients at the Sir Run Run Shaw Hospital affiliated with Zhejiang University staying in the hospital between December 2014 and April 2016. To eliminate possible confounding factors, our study only included patients 18 to 65 years old and who had not taken psychotropic medicine at least one month before registering in this study. [25,26] From 241 MDD patients who met the initial inclusion criteria listed about above, 70 patients declined to participate in this study and 171 patients provided informed consent. 103 patients met the final criteria for inclusion in this study, amongst which 46 were males and 57 were females with a mean (sd) age of 46.6 (13.4). Details of the final criteria are listed below:

Inclusion criteria for the MDD group were the following: (1) 18 to 65 years old; (2) provided written informed consent; (3) met the diagnostic criteria for MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and passed assessment using the Structured Clinical Interview for DSM-IV, Axis I Disorders (SCID-I/P); [27] (4) score on the Hamilton Depression Scale (HAMD) of greater than 10 points; (5) no psychotropic medications used in past one month. Exclusion criteria were the following: (1) having an autoimmune disease, infection, severe systemic diseases, epilepsy, diabetes mellitus, hypertension, or other kind of cardiovascular disease as well as liver and kidney diseases; (2) Mental retardation or neurodevelopment disorders, traumatic brain injuries and pregnancy; (3) history of dependence or abuse of alcohol, tobacco and other kinds of substances related disorders; (4) Body Mass Index (BMI) greater than 30kg/m^2 or taking any kind of medication.

Healthy control group was the following: 216 people were recruited from the Health Examination Center, Sir Run Run Shaw Hospital, 52 of them declined to participate and 164 agreed to participate. Ultimately 106 people were selected, including 47 males and 59 females, with a mean (sd) age of 46.6(12.9) years. Inclusion criteria for the healthy control group was the

Figure 1. Flowchart of the study



following: (1) aged 18 to 65 years; (2) screened by SCIDI/P assessment and no DSM-IV axis I mental disorders were found; (3) three generations of relatives without mental disorders or hereditary neurological diseases. Exclusion criteria were the following: (1) have a past or present history of any kind of substance dependence; (2) took any kind of psychotropic agents in the past one month; (3) having any kind of physical disease; (4) mental retardation or neurodevelopmental disorders, pregnancy and BMI>30 kg/m^2.

No significant difference was found between participants in the MDD group and control group in any of the following areas: gender (x^2=0.002, p=0.963), age (F=0.002, p=0.990), education (x^2=2.614, p=0.106), marital status (x^2=0.077, p=0.782) or BMI (F=5.307, p=0.5). All participants accepted a Complete Blood Count and blood analysis test at 6am on the first day after admission to the inpatient unit and gave 3 ml venous blood into a container containing anticoagulants of EDTA.

2.2 Assessment

Clinical symptoms were assessed by a team of trained psychometric specialists. They showed good reliability and consistency (average Kappa > 0.80), after evaluating 5 patients continuously. The Hamilton Depression Scale (HAMD, showed reliability from 0.88 to 0.99 and validity of 0.92 and the Hamilton Anxiety Scale (HAMA, reliability 0.83 to 1.00 and validity 0.36) was applied in the assessment.[28]

2.3 Laboratory

Following items of blood cytology were measured: neutrophil count, hemoglobin, red blood cell distribution width, mean platelet volume, mean hemoglobin contribution, mean hemoglobin content, lymphocyte count, leukocyte count, erythrocyte count, mean erythrocyte content, erythrocyte hematocrit, platelet count and plateletcrit. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were calculated. All blood samples were sent to laboratory of Sir Run Run Shaw Hospital and analyzed through LH 780 Hematology Analyzer of Beckman Coulter Inc.

2.4 Statistical analysis

SPSS 16.0 was used for data analysis. Continuous data was described as x ±s. Chi-square test was used to analyze discreet data. Shapiro-Wilk test were used for the normality test of continuous data. Differences in normally distributed continuous data between groups were analyzed by independent sample t-test. For non-normally distributed continuous data, we used Mann-Whitney U-test. The spearman method was introduced for the need of correlation analysis. Results with $p<0.05$ were considered as significantly different.

3. Results

3.1 Comparison of clinical features between groups (gender, age, educational level, marriage status and BMI, see table 1)

Table 1 shows that there was no significant difference in gender, age, education, marital status and BMI between MDD patients and controls.

3.2 Comparison of cytological indicators of blood analysis between groups

Results are shown in table 2 and table 3. These results suggest that for MDD patients, the indicators of leukocyte count, neutrophils count, red blood cell distribution width, mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, plateletcrit were significantly higher than the healthy controls. For the control group, their lymphocyte count, hemoglobin, mean hemoglobin content, erythrocyte count and erythrocyte hematocrit were greater than the MDD group. Both differences were significant.

3.3 Result of Spearman relativity analysis of mean platelet volume, total course of disease and HAMD score

Spearman correlation analysis was used to analyze the correlation between the platelet volume and total course of disease and HAMD score of the MDD group, respectively. The results did not show any correlation between platelet volume and total course of disease(r=0.031, p=0.768), and HAMD score (r=0.002, p=0.987).

4. Discussion

4.1 Main findings

Clinical trials have found that inflammation is involved in the etiology of MDD,[10] and inflammatory biomarkers can reflect the status of inflammation response in systemic diseases. This study compared blood cell markers of inflammation in depressed patients and healthy individuals. The results showed

Table 1. Basic features of patients with major depressive disorder and normal healthy controls

characteristic	MDD group (n=103)	Control group (n=106)	Statistic	*p*-value
age				
range	18-65	18-65		
mean (standard deviation)	46.58(13.38)	46.56(12.94)	F=0.002	0.990
BMI				
mean (standard deviation)	22.00(3.1)	21.73(2.24)	F=5.307	0.500
Gender				
male/female	46/57	47/59	0.002	0.963
education level			2.614	0.106
0-8 years	41	54		
> 8 years	62	52		
marriage				
married	81	85		
unmarried	22	21	0.077	0.782

significantly different: $p<0.05$.

Table 2. Comparison of blood analysis between depressive patients and normal controls, mean (sd)

	MDD group (n=103)	Control group(n=106)	*F*	p-value
WBC count(10^9/L)	6.11(1.12)	5.67(0.98)	0.443	**0.004***
Lymphocyte count (10^9/L)	1.67 (0.39)	1.85(0.47)	3.826	**0.004***
Red blood cell count (10^{12}/L)	4.34(0.43)	4.63(0.41)	0.248	**<0.001***
Mean corpuscular volume (FL)	90.19 (3.07)	91.6(3.45)	0.702	**0.003***
Hematocrit (%)	39.78(3.87)	41.74(3.85)	0.000	**<0.001***
Plateletcrit (%)	0.22 （0.02）	0.175(0.29)	8.300	**<0.001***
Platelet count (10^9/L)	217.7(42.92)	209.48(39.76)	0.010	0.166

*significantly different: *p<0.05.*

***single t-test used for normally distributional data*

Table 3. Comparison of blood analysis between depressive patients and normal controls, mean (sd)

	MDD group (n=103)	Control group(n=106)	*Z*	p-value
platelet/lymphocyte ratio	128.69(29.73)	118.79(32.84)	-2.469	**0.014***
neutrophil/lymphocyte ratio	2.28 (0.62)	2.0 (0.73)	-6.063	**<0.001***
the neutrophil count (10^9/L)	3.85 (0.77)	3.27(0.82)	-5.062	**<0.001***
platelet distribution width (%)	15.80 (2.12)	14.04 (3.97)	-1.789	0.074
mean platelet volume (FL)	9.39 (0.6)	9.06(0.85)	-2.668	**0.008***
mean hemoglobin (pg.)	30.45 (1.30)	30.98(1.26)	-3.005	**0.003***
mean hemoglobin concentration (g/L)	33.57 (0.85)	33.61 (0.45)	-0.069	**0.945**
red blood cell distribution width (%)	13.29 (0.94)	12.97 (0.49)	-2.481	**0.013***
hemoglobin (g/dl)	13.38 (1.33)	14.22(2.17)	-3.876	**<0.001***

*significantly different: *p<0.05.*

***Mann-Whitney test used for non-normally distributed data*

that the white blood cell count, neutrophil count, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, erythrocyte distribution width, mean platelet volume and plateletcrit were higher in the depressive group than in the control group. While the lymphocyte count, hemoglobin, mean hemoglobin, red blood cell count and hematocrit of patients with depression were lower than those of normal healthy controls.

Chronic inflammatory response may impair cognitive function in patients with mood disorders, and affects sleep, mood and mental status.[29] Animal studies have also confirmed that immune and inflammatory responses to the nervous system also cause psychiatric symptoms.[30-34] An example of this is that an injection of exogenous inflammatory cytokines in animals will be accompanied by feelings of loneliness and depressed mood.[32] MDD patients often have comorbid autoimmune inflammatory diseases, such as diabetes, malignancies, autoimmune hypothyroidism, multiple sclerosis, rheumatoid arthritis, etc.[31-33, 35-37] At the same time, suffering from autoimmune diseases can increase the risk of MDD incidence.[30-32] All this evidence suggests that immune and inflammatory reactions affect the brain's neurological function.[30-32] Further studies have confirmed that the inflammatory response is through the inflammatory cytokines that affect the central nervous system function. Inflammatory cytokines can cause changes in the neurotransmitters of the central nervous system and cause synaptic plasticity dysfunction, such as impacting brain 5-HT neurotransmitter generation and metabolism.[32] Moreover, inflammatory cytokines also trigger the hypothalamus-pituitary-adrenal axis, and decrease the sensitivity of it to glucocorticoid.[37] Indicating that the inflammatory response can lead to dysfunction of the central nervous system and abnormality of brain structure.[38]

It is possible to use serum contribution levels of inflammatory markers to assess a disease's inflammatory response. In a Major Depressive Episode, the concentration of white blood cells, neutrophils, C-reactive protein levels in the peripheral blood escalate, and can increase the symptoms of depression.[39] The neutrophil/lymphocyte ratio, platelet/lymphocyte ratio,

and red blood cell distribution width are inflammatory markers that monitor the inflammatory state of a disease.[16-18] In this study, we found that the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and red blood cell distribution width of depressive patients were significantly higher than those of the normal controls. These results are consistent with previous research.[21,22] Furthermore, we found that the blood inflammatory cells (i.e. white blood cell count, neutrophil count) of patients with depression were significantly higher than those of the normal control group, which indicates that there was an inflammatory reaction in MDD. However, their lymphocyte counts were lower than those in the normal controls, which may be inflammatory or chronic stress-induced cellular immunosuppression, resulting in elevated neutrophils and leukocytes and a relatively reduced lymphocyte count.[10,40,41] It has been reported in previous research that the mean platelet volume levels in some inflammatory diseases is elevated and can be used as a potential inflammatory marker. [18,42] The results of this study found that the mean platelet volume in patients with MDD was significantly higher than those of the healthy control group, suggesting that mean platelet volume, as well as neutrophil/lymphocyte ratio and platelet/lymphocyte ratio, may also be useful as markers of inflammation in MDD patients. In addition, our study also found that in patients with MDD, hemoglobin, mean hemoglobin, red blood cell count and hematocrit were lower in the MDD group than the control group. These changes are probably related to the inflammatory state that patients in the MDD group were in, and that systemic inflammation inhibited the erythropoiesis, resulting in inflammatory anemia in MDD patients.[43] But this may also be a result of long-term poor appetite seen in the individuals with MDD, which leads to decreased hemoglobin.[44,45]

There was no correlation between mean platelet volume and total course of disease and HAMD scores. This result is consistent with previous findings that there is no correlation between the severity of depressive symptoms and the immunoinflammatory response.[46-48] However, research has found that severe depressive symptoms and immunosuppression are related.[49] Another study suggested that the severity of depressive symptoms is associated with changes in autoimmune system functioning, and the lymphocyte count decreases as depressive symptoms increase. [50] Results of our study found no correlation between the mean platelet volume and the severity of depressive symptoms. Possible reasons could be small sample size, or the heterogeneity of inflammatory responses that exist in MDD. For example, Yirmiya and colleagues[51] concluded that activation or attenuation of microglia could also be a potential cause of depression. Further studies are required.

4.2 Limitations

This study has several major limitations that should be considered when interpreting the results. First, the sample size was quite small. Second, we did not include inflammatory cytokines associated with immunological function in the statistical analysis and did not perform correlation analysis with the HPA axis, therefore the data is not sufficient to use mean platelet volume as an independent marker for MDD. Moreover, this is a retrospective study so no causal relationship can be drawn between mean platelet volume and MDD. Further studies require follow-up analysis with larger samples of patients with MDD.

4.3 Implications

Our results suggests that the concentration of inflammatory cells in blood analysis (white blood cells, neutrophils, platelet, mean platelet volume) and ratio between counts (neutrophil/lymphocyte ratio, platelet/lymphocyte ratio) were significantly higher in MDD patients than in healthy controls, implying that inflammation probably plays an important role in the pathogenesis of MDD, and may lead to its recurrence and affect the therapeutic effect of pharmacological treatments. Mean platelet volume may also serve as a biomarker of the inflammatory state of depression. This provides a basis for future studies of MDD treatment. Recurrent episodes and poor treatment of MDD may be due to immune and inflammatory response.

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Conflict of interest statement

The authors declare no conflict of interest.

Informed consent

Each participant in this study signed a consent form or provided oral consent at the beginning of the study.

Ethics approval

This study has been approved by the Ethics Committee of Run Run Shaw Hospital, Zhejiang University School of Medicine.

Authors' contributions

CL was the principal investigator and was responsible for the collection of cases and data, statistical analysis and writing of the manuscript; XL and WL participated in the case collection and data processing; CW was in charge of project design, writing of the paper and editing.

平均血小板体积与抑郁症的相关性

蔡利强，许洛伊，魏丽丽，陈炜

背景：研究发现抑郁症存在免疫炎症反应，但是其炎症反应的病理机制仍不完全清楚。

目标：探讨抑郁症血液炎症细胞标志物水平，观察平均血小板体积水平能否反映抑郁症免疫炎症程度。

方法：选取 103 例符合 DSM-IV 诊断标准的抑郁症患者作为研究对象，以 106 例健康者作为对照。采集所有参与者的外周血进行全血细胞分析，比较两组血细胞指标水平的差异。非正态分布的数据（中性粒和淋巴细胞比值、中性粒细胞计数、血小板 / 淋巴细胞比值、血红蛋白、红细胞分布宽度、平均血小板体积、平均血红蛋白浓度、平均血红蛋白量、血小板分布宽度）采用 Mann–Whitney U-test 进行分析。符合正态分布的数据（如年龄、体重指数、淋巴细胞计数、白细胞计数、红细胞计数、红细胞压积、血小板计数、平均红细胞体积、血小板压积）采用独立样本 t 检验。

结果：（1）抑郁症组白细胞计数 (F=0.443, p=0.004)、血小板压积 (F=8.3, p<0.001)、中性粒和淋巴细胞比值 (Z=-6.063, p<0.001)、中性粒计数 (Z =-5.062, p<0.001)、血小板 / 淋巴细胞比值 (Z =-2.469, p=0.014)、红细胞分布宽度 (Z=-2.481, p=0.013)、平均血小板体积 (Z =-2.668, p=0.008) 高于正常对照组。（2）正常对照组血红蛋白 (Z=-3.876, p<0.001)、平均血红蛋白量 (Z=-3.005, p=0.003)、红细胞计数 (F=0.248, p<0.001)、淋巴细胞计数 (F=3.826, p=0.004)、红细胞压积 (F=0.000, p<0.001) 高于抑郁症患者组。

结论：抑郁症存在血液炎症反应，平均血小板体积可能是炎症状态的生物学指标。

关键词：抑郁症，平均血小板体积，炎症

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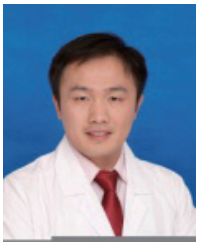

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