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Evaluation of Complete Blood Cell Count Parameters and Their Role in Inflammation in Patients with Methamphetamine and Synthetic Cannabis Use Disorder

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ABSTRACT

Background: The aim of this study was to compare the complete blood cell count parameters of patients with methamphetamine and synthetic cannabis use disorder (MCUD), a condition that has recently exhibited a gradual increase in prevalence, with those of healthy subjects.
Methods: In total, 76 patients diagnosed with MCUD and 78 healthy controls were included in the study. Venous blood samples were collected from all participants at presentation for laboratory examination.
Results: The rate of mono- and poly-substance users in the patient group was 14.5% and 85.5%, respectively. The average duration of methamphetamine (METH) use in the patient group is 3.0 ± 1.9 years. White blood cell ($P < .001$), PLT ($P = .005$), monocyte count ($P < .001$), basophil count ($P < .001$), neutrophil count ($P < .001$), lymphocyte count ($P < .001$) basophil/lymphocyte ratio (BLR) ($P = .04$), SII ($P = .006$), and SIRI ($P = .001$) values were significantly higher. In contrast Hgb ($P = .043$), Hct ($P = .002$), monocyte percentage ($P = .004$), and RBC ($P = .021$) values were significantly lower in the MCUD group compared to the control group. There was a significant positive correlation between neutrophil/lymphocyte ratio and platelet/lymphocyte ratio ($r = .552$ $P < .001$) and between systemic immune inflammatory index (SII) and systemic inflammation response index (SIRI) ($r = 0.580$ $P < .001$).
Conclusion: Methamphetamine and cannabis may affect the levels of inflammatory markers and SII and SIRI values through various mechanisms. To the best of our knowledge, this is the first study in the relevant literature, which investigated SII and SIRI values in patients with MCUD, therefore, the results can contribute to the future development of immune system-related markers in this field.

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INTRODUCTION

Methamphetamine (METH) is a psychostimulant that induces the release of monoamine neurotransmitters such as dopamine, norepinephrine, and serotonin, and is the most widely used narcotic substance after cannabis derivatives.[1] Mostly smoked or snorted, METH use was associated with cardiovascular diseases, immune system disorders, as well as mental health problems, including cognitive disorders, depression, and psychosis. [2,3] Subclinical inflammatory changes were also reported in individuals diagnosed with methamphetamine use disorder (MUD), which has an ever-increasing prevalence.[4] It is well-established that there is strong evidence indicative of the involvement of inflammatory processes in the etiopathogenesis of a number of mental disorders.[5] Substance use disorders (SUD) also make the central nervous system vulnerable to inflammation.[6] For psychostimulants, especially METH, neurotoxicity is triggered by damaging the blood-brain barrier and inflammation mechanisms are initiated by means of immune activation.[7] Furthermore, METH is associated with a disruption of peripheral nervous system functions as well as that of the central nervous system. A study in mice found that METH impaired the peripheral and central nervous system immune response and induced cytokine release (IL-6, IL-2, TNF-α, and IL-β) in both brain regions and peripheral plasma.[8] High pro-inflammatory cytokines are associated with worse cognitive functions in SUDs.[9] Available

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data suggest that METH use induces inflammation by causing changes in chemokines, cytokines, and other factors in the peripheral immune system.[10] It was reported that metha mphetamine-induced IL-1β, TNF-α, and IL-6 peripheral blood plasma changes can be sustained at elevated levels even during abstinence periods, and this level could be maintained for at least 2 years. Therefore, it was even suggested whether peripheral blood plasma count could be used as a marker for METH addiction.[11,12] Nevertheless, the use of the aforementioned parameters may not prove to be practical in all cases. Accordingly, more convenient methods, including whole blood count can be considered.

Peripheral blood cell count was considered a low-cost and convenient indicator of inflammation.[13] In addition to blood cells, the results of certain parameters, including NLR, MLR, BLR, ELR, and PLR, are additionally taken into consideration. Baykara et al,[14] which investigated inflammation in substance use with 140 patients diagnosed with opioid use disorder and 140 healthy controls, reported that complete blood count and related parameters [white blood cell (WBC), neutrophil, lymphocyte, monocyte, platelet count, neutrophil, basophil percentage, NLR, MLR] were significantly higher in the patient group. Another study used NLR and PLR to investigate inflammation in SUD, and those parameters were lower in patients diagnosed with SUD compared to the healthy control group.[15] Systemic immune inflammatory index (SII) and systemic inflammation response index (SIRI) are novel markers, which were suggested to reflect inflammation and immune response better compared to NLR and MLR.[16,17] Systemic inflammation response index level is calculated by monocyte, lymphocyte, and neutrophil counts. Despite it being originally used in relation to cancer inflammation and prognosis, it is now considered a promising marker for inflammation in other diseases.[17,18,19] It was suggested that these 2 new markers played an important role in the interaction of inflammation, immunity, and thrombocytosis, and were easy to calculate.[20] The present study focused on this whole blood count and its parameters on the grounds it was convenient to calculate and collect. Turan et al[21] measured serum thiol/disulfide balance, ischemia-modified albumin, and IL-6 levels, which are oxidative stress and inflammatory biomarkers, in subjects with MUD. In addition, hemogram parameters were evaluated. As a result, it was interpreted that hemogram examination may indicate systemic inflammation in patients with MUD. Another study demonstrated low NLR and PLR levels in 81 male and 3 female patients. A comprehensive examination of the literature did not reveal any studies that assessed SII, SIRI, NLR, MLR, BLR, ELR, and PLR values in MUD patients.[15] There are no previous studies in the literature reporting SIRI and SII values in methamphetamine use disorder. Therefore, we deemed evaluating SII, SIRI, NLR, MLR, BLR, ELR, and PLR values in patients with MCUD will contribute to the literature.

In cases of methamphetamine and cannabis use disorder, where inflammation occurs and each of the following blood components (neutrophils, monocytes, lymphocytes, and platelets) plays a role in inflammation, this study aimed to determine the values of SII, SIRI, NLR, MLR, BLR, ELR, and PLR and to contribute to their potential use as biomarkers for SUD.

MAIN POINTS

- Methamphetamine and cannabis may affect inflammatory markers, especially systemic immune inflammatory index and systemic inflammation response index values.
- White blood cell, neutrophil, and lymphocyte values were found to be significantly higher in methamphetamine and cannabis users.
- BLR, SII and SIRI values were found to be significantly higher in methamphetamine and cannabis users.

MATERIAL AND METHODS

Sample and Method

The present study was approved upon decision by the Adıyaman University Non-Interventional Clinical Research Ethics Board (Approval Number: 2022/8-25; Date: November 15, 2022) and conducted pursuant to the Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects by the World Medical Association (WMA) (1983). The study was performed between December 1, 2022, and March 15, 2023, with outpatients admitted to alcohol and drug addiction treatment and research center and Probation outpatient clinics at the psychiatry department of the hospital.

The combined use of METH and cannabinoids and synthetic cannabinoids is prevalent in patients diagnosed with SUD, who present to the psychiatry outpatient clinic.[22] Therefore, individuals, who used cannabinoids and synthetic cannabinoids along with METH were included in the study. In addition, only methamphetamine and cannabis users were selected in the sample to minimize confounding factors. The healthy control group included individuals without any psychiatric disorder or treatment history, who matched the patient group by age and sex and who presented to the psychiatry outpatient clinic for routine health committee report procedures during the same period. The cohort designated as the healthy control group comprised individuals who volunteered, possessing no record of physical or psychiatric disorders. These participants sought routine annual check-ups through the health committee and willingly consented to partake in the study. The NLR, PLR, MLR, SII, and SIRI values were calculated by the authors. Six patients with SUD were excluded from the study because of incomplete data, and 3 individuals the healthy control group were excluded since they declined to participate in the study. The study

group consisted of 76 patients diagnosed with SUD and 78 healthy controls. Written consent of all the participants were collected prior to the onset of the study. Data from both groups were analyzed and compared.

Exclusion criteria include medical disorders that may affect inflammation (acute or chronic endocrinological, inflammatory, infectious, autoimmune diseases), active infection, use of steroids and similar immune modulator drugs, organic brain pathology, mental retardation, another axis I disorder, people who have consumed alcohol in the last 6 months, cannabinoid, and use of additional substances other than synthetic cannabinoids, and ages below 18 years.

Data Collection Tools

Socio-demographic data form: A sociodemographic and clinical data form developed by the authors based on clinical experience and information as a result of literature review was used for the purposes of this study. In addition to demographic information, including age and marital status, the demographic and clinical data form also included clinical assessment questions such as crimes committed by the participants and their treatment.

Laboratory Samples

Venous blood samples were collected from the antecubital vein. Thereafter, venous blood samples were collected from all the participants by the antecubital vein into a purple-capped tube containing EDTA potassium for hemogram analysis, and the samples were analyzed at the biochemistry laboratory of the hospital. Samples were processed using the Abbott Cell Dyn Ruby Analyser (Abbott, Abbott Park, Ill, USA) device within half an hour, and the results of the patients were uploaded to the patient record system within 2 hours at the latest. For this device, the reference range for neutrophils is 1.82-7.42 (10e3/μL), for lymphocytes 0.6-3.4 (10e3/μL), for platelets 142-424 (10e3/μL), where the reference range for mean platelet volume (MPV) is 6-10 fL. Following formulae were used for calculations: SIRI = neutrophil count × monocyte/lymphocyte count, and SII = platelet count × monocyte/lymphocyte count.

Statistical Analysis

The data were evaluated in Statistical Package for the Social Sciences (SPSS®) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) package program. In the study, descriptive data were presented with n, % values for categorical data, and mean ± SD and median (25%-75%) values for continuous data. Chi-square analysis (Pearson chi-square) was used to compare categorical variables between groups. The conformity of continuous variables with normal distribution was evaluated by Kolmogorov–Smirnov test. Mann–Whitney *U*-test was used to compare the measurement data of 2 separate groups. Spearman correlation coefficient were applied to examine the relationship between the measured data. $P < .05$ was accepted as statistically significant in all analyses.

RESULTS

A total of 154 participants, 76 substance users (MCUD group) and 78 non-users (control group), were included in the study. All patients in the MCUD and control groups were male. The mean age of the individuals included in the MCUD group was 28.9 ± 7.1 years, where the same was 26.7 ± 5.6 years in the control group, there was no significant intergroup difference by mean age ($P = .065$). The rate of employment in the case group (82.9%) was significantly higher than the rate of employment in the control group (66.7%) ($P = .021$). The smoking rate of the individuals included in the MCUD group (97.5%) was significantly higher compared to that of the healthy controls (65%) ($P < .001$). There was no significant difference between the groups by other general characteristics ($P > .05$) (Table 1).

The MCUD group included of 51.3% of the individuals with use of alcohol, and the rate of mono- and poly-substance use was 14.5% and 85.5%, respectively. The average duration of METH use in the MCUD group was 3.0 ± 1.9 years. It was found that 44.7% of the patients engaged in substance use for less than 5 years, 30.3% for 5-10 years, and 25% for more than 10 years. In addition, the MCUD group included 57.9% of the individuals, who previously received substance abuse treatment, 67.1% had an additional psychiatric diagnosis and 10% had a chronic disease. Patients with a family history of substance abuse formed 17.1% of the group. The rate of attempted suicide and self-mutilation in the patient group was 35.5% and 43.4%, respectively (Table 2).

WBC ($P < .001$), PLT ($P = .005$), monocyte count ($P < .001$), basophil count ($P < .001$), neutrophil count ($P < .001$), lymphocyte count ($P < .001$) basophil/lymphocyte ratio (BLR) ($P = .04$), SII ($P = .006$) and SIRI ($P = .001$) values were significantly higher while Hgb ($P = .043$), Hct ($P = .002$), monocyte percentage ($P = .004$) and RBC ($P = .021$) values were significantly lower in the MCUD group compared to the control group (Table 3).

The percentage values of neutrophil ($P = .04$), NLR ($P = .044$), MLR ($P = .005$) and BLR ($P = .038$) in METH only users were significantly higher, where lymphocyte ($P = .002$), eosinophil ($P = .028$), eosinophil percentages ($P = .014$) and ELR percentage ($P = .042$) were significantly lower compared to the individuals engaged in polysubstance use (Table 4).

There was a significant positive relationship between age and duration of substance use. There was a significant positive correlation between the duration of methamphetamine use and the duration of substance use and MPV. There was a significant positive relationship between NLR and PLR, and SII and SIRI. There is a significant positive correlation

Table 1. Comparison of General Characteristics of the Groups

		Case (n=76)		Control (n=78)		*P*
		n	%	n	%	
Age, mean ± SD		28.9±7.1		26.7±5.6		**.065****
Marital status	Single	30	39.5	38	48.7	.248
	Married	46	60.5	40	51.3	
Education	Middle school and below	41	53.9	32	41.0	.108
	High school and above	35	46.1	46	59.0	
Employment status	Working	63	82.9	52	66.7	**.021**
	Not working	13	17.1	26	33.3	
Who is he/she living with	Alone	9	11.8	5	6.4	.241
	Family	67	88.2	73	93.6	
Economic status	Low	38	50.0	54	69.2	.052
	Medium	20	26.3	13	16.7	
	High	18	23.7	11	14.1	
Residence	Province	63	82.9	62	79.5	.589
	District	13	17.1	16	20.5	
Smoking	Yes	74	97.4	50	64.1	**<.001**
	No	2	2.6	28	35.9	

Values in bold indicate statistical significance.
*Chi-square analysis.
**Mann-Whitney *U*-test was applied.

between PLR and SII and SIRI; SIRI and MPV; and SII and SIRI (Table 5).

DISCUSSION

Inflammation is considered a process characterized by the activation of immune and non-immune cells. A number of mental disorders affecting the nervous system activate degenerative processes and inflammatory mechanisms. Substance use induces a cascade of inflammatory responses, including interleukins (ILs), chemokines, interferons (IFNs), tumor necrosis factors (TNF), and lymphokines. It was reported that substance use disrupted cognitive control through inflammatory processes, and this contributed to problematic behaviors, including increased substance use.[23] Neuroimaging studies reported evidence associated with METH-induced neuroinflammation. METH triggers undesirable levels of dopamine and glutamate release. Excess dopamine can cause oxidative stress and mitochondrial dysfunction at cellular level. In addition, excessive prefrontal glutamate release is associated with an increase in the expression of cellular pro-inflammatory cytokines.[24,25] Magnetic resonance spectroscopy studies with METH user reported decreases in the creatine plus phosphocreatine (Cr+PCr)/choline-containing compound (Cho) ratio and N-acetyl aspartate (NAA) concentrations, favoring neurotoxicity.[26] Nevertheless, these markers are neither practical, nor cost-effective. Although the central state does not directly imply the peripheral state, it may reflect it to a certain extent. This is because it was shown that neuroinflammation-induced cognitive impairment was associated with peripheral markers.[27] For the purposes of the present study, peripheral indicators were considered more easy-to-measure and more practical. As a matter of fact, whole blood count is the most widely used laboratory measurement today. And recently, new and more specific

Table 2. Characteristics of the Case Group

		n	%
Alcohol	Yes	39	51.3
	No	37	48.7
Substance use	Single	11	14.5
	Multiple	65	85.5
Methamphetamine use duration, mean ± SD		3.0±1.9	
Duration of substance use	<5 years	34	44.7
	6-10 years	23	30.3
	>10 years	19	25.0
Previous substance treatment	Yes	44	57.9
	No	32	42.1
Additional psychiatric diagnosis	Yes	51	67.1
	No	25	32.9
Presence of chronic disease	Yes	7	9.2
	No	69	90.8
Substance use in the family	Yes	13	17.1
	No	63	82.9
Suicide attempt	Yes	27	35.5
	No	49	64.5
Self-mutilation	Yes	33	43.4
	No	43	56.6

Table 3. Comparison of Blood Parameters of the Groups

	Case (n=76)	Control (n=78)	P*
	Median (Q1, Q3)	Median (Q1, Q3)	
WBC	9.5 (8.1-11.1)	6.9 (5.7-8.5)	**<.001**
Hgb	15.5 (14.5-16.2)	15.8 (14.9-16.7)	**.043**
Hct	48.9 (46.7-50.5)	50.3 (47.8-52.4)	**.002**
PLT	260.3 (218.4-315.8)	238.2 (191.0-270.0)	**.005**
Monocyte	0.69 (0.52-0.85)	0.56 (0.44-0.67)	**<.001**
Basophil	0.07 (0.05-0.10)	0.05 (0.03-0.07)	**<.001**
Neutrophil	5.7 (4.5-7.0)	3.7 (2.9-5.1)	**<.001**
Lymphocyte	2.8 (2.4-3.4)	2.2 (1.8-2.5)	**<.001**
Eosinophil	0.18 (0.09-0.30)	0.13 (0.08-0.22)	.153
MCV	89.1 (86.3-92.3)	89.0 (86.7-92.2)	.817
Neutrophil %	59.1 (52.8-64.2)	56.4 (51.4-60.7)	.058
Basophil %	0.80 (0.55-1.08)	0.72 (0.41-1.01)	.130
Eosinophil %	1.8 (1.1-3.2)	2.1 (1.1-3.3)	.223
Lymphocyte %	31.6 (25.9-34.7)	31.6 (27.7-37.3)	.205
Monocyte %	7.2 (5.8-8.7)	8.0 (6.9-9.4)	**.004**
RBC	5.5 (5.2-5.7)	5.6 (5.4-5.9)	**.021**
MPV	10.0 (7.7-11.0)	9.7 (7.9-10.8)	.744
NLR	1.9 (1.6-2.5)	1.8 (1.4-2.2)	.178
NLR %	1.9 (1.6-2.5)	1.8 (1.4-2.2)	.157
MLR	0.24 (0.18-0.31)	0.25 (0.18-0.31)	.764
MLR %	0.23 (0.19-0.31)	0.25 (0.20-0.32)	.263
BLR	0.03 (0.02-0.04)	0.02 (0.01-0.03)	**.040**
BLR %	0.03 (0.02-0.04)	0.02 (0.01-0.03)	.067
ELR	0.06 (0.03-0.10)	0.06 (0.04-0.11)	.439
ELR %	0.06 (0.03-0.10)	0.06 (0.04-0.11)	.376
PLR	95.4 (70.9-125.7)	107.3 (87.1-124.9)	.104
SII	512.1 (360.0-674.1)	404.9 (304.7-526.2)	**.006**
SIRI	1.2 (0.9-1.9)	0.9 (0.6-1.4)	**.001**

Values in bold indicate statistical significance.
*Mann-Whitney *U*-test was applied.

Table 4. Comparison of Blood Parameters According to the Type of Substance Use in the Case Group

	Single (n=11)	Multiple (n=65)	P*
	Median (Q1, Q3)	Median (Q1, Q3)	
WBC	9.5 (6.8-11.1)	9.5 (8.2-11.7)	.521
Hgb	15.9 (14.6-16.4)	15.4 (14.5-16.1)	.345
Hct	49.7 (46.9-49.9)	48.9 (46.6-50.5)	.825
PLT	240.0 (220.9-342.8)	263.0 (217.0-314.7)	.729
Monocyte	0.79 (0.61-0.91)	0.68 (0.51-0.84)	.425
Basophil	0.09 (0.05-0.11)	0.07 (0.05-0.10)	.505
Neutrophil	6.1 (4.0-8.4)	5.7 (4.5-6.9)	.729
Lymphocyte	2.2 (1.7-2.7)	3.0 (2.5-3.5)	**.002**
Eosinophil	0.09 (0.03-0.17)	0.18 (0.10-0.33)	**.028**
MCV	88.3 (87.9-92.5)	89.2 (85.7-92.2)	.918
Neutrophil %	64.7 (58.4-75.1)	58.0 (52.7-62.1)	**.040**
Basophil %	0.86 (0.58-1.53)	0.76 (0.55-1.06)	.341
Eosinophil %	0.7 (0.2-1.8)	2.2 (1.3-3.3)	**.014**
Lymphocyte %	24.7 (15.4-35.5)	31.7 (27.6-34.6)	.059
Monocyte %	7.7 (5.8-10.7)	7.1 (5.8-8.5)	.356
RBC	5.6 (5.3-5.6)	5.5 (5.2-5.7)	.621
MPV	10.0 (7.4-11.2)	10.0 (7.7-10.9)	.668
NLR	2.6 (1.6-4.9)	1.8 (1.6-2.2)	.056
NLR %	2.6 (1.6-4.9)	1.8 (1.6-2.2)	**.044**
MLR	0.26 (0.14-0.44)	0.24 (0.18-0.31)	.384
MLR %	0.41 (0.28-0.50)	0.22 (0.19-0.28)	**.005**
BLR	0.04 (0.02-0.06)	0.03 (0.02-0.04)	**.047**
BLR %	0.04 (0.02-0.06)	0.03 (0.02-0.04)	**.038**
ELR	0.03 (0.02-0.06)	0.06 (0.03-0.11)	.097
ELR %	0.03 (0.02-0.06)	0.06 (0.03-0.11)	**.042**
PLR	105.2 (89.0-165.6)	94.1 (65.8-119.8)	.123
SII	544.5 (363.6-1767.7)	505.2 (358.5-640.5)	.413
SIRI	1.8 (0.9-4.2)	1.2 (0.9-1.7)	.191

Values in bold indicate statistical significance.
*Mann-Whitney *U*-test was applied.

parameter were suggested for the detection of systemic inflammation. PLR, NLR, MLR, BLR, SIRI, and SII are among the most important of aforementioned parameters.[28] Despite, it originally found wide use in cancer research, it was gradually extended to other diseases involving inflammation. Accordingly, these markers were studied in schizophrenia and bipolar patients, where inflammation was known to have involved in etiopathogenesis in psychiatry. Higher SII, SIRI, neutrophils, and monocyte values were found in patients with schizophrenia and bipolar disorder, which were characterized by high inflammation burden, compared to healthy individuals. Previous studies suggested certain measures, which could be used as a reference during the identification and differential diagnosis of schizophrenia and bipolar disorder, indicating the biomarker potential thereof.[29] In the present study, white blood cell, platelet, basophil, monocyte, neutrophil, lymphocyte, SII, SIRI, and BLR values were significantly higher in patients diagnosed with SUD compared to healthy controls. A 2021 study investigated peripheral immune parameters in patients diagnosed with SUD and did not report any significant difference in the patients' leukocyte and platelet counts, and concluded that the study results were associated with the limited number of studies on peripheral inflammation markers in the scope of substance use disorders in the relevant literature.[15] METH is associated with permanent changes in neuroplasticity due to the disruption of the blood-brain barrier. It was suggested that this was induced by modifications in the immune system cells themselves and the signaling pathways used thereby. Therefore, METH is associated with inflammation.[30,31]

Albeit the difference between the patient and control groups in the present study by MPV values, this difference

Table 5. Correlation Analysis

		Age	Duration of Methamphetamine Use	Duration of Substance Use	NLR	PLR	MPV	SII
Duration of methamphetamine use	*r*	0.014						
	P	.902						
Duration of substance use	*r*	0.273	0.485					
	P	**.017**	**<.001**					
NLR	*r*	0.117	0.018	0.043				
	P	.314	.878	.709				
PLR	*r*	−0.073	0.092	0.003	0.552			
	P	.533	.427	.980	**<.001**			
MPV	*r*	−0.128	0.236	−0.052	0.138	−0.042		
	P	.271	**.040**	.653	.233	.720		
SII	*r*	0.070	0.155	0.095	0.803	0.793	0.010	
	P	.549	.180	.417	**<.001**	**<.001**	.929	
SIRI	*r*	0.109	0.058	0.161	0.700	0.251	0.323	0.580
	P	.348	.617	.164	**<.001**	**.029**	**.004**	**<.001**

Values in bold indicate statistical significance.

was not significant. Nevertheless, as the MPV value increased, the SIRI value increased significantly. Previous studies, which compared the MPV value in schizophrenia patients with healthy controls, reported higher MPV values in the patients.[32-34] Another study with patients with schizophrenia and bipolar disorder, who used antipsychotics, reported that SII values were significantly higher compared to healthy controls. The same study suggested that the antipsychotic drugs use in the patients may have accounted for lower MPV values in schizophrenia patients.[32] MPV value is a reflection of inflammation, and accordingly, previous studies reported that it increased in low-grade inflammations and began to decrease in high-level inflammations. In addition, it is affected by age, sex, body mass index, and antipsychotic drug use. Because the patients in this study were newly diagnosed and had not received any prior treatment and given that the patient group was matched with healthy controls by age and sex, the MPV value and its association with SIRI could indicate early signs of high inflammation in these patients.

Furthermore, the majority of patients used marijuana and synthetic cannabinoids. The oxidative load associated with additional substance abuse may prevent specific interpretation of the study results, therefore, certain properties of cannabinoids are reviewed below. These substances use the peripheral receptor CB2r (cannabinoid 2 receptor) of the endocannabinoid system and have an important role in immune modulation.[35] A study reported that the pro-inflammatory chemokine CCL11 (eotaxin-1) level was higher in patients with current cannabis use compared to healthy controls, yet there was no difference between addicts, who had not used cannabis for 2 months or longer, and healthy controls.[36] Certain previous studies found no significant differences by inflammatory marker levels, including IL-1β, IL-6, and TNF-α, between cannabis users and healthy controls.[37] Furthermore, current marijuana users had lower CRP levels compared to those never used marijuana for a 1-year period, based on the National Health and Nutrition Examination Survey (NHANES), one of the studies which used C-reactive protein (CRP) to investigate the association between marijuana use and systemic inflammation. Therefore, previous studies suggested that cannabis had an anti-inflammatory effect.[38]

Similarly, another study reported lower biomarkers of systemic inflammation, including CRP, IL-6, and fibrinogen, in patients, who reported marijuana use in the past 30 days.[39] Continued use of cannabis within the last 30 days may provide a stronger anti-inflammatory effect compared to not using cannabis for 1 year (compared to older cannabis use).[40] All the above reports cast a shadow over the inflammatory burden of cannabis. In the respect thereof, when compared to other reports, there is far precise, clear, and numerous data indicative of the fact that METH is associated with inflammation. In addition, another point of consideration was that the patients included the study sample primarily used METH and consumed cannabis less frequently and in lower amounts. However, it is important to recognize that multiple substance use may interact with each other, potentially influencing the parameters we analyzed. In addition, the fact that METH-only users had significantly higher percentages of NLR, MLR, BLR, ELR, and neutrophil values compared to patients using METH + cannabinoid was consistent with above suggestion that METH was associated with inflammation. There was no significant difference by PLR value. Upon a review of previous studies with these parameters, a meta-analysis study in 2018 reported NLR, PLR, and MLR values as indicators of inflammatory activation in mood disorders.[41]

Whereas, schizophrenia studies reported that the NLR value was higher.[42,43] In a study conducted on heroin addicts, NLR and PLR were higher in heroin addicts compared to controls, and it was shown that these values were associated with the duration of substance use.[44] Another study compared patients with cannabinoid use disorder and opioid use disorder with healthy controls, and reported that there was no difference by NLR, where there was significantly lower PLR in the opioid use disorder group, and significantly higher MLR in the cannabinoid use disorder group compared to the opioid use disorder group.[45] Another study reported that NLR was significantly higher in individuals using synthetic cannabinoids compared to the control group, yet there was no significant difference was found in terms of PLR.[46] Nevertheless, in most of these studies, there is an issue associated with the limitation of confounding factors, and there were varied drug dose amounts and durations in the patients. In our study, almost half of the patients used METH regularly for nearly 5 years. In addition, there was a significant positive correlation between the duration of METH use and MPV. As is well known, platelets increase in size when activated and release inflammatory factors such as cytokines, chemokines, and coagulation factors. Increased MPV values indicate increased platelet function and are associated with inflammation.[47] Both acute and chronic METH use is associated with inflammation, and it is even mentioned that chronic use impairs both B and T cell functions of the immune system, making it vulnerable to opportunistic pathogens.[48] Moreover, indicators of high inflammation have been found in METH users even 12 months after discontinuation of METH.[49] There is more evidence pointing to an anti-inflammatory effect of cannabis use, even in chronic use.[50-53] A cross-sectional study involving long-term cannabis users found higher levels of circulating CRP and correlated this with 18 kDa translocator protein (TSPO) levels, emphasizing neuroinflammation.[51] Ongoing cannabis use (e.g., last 30 days) may provide a more potent anti-inflammatory effect than more distant use (e.g., last 12 months).[40] Nevertheless, the effects of chronic and long-term use of both substances on inflammation vary from person to person and often interact with other factors.

Cigarette smoking increases oxidative stress and systemic inflammation in general, which may lead to changes in SIRI levels. Smoking may also indirectly affect SIRI levels as it may contribute to the development of various chronic diseases. According to studies, NLR and MPV/PLT ratios are higher whereas PLR is lower in smokers compared to the general population.[54,55] In smokers, high NLR and ELR and low LMR (lymphocyte/monocyte ratio) are associated with smoking.[56] On another note, a study by Lin et al[57] found that MLR was associated with smoking. A 2024 review reported that passive smoking was both associated with depressive symptoms and increased risk of inflammation. Another important finding of the same examination was that high blood cotinine levels (a nicotine metabolite) significantly increased SII and SIRI levels.[58] In our study, the majority of the sample were smokers, and smoking rates were significantly higher in patients compared to the control group. Although we excluded additional medical conditions that indicate a high inflammatory burden in the sample, we should mention smoking as a limitation.

The strength of the study was that the sample group did not have any additional psychiatric disorder. Patients with additional mental disorders that met the diagnostic criteria were excluded from the study, contributing to selective formation of the study sample. It is well established that SUD is accompanied by comorbid mental disorders, including depression and alcoholism disorder, to a high degree. Excluding this important confusing factor contributed to the relevance of the study data. Another strength of the study is that METH only use as well as the combined use cannabinoids and synthetic cannabinoids were considered in the sample selection. Other substances that were considered to facilitate inflammation, including opiates, hallucinogens, and sedative hypnotics, were not included. In addition, the patients in the sample were not previously administered psychotropic medication. This is because of the fact that psychotropic treatment might change immune function by altering the inflammatory and anti-inflammatory cytokine levels.[59,60]

The limitations of the present study included the fact that poly-substance use could not be limited and parameters such as body mass index and smoking were not included. In addition, since alcohol use often accompanies substance use, this study ensured to only include patients who have not consumed alcohol in the last 6 months.[61] However, another limitation of our study is that individuals who have not used alcohol in the last 6 months were identified through self-report. Additionally, since it was a cross-sectional study, the study results cannot be generalized outside the sample.

To the best information of the authors, this is the first study to report SIRI and SII values for SUD, i.e., the systemic inflammation markers in whole blood biochemistry. White blood cell, neutrophil, lymphocyte, BLR, SII, and SIRI values were significantly higher in MCUD patients. The NLR, MLR, BLR, ELR, and neutrophil percentage were significantly higher in patients with methamphetamine use only compared to patients using METH + cannabinoids and synthetic cannabinoids. These results indicate that methamphetamine and cannabis exposure affect blood parameters by elevating inflammatory markers through various mechanisms.

Inflammatory cytokines and inflammation cascades maintain their place in the etiopathogenesis of mental disorders with their effects on the central nervous system. The present study provides important data for further research on immune system mechanisms in substance use disorders, including SUD, and to develop convenient

methods and markers that can detect these disorders to a certain extent.

BLR, PLR, NLR, MLR, SIRI, and SII are simple, noninvasive, inexpensive, and reproducible laboratory parameters that indicate systemic inflammation. There is a need for easily measurable biomarkers in mental disorders. We believe that furthermore comprehensive studies in this field, especially those that can establish a causal relationship, will strengthen the body of evidence.

Ethics Committee Approval: This study was approved by Ethics Committee of Adıyaman University (Approval Number: 2022/8-25; Date: November 15, 2022).

Informed Consent: Informed consent was obtained from the participants who agreed to take part in the study.

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