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CLINICAL STUDY

Neutrophil/lymphocyte, platelet/lymphocyte, monocyte/lymphocyte ratios and systemic immune-inflammation index in patients with depression

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ABSTRACT

BACKGROUND: Evidence suggest immunity abnormalities and inflammation might play an important role in the pathophysiology of depression. This study explored the relationship between inflammation and depression using neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) as inflammatory markers.

METHODS: We collected the full blood count results of 239 patients with depression and 241 healthy controls. Patients were divided into three diagnostic subtype groups: severe depressive disorder with psychotic symptoms, severe depressive disorder without psychotic symptoms, and moderate depressive disorder. We analyzed the Participants' neutrophil (NEU), lymphocyte (LYM), monocyte (MON), and platelet (PLT) counts, compared the differences in NLR, MLR, PLR and SII, and explored the relationships between depression and these indicators.

RESULTS: There were significant differences in PLT, MON, NEU, MLR, and SII among the four groups. MON and MLR were significantly higher in three groups of depressive disorders. SII was significantly increased in two severe depressive disorder groups, while the SII in the moderate depressive disorder group showed an increasing trend.

CONCLUSION: Increased MON, MLR and SII, as signs of inflammatory response, were not different among three subtypes of depressive disorders, and may be biological indictors of depressive disorders *(Tab. 1, Ref. 17)*. Text in PDF *www.elis.sk*

KEY WORDS: depression, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII).

Introduction

Depression is a psychiatric disorder that has received widespread attention, with a lifetime prevalence of 15–18 % (1). Depression diminishes individuals' quality of life and limits their psychosocial functioning (1). Research suggests that inflammation is involved in the etiology of depression and may contribute to the manifestations of different depression subtypes and treatment responses (2).

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Inflammatory markers are abnormal in patients with depression, such as IL-1β, IL-6, TNF, and C-reactive protein in peripheral blood (3). A neuroimaging study also finds evidence of immune activation in central nervous system of patients with depression (4), while others find that the application of anti-inflammatory aversion could relieve depressive symptoms(2). Given the strong link between depression and inflammation, inflammatory markers could serve as one of the biomarkers of depression (3).

Some convenient indicators have received much attention in recent years; these include the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII). These indicators can well reflect an individual's inflammatory state and have been widely recognized in the research of chronic inflammation-related diseases (5). SII, in particular, is regarded as ideal indicator of the inflammatory state (6). These indicators are completely derived from a full blood count. As a routine examination method, a full blood count will not add additional blood collection burden to patients. The low-cost method does not increase the medical insurance burden, it can be performed even in hospitals with less advanced equipment, and data can be obtained

retrospectively (7, 8). These advantages set it apart from indicators such as interleukin and C-reactive protein.

Studies show that elevated MLR (9) or NLR (10) is linked to major depressive episodes, and elevated SII is associated with depression (11–13). However, there is heterogeneity in the research among subtypes of depression. One study reports that NLR is associated with the severity of depressive symptoms (14), another study reports that elevated NLR only exists among older adults with first-episode depression(15), while another study reports no significant differences of NLR among subtypes of depressive disorders (16). Differences in study design or participants (sex or race differences) may contribute to the heterogeneity.

In order to further clarify the relationship between depression and the convenient inflammation indicators including MLR, NLR, PLR, and SII, and whether different subtypes of depression are different in the state of inflammation, we conducted this study. To the best of our knowledge, this is the first study investigating these convenient indicators in Chinese patients with unipolar depression. The expected findings might contribute to understanding the mechanism of etiology of depression.

Materials and methods

Participants

Our cross-sectional study included the full blood count results of inpatients diagnosed with depression, according to the International Classification of Diseases 10, codes F20–F29, at a hospital in Beijing from January to December 2019. Our data were collected from hospitalized patients and as patients with mild depression are rarely hospitalized, we included only patients with severe or moderate depressive episodes. The healthy control group comprised health examiners from the same hospital in 2019. We checked medical records and excluded participants with chronic physical diseases or those taking anti-inflammatory drugs such as antibiotics, glucocorticoids, and immunosuppressants.

Finally, 241 healthy controls and 239 inpatients with depression were included. The 241 patients were divided into three subgroups according to their diagnosis on admission: group D1 comprised 56 patients diagnosed with severe depressive episode with psychotic symptoms; group D2 comprised 127 patients diagnosed with severe depressive episode without psychotic symptoms; and group D3 comprised 56 patients diagnosed with moderate depressive episode.

Variables and measurements

SYSMEX XN-3000 assembly line (Sysmex Corporation, Japan) laboratory equipment was used to obtain full blood count data. The quality control and testing requirements strictly followed the operation manual.

For recruited inpatients, to ensure that blood indicators can accurately reflect patients' status at the time of diagnosis, we used data collected in three days after the admission to mental hospital. All blood samples were taken in the morning before breakfast and data were collected from the laboratory's electronic database. Neutrophil counts, lymphocyte counts, platelet counts, and monocyte counts were recorded, and the NLR, PLR, MLR, SII were calculated according to the following formulas (17):

NLR = neutrophil counts/lymphocyte counts;
MLR = monocyte counts/lymphocyte counts;
PLR = platelet counts/lymphocyte counts;
SII = platelet counts*monocyte counts/lymphocyte counts.

The data to the right of the equal sign in each formula are from the same test. The above results were kept to two decimal places.

Ethics statement

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration. This research was approved by the Human Research Ethics Committee of the authors' affiliate institute.

Tab. 1. Participant demographics and clinical characteristics.

	Patients			HC	statistics	Significant	post hoc test
	D1(n=56)	D2(n=127)	D3(n=56)	(n=241)	(F)		
AGE	39.55±11.19	40.43±11.04	40.34±10.25	40.52±8.61	0.149	0.930	
Sex(Male%)	39.3%	38.6%	39.3%	38.6%	0.006	0.999	
PLT(10^9/L)	249.82±56.76	235.24±61.56	223.98±45.26	252.13±52.18	4.435	0.004**	HC-D3**, D2-D3**
MON(10^9/L)	0.46±0.17	0.41±0.12	0.39±0.12	0.28±0.08	59.664	<0.001**	HC-D1**, HC-D2**, HC-D3**
LYM(10^9/L)	1.89±0.48	1.81±0.48	1.82±0.52	1.80±0.46	0.605	0.612	
NEU(10^9/L)	4.56±1.94	3.89±1.42	3.77±1.20	3.88±1.17	4.267	0.005**	
NLR	2.58±1.33	2.45±1.19	2.27±1.04	2.31±1.02	1.113	0.343	
MLR	0.26±0.11	0.24±0.09	0.23±0.09	0.17±0.06	36.125	<0.001**	HC-D1**, HC-D2**, HC-D3**
PLR	140.93±48.58	148.05±50.86	132.33±45.07	149.27±49.38	2.068	0.104	
SII	64.64±35.04	59.28±25.00	50.23±21.15	42.02±17.57	24.786	<0.001**	HC-D1**, HC-D2**, HC-D3(p = 0.051)

D1 – patients diagnosed with (recurrent or not) severe depressive episode with psychotic symptoms; D2 – patients diagnosed with (recurrent or not) severe depressive episode without psychotic symptoms; D3 – patients diagnosed with (recurrent or not) moderate depressive episode. HC – healthy controls. PLT – platelets; MON – monocyte; LYM – lymphocyte; MEU – neutrophil; NLR – neutrophil/lymphocyte; MLR – monocyte/lymphocyte; PLR – platelet/lymphocyte; NA – not applicable; SII – platelet*monocyte/lymphocyte. All data are reported as mean ± standard deviation. *p < 0.05, **p < 0.01

Statistical analysis

IBM SPSS Statistics for Windows Version 22.0 (IBM Corp., Armonk, NY, USA) were used to perform data analyses.

As the blood count data of the participants in each group were in line with the normal distribution in the Q-Q plot test, a one-way ANOVA was used to compare the differences between groups. As the data of multiple groups did not pass the homogeneity of variance test, we used Tamhane's T2 to conduct post hoc test for pairwise differences between groups. A 5 % significance level ($p < 0.05$) with two-tail was set. All data were presented as mean ± standard deviation.

Results

The one-way ANOVA yielded no statistically significant differences in age and sex between the three subgroups of patients and the control group. There were significant differences in PLT, MON, NEU, MLR, and SII among the four groups ($p < 0.05$), but no significant differences in LYM, NLR, and PLR (Tab. 1).

We performed a post hoc test and found that compared with healthy controls, MON and MLR were significantly higher in 3 subgroups of patients ($p < 0.01$); SII was significantly higher in groups D1 and D2 ($p < 0.01$), and the SII in group D3 showed an increasing trend ($p = 0.051$) than that in healthy controls. The PLT in group D3 was significantly lower than healthy controls and group D2 ($p < 0.01$). There were no significant differences in other indicators.

Discussion

In this study, 239 inpatients with depression and 241 healthy controls were recruited, and findings indicated that MON, MLR, and SII were elevated in all 3 groups of inpatients with different subtypes of depression. Previous studies report elevated MLR (9) and SII (12) were associated with depression among individuals with or without chronic physical diseases, and our findings support these views. It indicates that the presence of depression was associated with elevated inflammatory reaction, which could be revealed in convenient indicators, such as MON, MLR, and SII.

Depression, as a fluctuating and recurrent disease, could be classified into different subtypes, according to clinical features. In our study, patients were divided into three subtypes, i.e., severe depression with psychotic symptoms, severe depression without psychotic symptoms, and moderate depression. Psychotic symptoms are one of the common clinical manifestations of major depressive disorder. Previous studies confirm that inflammatory markers in patients with schizophrenia differ from those in healthy individuals (17). Another study compares PLR and NLR in patients with different subtypes of depression (16), the results indicate that the PLR in depressed patients with psychotic symptoms is higher than that in other subtypes. Howbeit, our study did not find any significant difference of inflammatory indicators between depressed inpatients with or without psychotic symptoms. It implied that the alteration in inflammatory markers is not psychotic symptom specific. Elevated inflammatory reaction might be common pathophysiology of depressive disorders and psychotic disorders.

Our findings showed that inpatients with different subtypes of depression were not different from each other for all inflammatory reaction measures, except for the PLT. This suggests that inflammatory status depends on the presence of depression and is not changed across subtypes. However, as this study was cross-sectional, we can only speculate that these indicators may be stable biological signatures of depressive episodes. This conclusion would be more convincing if we could follow up the patients and obtain data on different disease stages.

This study has certain strengths. We innovatively detected blood routine inflammatory markers in Chinese inpatients with depression. The low-cost and convenient method is easy to generalize to clinical settings of mental illness, even in rural areas with limited medical resources. This study also has many limitations. As a cross-sectional study, it can't infer causality. In this study, we lacked information on patients' treatment at the time of specimen collection. We did not quantitatively assess patients' psychiatric symptoms, as their in-hospital diagnosis was sufficient to make qualitative judgments about the severity of their depressive symptoms and the presence of psychotic symptoms at the time of blood collection. This partially compensates for the limitations of this study. As the patients included in this study were all hospitalized patients, and patients with mild depression were rarely hospitalized, only patients with severe and moderate depression were included. The study will be more complete if data on patients with mild depression can be obtained in the future.

In summary, our results suggest that increased MON, MLR, and SII may be the underlying mechanism of depressive disorders. Widespread usage of these off-the-shelf indicators will get enough clinical benefit in developing effective measures for diagnosis and treatment for depression.

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