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Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Methamphetamine Use Disorder

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ABSTRACT

Objective: Methamphetamine (METH) is a potent central nervous system (CNS) stimulant that rapidly enhances the release of neurotransmitters, including adrenaline, dopamine, and serotonin. It is also one of the most popular illicit drugs of choice worldwide known as "ice". In this study, we examined the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) levels in patients with methamphetamine use disorder.

Materials and Methods: This study included a total of 84 patients with only methamphetamine use and 81 healthy individuals. Participants who had hematological disorders and other chronic diseases were excluded from the study. White blood cell, neutrophil, lymphocyte, and platelet count were compared between groups. NLR and PLR values were calculated and compared between groups.

Results: The patient group comprised 81 males and 3 females with the mean age of 26.37 ± 5.99 years. There was no significant difference between patient and control group in terms of age, sex, BMI, smoking status, and alcohol consumption. NLR and PLR ratios were lower in the patient group than controls. NLR and PLR values were positively correlated with daily dosage of METH use ($r=0.227$ $P=.038$, $r=0.228$ $P=.037$, respectively).

Conclusion: To the best of our knowledge, our study is the first study examining the relationship between NLR and PLR in patients with METH use disorder. NLR and PLR were found to be lower in patients with METH use disorder. The effects of METH on the immune system should be considered. Prospective, longitudinal studies involving intoxication-detoxification-remission periods are needed.

ARTICLE HISTORY

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INTRODUCTION

Methamphetamine (METH) is a potent central nervous system (CNS) stimulant that rapidly enhances the release of neurotransmitters, including adrenaline, dopamine, and serotonin. It is also one of the most popular illicit drugs of choice worldwide known as "ice".[1] Methamphetamine is available in different pharmacokinetic properties in different forms such as ice, powder, and pills.[2] Also, methamphetamine that is known as ice is a crystalline and highly pure form of METH. According to the world drug report (2019), methamphetamine consumption shows a steep increase.[3] Also, according to the Substance Abuse Survey conducted by TUBIM (Turkey Monitoring Center for Drugs and Drug Addiction) in Turkey, the number of methamphetamine related events has increased since 2009. In fact, this increase is 67.98% more in 2018 than in the previous year.[4] In parallel with increased events, the admission rates for substance misuse treatment services in patients 12 years and older increased from 5.6% in 2005 to 8.4% in 2010 for primary methamphetamine/amphetamines.[5-7]

There is evidence about the existence of subclinical inflammation and/or immune system alterations in most of the psychopathologies. The role of subclinical inflammation in those mental disorders is not yet fully understood. However, the immune system modulates central nervous system functions through a variety of signaling mechanisms, and a relationship between inflammation and neurotransmitters was shown in previous studies. Proinflammatory cytokines interact with the cytokine network in the central nervous system. Such effects of the immune system in the brain can cause behavioral consequences and neuropsychiatric disorders.[8,9] This immune system alteration is also shown in patients with substance use disorder (SUD) including methamphetamine use disorder like other psychopathologies.[10]

METH abuse causes dysregulation in the peripheral immune response, leading to an imbalanced expression in cytokines, chemokines, and other molecular factors. Alterations in IL-6, IL-10, Cox-2, TNF-alpha, and IL1-beta in the immune response to methamphetamine induces neurotoxicity.[11] The

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data even support that METH lowers an effective immune response in humans and leads to the susceptibility to sexually transmitted diseases and infections.[11,12]

Another determinant of inflammation is the number of white blood cells and its subtypes. The neutrophil/lymphocyte ratio (NLR) is a new parameter indicating a systemic inflammatory response.[13] Recently, the platelet/lymphocyte ratio (PLR) has also been used to determine inflammation.[14,15] Neutrophil/lymphocyte ratio (NLR) and PLR are simple, inexpensive peripheral inflammation markers that show chronic subclinical inflammation and are used as indicators of clinical course in neuroimmune disorders, obtained by dividing the number of neutrophils and platelets by the number of lymphocytes. Increased NLR and PLR have been shown in mental disorders like bipolar disorder, major depression, catatonia, and psychotic disorders.[15-19] NLR was found to increase in these disorders and was considered to be an indicator of increased inflammation. Studies investigating NLR and PLR in substance use disorders are recent. In a literature review, there are studies examining the NLR, PLR, and monocyte-lymphocyte ratio (MLR) in heroin, cannabis addicts, and those with synthetic cannabinoid use disorder, but there are no studies conducted in those with METH use disorder. In general, little information is available, except for the short-term effects of METH. Understanding how METH affects the immune system in the long term can help strengthen our current perspective on METH, inform and guide public policy, and report on influencing the prevalence of communicable and noncommunicable diseases. In this study, we aimed to investigate the NLR and PLR in patients with methamphetamine use disorder.

MATERIALS AND METHODS

Study Design

This retrospective study included patients diagnosed with methamphetamine use disorder who were hospitalized between January 1 and December 31, 2019 in the Alcohol and Substance Addiction Treatment Training Center (AMATEM) in 25 December State Hospital. The study was approved by the Clinical Trials Ethics Committee of Sanko University (Ethics code: 2019/06-03).

Data Collection

All patients admitted to the AMATEM clinic were examined by an experienced psychiatrist and evaluated according to DSM-5 diagnostic criteria for substance use disorder diagnosis.[20] Urine toxicology tests and hematological tests are routinely performed on the first day of all hospitalized patients. There are social interview forms, identity and background information, doctor and nurse registration forms in the patient files. Sociodemographic and clinical data were obtained from these sources.

Sample Size

Power analysis was performed to determine the sample size. G*Power (Foul, Erdfelder, Lang, and Buchner. 2007) program was used to calculate the sample size. Independent *t*-test was done for repeat measurements with the program The minimum sample size was calculated as minimum 88 for 0.54 effect size, 5% margin of error, 95% confidence interval for the two groups. In a study that previously investigated the NLR ratio in synthetic cannabinoid users, it was observed that the effect size was 0.54 and the sample size was 80.[21]

Sample

The sample consisted of 190 patients. When 102 cases of other substance use in combination with METH and 4 cases with acute or chronic general medical disease were excluded from the study, the remaining 84 cases were included in the study. All of these cases are those who have been using methamphetamine for at least 1 year and were only METH positive in the urine toxicology test on the first day of hematological measurement. Since smoking is common in individuals with substance use disorders, the control sample group was formed in accordance with patients' smoking status. In addition, those who were similar to the study group in terms of age, gender, and body mass index (BMI), and those without a history of physical and mental illness were determined as the control group. While forming the control group, those with acute and chronic medical diseases (neurological, endocrinological, immunological diseases, autoimmune diseases, diabetes mellitus, hypertension, hyperlipidemia, asthma, liver-kidney failure, and heart diseases) were excluded. During the hemogram analysis, patients with diseases (malignancy, acute infection, chronic inflammatory diseases, and hematopoietic disease) that could affect the leukocyte count were excluded. Those using antibiotics, anti-inflammatory, immunomodulators, chemotherapy, and steroids were excluded. In addition, those with a BMI above 30 kgm^2 and those during pregnancy and lactation were excluded. Eventually, the sample of the study consisted of 165 people, 84 patients, and 81 controls. The patient group comprised 81 males and 3 females, and the healthy control group comprised 79 males and 2 females. The mean age of the patients was 26.37 ± 5.99 years and the mean age of the control group was 24.36 ± 2.53 years.

Laboratory Analysis

On the first day of their hospitalization, EDTA blood samples (BD Vacutainer K2EDTA Plus plastic tubes) were collected from each patient at the time of admission and hemogram parameters were measured using a Sysmex XE-2100 hematology analyzer (Sysmex Corp. Kobe, Japan). The same procedure was applied for the control group.

The NLR was calculated by dividing the absolute neutrophil count by the absolute number of lymphocytes. The PLR

was calculated by dividing the absolute platelet count by the absolute number of lymphocytes.

The urine toxic screening tests (UTS) are performed in the Clinical Biochemistry Laboratory with Architect C4000® (Abbott Diagnostics, Abbott Park, IL) by taking at least 30 mL of urine samples under audit chain application. The validation tests for positive results were performed by using LC-MS-MS (Liquid chromatography-mass spectrometry). A total of 8 types of psychoactive substances were investigated in the urine: amphetamine, methamphetamine, cocaine, opioid, tetrahydrocannabinol (THC), benzodiazepines, synthetic cannabinoids (K2-1 and K2-2), and buprenorphine. The minimum substance levels based on these analyses are as follows: 500 µg/L for amphetamine; 500 µg/L for methamphetamine; 150 µg/L for cocaine; 2000 µg/L for opioid; 50 µg/L for THC; 300 µg/L for benzodiazepines; 20 µg/L for K2-1, 10 µg/L for K2-2 synthetic cannabinoids, and 5 µg/L for buprenorphine.

Statistical Analyses

The descriptive characteristics of the data obtained in the study are given with frequency, percentage distribution, and mean and standard deviation values. In addition, *x2* test was used to compare categorical variables. The Kolmogorov–Smirnov test was used to determine whether the parameters are normally distributed. The age and NLR variables did not distribute normal for the Kolmogorov test ($P < .05$). The *t*-test was used for comparison of normally distributed variables between the patient and control groups. The Mann-Whitney U test was used for comparison of non-normal distributed variables between the patient and control groups. The linear associations between the normally distributed variables (BMI, white blood cell count, neutrophil count, lymphocyte count, platelet count, and PLR) were evaluated with a Pearson correlation test. The linear associations between the non-normally distributed variables (age and NLR) were evaluated with a Spearman correlation test. All significant levels were two-tailed and set at the level of 0.05. SPSS 22.0 (IBM Corporation, Armonk, NY) software was used in the analysis of variables.

RESULTS

Characteristics of the groups and their comparison are given in Table 1. There was no significant difference between patient and control group in terms of age, sex, BMI, smoking status, and alcohol consumption.

The mean age of patients starting to use METH was 21.45 ± 5.34 years, and the mean duration of METH use was 3.84 ± 2.08 years.

The comparison of the blood parameters of the control group and the patient group with the *t*-test and Mann Whitney U-test is given in Table 2. While the leukocyte count was 7.34 ± 1.43 in the patient group, it was found to be 7.48 ± 1.78 in the control group. Leukocyte count did not differ statistically between the groups ($t(163) = -.56$, $P > .05$). There was a significant difference between the groups in terms of neutrophil and lymphocyte counts. The neutrophil count was lower, and the lymphocyte count was higher in the patient group than the control group ($t(163) = -5.21, P < .001$; $t(163) = 7.32, P < .001$ respectively). Platelet count did not differ between the patient and control groups. NLR and PLR differed significantly between the groups, and the NLR and PLR ratios were lower in the patient group.

Clinical features and NLR-PLR correlations are given in Table 3. In Pearson and Spearman correlation analysis of NLR and PLR with clinical features, it was observed that a positive and statistically significant relationship was determined between the NLR and daily dosage of METH

Table 1. Characteristics of Groups and Their Comparison with t-test, Mann Whitney U-test and Chi-square Test

Characteristics	Groups		*t(163)*	*U*	x^2	*P*
	Patients M ± SD or *N* (%)	Control M ± SD or *N* (%)				
Age (year)	26.37 ± 5.99	24.36 ± 2.53		-1.808†		.071
Sex						
Female	3 (%2.5)	2 (%2.5)			0.171	.680
Male	81 (%97.5)	79 (%97.5)				
BMI	23.71 ± 2.20	23.19 ± 1.97	1.592*			.113
Smoker						
Yes	83 (%96.8)	76 (%93.8)			2.921	.087
No	1 (%1.2)	5 (%6.2)				
Alcohol Drinking						
Yes	16 (%19.1)	11 (%13.6)			0.901	.343
No	68 (%80.9)	70 (%86.4)				

Values are presented as M ± SD (mean ± standard deviation) or *N* (count), %. **t*: *t*-test; †*U*: Mann-Whitney U-test,*x2*: Chi square test value. Sociodemographic and characteristics variables for 84 METH user and 81 healthy controls were compared. *P* value of <.05 considered statistically significant. BMI: Body mass index.

Table 2. Comparison of Blood Counts Parameters between Patient and Control Groups with T Test and Mann-Whitney U Test

Parameter	Groups		*t(163)*	*U*	*P*	Cohen's *d*
	Patients M ± SD	Control M ± SD				
White blood cell count (10^3/mm^3)	7.34 ± 1.43	7.48 ± 1.78	-.565*		.573	0.09
Neutrophil (10^3/mm^3)	3.28 ± 1.04	4.33 ± 1.49	-5.214*		<.001	0.82
Lymphocyte (10^3/mm^3)	3.09 ± 0.82	2.28 ± 0.57	7.328*		<.001	1.14
Platelet (10^3/mm^3)	242.3 ± 48.7	232.3 ± 44.7	1.370*		.172	0.21
NLR	1.14 ± 0.58	1.99 ± 0.76		-1005.5†	<.001	1,26
PLR	82.77 ± 22.6	106.5 ± 28	-5.983*		<.001	0.93

Values are presented as M (mean) ± SD (standard deviation). *t: t-test; †U: Mann-Whitney U test.
NLR: neutrophil- lymphocyte ratio; PLR: platelet-lymphocyte ratio.

Table 3. Pearson and Spearman Correlation Analysis of Clinical Features with NLR and PLR

		NLR	PLR	Age	Duration of disorder (year)	Amount of usage (gram/day)
NLR	*r*		0.548**	0.058	0.097	0.227*
PLR	*r*	0.548**		-0.072	-0.120	0.228*

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio, *r*: Correlation coefficient.
*$P < .05$, **$P < .001$.

use ($r(84) = 0.23$, $P < .05$). Also a positive and statistically significant relationship was determined between the PLR and the daily dosage of METH use ($r(84) = 0.23$ $P < .05$). However, there were no statistically significant correlations between age, duration of use, and NLR, PLR ($P > .05$).

DISCUSSION

In our study, we investigated the peripheral subclinical systemic inflammation markers (NLR and PLR) in patients diagnosed with methamphetamine use disorder by comparing them with healthy controls. To the best of our knowledge, our study is the first study evaluating NLR and PLR in methamphetamine use disorder. Although the leukocyte and platelet counts did not differ significantly between the patient and control groups in our results, the NLR and PLR values were significantly lower in patients than controls.

Inflammation, which is attributed to the etiology of many psychiatric disorders, has been investigated using NLR and PLR in patients with psychiatric disorders. In a study conducted with patients with major depression, it was shown that NLR rates were significantly higher in patients compared to controls, and NLR decreased statistically significantly in remission after treatment.[22] However, no statistically significant difference was found in a study comparing NLR and PLR in major depression patients with healthy controls[23] In the study in which bipolar disorder and schizophrenia patients were examined in terms of NLR and PLR, it was found that both parameters were higher than controls.[16] In another study involving patients with bipolar disorder, while NLR was significantly higher in patients compared to controls, no significant difference was found in terms of the PLR. In a study in which NLR was evaluated in those who attempted suicide, it was found that NLR, neutrophil, and leukocyte values were significantly higher in the patient group.[24] In another study, no significant difference was found between patients with panic disorder and the control group in terms of NLR and PLR.[25] A study involving patients with catatonia, NLR was significantly higher in patients compared to healthy controls. But no difference was found between the patient and the control group in terms of MLR and PLR[19] It is seen in the literature that the rates of NLR and PLR in psychiatric disorders are very different, and there is no clarity that they can be used as a marker of psychiatric symptoms.

The popularity of the immune system and inflammation has increased with studies on the etiology and clinical effects of psychiatric disorders. Based on this, the effects of a substance on the immune system can affect the addictive properties and the clinic. These effects may interfere with the immune effects of another substance use disorder, neurotic-psychotic disorders, and chronic infections.[10]

Substance abuse has measurable and reciprocal effects on immune system cytokines, which are effective regulators of neuropsychiatric function.[10] It has been shown that IL-1ß and IL-6 increase natural clays (NK) cell activity and lymphocyte proliferation and decrease nitric oxide production in patients with opioid use disorder.[26] A decrease in T and B lymphocyte count and an increase in eosinophil count were found in patients with THC addiction.[27] METH's effects on the immune response have not yet been fully determined, but there is increasing evidence that it suppresses and modulates the immune system.[11] In

human and animal studies, it has been shown that METH increases IL-1β, IL-6, IL-6R (interleukin-6 receptor), IL-2, IL-8, and IL-10.[11,28] METH has been shown to increase the striatal expression of COX-2 protein, although it is suggested that TNF-α expression increases in microglia, and further studies are required.[11,29] When the effects of METH on immune cells are examined, it has been shown that METH increases NK cell activity, decreases splenic NK lymphocytes, and decreases T cell proliferation and CD4 +, CD8 + T cell frequency.[11,30]

Studies evaluating peripheral inflammation markers in substance use disorder are limited in the literature and different findings have been obtained. In a study examining NLR and PLR in heroin addicts, NLR and PLR were found to be higher in heroin addicts compared to controls, and these values were shown to be correlated with substance use duration.[31] In another study, including patients with heroin addicts, monocyte-lymphocyte ratio (MLR) and PLR were measured, and MLR and PLR were found to be significantly lower in the patient group compared to the control group.[32] In a recent study by Orum et al.,[26] cannabis use disorder, opioid use disorder, and control groups were compared in terms of NLR, PLR, and MLR[26] In this study, while NLR did not differ between groups, PLR was significantly lower in the group with opioid use disorder, and MLR was found to be significantly higher in the group with cannabis use disorder than in the group with opioid use disorder. In another study, while NLR was statistically significantly higher in people using synthetic cannabinoids compared to the control group, no significant difference was found in terms of PLR.[21] In our study, NLR and PLR were found to be significantly lower in the patient group compared to the control group. In addition, NLR and PLR were found to be slightly correlated with the daily dosage of METH use. Our results may be related to the effects of METH on the immune system and/or possible toxic effects. All of our patients in our study had been using METH for more than 1 year and when hematological measurements were evaluated, methamphetamine was positive in urine tests. A comparison study of the samples of patients taken after detoxification and in remission will be very valuable for future research.

Substance use characteristics, addiction level, and other clinical findings in patients with substance use disorder cannot be fully revealed due to denial, advocacy, or secondary gain (extra drug supply, higher dose drug use, abolition of judicial and criminal responsibilities, etc.). These handicaps are seen when self-report tests such as addiction severity index, addiction profile index, and drug abuse screening test are used. Therefore, laboratory tests that can demonstrate these issues concretely will be both cheap and easy. The low NLR and PLR rates we detected in people with METH use disorder may be important in this sense. Increasing studies to create biomarkers in this field will facilitate the planning of the follow-up and treatment of these patients, increase their use in judicial events, and distinguish acute-chronic conditions.

The most important limitation of our study is its retrospective design. Also, data consisting of larger samples should be evaluated in terms of age and gender groups. The diagnosis of substance use disorder was made according to the DSM-5, and a clinical examination was performed by senior psychiatrists. But structured psychiatric assessments, such as the SCID II, were not performed. Smoking, which is shown to have important effects on hematological parameters, has been a serious confounding factor in previous studies.[33] We eliminated this confounding factor as the strength of the study, but we admit that there may be other confounding factors such as nutritional effects, patients' lifestyle, etc., in such studies.

CONCLUSIONS

To the best of our knowledge, our study is the first study examining the relationship between NLR and PLR in patients with METH use disorder. NLR and PLR ratios were found to be low in patients with METH use disorder. Some adverse results have been obtained in studies of NLR and PLR in substance use disorders. Prospective, longitudinal studies, and studies involving intoxication-detoxification-remission periods are needed to validate our current results and to understand the underlying mechanisms.

Ethical Committee Approval: Ethical Committee Approval was received from the clinical trial ethics committee of Sanko University for this study (2019/06-03).

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Conflict of Interest: The authors have no conflicts of interest to declare.

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