

ORIGINAL PAPER: RESEARCH ARTICLE

An investigation of various lymphocyte-related ratios in patients with opioids dependence syndrome

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Abstract

Background & Aim: Opioid Dependence Syndrome (ODS) features not only neuropsychological effects, but also immune dysregulation and systemic inflammation. Hematological indices including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) may be useful and readily available markers of these immune changes. We aim to evaluate the diagnostic usefulness of lymphocyte-related ratios and socio-demographic and clinical characteristics in patients with opioid dependence syndrome. **Method:** The cross-sectional study included 50 male ODS patients (ICD-10 criteria) and 50 healthy controls matched for age. Hematological parameters were assessed using a standard analyzer. Group differences were compared, along with correlations with the length of duration of use and the route of opioid use using statistical comparison. **Results:** ODS patients had significantly higher WBC counts, lymphocyte counts, and NLR, and significantly lower PLR and MLR, compared to controls. There were no significant differences in basophil-to-lymphocyte ratio (BLR). Increased duration of opioid use was associated with increased values of WBC, NLR, and MLR, suggesting a cumulative inflammatory effect. No hematological differences were found across the routes of opioid administration. **Conclusions:** Systemic inflammation and immune dysfunction are related to opioid use disorder, showing differences in NLR, PLR, and MLR. These ratios may provide easy, inexpensive, clinical markers and follow-up in opioid-dependent patients.

Keywords: Substance use disorders, immunological factors

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INTRODUCTION

Opioid Dependence Syndrome (ODS) is a chronic, relapsing disorder characterized by compulsive opioid use, impaired control over consumption, craving, and physiological features such as tolerance and withdrawal symptoms¹. Opioids are a broad class of psychoactive substances that include naturally occurring opiates like morphine and codeine, semi-synthetic derivatives such as heroin (diacetylmorphine), and synthetic opioids like fentanyl and methadone². These substances act primarily on mu (μ), kappa (κ), and delta (δ) opioid receptors within the central and peripheral nervous systems, modulating pain and reward pathways³. However, their long-term use leads to neuroadaptations that underpin dependence and addiction.

The global burden of opioid use has become a significant public health concern. According to the United Nations Office on Drugs and Crime (UNODC), over 60 million people worldwide used opioids in 2021, with a substantial proportion developing opioid use disorder (OUD)⁴. In India, the 2019 national survey conducted by the Ministry of Social Justice and Empowerment (MoSJE) in collaboration with AIIMS reported that approximately 2.06% of the Indian population were current opioid users. Among them, heroin accounted for the most frequently used opioid (1.14%), followed by pharmaceutical opioids (0.96%) and opium (0.52%)⁵. Notably, the state of Assam recorded an opioid use prevalence of 0.9%, reflecting the rising trend of substance use even in the northeastern regions⁵.

Beyond the neurological and behavioral dimensions, opioids have significant immunomodulatory effects. They influence the immune system both directly, via opioid receptors present on immune cells, and indirectly, through neuroendocrine pathways⁶. Chronic opioid exposure has been associated with alterations in lymphocyte subpopulations and immune suppression, increasing vulnerability to infections and systemic inflammation⁷. Consequently, there is growing interest in identifying hematological biomarkers that reflect systemic immune changes in individuals with opioid dependence. Among these markers, lymphocyte-related ratios such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and basophil-to-lymphocyte ratio (BLR) have emerged as cost-effective and easily accessible indicators of systemic inflammation and immune dysregulation^{8,9}. These ratios, derived from routine complete blood counts, have been investigated in various psychiatric, infectious, and autoimmune disorders and may offer diagnostic and prognostic value in ODS as well¹⁰.

This study is designed to explore the diagnostic utility of lymphocyte-related inflammatory ratios in patients with opioid dependence. By evaluating these hematological indices, the study aims to provide insight into immune alterations associated with opioid use and assess their potential role as adjunctive tools in clinical assessment.

METHOD

The aim of the study was to observe the diagnostic value of various lymphocyte-related ratios in patients diagnosed with opioid dependence syndrome. The objectives of the study were to observe the various socio-demographic variables in patients with opioid dependence syndrome and to observe the clinical characteristics of patients with opioid dependence syndrome.

- The study included 50 patients diagnosed as opioid dependence syndrome, according to ICD-10, aged between 18-65 years of age and 50 subjects with no past history of opioid use, aged between 18-65 years of age.
- The study excluded patients with other psychiatric, hormonal, inflammatory, auto-immune disorder or on treatment with anti-inflammatory or immunosuppressive drugs, presence of

any active infection or any severe medical illness or patients with any additional substance use disorder (except tobacco).

- The diagnosis was made as per ICD-10 classification of mental and behavioural disorders in consultation with senior Psychiatrist.
- Patients were included after approval from SMCH, Institutional Ethical Committee and informed consent.
- The socio-demographic profile and clinical data was collected.
- Blood samples were collected and assessed.
- Tools - Structured interview, Semi-structured interview
- Blood collected were measured using Hematology analyzer Erba Elite 580 of the Department of Pathology, Silchar Medical College & Hospital.

Duration of study: From July 2024 to December 2024.

STATISTICAL ANALYSIS

The numerical data are presented with means and standard deviations. The categorical data are presented with frequencies and percentages. The p value ≤ 0.05 is considered statistically significant.

RESULTS

Our study comprises of 50 cases and 50 controls.

SOCIO-DEMOGRAPHIC VARIABLES

	Sociodemographic Parameters	No. of individuals	
		n=50	%
Age Group (Years)	18-25	15	30%
	26-33	20	40%
	34-41	10	20%
	42-49	05	10%
Marital Status	Married	20	40%
	Separated	01	2%
	Single	29	58%
Religion	Hindu	15	30%
	Muslim	30	60%
	Christian	05	10%

Education	Primary	18	36%
	Secondary	25	50%
	Graduate	07	14%
Employment	Employed	45	90%
	Unemployed	05	10%
Socio-economic Status	Upper Middle	08	16%
	Lower Middle	30	60%
	Upper Lower	12	24%

COMPARISON OF HEMATOLOGICAL PARAMETERS BETWEEN OPIOID DEPENDENCE PATIENTS AND CONTROLS

Hematological Values	Case (n-50)		Control (n-50)		p-value
	Mean	SD	Mean	SD	
WBC (mm ³)	7710	1780	6970	1550	0.03
Platelet (Lakhs/mm ³)	1.96	0.38	2.04	0.08	0.14
Absolute Neutrophil count (10 ³ /μL)	4.58	1.62	4.08	1.38	0.09
Absolute Lymphocyte count (10 ³ /μL)	2.42	0.55	2.16	0.53	0.02
Absolute Monocyte count (10 ³ /μL)	0.45	0.12	0.49	0.13	0.11
Absolute Basophil count (10 ³ /μL)	0.07	0.02	0.07	0.06	1.00
Platelet Lymphocyte ratio	70.87	18.88	83.41	23.91	0.004
Neutrophil Lymphocyte ratio	2.12	0.86	1.82	0.46	0.03
Monocyte Lymphocyte ratio	0.16	0.04	0.20	0.09	0.01
Basophil Lymphocyte ratio	0.02	0.01	0.03	0.05	0.17

COMPARISON OF HEMATOLOGICAL PARAMETERS BETWEEN PATIENTS WITH DURATION OF OPIOID USE

Hematological Values	>5years(n-28)		<5 years(n-22)		p-value
	Mean	SD	Mean	SD	
WBC (mm ³)	8780	2090	7430	1910	0.02
Platelet (Lakhs/mm ³)	2.57	0.74	2.44	0.59	0.50
Absolute Neutrophil Count (10 ³ /μl)	5.63	1.92	4.14	1.46	0.003
Absolute Lymphocyte Count (10 ³ /μl)	2.23	0.79	2.45	0.71	0.30
Absolute Monocyte Count (10 ³ /μl)	0.80	0.33	0.54	0.20	0.001
Absolute Basophil Count (10 ³ /μl)	0.04	0.04	0.04	0.02	1.00
Platelet Lymphocyte Ratio	149.65	140.34	106.36	34.86	0.12
Neutrophil Lymphocyte Ratio	3.57	3.19	1.81	0.85	0.007
Monocyte Lymphocyte Ratio	0.42	0.27	0.23	0.08	0.001
Basophil Lymphocyte Ratio	0.02	0.01	0.02	0.03	1.00

COMPARISON OF HEMATOLOGICAL PARAMETERS BETWEEN PATIENTS WITH ROUTE OF OPIOID USE

Hematological Values	Inhalation (n-8)		Injectable(n-42)		p-value
	Mean	SD	Mean	SD	
WBC (mm ³)	7.47	2.45	7.87	2.17	0.64
Platelet (Lakhs/mm ³)	1.73	0.64	1.87	0.49	0.49
Absolute neutrophil count (10 ³ /μL)	4.3	1.42	4.58	1.26	0.57
Absolute lymphocyte count (10 ³ /μL)	2.61	0.85	2.75	0.76	0.64
Absolute monocyte count (10 ³ /μL)	0.27	0.08	0.28	0.08	0.75
Absolute basophil count (10 ³ /μL)	0.03	0.03	0.03	0.01	1.00
Platelet lymphocyte ratio	70.23	37.01	75.13	34.97	0.72
Neutrophil lymphocyte ratio	1.67	0.61	1.70	0.82	0.92
Monocyte lymphocyte ratio	0.10	0.06	0.10	0.04	1.00
Basophil lymphocyte ratio	0.02	0.01	0.03	0.05	0.57

DISCUSSION

This cross-sectional comparative analysis characterized hematological changes in a cohort of 50 male opioid-dependent patients as per ICD-10, and 50 healthy control subjects equally matched for age without current or prior substance use disorder. The hematological findings revealed a variety of more pronounced effects in the opioid-dependent group of patients, most notably a statistically significant elevation in white blood cells (WBC) and lymphocytes, which indicated systemic inflammation or a systemic immune response. The increase in WBC counts was corroborated with Liu *et al.*, who reported immune changes following opioid use including elevated white blood cells in heroin users¹¹. The increase in lymphocytes was similar to results reported by Quraishi *et al.* where they noted an increase in lymphocytes and inflammatory markers from opioids and considered it indicative of either compensatory immune activation or a lymphoproliferative response¹².

In addition, the study demonstrated a statistically significant increase in the neutrophil-to-lymphocyte ratio (NLR) and statistically significant decreases in both the platelet-to-lymphocyte ratio (PLR) and the monocyte-to-lymphocyte ratio (MLR) in the patients. The statistically significant decrease in PLR supports the findings of Orum *et al.*, who found that PLR is a sensitive marker of systemic inflammation and immune dysregulation in heroin users¹³, while the statistically significant increase in NLR confirmed the findings of Cıçek Erdinc *et al.* who similarly examined opioid users¹⁴. The decrease in MLR reflects the observations Orum *et al.* (2018) made when they observed lower MLR values in chronic opioid users to reflect innate immune dysfunction¹⁵. No statistically significant differences in the basophil-to-lymphocyte ratio (BLR) were found between the groups.

Our analyses confirmed a direct association with duration of opioid use, for WBC count, NLR, and MLR, providing evidence of a cumulative inflammatory load over time, something seen by Quraishi *et al.*¹². We also found no differences in hematological parameters in relation to the route of opioid use. The results of the study support the possible use of simple and inexpensive hematological indices (NLR, PLR, MLR) as markers for systemic inflammation with patients who present with opioid dependence syndrome. These indices are less invasive than the standard laboratory markers of systemic inflammation and may be useful clinical adjuncts in resource-limited settings.

Conclusion

The current study identifies the strong influence that opioid dependence has upon hematological values, therefore exhibiting direct and indirect effects to immune function. Specifically, opioid dependence was significantly associated with systemic inflammatory markers, namely the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR), but not with the basophil-to-lymphocyte ratio (BLR). These findings are in keeping with emerging literature highlighting immune dysregulation and systemic inflammation in opioid dependence^{16,17,18}. Furthermore, among the noted changes, the absolute increase seen within the NLR could indicate chronic low-grade inflammation and ongoing immune activation and is aligned with earlier work suggesting elevated NLR in psychiatric disorders and substance use^{17,19}. This expansion of neutrophil-driven responses may also be influenced by the oxidative stress, repeated infections, or tissue damage that is common among many long-term opioid users²⁰.

In contrast, the decrease in PLR and MLR values may represent disturbances in immune homeostasis such as reverse platelet role and inhibited monocytic response. because platelets and monocytes play key roles in immune-regulation, these alterations may contribute to the increased risk for infections and inflammatory diseases observed in opioid users^{21,22}. Advanced duration of use showed a progressive increase in both NLR and MLR, suggestive of a time-dependent, accumulating

inflammatory response. This is consistent with reports of extending use of opioids exacerbating immune dysfunction over time^{17,23}. An extended duration showing persistently elevated NLR, may indicate underlying, unrecognised, subclinical infections, or unresolved inflammatory states that are unseen by users and often undiagnosed due to reduced health service engagement from opioid users²⁰.

In summary, these findings strongly support the existing literature on systemic inflammation as a key determinant in the pathophysiology of opioid dependence. Blood-based indices such as NLR, PLR, and MLR, collected easily and used routinely, may represent cost-effective non-invasive markers of immune dysregulation in clinical practice. Future prospective longitudinal studies should examine the prognostic utility of these indices, and their utility in monitoring treatment responses and disease progression.

AUTHOR CONTRIBUTIONS

NSM: Definition of intellectual content, data acquisition, manuscript preparation, guarantor; **RM:** Design, clinical studies, statistical analysis, manuscript editing, guarantor; **HD:** Concepts, data analysis, manuscript review, guarantor; **KN:** Concepts, data analysis, manuscript review, guarantor

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