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The predictivity of hematological parameters and related inflammatory biomarkers of male subjects with chronic polysubstance use disorder

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ABSTRACT

Background: Polysubstance use disorder (PSUD) is a chronic disease with adverse clinical outcomes. Hematological properties and related inflammatory biomarkers have not been investigated in PSUD. This study aimed to investigate the alterations in hematologic and related inflammatory parameters among subjects with PSUD.
Methods: A total of sixty subjects were included, thirty chronic PSUD subjects and thirty control subjects. Venous blood was withdrawn from participants, and complete blood count was conducted. Related inflammatory biomarkers were calculated, including neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-monocyte ratio (NMR), derived neutrophil-to-lymphocyte ratio (dNLR), and systemic inflammation index (SII).
Results: Between study groups, we reported significant differences in red cell count, hematocrit, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration ($P < 0.001$). As compared to control subjects, PSUD subjects had significantly higher neutrophil counts that coincided with significantly lower monocyte counts ($P < 0.001$). These findings corresponded to significantly higher NLR (2.88 ± 0.21 vs. 1.92 ± 0.13), dNLR (2.39 ± 0.97 vs.1.43 ± 0.08), NMR (35.1 ± 4.8 vs.8.3 ± 0.5), LMR (13.3 ± 1.7 vs. 4.6 ± 0.3) and SII (683.0 ± 56.9 vs. 424.3 ± 30.2) among PSUD subjects ($P < 0.001$). Receiver operating characteristic analysis revealed areas under the curves for NMR, LMR, dNLR, NLR, and SII of 0.983, 0.829, 0.811, 0.766, and 0.779, respectively ($P < 0.001$).
Conclusion: Chronic PSUD alters erythrocyte indices that define mild erythrocytic hyperchromasia and may suggest membrane damage. Furthermore, higher hematological inflammatory biomarkers imply the contribution of systemic inflammation in the pathophysiology of PSUD and suggest their diagnostic predictivity of the disease.

1. Introduction

Polysubstance use disorder (PSUD) is an expanding chronic disease that correlates with adverse clinical outcomes and higher mortality rates (Rodriguez-Cano et al., 2023; Gjersing et al., 2018). According to the International Classification of Diseases, polysubstance dependence is defined as the simultaneous or concurrent use of more than one substance without evidence on which substance contributes the most to dependence (Shearer et al., 2022). Through poorly identified mechanisms, PSUD is associated with acute toxicity where synergistic and antagonistic drugs interactions contribute to several adverse behaviors and clinical manifestations (Crummy et al., 2020). Mediated by their bioactive constituents and/or intermediate metabolites, drug use triggers the generation of reactive oxygen species, leading to subsequent development of oxidative stress (Kovacic, 2005). Oxidative stress and inflammation are interrelated (Hussain et al., 2016). Clinical studies have shown that drug administration induces the release of proinflammatory cytokines and chemokines, resulting in systemic inflammation, including neuroinflammation (Morcuende et al., 2021; Kohno et al., 2019).

Hematological complete blood count (CBC) is a non-invasive and unexpensive laboratory approach that is routinely conducted in the context of a wide variety of diseases. Novel hematologic related inflammatory biomarkers have been identified as useful diagnostic and

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prognostic tools of several benign and malignant disorders (Embaby et al., 2023). These biomarkers include neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-monocyte ratio (NMR), derived neutrophil-to-lymphocyte ratio (dNLR), systemic inflammation index (SII), Systemic Inflammation Response Index (SIRI), and aggregate index of systemic inflammation (AISI).

Inflammation is implicated in the pathogenesis and the clinical outcomes of a variety of benign and malignant diseases, including neuropsychiatric disorders (Bauer and Teixeira, 2019; Abdoli et al., 2020). Therefore, inflammatory biomarkers have been suggested as diagnostic and prognostic tools of such disorders including schizophrenia, autism, anxiety disorders and mood disorders (Yuan et al., 2019; Abi-Dargham et al., 2023). For instance, in patients with schizophrenia, hematologically derived inflammatory biomarkers have been highlighted as potential prognostic tools of associated clinical outcomes. PLR helps in the differential diagnosis of treatment-resistant and non-treatment resistant forms of schizophrenia and MLR demonstrated significant association with higher score of positive and negative severity scales of the disease (Khoodoruth et al., 2025). Though, higher NLR, MLR and PLR were associated with severe clinical manifestations of major depressive disorder, restoring the baseline levels did not provide significant predictivity of patient's responsiveness to antidepressant treatments and symptoms improvement (Elbakary et al., 2025).

Several studies have investigated rheological blood features in response to drug administration, with major emphasis on the immunological properties of leukocytes. Opioid receptors are expressed on the surface of leukocytes and erythrocytes, making them highly vulnerable to pathological effects on blood cells (Zeiger et al., 2002). Inflammation and routine inflammatory biomarkers in response to cannabinoids and opioids have been investigated. However, to our knowledge, no studies have investigated the modulation of hematologic inflammatory biomarkers in response to polysubstance abuse. Based on the established relationship between psychiatric disorders and inflammation, we hypothesized that systemic inflammation contributes to the pathophysiology of chronic PSUD, and so hematological inflammatory biomarkers can be useful tools for the diagnostic predictivity of the disease. So, this is a hypothesis testing study that primarily aimed to investigate the alteration of hematological parameters and related inflammatory biomarkers among subjects with chronic PSUD and to evaluate their diagnostic performance to classify subjects with the disease.

2. Materials and methods

2.1. Study subjects and samples collection

This study was conducted on subjects with PSUD who were admitted to addiction rehabilitation centers in collaboration with the Drug Enforcement Administration/Public Security Department. Regardless of the types, dosages and routes of administration, chronic PSUD subjects were defined by prolonged and repeated administration patterns of at least two addictive substances. None of the included PSUD subjects had reported psychiatric comorbidities and subjects with active infections, chronic diseases including inflammatory disease, cardiovascular diseases and diabetes mellitus, were excluded from participation. Upon their admission to the rehabilitation center and prior to the initiation of withdrawal treatment, PSUD subjects were recruited to participate. For comparative purpose, an age and sex-matched group of control subjects with no history of PSUD including nicotine (non-smokers) and no medical history of psychiatric disorders, chronic inflammatory diseases, or evident active infections.

Under aseptic conditions, non-fasting midday venous blood samples were withdrawn form participants in Ethylenediaminetetraacetic Acid (EDTA) collection tubes. Blood samples were immediately transferred to a diagnostic laboratory for hematologic analysis. This study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. All participants were informed about the study and following their approval, they were asked to read and sign a consent form in that regard. The study was reviewed and approved by the Institutional Review Board (IRB) (approval number 36/150/2022) and the Deanship of Research at Jordan University of Science and Technology.

2.2. Complete blood count

Complete blood count (CBC) analysis was conducted using an automated cell counter (LH 780 Analyzer; Beckman Coulter, CA, USA). The measured red cell indices included red cell count (RBC), hemoglobin concentration ([Hb]), hematocrit (Hct), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW). Total leukocyte and platelet count, and absolute and relative differential counts of neutrophils, lymphocytes, monocytes, basophils, and eosinophils were also measured.

2.3. Hematological-related inflammatory biomarkers

Using complete blood count parameters, hematologic inflammatory biomarkers were calculated and compared between study groups. The investigated biomarkers included the NLR, LMR, NMR, dNLR, SII, SIRI, AISI. These parameters were calculated in accordance with the following formulas:

$$NLR = Neutrophils\ count / Lymphocytes\ count$$

$$LMR = Lymphocyte\ count / Monocytes\ count$$

$$NMR = Neutrophils\ count / Monocytes\ count$$

$$SII = Neutrophils\ count \times Platelets\ count / Lymphocytes\ count$$

$$dNLR = Neutrophils\ count / (Total\ leukocytes\ count - Neutrophils\ count)$$

$$SIRI = (Neutrophils\ count \times Monocytes\ count\ /\ Lymphocytes\ count$$

$$AISI = (Neutrophils\ count \times Monocytes\ count \times Platelets\ count\ /\ Lymphocytes\ count$$

2.4. Statistical analysis

A Priori calculation of sample size was conducted using G*power software (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). Calculation was based on the two-tailed model of independent comparative testing with a large effect size of 0.80, a significance level (α) of 0.05, a power value (1-β) of 0.80, and an allocation ratio (N2/N1) equals 1. To further validate the reliability of our comparative findings, univariate general linear model (GLM) analysis was used to determine the value of partial Eta squared and the observed power were determined for significantly different comparisons.

Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corporation, New York, USA). Descriptive outputs are presented as the mean ± standard error of the mean (SEM). The independent two-tailed Student's t-test was used for comparative analysis of the study parameters between the control and PSUD subjects. Normality (goodness of fit) testing was conducted using Shapiro-Wilk test and for non-normally distributed data, non-parametric comparative analysis was conducted using Mann-Whitney *U* test. Comparative results were considered significant when the P-value was less than 0.05. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic ability of inflammatory biomarkers to discriminate between subjects with PSUD and control subjects. Graphical illustration, of ROC curves, was prepared using GraphPad Prism 9 (Boston, MA, USA).

3. Results

This study included a total of sixty voluntarily participants (N = 60) of whom thirty participants were male PSUD subjects (n = 30) with an average age of 27.8 ± 5.0 years (age range was 19–37 years) and thirty male control subjects (n = 30) with an average age of 29.5 ± 4.7 years (age range was 18–40 years) (P > 0.05). According to sample size calculation, a study sample size of at least fifty-two participants (twenty-six subjects per study group) is required. Furthermore, partial Eta squared and observed power values validate the adequacy of our sample size to provide statistical significance, and clinical reliability of obtained outputs. PSUD subjects were males with an average of 4.1 ± 3.4 years of polysubstance use to a combination of at least two addictive substances including nicotine (n = 30, 100 %), intravenous heroin (n = 18, 60 %), Crystal Methamphetamine (n = 15, 50 %), Fenethylline/Captagon (n = 15, 50 %), Hashish/Cannabis (n = 13, 43.3 %), and misused prescription medical drugs (n = 10, 33.3 %).

Table 1 demonstrates the results of comparative analyses between PSUD and control subjects of CBC parameters including, blood cell count, red cell indices as well as the absolute and relative differential count of white blood cells subtypes. Compared to the corresponding values among control subjects, PSUD subjects had significantly lower averages of red blood cell count and hematocrit (P < 0.001), which coincided with significantly higher averages of MCH and MCHC (P < 0.001) and insignificantly different averages of MCV and RDW (P > 0.05). Furthermore, a significantly higher average of white blood cell count was evident among PSUD subjects (P = 0.01), whereas there was no significant difference in the average circulatory platelet count (P > 0.05).

Comparative analysis of differential white blood cell counts demonstrates that PSUD subjects had significantly higher average neutrophil counts (P < 0.001) and significantly lower average monocyte counts (P < 0.001). On the other hand, although PSUD subjects had significantly lower relative counts of lymphocytes (P < 0.01) and eosinophils (P < 0.05), there were no significant differences in the averages of the absolute counts of these cells (P > 0.05). Finally, PSUD and control subjects had no significant differences in the relative and absolute counts of basophils (P > 0.05). To evaluate the inflammatory status among PSUD subjects, hematologic inflammatory biomarkers were calculated and the results of comparative analysis between PSUD and control subjects are shown in Table 2. Compared to control subjects, significantly higher NLR, dNLR, NMR, LMR, and SII were observed among PSUD subjects (P < 0.001). Conversely, there were no significant differences in the average SIRI (P = 0.551) and AISI (P = 0.751).

It has been postulated that, even with non-normally distributed data, two-tailed parametric comparative analysis can still be conducted, if sufficient sample size was provided (Kim and Park, 2019). Despite the validity of the sample size of our study groups, normality testing was conducted, and results are illustrated in Table 3. Non-parametric Mann-Whitney U testing was conducted for data sets that were not normally distributed, and results are presented in Table 3. Except for basophils count and RDW, the results agree with the results of parametric comparative analysis. Regarding basophils count, PSUD subjects had significantly higher mean rank of absolute basophils count, as compared control subjects (p < 0.05). On the other hand, a lower mean rank of RDW was evident among PSUD subjects as compared to the corresponding mean rank among control subjects (P < 0.05).

To evaluate the statistical predictivity of NLR, dNLR, NMR, LMR, and SII in discriminating subjects with PSUD, ROC analysis was conducted. The area under curve (AUC) of the ROC signifies the diagnostic performance and predictive ability of the investigated inflammatory biomarkers to distinguish PSUD subjects. It has been postulated that an AUC value of ≥0.9 indicates excellent predictivity, and a value that is ≥ 80 and <0.9 indicates a considerable (good) predictivity. This is compared to a fair, poor and failed predictivity when the corresponding AUC value is: 0.7 ≥ AUC <0.8, 0.6 ≥ AUC <0.7, and AUC ≤0.5, respectively (Corbacioglu and Aksel, 2023). To further interpret the diagnostic performance of each biomarker, an optimal cut-off is determined as the coordinate ROC point with the maximum sum of both sensitivity (true positive rate) and specificity (true negative rate) (Corbacioglu and Aksel, 2023).

Accordingly, the results of the ROC analysis are represented in Fig. 1. As demonstrated, NMR had the highest AUC which indicates its excellent discrimination and reliable predictivity of subjects with PSUD. At a

Table 1
Comparative analysis of complete blood count; red cell indices and differential white blood cells counts among chronic PSUD and control subjects. (A) PSUD subjects had significantly lower averages of RBCs count and hematocrit that coincide with significantly higher averages of MCH and MCHC. Additionally, significantly higher WBCs count was shown among PSUD subjects. Regarding differential white blood cells count, PSUD subjects had significantly higher count and percentage of neutrophils that coincide with significantly lower count and percentage of monocytes. The relative percentage of lymphocytes and eosinophils were significantly lower among PSUD subjects. **(B)** Generalized linear model results of effect size (partial Eta squared) and observed power of clinically significance findings are demonstrated.

Indices (Unit)		(A) Comparative student t-test			(B) Effect size	
		Control Mean ± SEM	PSUD Mean ± SEM	P value	Partial Eta (η) squared (P value)	Observed power
RBC count (10^6 cell/μL)		5.33 ± 0.07	4.80 ± 0.08	<0.001*	0.318 (<0.001)	0.999
Hb (g/dL)		15.5 ± 0.2	15.2 ± 0.3	0.217	N/A	N/A
Hct (%)		46.1 ± 0.5	42.5 ± 0.8	<0.001*	0.203 (<0.001)	0.965
MCV (fL)		86.6 ± 0.8	88.4 ± 1.3	0.227	N/A	N/A
MCH (pg)		29.2 ± 0.4	31.7 ± 0.5	<0.001*	0.213 (<0.001)	0.973
MCHC (g/dL)		33.7 ± 0.2	35.8 ± 0.4	<0.001*	0.341 (<0.001)	1.00
RDW (%)		13.3 ± 0.1	13.1 ± 0.3	0.534	N/A	N/A
WBC		6.90 ± 0.30	8.56 ± 0.54	<0.05 *	0.112 (<0.01)	0.757
Platelets		221.7 ± 7.0	237.5 ± 10.0	0.20	N/A	N/A
Neutrophils	Percentage (%)	57.6 ± 1.3	68.3 ± 1.5	<0.001*	0.326 (<0.001)	0.999
	Count (10^6 cell/μL)	4.01 ± 0.22	5.98 ± 0.46	<0.001*	0.202 (<0.005)	0.965
Lymphocytes	Percentage (%)	32.2 ± 1.2	26.7 ± 1.5	<0.01*	0.126 (=0.005)	0.813
	Count (10^6 cell/μL)	2.18 ± 0.10	2.15 ± 0.12	>0.05	N/A	N/A
Monocytes	Percentage (%)	7.46 ± 0.38	3.07 ± 0.33	<0.001*	0.569 (<0.001)	1.00
	Count (10^6 cell/μL)	0.511 ± 0.031	0.268 ± 0.037	<0.001*	0.305 (<0.001)	0.999
Eosinophils	Percentage (%)	2.28 ± 0.26	1.57 ± 0.13	<0.05*	0.094 (<0.05)	0.674
	Count (10^6 cell/μL)	0.164 ± 0.023	0.132 ± 0.014	>0.05	N/A	N/A
Basophils	Percentage (%)	0.387 ± 0.029	0.367 ± 0.102	>0.05	N/A	N/A
	Count	0.026 ± 0.003	0.031 ± 0.008	>0.05	N/A	N/A

Hb; hemoglobin concentration, Hct; Hematocrit, MCV; mean corpuscular volume, MCH; mean corpuscular hemoglobin, MCHC; mean corpuscular hemoglobin concentration, RDW; red cell distribution width, WBC: white blood cells. N/A: Not applicable. * Indicates significant difference between PSUD and control groups.

Table 2
Comparative analysis of hematologic inflammatory biomarkers among PSUD and control subjects. (A) As compared to control subjects, PSUD subjects had significantly higher averages of NLR, dNLR, NMR, LMR and SII. **(B)** Generalized linear model results of effect size (partial Eta squared) and observed power of clinically significance findings are demonstrated.

Inflammatory Biomarker	(A) Comparative student t-test			(B) Effect size	
	Control Mean ± SEM	PSUD Mean ± SEM	P-value	Partial Eta (η) squared (P value)	Observed power
NLR	1.92 ± 0.13	2.88 ± 0.21	<0.001*	0.205 (<0.001)	0.967
dNLR	1.43 ± 0.08	2.39 ± 0.97	<0.001*	0.292 (<0.001)	0.998
NMR	8.3 ± 0.5	35.1 ± 4.8	<0.001*	0.351 (<0.001)	1.00
LMR	4.6 ± 0.3	13.3 ± 1.7	<0.001*	0.297 (<0.001)	0.998
SII	424.3 ± 30.2	683.0 ± 56.9	<0.001*	0.218 (<0.001)	0.977
SIRI	0.93 ± 0.08	0.83 ± 0.0.15	0.551	N/A	N/A
AISI	221.0 ± 22.9	207.7 ± 42.7	0.785	N/A	N/A

NLR: neutrophils to lymphocytes ratio; dNLR: Derived neutrophils to lymphocyte ratio; NMR: neutrophils to monocytes ration; LMR: Lymphocytes to monocytes ration; SII: systemic inflammation index; SIRI Systemic Inflammation Response Index; AISI: aggregate index of systemic inflammation. N/A: Not applicable. * Indicates significant difference between PSUD and control groups.

Table 3
Test of normality (Shapiro-Wilk test) and non-parametric comparative analysis (Mann-Whitney *U* test) of investigated parameters between PSUD and control groups. For data sets that are not normally distributed ($P < 0.05$), non-parametric comparative analysis demonstrates patterns of significant differences that are in consistence to the outputs of parametric analysis. The additive finding is the significantly differential count and percentage of basophils was significantly higher in PSUD as compared to control subjects.

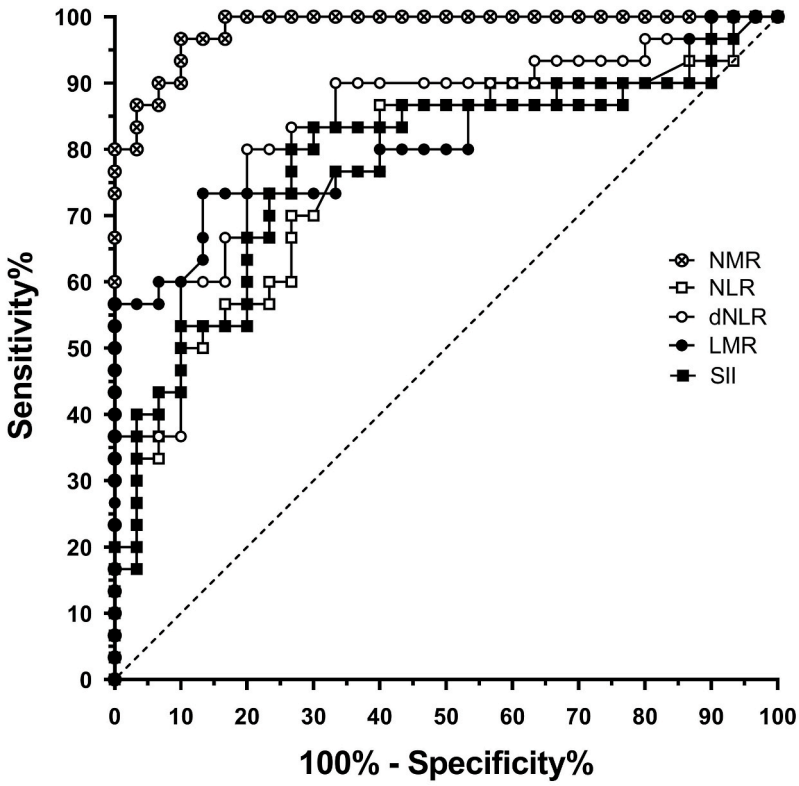
Parameter		Median (IQ range)		Shapiro-Wilk test		Mann-Whitney *U* test				
		Control	PSUD	P value		Mean Rank		U	Z	P
				Control	PSUD	Control	PSUD			
RBC count		5.36 (5.08–5.62)	4.76 (4.50–5.11)	0.604	0.619	N/A	N/A	N/A	N/A	N/A
Hb		15.5 (15.0–16.3)	15.3 (14.4–16.1)	0.905	0.086	N/A	N/A	N/A	N/A	N/A
Hct		45.9 (44.1–48.3)	42.7 (39.5–45.5)	0.894	0.893	N/A	N/A	N/A	N/A	N/A
MCV		87.2 (83.4–90.1)	89.9 (85.1–91.1)	0.126	0.094	N/A	N/A	N/A	N/A	N/A
MCH		29.4 (28.1–30.7)	32.2 (29.6–33.0)	0.373	0.325	N/A	N/A	N/A	N/A	N/A
MCHC		33.8 (33.2–34.2)	36.1 (35.0–37.5)	0.801	0.010*	21.40	39.60	177.0	−4.038	<0.001*
RDW		13.2 (12.9–13.8)	12.6 (12.2–13.5)	0.615	0.000*	36.75	24.25	262.5	−2.775	0.006
WBC		6.40 (5.70–8.42)	7.80 (6.40–10.88)	0.031*	0.114	25.28	35.72	293.5	−2.315	0.021*
Platelets		215.5 (198.5–245.8)	228.0 (200.8–288.3)	0.168	0.435	N/A	N/A	N/A	N/A	N/A
Neut	**%**	57.9 (52.8–63.0)	67.0 (65.0–75.0)	0.915	0.589	N/A	N/A	N/A	N/A	N/A
	Count†	3.67 (3.17–4.83)	5.34 (4.26–7.56)	0.344	0.046*	22.90	38.10	222.0	−3.371	= 0.001*
Lymph	**%**	32.8 (27.7–37.5)	26.5 (19.8–31.0)	0.850	0.083	N/A	N/A	N/A	N/A	N/A
	Count†	2.06 (1.82–2.41)	1.98 (1.67–2.52)	0.068	0.117	N/A	N/A	N/A	N/A	N/A
Mono	**%**	7.20 (5.80–8.35)	3.0 (1.0–5.0)	0.013*	0.001*	44.27	16.73	37.0	−6.130	<0.001*
	Count†	0.488 (0.366–0.633)	0.182 (0.105–0.403)	0.237	0.002*	40.13	20.87	161.0	−4.273	<0.001*
Eos	**%**	2.20 (1.20–2.75)	2.00 (1.00–2.00)	0.028*	0.000*	35.40	25.60	303.0	−2.198	= 0.028*
	Count†	0.139 (0.083–0.199)	0.128 (0.073–0.160)	0.000*	0.025*	31.85	29.15	409.5	−0.599	0.549
Baso	**%**	0.30 (0.30–0.50)	0.0 (0.0–1.0)	0.017*	0.000*	35.50	25.50	300.0	−2.274	0.023*
	Count†	0.025 (0.020–0.029)	0.0 (0.0–0.06)	0.000*	0.000*	25.30	35.70	294.0	−2.350	0.019*
NLR		1.76 (1.41–2.27)	2.55 (2.06–3.67)	0.353	0.146	N/A	N/A	N/A	N/A	N/A
dNLR		1.38 (1.12–1.71)	2.03 (1.86–3.00)	0.080	0.030*	20.63	40.37	154.0	−4.378	<0.001*
NMR		7.80 (6.56–9.93)	20.8 (14.7–65.5)	0.695	0.000*	16.00	45.00	15.0	−6.432	<0.001*
LMR		4.49 (3.55–4.89)	11.2 (4.95–19.0)	0.044*	0.002*	21.17	39.83	170.0	−4.140	<0.001*
SII		384.3 (336.3–485.7)	656.8 (474.1–896.5)	0.010*	0.127	22.13	38.87	199.0	−3.711	<0.001*
SIRI		0.891 (0.584–1.119)	0.616 (0.232–1.081)	0.071	0.000*	34.10	26.03	316.0	−1.804	0.071
AISI		193.6 (135.2–292.4)	113.7 (45.1–299.5)	0.023*	0.000*	34.30	26.70	336.0	−1.685	0.092

Hb; hemoglobin concentration, Hct; Hematocrit, MCV; mean corpuscular volume, MCH; mean corpuscular hemoglobin, MCHC; mean corpuscular hemoglobin concentration, RDW; red cell distribution width, WBC: white blood cells. Neut: Neutrophils, Lymph: Lymphocytes, Mono: Monocytes, Eos: Eosinophils, Baso: Basophils, %: percentage, NLR: neutrophils to lymphocytes ratio; dNLR: Derived neutrophils to lymphocyte ratio; NMR: neutrophils to monocytes ration; LMR: Lymphocytes to monocytes ration; SII: systemic inflammation index; SIRI Systemic Inflammation Response Index; AISI: aggregate index of systemic inflammation. N/A: Not applicable. * Indicates significant difference between PSUD and control groups. * Indicates significant difference between PSUD and control groups. † cell count in (106 cell/μL).

cut-off ratio of 11.92, NMR is associated with 96.7 % sensitivity and 90.0 % specificity of predictivity of PSUD subjects. On the other hand, dNLR and LMR have good predictive ability, while NLR and SII have fair ability to predict subjects with PSUD.

4. Discussion

Hematological changes in substance use disorders have been previously reviewed, where controversial findings have been reported among subjects with chronic opioids or cannabinoids administration (Jain and Narnoli, 2020). To the best of our knowledge, no studies have investigated alterations of hematological parameters in response to PSUD. Although they were all within the normal ranges, PSUD subjects had significantly lower average red cell counts, and hematocrit that coincided with significantly higher averages of MCH and MCHC. Among PSUD subjects, the reported non-parametric significance of lower RDW may not indicate any clinical significance. With a reference range of 11.5 %–15.0 %, low RDW has not been implicated in the pathological contexts of diseases (Hu et al., 2020). These findings can be explained by possible hemolytic events in consequence to trivial oxidative effects on red cells (Bani-Ahmad et al., 2022). Though that red cells are vulnerable to oxidative stress, clinically insignificant impacts are evident in favor to



Biomarker	AUC	St. Error	P value	95% CI	Cutoff	Sensitivity	Specificity
NMR	0.983	0.012	<0.001	0.961-1.000	11.92	0.967	0.900
NLR	0.766	0.062	<0.001	0.644-0.888	1.92	0.867	0.600
dNLR	0.829	0.055	<0.001	0.722-0.936	1.79	0.800	0.800
LMR	0.811	0.058	<0.001	0.697-0.926	6.00	0.733	0.867
SII	0.779	0.062	<0.001	0.656-0.901	459.1	0.833	0.700

Fig. 1. Receiver Operating Characteristics of inflammatory biomarkers among study subjects. NMR is characterized by the highest area under curve (AUC) that suggests its excellent predictivity of PSUD subjects. NLR: neutrophils to lymphocytes ratio; dNLR: Derived neutrophils to lymphocyte ratio; NMR: neutrophils to monocytes ration; LMR: Lymphocytes to monocytes ration; SII: systemic inflammation index.

their professional antioxidant mechanisms as well as their high turnover rate (Bani-Ahmad et al., 2022). Mild elevation in MCH and MCHC are indicators of clinically asymptomatic elevation in the percentage of hyperchromic red cells (Deuel et al., 2012). Notably, asymptomatic hyperchromasia of RBCs is associated with a mild loss of red cell membrane integrity and limited hemolytic events that are accompanied by a variety of pathological conditions, including cytotoxicity in oxidant injuries, liver diseases, poisons, and viral infections (Deuel et al., 2012).

On the other hand, chronic substance use triggers the adaptation of peripheral immunity that significantly contributes to the induced neuroinflammatory response (Harricharan et al., 2017). In turn, chronic neuroinflammation is implicated in the pathological manifestation of the use of substances including methamphetamine, cocaine, and cannabis (Agarwal et al., 2022; Doggui et al., 2021). Acute inflammation triggers the innate response by the infiltration of neutrophils into the affected tissues (Kantari et al., 2008). However, upon prolonged and persistent stimulation of innate response, a dramatic shift to the infiltration of macrophages and lymphocytes aggravates tissue damage, which ultimately results in multiple pathological consequences (Doggui et al., 2021; Ingersoll et al., 2011). It is worth mentioning that inflammation and oxidative stress are interrelated and are the main determinants of the pathological consequences of substance use disorders, which are represented by multisystem toxicity (Bachi et al., 2017).

Here in, the higher count of neutrophils as compared to decreased monocyte count, among PSUD subjects, can be explained by the rapid transmigration of monocytes into inflamed tissues due to the chronic inflammatory response (Ingersoll et al., 2011). The systemic nature of chronic inflammatory diseases is characterized by the altered distribution and proportion of inflammatory cells, specifically neutrophils and monocytes (Kantari et al., 2008; Obaid et al., 2023). Although neutrophils and monocytes share innate immune functions with potential cooperative roles in inflammation, their dynamic interactions with immunity are sophisticated (Prame Kumar et al., 2018). Dysfunctionality of monocytes is a frequent manifestation of chronic inflammatory disease that ultimately results in immune hypo-responsiveness and paralysis (Austermann et al., 2014). The chronic abuse of addictive substances contributes to the development of neuroinflammation and is implicated in the pathophysiological consequences including related psychiatric disorders (Agarwal et al., 2022). Earlier studies have revealed that opioid administration is associated with immune dysfunction through indirect neuroinflammatory response or direct interaction with opioids receptors on lymphocytes and macrophages (Chan et al., 2015). According to non-parametric comparative analysis, the slightly higher absolute basophils count may indicate their trivial

immunological contribution to the pathogenesis of PSUD. In addition to allergic and hypersensitivity responsiveness, basophils have been demonstrated to be involved in the pathogenesis of a broad spectrum of immune-mediated diseases including infections, autoimmune disorders, and malignant diseases (Cromheecke et al., 2014). Patients with anxiety disorders had lower basophils counts that inversely correlate to anxiety outcomes (Baek et al., 2016). On the contrary, higher counts of circulatory basophils was reported in patients with panic disorders (Gurok et al., 2019).

To further investigate the inflammatory status among study subjects, hematologic inflammatory biomarkers were calculated and compared between the two groups. The assessment of hematologic inflammatory biomarkers is advantageous over single inflammatory cell counts for evaluating the status of systemic inflammation (Chen et al., 2021). These biomarkers reflect local and systemic inflammatory responses and are significantly associated with the severity of adverse clinical outcomes of a variety of diseases including psychotic and neurodegenerative disorders (Ng et al., 2024). Our reported high levels of NLR, dNLR, NMR, LMR, and SII, among PSUD subjects, may define a severe form of inflammatory responses and may correlate with higher risks of adverse health impacts of PSUD.

ROC analysis defines the significant contribution of these biomarkers in the reliable discrimination of subjects with PSUD, in consequence to the inflammatory impacts of substances abuse. Considering that NMR was significantly four-fold higher in PSUD, ROC analysis defines NMR as the most reliable predictive of PSUD with the highest sensitivity and specificity compared to the other biomarkers. NMR is a prominent neuroinflammatory biomarker that reflects imbalanced innate and adaptive immunity, and is significantly correlated with the clinical features of Alzheimer's disease (Mehta et al., 2023). Similar findings have been reported in patients with rheumatoid arthritis where NMR demonstrated a better diagnostic performance of patients, in comparison to both LMR and NLR (Obaid et al., 2023). In hospitalized patients with severe Covid-19 infection, NMR has been shown to be an accurate prognostic predictor of mortality among patients (Rizo-Tellez et al., 2020). In agreement with findings on benign and malignant diseases, our study emphasizes the significant contribution of NMR as diagnostic and prognostic hallmark of inflammatory associated diseases, including PSUD.

As it represents the balance between innate and adaptive immunity, NLR is an indicator of evoked inflammatory complications and is correlated to a high overall mortality rate among patients with chronic diseases (Song et al., 2021; Zahorec, 2021). A recent review has defined NLR as a robust biomarker of immune derangement in the context of various diseases and may serve as a prognostic tool of related severity and mortality among patients (Buonacera et al., 2022). High NLR is evident among subjects with heroin and synthetic cannabinoids administration (Ozkan et al., 2017). As compared to NLR, our reported higher predictivity of dNLR can be explained by the incorporation of total leukocytes count that makes dNLR a more comprehensive inflammatory biomarker (Sugimoto et al., 2024). Several studies demonstrated that dNLR has a valuable diagnostic and prognostic significance in the contexts of a variety of malignant diseases (Citu et al., 2022).

In consequence to concurrent increased lymphocytes count and decreased monocytes count, LMR significantly correlates with the clinical outcome and mortality rates of malignant diseases, (Goto et al., 2018). It is obvious that the higher LMR, among PSUD subjects, is a result of the significantly decreased monocytes where lymphocytes count was not different. The reported decrease in circulatory monocytes might be in consequence to their transmigration into inflamed neurologic tissues among PSUD subjects (Ingersoll et al., 2011). Stress-induced monocytes redistribution contributes in priming central inflammation as well as the development and persistence of anxiety related behaviors (Wohleb et al., 2014). It is worth mentioning that dopamine, a key neurobiological effector in addictive disorders, enhances the transmigration of monocytes into the CNS through blood brain barrier (Gaskill et al., 2013). LMR demonstrates significant association to pathogenesis and clinical outcomes of psychiatric disorders, such as schizophrenia and major depressive disorder (Khoodoruth et al., 2025; Elbakary et al., 2025).

Despite that SII is a biomarker that reflects both immune and inflammatory status (Vural et al., 2023), earlier studies have reported contradictory findings regarding its contribution as prognosis of diseases such as the overall survival in solid tumors, and mortality rates cardiovascular diseases (Zhong et al., 2017; Yin et al., 2024). In adolescents with depressive disorders, SII has been proposed as an inflammatory biomarker of severe symptoms, but not the early-onset of depression symptoms (Schumacher et al., 2025). SIRI and AISI are relatively new indices that provide more comprehensive assessment of the dysregulated balance between systemic pro-inflammatory and anti-inflammatory responses (Tang et al., 2025). Therefore, both SIRI and AISI are potential prognostic markers of malignant diseases (Ginesu et al., 2022; Zinellu et al., 2021). The insignificant differences in SIRI and AISI revealed their irrelevant contribution in the pathogenesis of PSUD. Considering that they are newly found inflammatory biomarkers, most studies emphasized the predictivity of other inflammatory biomarkers in the context of psychiatric disorders while SIRI and AISI are less investigated (Jiang et al., 2025).

This study has both strengths and limitations. The study design is a strength as it relies on simple and clearly described objectives that investigated the added significance and diagnostic predictivity of routinely conducted, noninvasive and unexpensive CBC analysis to the pathological impacts of PSUD. Furthermore, another strength to the study emanates from the inclusion of chronic PSUD subjects at the time of their admission and before the initiation of withdrawal procedures. On the other hand, the study has some potential limitations among which the small sample size is the most concerning, despite the statistically demonstrated reliability and appropriateness of our included sample size. The non-probability sampling method and the inclusion of only male subjects are further limitations that may induce bias and may restrict representativeness and generalizability of the study outcomes. Another limitation is the lack of clinical neuropsychiatric status, socioeconomic status, alcohol consumption, and substance administration pattern including dosage, route, and purity of abused substances. These are confounding factors that may potentially contribute to the clinical impacts of PSUD and may provide a better interpretation of obtained findings. Finally, the lack of conventional key measures of inflammatory biomarkers, such as C reactive protein, is a limitation. These data justify the inflammatory status in PSUD and may aid in the correlation of our investigated biomarkers to the clinical outcomes of the disease.

5. Conclusion

In conclusion, chronic PSUD is associated with alterations in the hematological properties of erythrocytes and leukocytes. Mild erythrocytic hyperchromasia may reflect toxic effects on the integrity of the red cell membrane. Furthermore, the relative proportions of neutrophil and monocyte, along with higher hematologic inflammatory biomarkers were consistent with chronic systemic inflammation among PSUD subjects. Our findings support the significant contribution of inflammatory response in the pathogenesis of PSUD and the implication of hematologically-derived inflammatory biomarkers, specifically NMR and dNLR, as characteristic hallmarks of PSUD. Our study provides preliminary evidence on the suggested usefulness of routinely conducted CBC analysis in evaluating the clinical status of PSUD subjects. This can be helpful for health-providers and policymakers in establishing a suitable withdrawal treatment regimen and monitoring the progress of the related clinical outcomes.

To validate our obtained findings, further investigation is required into a larger sample size, where subjects of both sexes should be included. Clinical assessment of neuropsychiatric status of PSUD patients and inflammatory status, parallel with multiple-point

measurement, should highlight the diagnostic and prognostic value of hematologic inflammatory biomarkers in PSUD.

CRediT authorship contribution statement

Mohammad A. Bani-Ahmad: Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Belal A. Al-Husein:** Writing – review & editing, Validation, Supervision, Software, Resources, Investigation, Funding acquisition. **Diala Q. Alshaabi:** Writing – review & editing, Methodology, Investigation, Data curation. **Duaa A. Aldmour:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Yasmeen E. Ghanim:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Rahaf F. Al Deqah:** Writing – review & editing, Methodology, Formal analysis, Data curation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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