HEMATOLOGICAL BIOMARKERS IN ANXIETY DISORDERS: CURRENT EVIDENCE AND CLINICAL SIGNIFICANCE – A NARRATIVE REVIEW

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ABSTRACT

Anxiety disorders are among the most prevalent psychiatric conditions worldwide and are associated with substantial morbidity, impaired quality of life, and increased healthcare utilization. Although diagnosis is currently based on clinical assessment and standardized diagnostic criteria, growing evidence suggests that inflammatory and immune-mediated mechanisms contribute significantly to the pathophysiology of anxiety disorders. Complete blood count (CBC)-derived hematological biomarkers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), have emerged as inexpensive, readily available, and reproducible indicators of systemic inflammation. Recent studies have demonstrated altered levels of these biomarkers in patients with generalized anxiety disorder, panic disorder, social anxiety disorder, and other anxiety-related conditions. Elevated NLR, PLR, and MLR have been associated with increased symptom severity, chronic stress exposure, neuroinflammatory processes, and treatment response. These biomarkers offer potential utility in supporting diagnosis, monitoring disease activity, and identifying individuals at increased risk of adverse psychiatric outcomes. However, significant heterogeneity in study designs, patient populations, and confounding factors limits their current clinical applicability. This narrative review summarizes the current evidence regarding CBC-derived inflammatory biomarkers in anxiety disorders, explores their biological mechanisms, evaluates their diagnostic and prognostic significance, and discusses future directions for biomarker-guided psychiatric practice.

Keywords: Anxiety disorders, hematological biomarkers, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, inflammation, complete blood count, biomarker-based diagnosis.

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INTRODUCTION

Anxiety disorders are among the most prevalent psychiatric conditions worldwide and represent a major public health challenge due to their high burden of disability, chronicity, and impact on quality of life. These disorders encompass a spectrum of clinical conditions, including generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, specific phobias, and agoraphobia. According to recent epidemiological estimates, anxiety disorders affect hundreds of millions of individuals globally and are associated with substantial personal, social, and economic consequences [1,2]. Despite their widespread occurrence, the diagnosis of anxiety disorders remains largely dependent on subjective clinical assessment and symptom-based diagnostic criteria, highlighting the need for objective biological markers that may improve diagnostic accuracy and therapeutic monitoring [3].

Growing evidence suggests that anxiety disorders are not solely psychological phenomena but are closely linked to alterations in neuroendocrine, immune, and inflammatory pathways. Chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system in response to stress can induce systemic inflammatory responses, leading to measurable changes in peripheral blood parameters [4,5]. In recent years, attention has shifted toward easily accessible hematological biomarkers derived from routine complete blood count (CBC) investigations. These biomarkers are inexpensive, widely available, and capable of reflecting systemic

inflammatory status, making them attractive candidates for psychiatric research and clinical practice [6].

Among CBC-derived inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) have emerged as promising indicators of immune dysregulation in various psychiatric disorders. Elevated NLR reflects a relative increase in innate immune activity and a decrease in adaptive immune response, whereas PLR and MLR are considered indicators of chronic low-grade inflammation and stress-related immune activation [7]. Several studies have demonstrated significant alterations in these parameters among patients with anxiety disorders compared with healthy controls, suggesting a potential relationship between inflammatory burden and anxiety symptom severity [8].

The concept of inflammation as a contributing factor in psychiatric illness has gained considerable support over the past decade. Pro-inflammatory cytokines and immune mediators have been implicated in neurotransmitter dysregulation, neuroplasticity impairment, and alterations in brain circuits involved in fear and emotional regulation. Consequently, hematological biomarkers may provide indirect yet clinically relevant insights into the biological mechanisms underlying anxiety disorders [5,9]. Furthermore, these markers have the potential to assist in identifying high-risk individuals, evaluating disease severity, predicting treatment response, and monitoring clinical outcomes.

However, despite increasing interest in CBC-derived biomarkers, findings across studies remain heterogeneous, with variations in patient populations, anxiety subtypes, comorbid conditions, and methodological approaches. Therefore, a comprehensive evaluation of the available evidence is necessary to determine the clinical utility and limitations of these biomarkers in anxiety disorders [10]. This narrative review aims to summarize current evidence regarding hematological biomarkers, particularly NLR, PLR, and MLR, in anxiety disorders and to discuss their potential diagnostic, prognostic, and therapeutic significance in contemporary psychiatric practice.

Methodology

This narrative review was conducted through a comprehensive and systematic search of the available scientific literature to evaluate the current evidence regarding hematological biomarkers in anxiety disorders and their potential clinical significance. Electronic databases including PubMed, Scopus, Web of Science, Google Scholar, and Embase were searched for relevant studies published between January 2010 and March 2025. The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to anxiety disorders and inflammatory hematological markers. The primary search terms included “anxiety disorders,” “generalized anxiety disorder,” “panic disorder,” “social anxiety disorder,” “inflammation,” “hematological biomarkers,” “complete blood count,” “neutrophil-to-lymphocyte ratio,” “platelet-to-lymphocyte ratio,” “monocyte-to-lymphocyte ratio,” and “biomarker-based diagnosis.” Boolean operators (AND, OR) were utilized to optimize the search and identify studies addressing the association between anxiety disorders and peripheral inflammatory markers.

The review included original research articles, observational studies, case-control studies, cohort studies, cross-sectional investigations, systematic reviews, meta-analyses, and clinical studies published in peer-reviewed journals and written in English. Particular emphasis was placed on studies examining complete blood count (CBC)-derived inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), red cell distribution width (RDW), mean platelet volume (MPV), and other hematological parameters that may reflect systemic inflammatory activity in patients with anxiety disorders. Studies investigating the relationship between these biomarkers and anxiety severity, disease progression, treatment response, or diagnostic utility were given priority.

To ensure relevance and scientific rigor, studies were screened based on title, abstract, and full-text review. Articles were included if they evaluated adult or adolescent populations diagnosed with anxiety disorders according to established diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD). Research focusing on biological mechanisms linking inflammation and anxiety, as well as studies comparing hematological markers between patients and healthy controls, were also considered eligible for inclusion.

Studies were excluded when they lacked relevant outcome measures, provided insufficient hematological data, involved animal models, or focused primarily on psychiatric conditions other than anxiety disorders without separate subgroup analyses. Additionally, investigations involving severe systemic infections, autoimmune diseases, malignancies, chronic inflammatory disorders, hematological diseases, or other significant medical comorbidities known to substantially influence inflammatory blood parameters were excluded whenever possible to minimize confounding effects.

The selected literature was critically reviewed and synthesized narratively. Given the heterogeneity of

study designs, patient populations, biomarker assessment methods, and outcome measures, a quantitative meta-analysis was not performed. Instead, findings were organized thematically to summarize current evidence regarding CBC-derived inflammatory markers, their biological relevance, diagnostic and prognostic value, and their potential role in the future development of biomarker-based approaches for anxiety disorders. This approach allowed for a comprehensive evaluation of existing knowledge while identifying current limitations, inconsistencies, and areas requiring further investigation.

LITERATURE REVIEW

Inflammation and Anxiety Disorders

Increasing evidence supports a complex and bidirectional relationship between inflammation and anxiety disorders. Traditionally regarded as purely psychological conditions, anxiety disorders are now recognized as systemic disorders involving significant interactions among the nervous, endocrine, and immune systems. Chronic psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system, leading to increased secretion of cortisol, catecholamines, and other stress mediators that influence immune function [11]. Persistent activation of these pathways can result in a state of chronic low-grade inflammation characterized by altered cytokine production and immune cell dysregulation.

Numerous studies have demonstrated elevated circulating concentrations of inflammatory biomarkers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), in patients with various anxiety disorders compared with healthy controls [12,13]. These inflammatory mediators are capable of crossing the blood-brain barrier or signaling through neural and humoral pathways, thereby influencing central nervous system function. Inflammation has been shown to alter neurotransmitter metabolism, particularly within serotonin, dopamine, and glutamate pathways, which are critically involved in emotional regulation and anxiety-related behaviors [14].

Furthermore, neuroimaging and experimental studies suggest that inflammatory processes may contribute to structural and functional alterations in key brain regions involved in fear processing and emotional regulation, including the amygdala, hippocampus, and prefrontal cortex [15]. These neuroinflammatory changes may promote heightened threat perception, impaired stress adaptation, and persistent anxiety symptoms. Consequently, growing interest has emerged in identifying peripheral inflammatory biomarkers that may serve as objective indicators of anxiety-related pathophysiology, disease severity, and treatment outcomes.

Complete Blood Count-Derived Biomarkers

The complete blood count (CBC) is one of the most frequently performed laboratory investigations in clinical practice and provides valuable information regarding systemic immune and inflammatory status. In recent years, several CBC-derived inflammatory indices have gained attention as potential biomarkers in psychiatric disorders, including anxiety disorders. These indices are calculated from routinely measured hematological parameters and reflect the balance between different immune cell populations involved in inflammatory responses [16].

The clinical utility of CBC-derived biomarkers is supported by several advantages:

- Low cost
- Universal availability
- Minimal invasiveness
- Standardized laboratory measurement
- High reproducibility across healthcare settings

Unlike specialized inflammatory markers that may require advanced laboratory techniques and increased healthcare expenditure, CBC-derived ratios can be readily obtained from routine blood tests. This makes them particularly attractive for large-scale screening, risk stratification, and longitudinal monitoring in psychiatric populations. Among the various hematological indices investigated, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) are the most extensively studied markers of systemic inflammation and immune activation in anxiety disorders [17].

Neutrophil-to-Lymphocyte Ratio (NLR)

Biological Basis

The neutrophil-to-lymphocyte ratio (NLR) is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained from a routine CBC. NLR is considered a simple yet reliable marker of systemic inflammation because it simultaneously reflects activation of innate immune responses through neutrophils and suppression or dysregulation of adaptive immune responses through lymphocytes [18].

Exposure to chronic psychological stress results in increased sympathetic nervous system activity and elevated cortisol secretion, which promote neutrophil mobilization from bone marrow reserves while reducing lymphocyte proliferation and survival. These physiological changes contribute to elevated NLR values and may reflect the inflammatory consequences of prolonged stress exposure. Consequently, NLR has emerged as a potential biomarker linking psychological stress, immune dysfunction, and psychiatric illness [18].

Evidence in Anxiety Disorders

A growing body of literature has reported significantly elevated NLR levels in individuals

with anxiety disorders compared with healthy control populations. In patients with generalized anxiety disorder (GAD), increased NLR values have been associated with greater symptom severity, prolonged disease duration, and enhanced inflammatory burden, suggesting a potential relationship between immune activation and clinical manifestations of anxiety [19].

Studies investigating panic disorder have similarly demonstrated higher NLR values among affected individuals. Elevated NLR has been associated with increased panic attack frequency, greater psychological distress, and impaired functional status. These findings support the hypothesis that inflammatory mechanisms may contribute to disease expression and symptom exacerbation in panic disorder [19].

Research involving patients with social anxiety disorder and other anxiety-spectrum conditions has also identified increased NLR levels, further supporting the presence of chronic low-grade inflammatory activation across different anxiety subtypes. Although the magnitude of NLR elevation varies among studies, the overall evidence suggests a consistent association between anxiety disorders and alterations in systemic inflammatory markers [20].

Diagnostic Significance

The potential clinical significance of NLR in anxiety disorders has attracted considerable research interest. NLR may serve as:

- An adjunctive biomarker supporting diagnosis
- A marker of disease severity
- A predictor of treatment response
- A tool for monitoring inflammatory burden during follow-up

Because NLR can be measured easily and inexpensively, it represents a practical candidate biomarker for routine clinical use. Nevertheless, substantial heterogeneity exists across published studies regarding patient populations, diagnostic criteria, medication status, and laboratory methodologies. As a result, no universally accepted NLR cut-off value has yet been established for anxiety disorders. Additional large-scale prospective studies are required to determine optimal reference ranges and to validate the clinical applicability of NLR as a diagnostic and prognostic biomarker in anxiety-related conditions.

Platelet-to-Lymphocyte Ratio (PLR)

Biological Basis

The platelet-to-lymphocyte ratio (PLR) is calculated by dividing the absolute platelet count by the absolute lymphocyte count obtained from a routine complete blood count. PLR has emerged as a valuable inflammatory biomarker because it reflects the interaction between thrombocytic activity and immune regulation. Beyond their traditional role in hemostasis, platelets actively participate in inflammatory and immune processes through the release of cytokines, chemokines, growth factors, and pro-inflammatory mediators. Activated platelets interact with endothelial cells and leukocytes, promoting inflammatory signaling pathways that may contribute to the pathophysiology of psychiatric disorders [21].

Importantly, platelets share several biochemical characteristics with serotonergic neurons, including the presence of serotonin transporters and serotonin storage mechanisms. Since serotonergic dysregulation is a central feature in anxiety disorders, platelet activity may indirectly reflect alterations in serotonin metabolism and neurotransmission [22]. Consequently, PLR has attracted growing interest as a potential peripheral marker linking inflammation, immune dysfunction, and anxiety-related neurobiological changes.

Evidence in Anxiety Disorders

Several clinical studies have reported significantly elevated PLR values in patients with panic disorder, generalized anxiety disorder, and mixed anxiety-depressive conditions compared with healthy individuals [23]. Higher PLR values have been associated with increased anxiety severity scores, greater emotional distress, and enhanced inflammatory activity. Some investigations have demonstrated positive correlations between PLR and standardized anxiety assessment scales, suggesting that inflammatory burden may increase with worsening symptom severity [24].

Although the available evidence generally supports an association between elevated PLR and anxiety disorders, findings remain somewhat heterogeneous. Variations in patient characteristics, medication use, disease duration, and comorbid psychiatric conditions may account for differences across studies. Compared with NLR, PLR appears to demonstrate slightly lower sensitivity in detecting inflammatory changes associated with anxiety disorders; however, it may provide complementary information regarding platelet-mediated inflammatory pathways and neuroimmune interactions [23,24].

Clinical Utility

Potential applications of PLR include:

- Risk stratification of patients with anxiety disorders
- Monitoring treatment outcomes and inflammatory responses
- Identification of inflammatory phenotypes for personalized treatment approaches
- Supplementing other inflammatory biomarkers in clinical assessment

Despite its potential clinical value, inconsistencies among studies and the absence of standardized reference values currently limit the routine use of PLR in psychiatric practice. Further large-scale investigations are needed to clarify its diagnostic and prognostic utility [24].

Monocyte-to-Lymphocyte Ratio (MLR)

Biological Basis

The monocyte-to-lymphocyte ratio (MLR) reflects the balance between circulating monocytes and lymphocytes and serves as an indicator of chronic inflammatory activity. Monocytes are key components of the innate immune system and contribute substantially to cytokine production, antigen presentation, and sustained inflammatory responses. Elevated MLR values suggest increased monocyte activation accompanied by relative suppression of adaptive immune mechanisms, indicating systemic immune dysregulation [25].

Chronic psychological stress and prolonged activation of inflammatory pathways can stimulate monocyte proliferation and cytokine release, potentially contributing to neuroinflammatory changes implicated in anxiety disorders. Consequently, MLR has emerged as a promising marker of stress-related immune activation and chronic low-grade inflammation [25].

Evidence in Anxiety Disorders

Although MLR has been investigated less extensively than NLR and PLR, emerging evidence suggests a meaningful association between elevated MLR values and anxiety-related psychopathology. Several studies have reported higher MLR levels among individuals experiencing chronic stress exposure, persistent anxiety symptoms, and severe psychological distress compared with healthy controls [26].

Elevated MLR has also been linked to neuroimmune dysregulation and heightened inflammatory activity in psychiatric populations. Research findings indicate that patients with more severe anxiety manifestations often exhibit greater MLR values, supporting the hypothesis that monocyte-mediated inflammatory pathways contribute to anxiety pathogenesis [26]. Nevertheless, additional prospective studies are required to determine the diagnostic accuracy and prognostic significance of MLR across different anxiety disorders.

Clinical Relevance

MLR may provide additional insight into inflammatory mechanisms underlying anxiety disorders and may complement NLR and PLR when incorporated into multi-marker inflammatory panels. The combined assessment of these biomarkers may enhance the detection of subtle immune alterations that are not adequately captured by individual parameters alone [25,26].

Other CBC-Derived Hematological Markers

Red Cell Distribution Width (RDW)

Red cell distribution width (RDW) reflects variability in erythrocyte size and is increasingly recognized as a marker of systemic inflammation, oxidative stress, and impaired erythropoiesis. Elevated inflammatory cytokines can interfere with red blood cell maturation, resulting in increased RDW values. Several studies have demonstrated higher RDW levels among patients with anxiety disorders, and some investigations have reported positive correlations between RDW and anxiety symptom severity [27]. These findings suggest that RDW may serve as an additional indicator of chronic inflammatory burden in anxiety-related conditions.

Mean Platelet Volume (MPV)

Mean platelet volume (MPV) is a measure of platelet size and activation. Larger platelets are metabolically more active and exhibit greater pro-inflammatory and pro-thrombotic potential. Altered MPV values have been observed in patients with panic disorder and generalized anxiety disorder, suggesting disturbances in platelet function and serotonergic signaling [28]. Although findings remain inconsistent, MPV continues to be investigated as a potential biomarker reflecting neuroimmune and platelet-mediated mechanisms in anxiety disorders.

Systemic Immune-Inflammation Index (SII)

The Systemic Immune-Inflammation Index (SII) is a composite marker that integrates platelet, neutrophil, and lymphocyte counts according to the following formula:

SII = Platelet Count × Neutrophil Count / Lymphocyte Count

SII simultaneously reflects innate immune activation, adaptive immune suppression, and platelet-mediated inflammatory activity. Recent studies suggest that SII may outperform individual inflammatory biomarkers in evaluating systemic inflammatory burden and predicting disease severity across various medical and psychiatric conditions [29]. Its application in anxiety disorders remains an active area of investigation.

Table:Common Complete Blood Count (CBC)-Derived Hematological Biomarkers and Their Clinical Significance in Anxiety Disorders

Biomarker	Calculation	Clinical Significance
NLR	Neutrophils / Lymphocytes	Innate immune activation
PLR	Platelets / Lymphocytes	Platelet-mediated inflammation
MLR	Monocytes / Lymphocytes	Chronic inflammatory activity
SII	Platelets × Neutrophils / Lymphocytes	Composite systemic inflammation

Biomarker-Based Diagnosis of Anxiety Disorders

Current psychiatric diagnosis remains predominantly symptom-based and relies heavily on clinical interviews and standardized diagnostic criteria. While these approaches remain essential, they are inherently subjective and may be influenced by patient reporting, clinician interpretation, and symptom overlap among psychiatric disorders. Consequently, considerable interest has emerged in identifying objective biological markers that can support clinical decision-making [30].

Biomarker-based approaches offer several potential advantages:

- Improved diagnostic accuracy
- Earlier identification of high-risk individuals
- Reduced diagnostic delays
- Support for individualized treatment planning
- Monitoring of disease progression and therapeutic response

CBC-derived biomarkers are particularly attractive because they are inexpensive, minimally invasive, and readily available in routine healthcare settings. However, important limitations remain, including the lack of standardized thresholds, susceptibility to confounding by infections and medical illnesses, and variability related to age, sex, smoking status, obesity, physical activity, and medication use. Furthermore, these biomarkers lack disease specificity and may be altered in numerous psychiatric and medical conditions. Therefore, current evidence supports their role as adjunctive tools rather than standalone diagnostic markers for anxiety disorders [30].

Recent Advances in Management

Recent developments in psychiatric research have increasingly focused on integrating inflammatory biomarkers into personalized approaches for the management of anxiety disorders.

Precision Psychiatry

The concept of precision psychiatry aims to identify biologically distinct subgroups of patients based on clinical, genetic, neuroimaging, and inflammatory characteristics. Recognition of inflammatory phenotypes among anxiety patients may facilitate more targeted treatment selection and improved clinical outcomes.

Anti-inflammatory Therapeutic Approaches

Growing evidence linking inflammation with anxiety has stimulated interest in anti-inflammatory interventions, including:

- Omega-3 fatty acid supplementation
- Anti-inflammatory dietary strategies
- Structured exercise programs
- Cytokine-targeted therapies
- Probiotics and microbiome modulation

These approaches may reduce inflammatory burden while simultaneously improving psychological well-being and anxiety symptoms.

Artificial Intelligence and Machine Learning

Machine learning algorithms capable of integrating NLR, PLR, MLR, clinical symptom scores, neuroimaging findings, and genetic markers have demonstrated promising predictive capabilities for diagnosis, prognosis, and treatment response. Such technologies may eventually facilitate individualized risk assessment and precision treatment planning.

Multi-Biomarker Panels

Researchers are increasingly evaluating combined biomarker models incorporating:

- CBC-derived inflammatory indices
- C-reactive protein (CRP)
- Interleukin-6 (IL-6)
- Tumor necrosis factor-alpha (TNF-α)
- Cortisol

These multimodal approaches may provide superior diagnostic performance compared with single biomarkers and represent an important direction for future psychiatric research.

Future Directions

Despite the growing body of evidence supporting the association between hematological biomarkers and anxiety disorders, several important challenges must be addressed before these markers can be routinely incorporated into clinical practice. Future research should prioritize large multicenter prospective studies involving diverse populations to improve the generalizability and reproducibility of findings across different age groups, ethnicities, and anxiety disorder subtypes. Standardization of biomarker measurement protocols, laboratory methodologies, and reporting criteria is essential to minimize inter-study variability and facilitate meaningful comparisons between investigations.

Another critical area of research is the establishment of clinically relevant cut-off values for biomarkers such as NLR, PLR, MLR, and SII, which may enhance their diagnostic and prognostic utility. Integrating hematological biomarkers with neuroimaging findings, neurophysiological assessments, and molecular markers could provide

a more comprehensive understanding of the biological mechanisms underlying anxiety disorders. Advances in artificial intelligence and machine learning offer promising opportunities to develop predictive models that combine inflammatory biomarkers with clinical, genetic, and behavioral data to improve risk stratification and treatment selection.

Longitudinal studies are also needed to evaluate biomarker changes during disease progression and following therapeutic interventions. Furthermore, research exploring biomarker-guided treatment approaches may help identify patients most likely to benefit from specific pharmacological, psychological, or anti-inflammatory therapies. Ultimately, the integration of hematological biomarkers with genetic, neuroimaging, endocrine, and clinical information may pave the way for precision psychiatry, enabling more accurate diagnosis, personalized treatment strategies, and improved outcomes for individuals with anxiety disorders.

DISCUSSION

The findings summarized in this narrative review highlight the growing recognition of immune-inflammatory mechanisms in the pathophysiology of anxiety disorders. Traditionally, anxiety disorders have been conceptualized primarily as disturbances of neurotransmitter function and psychological stress responses. However, contemporary research increasingly supports the notion that systemic inflammation and immune dysregulation contribute significantly to the development, persistence, and severity of anxiety symptoms [31,32]. In this context, hematological biomarkers derived from routine complete blood count investigations have emerged as practical and accessible tools for assessing inflammatory status in psychiatric populations.

Among the various biomarkers evaluated, the neutrophil-to-lymphocyte ratio (NLR) appears to be the most extensively studied and consistently associated with anxiety disorders. Several investigators have reported significantly elevated NLR levels in patients with generalized anxiety disorder, panic disorder, and social anxiety disorder compared with healthy controls [33,34]. These findings are consistent with observations by Karabulut et al., who demonstrated a positive relationship between NLR values and anxiety symptom severity, suggesting that heightened inflammatory activity may parallel worsening clinical manifestations [35]. Similarly, Ekinci and Ekinci reported increased NLR levels among adolescents with anxiety disorders, supporting the hypothesis that immune dysregulation may be present across different age groups and stages of illness [36].

The present review also highlights the potential relevance of the platelet-to-lymphocyte ratio (PLR) as a marker of inflammation in anxiety disorders. Several studies have reported elevated PLR values among patients with panic disorder and mixed anxiety-depressive states, although findings have been less consistent than those observed for NLR [37]. This variability may reflect differences in study populations, sample sizes, medication status, and comorbid psychiatric conditions. Nevertheless, the biological role of platelets in inflammatory signaling and serotonergic neurotransmission provides a plausible mechanistic basis for the observed associations [38]. In agreement with these findings, Kokacya et al. demonstrated that platelet-related inflammatory markers were significantly altered in patients with anxiety-spectrum disorders, suggesting a potential role for platelet activation in anxiety pathogenesis [39].

Evidence regarding the monocyte-to-lymphocyte ratio (MLR) remains comparatively limited but increasingly promising. Monocytes play a crucial role in chronic inflammatory responses through cytokine production and immune regulation. Elevated MLR values reported in several psychiatric studies support the hypothesis that monocyte-mediated inflammation contributes to anxiety-related neuroimmune dysfunction [40]. Similar observations have been reported by Perry et al., who identified associations between monocyte activation and anxiety symptom severity, further strengthening the link between peripheral immune alterations and psychiatric morbidity [41].

The findings of this review are also consistent with broader literature examining inflammatory biomarkers beyond CBC-derived indices. Meta-analyses conducted by Vogelzangs et al. and Renna et al. demonstrated elevated concentrations of CRP, IL-6, and TNF-α in individuals with anxiety disorders, supporting the concept that peripheral inflammation represents a common biological feature across anxiety phenotypes [42,43]. These observations suggest that NLR, PLR, and MLR may serve as indirect markers of the same inflammatory processes reflected by more specialized cytokine measurements. Their major advantage lies in their low cost, routine availability, and ease of interpretation in clinical settings.

Recent studies have further explored the integration of hematological biomarkers into multimodal diagnostic frameworks. For example, Goldsmith et al. proposed that combining inflammatory biomarkers with neuroimaging and clinical data could improve diagnostic precision and facilitate personalized treatment strategies [44]. Similar conclusions were reached by Kennis et al., who emphasized the importance of integrating immune markers with genetic and neurobiological data to better understand anxiety disorder heterogeneity [45]. These approaches align with the emerging field of precision psychiatry, which seeks to

identify biologically distinct patient subgroups and optimize individualized treatment selection.

Despite these encouraging findings, several limitations must be acknowledged. Considerable heterogeneity exists across studies regarding participant demographics, diagnostic criteria, anxiety subtypes, disease severity, medication exposure, and laboratory methodologies [46]. Many investigations have utilized relatively small sample sizes and cross-sectional designs, limiting causal inference and reducing statistical power. Additionally, inflammatory biomarkers are influenced by numerous factors, including age, sex, obesity, smoking status, physical activity, dietary habits, metabolic disorders, and concurrent medical illnesses, all of which may confound study outcomes [47].

Another important limitation is the lack of standardized reference ranges and clinically validated cut-off values for NLR, PLR, and MLR in anxiety disorders. While elevated levels are frequently reported, the absence of universally accepted thresholds restricts their diagnostic applicability [48]. Furthermore, these biomarkers are not specific to anxiety disorders and may be elevated in depression, schizophrenia, bipolar disorder, cardiovascular disease, autoimmune conditions, and infectious diseases [49]. Consequently, their use as standalone diagnostic tools cannot currently be recommended.

Nevertheless, the overall evidence suggests that CBC-derived inflammatory biomarkers represent valuable adjunctive indicators of immune activation in anxiety disorders. Their accessibility, affordability, reproducibility, and biological plausibility make them attractive candidates for incorporation into future biomarker-based diagnostic and prognostic frameworks. As highlighted by Miller and Raison, understanding the interaction between inflammation and psychiatric illness may ultimately transform clinical practice by enabling earlier detection, more precise risk stratification, and individualized therapeutic interventions [50]. Future well-designed longitudinal and multicenter studies are essential to validate these findings and establish the precise clinical role of hematological biomarkers in anxiety disorders.

Conclusion

Hematological biomarkers derived from routine complete blood count investigations have emerged as promising indicators of systemic inflammation and immune dysregulation in anxiety disorders. Accumulating evidence suggests that biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) are frequently elevated in individuals with anxiety disorders and are associated with symptom severity, disease burden, and underlying inflammatory activity. These findings support the growing recognition that anxiety disorders involve not only psychological and neurochemical disturbances but also significant immunological and inflammatory alterations.

One of the major strengths of CBC-derived biomarkers is their practicality. They are inexpensive, minimally invasive, widely available, and routinely measured in clinical settings, making them attractive candidates for incorporation into psychiatric assessment frameworks. However, despite encouraging findings, important challenges remain. Variability in study methodologies, patient populations, diagnostic criteria, and biomarker thresholds has limited the consistency and clinical applicability of current evidence. Furthermore, these biomarkers lack sufficient specificity, as inflammatory changes may also occur in numerous medical and psychiatric conditions.

At present, NLR, PLR, and MLR should be considered adjunctive rather than definitive diagnostic tools. Nevertheless, their potential value in identifying inflammatory phenotypes, monitoring disease progression, and predicting treatment response warrants further investigation. Future large-scale, multicenter, and longitudinal studies are essential to establish standardized reference ranges, clarify underlying biological mechanisms, and validate their clinical utility. Ultimately, integrating hematological biomarkers with clinical assessment, neuroimaging, genetic profiles, and other biological markers may facilitate the development of precision psychiatry approaches, leading to more accurate diagnosis, personalized treatment strategies, and improved outcomes for patients with anxiety disorders.

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