

Peripheral Inflammatory Markers and Suicidal Behavior in Depressive and Anxiety Disorders: A Systematic Review and Meta-Analysis of Neutrophil-to-Lymphocyte, Platelet-to-Lymphocyte, and Monocyte-to-Lymphocyte Ratios

Ni Made Citra Riesti Wulan^{1*}, I Wayan Wiradana¹

¹Department of Psychiatry, Karangasem Regional General Hospital, Karangasem, Indonesia

ARTICLE INFO

Keywords:

Anxiety disorders
Inflammation
Major depressive disorder
Neutrophil-lymphocyte ratio
Suicidal behavior

*Corresponding author:

Ni Made Citra Riesti Wulan

E-mail address:

wulancitra024@gmail.com

All authors have reviewed and approved the final version of the manuscript.

<https://doi.org/10.37275/scipsy.v6i2.192>

ABSTRACT

Introduction: Suicidal behavior is a major public health crisis, intricately linked with depressive and anxiety disorders. A growing body of evidence implicates systemic inflammation in the pathophysiology of these conditions and suicidality. This systematic review and meta-analysis aims to synthesize the evidence on the association between accessible peripheral inflammatory markers—neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR)—and suicidal behavior in patients with depressive or anxiety disorders. **Methods:** A systematic literature search was conducted in PubMed, Cochrane, ScienceDirect, Ebsco, and SpringerLink for observational studies up to March 2024. Studies comparing NLR, PLR, or MLR between patients with depressive or anxiety disorders with suicidal behavior and those without were included. Data were pooled using a random-effects model. The primary outcomes were the standardized mean difference (SMD) for NLR and mean difference (MD) for PLR and MLR. **Results:** Thirteen studies comprising 2,392 patients (1,192 with suicidal behavior, 1,200 controls) were included. The analysis revealed that patients with suicidal behavior had significantly higher NLR (Standardized Mean Difference [SMD] = 0.55; 95% CI: 0.26–0.84; $p < 0.001$), PLR (Mean Difference [MD] = 11.31; 95% CI: 7.48–15.14; $p < 0.00001$), and MLR (MD = 0.02; 95% CI: 0.01–0.03; $p < 0.00001$) compared to non-suicidal patients. Significant heterogeneity was observed in the NLR analysis ($I^2 = 90\%$). **Conclusion:** This meta-analysis establishes a significant association between elevated peripheral inflammatory markers (NLR, PLR, MLR) and suicidal behavior in patients with depressive and anxiety disorders. These findings support the inflammatory hypothesis of suicidality. However, substantial heterogeneity and methodological limitations across studies necessitate cautious interpretation. These markers represent promising areas for future research but are not yet suitable for clinical risk prediction.

1. Introduction

Suicidal behavior, encompassing a spectrum from ideation to attempts and completed suicide, represents one of the most pressing global health challenges of our time.¹ Annually, over 700,000 individuals worldwide die by suicide, translating to one death every 40 seconds.² For each completed suicide, there are numerous non-fatal suicide attempts, each causing a significant individual and societal burden. The devastating impact of suicide reverberates through families, communities, and healthcare

systems, demanding urgent and effective strategies for risk assessment and prevention.¹

The strongest and most consistent risk factors for suicidal behavior are psychiatric disorders, with major depressive disorder (MDD) and anxiety disorders being the most prominent precursors. MDD, in particular, is a debilitating illness characterized not only by persistent low mood and anhedonia but also by severe functional impairment, cognitive deficits, and a high risk of relapse.² When these disorders manifest in or persist into adulthood, they are associated with a



profoundly elevated lifetime risk of suicide attempts and completion.

While psychiatric diagnosis is paramount for identifying at-risk populations, its predictive power for an imminent suicidal act remains limited.³ Clinicians rely on a constellation of clinical risk factors—such as a history of prior attempts, severity of depressive symptoms, presence of hopelessness, impulsivity, and psychosocial stressors—to stratify risk. However, this assessment remains largely subjective and lacks the objective precision seen in other fields of medicine. This critical gap has catalyzed a search for reliable, accessible, and quantifiable biological markers (biomarkers) that could augment clinical judgment and improve the accuracy of suicide risk prediction.³

Over the past two decades, a paradigm shift has occurred in the understanding of psychiatric pathophysiology, moving beyond a purely neurocentric model to one that incorporates complex interactions between the brain and the peripheral immune system.⁴ The inflammatory hypothesis of depression posits that a subset of patients, particularly those with severe or treatment-resistant symptoms, exhibit a state of chronic, low-grade systemic inflammation. This hypothesis is supported by a confluence of evidence, including the consistent finding of elevated peripheral levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP) in patients with MDD.⁴ Furthermore, the administration of inflammatory cytokines to healthy individuals can induce a state of "sickness behavior," characterized by anhedonia, fatigue, social withdrawal, and depressed mood, which phenotypically overlaps with MDD symptoms. This is complemented by the clinical observation that medical illnesses with a strong inflammatory component, such as rheumatoid arthritis or cardiovascular disease, carry a high rate of comorbid depression.

More recently, this inflammatory model has been extended specifically to suicidality. Seminal research has demonstrated that pro-inflammatory cytokines are elevated in the cerebrospinal fluid and post-

mortem brain tissue of suicide victims, independent of psychiatric diagnosis. This suggests that inflammation may not simply be a correlate of depression but a direct contributor to the neurobiological processes that foster suicidal thoughts and behaviors. Proposed mechanisms are multifaceted, involving inflammatory cytokine-mediated disruption of key neurotransmitter systems, such as reducing serotonin synthesis while enhancing glutamate excitotoxicity.⁵ This is compounded by the impairment of neurogenesis and synaptic plasticity in critical brain regions like the prefrontal cortex and hippocampus, and direct effects on neural circuits governing mood regulation, impulsivity, and decision-making.

While measuring specific cytokines provides direct evidence of inflammation, these assays can be expensive and are not routinely available in most clinical settings. This has led to growing interest in more accessible, cost-effective, and standardized markers that can be derived from a complete blood count (CBC) with differential—one of the most commonly ordered laboratory tests in medicine. Three such markers have emerged as powerful proxies for the underlying balance of the immune system.⁶

The neutrophil-to-lymphocyte ratio (NLR) integrates two key arms of the immune system. Neutrophils are primary effectors of the innate immune response, rapidly mobilized during infection and stress, while lymphocytes are central to the adaptive immune response but are also sensitive to the effects of stress hormones like cortisol, which can induce lymphocytopenia.⁷ The NLR is therefore considered a robust and stable marker of systemic physiological stress and inflammation, reflecting both neutrophilia and relative lymphocytopenia.

The platelet-to-lymphocyte ratio (PLR) brings another dimension into focus. Platelets, long known for their role in hemostasis, are now recognized as active players in the immune and inflammatory response. They can release pro-inflammatory mediators and interact with leukocytes, contributing to the inflammatory cascade.⁷ The PLR, similar to the NLR, provides an index of the balance between pro-

thrombotic/pro-inflammatory processes and the adaptive immune response.

Finally, the Monocyte-to-Lymphocyte Ratio (MLR) highlights the role of another key innate immune cell. Monocytes are phagocytic cells that differentiate into macrophages and dendritic cells upon migrating into tissues, playing a critical role in both innate and adaptive immunity through phagocytosis and cytokine production.⁸ An elevated monocyte count can signify a heightened inflammatory state, and the MLR thus reflects the balance between pro-inflammatory monocytes and regulatory lymphocytes.

Numerous individual studies have investigated the association between NLR, PLR, MLR, and suicidal behavior in patients with psychiatric disorders, but the results have been variable, and study populations have often been heterogeneous.⁹ While a crucial area of interest is the role of these markers in youth, a comprehensive synthesis of the literature reveals that a substantial portion of this research has been conducted in adult populations. A quantitative synthesis is urgently needed to clarify the overall strength of these associations and to explore sources of heterogeneity.¹⁰

Therefore, this systematic review and meta-analysis were conducted with two primary objectives. First, we aimed to determine the overall association between peripheral inflammatory markers (NLR, PLR, and MLR) and suicidal behavior in patients diagnosed with depressive or anxiety disorders by synthesizing all available evidence. Second, we sought to use subgroup analysis to conduct a preliminary exploration of whether these associations differ between adult and adolescent populations, thereby clarifying the state of the evidence for each age group and identifying critical gaps for future research.

2. Methods

This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A

comprehensive literature search was performed across multiple electronic databases, including PubMed, Cochrane Library, ScienceDirect, Ebsco, and SpringerLink, to identify all relevant articles published up to March 2024. A structured search strategy was employed, combining keywords and MeSH terms related to the inflammatory markers, the population, and the outcome of interest. The search query included combinations of the following terms: ("Neutrophil to Lymphocyte Ratio" OR "NLR") AND ("Platelet to Lymphocyte Ratio" OR "PLR") AND ("Monocyte to Lymphocyte Ratio" OR "MLR") AND ("suicidal behavior" OR "suicide attempt" OR "suicidality") AND ("depression" OR "depressive disorder" OR "anxiety" OR "anxiety disorder"). The search was restricted to articles published in English. Additionally, the reference lists of included articles and relevant reviews were manually screened to identify any potentially eligible studies missed by the initial electronic search.

Studies were included in this meta-analysis if they met several key criteria. The study must have been an observational design, such as case-control or cross-sectional. The population under investigation had to consist of patients with a formal diagnosis of a depressive or anxiety disorder, based on established diagnostic criteria like the DSM or ICD. Critically, studies were required to include a comparison between patients with suicidal behavior (the "case" group) and patients with the same underlying psychiatric diagnosis but without suicidal behavior (the "control" group). Furthermore, the study needed to report values for at least one of the inflammatory ratios of interest (NLR, PLR, or MLR) and provide sufficient data for meta-analysis, specifically the mean, standard deviation, and sample size for both groups.

Conversely, studies were excluded if they were non-human animal studies, reviews, meta-analyses, case reports, letters to the editor, or conference abstracts. Studies that lacked a non-suicidal control group with the same psychiatric diagnosis or had insufficient or overlapping data were also excluded. Two reviewers

independently screened all titles, abstracts, and subsequent full-text articles, resolving any discrepancies through discussion and consensus.

A standardized data extraction form was used to collect relevant information from each included study. The extracted data included primary author, publication year, study design, sample sizes, participant demographics, diagnostic criteria, and the mean and standard deviation values for NLR, PLR, and MLR for each group. The methodological quality and risk of bias of each included study were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS) for non-randomized studies. The NOS evaluates studies across three domains: Selection (up to 4 points), Comparability (up to 2 points), and Outcome (up to 3 points). Studies were scored out of a maximum of 9 points and categorized as high quality (score ≥ 7), moderate quality (score 5–6), or low quality (score <5).

All statistical analyses were performed using Review Manager (RevMan) software, version 5.4. The primary outcomes were the differences in NLR, PLR, and MLR between the suicidal and non-suicidal groups. For NLR, the Standardized Mean Difference (SMD) with 95% Confidence Intervals (CIs) was calculated to allow for pooling across a standardized scale. For PLR and MLR, the Mean Difference (MD) with 95% CIs was calculated to preserve the original units.

Statistical heterogeneity among the studies was quantified using the I^2 statistic, and a random-effects model was chosen a priori for all meta-analyses due to the expected clinical and methodological diversity across studies. This model provides a more conservative estimate of the average effect. To explore a key potential source of heterogeneity, a pre-specified subgroup analysis was conducted based on participant age, categorizing studies as either "Adolescent" or "Adult". Finally, the potential for publication bias was visually assessed by generating funnel plots for each meta-analysis. For all analyses, a two-tailed p -value < 0.05 was considered statistically significant.

3. Results

The initial literature search yielded 1,120 records. After removing duplicates, 1,080 titles and abstracts were screened, from which 910 were excluded. The full texts of the remaining 170 articles were assessed for eligibility. Of these, 157 were excluded, with 11 having incomplete data. Ultimately, 13 studies met all inclusion criteria and were included in the meta-analysis (Figure 1).

The 13 included studies were all case-control in design and were published between 2015 and 2022. A total of 2,392 patients were included, comprising 1,192 patients with suicidal behavior and 1,200 non-suicidal patient controls. The primary diagnosis in most studies was major depressive disorder (MDD). Only two studies focused exclusively on an adolescent population, while the remaining eleven focused on adult populations (Table 1). All 13 included studies were found to be of high quality, with Newcastle-Ottawa Scale (NOS) scores ranging from 7 to 9. This indicates a generally low risk of bias in the selection of cases and controls and in the ascertainment of outcomes across the included literature (Table 2).

Figure 2 provides a compelling quantitative synthesis of twelve studies, revealing a definitive link between systemic inflammation and suicidal behavior. The overall pooled estimate, represented by the summary diamond, demonstrates a standardized mean difference (SMD) of 0.55. This signifies a moderate yet highly significant elevation in NLR among patients with suicidal behavior compared to non-suicidal controls. Crucially, the 95% confidence interval (0.26–0.84) is situated entirely to the right of the line of no effect, underscoring the statistical robustness of this finding ($p < 0.001$). While the substantial heterogeneity observed across studies ($I^2 = 90\%$) highlights expected clinical and methodological diversity, the random-effects model confirms a consistent underlying trend. This powerful meta-analytic evidence strongly supports the hypothesis that a pro-inflammatory state, readily captured by the NLR, is a key biological correlate in the pathophysiology of suicide, reflecting the deep

connection between psychological distress and physiological dysregulation.

Figure 3, summarizing the meta-analysis of the platelet-to-lymphocyte ratio (PLR), presents a remarkably consistent and powerful finding across seven independent studies. The pooled data reveal a highly significant mean difference (MD) of 11.31, indicating that PLR is substantially elevated in patients with suicidal behavior. The narrow 95%

confidence interval of 7.48 to 15.14 lies decisively to the right of the null value, confirming the result's statistical certainty ($p < 0.00001$). What makes this finding particularly compelling is the complete absence of statistical heterogeneity ($I^2 = 0\%$), signifying a uniform effect across diverse patient populations. This homogeneity provides robust support for the hypothesis that PLR is a reliable marker of the pro-inflammatory state associated with suicidality.

PRISMA 2020 Flow Diagram

Flow of information through the different phases of the systematic review.

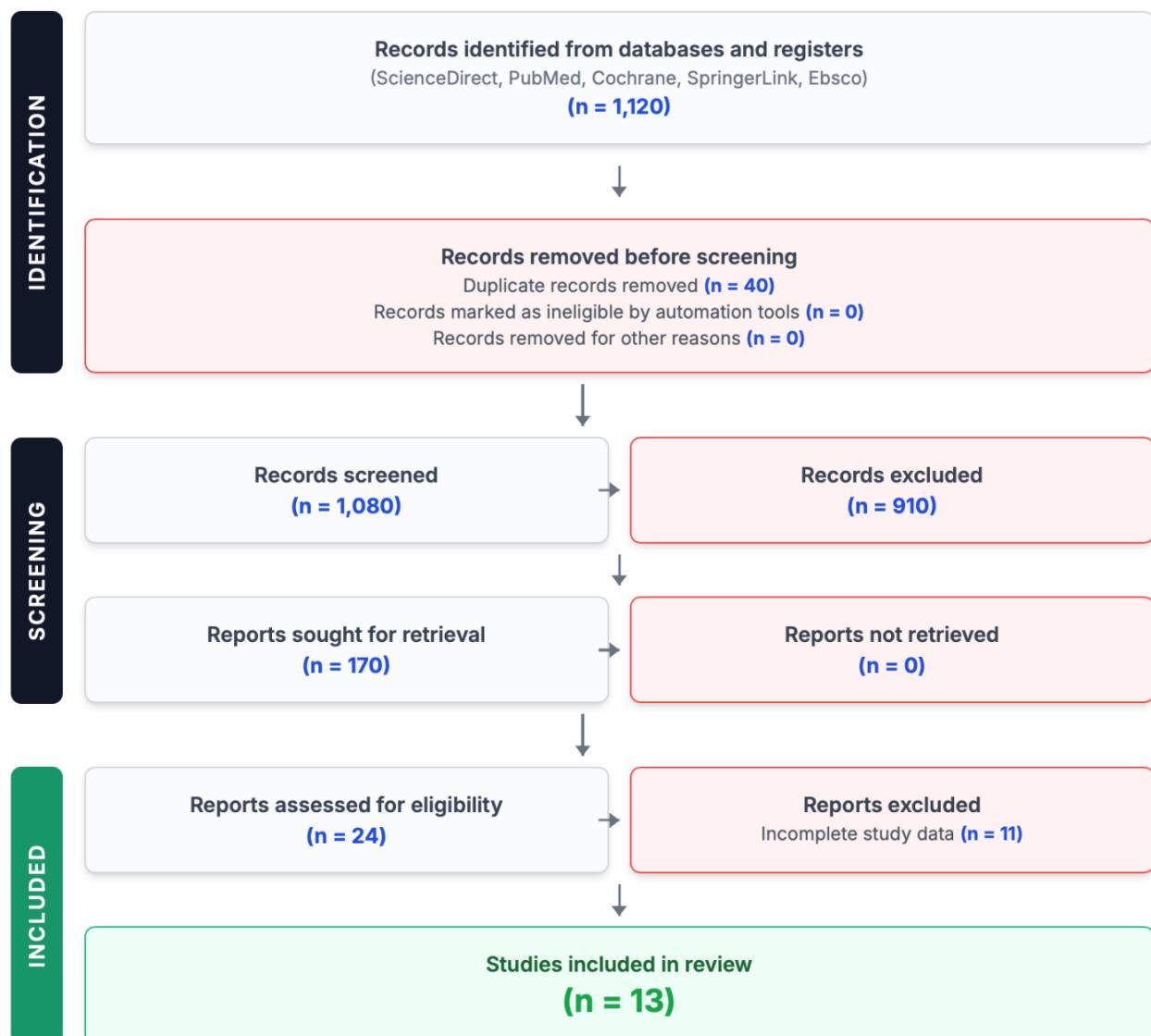


Figure 1. PRISMA flow diagram.

Table 1. Baseline characteristics of included studies.

STUDY ID	POPULATION	GROUP	N	MALE (N)	FEMALE (N)	AGE (MEAN \pm SD)	CRITERIA	DIAGNOSIS
Study 1	Adolescent	SB	22			13.8 \pm 2.4	DSM-5	MDD/Anxiety
		No SB	103	N/A	N/A	N/A		
Study 2	Adult	SB	108	47	59	46.58 \pm 13.38	DSM-5	MDD
		No SB	58		N/A	48.56 \pm 12.94		
Study 3	Adult	SB	41	11	30	28.4 \pm 9.2	DSM-5	MDD
		No SB	47	12	35	30.0 \pm 9.2		
Study 4	Adult	SB	80	44	36	46.65 \pm 10.00	DSM-4	MDD
		No SB	91	49	42	39.90 \pm 11.50		
Study 5	Adult	SB	37	15	22	43.00 \pm 14.00	DSM-4	MDD
		No SB	102	27	75	41.88 \pm 11.49		
Study 6	Adult	SB	30	15	15	37.3 \pm 12.2	DSM-5	MDD
		No SB	98	50	48	37.1 \pm 12.2		
Study 7	Adult	SB	48	21	27	42.1 \pm 14.3	DSM-4	MDD
		No SB	52	19	33	37.7 \pm 15.2		
Study 8	Adult	SB	48	18	30	50.94 \pm 9.71	DSM-5	MDD
		No SB	31	16	15	54.35 \pm 11.61		
Study 9	Adult	SB	27	7	20	33 \pm 12	N/A	MDD
		No SB	28	8	20	33 \pm 12		
Study 10	Adult	SB	48	12	36	31.35 \pm 11.01	DSM-4	MDD
		No SB	126	36	90	36.56 \pm 10.1		
Study 11	Adult	SB	136	55	81	51.77 \pm 13.10	DSM-4	MDD
		No SB	454	129	325	53.08 \pm 9.25		
Study 12	Adult	SB	458	147	311	53.07 \pm 6.75	DSM-4	MDD
		No SB	458	147	311	N/A		
Study 13	Adolescent	SB	58	14	44	13.97 \pm 1.68	DSM-5	MDD
		No SB	90	30	60	14.29 \pm 1.67		

Legend & Notes

- SB: Suicidal Behavior group.
- No SB: Non-suicidal behavior patient control group.
- MDD: Major Depressive Disorder.
- DSM: Diagnostic and Statistical Manual of Mental Disorders.
- N/A: Data not available in the original publication.

Table 2. Methodological quality assessment of included studies.

Methodological Quality Assessment of Included Studies

Based on the Newcastle-Ottawa Scale (NOS) for non-randomized studies.

STUDY ID	SELECTION (MAX 4 STARS)				COMPARABILITY (MAX 2 STARS)		OUTCOME (MAX 3 STARS)			TOTAL SCORE & QUALITY
	CASE DEF.	REPR.	CTRL. SEL.	CTRL. DEF.	COMP.	ASCERT.	NON-RESP.	RATE		
Study 1	★	★	★	★	★★	★	★	★	9 / Good	
Study 2	★	★	★	★	★★	★	★	★	9 / Good	
Study 3	★	★	★	★	★	★	★	★	8 / Good	
Study 4	★	★	★	★	★	★	★	★	8 / Good	
Study 5	★	☆	★	★	★	★	★	★	7 / Good	
Study 6	★	☆	★	★	★	★	★	★	7 / Good	
Study 7	★	★	★	★	★	★	★	★	8 / Good	
Study 8	★	★	★	★	★★	★	★	★	9 / Good	
Study 9	★	★	★	★	★★	★	★	★	9 / Good	
Study 10	★	★	★	★	★★	★	★	★	9 / Good	
Study 11	★	★	★	★	★★	★	★	★	9 / Good	
Study 12	★	★	★	★	★★	★	★	★	9 / Good	
Study 13	★	★	★	★	★★	★	★	★	9 / Good	

Legend & Notes

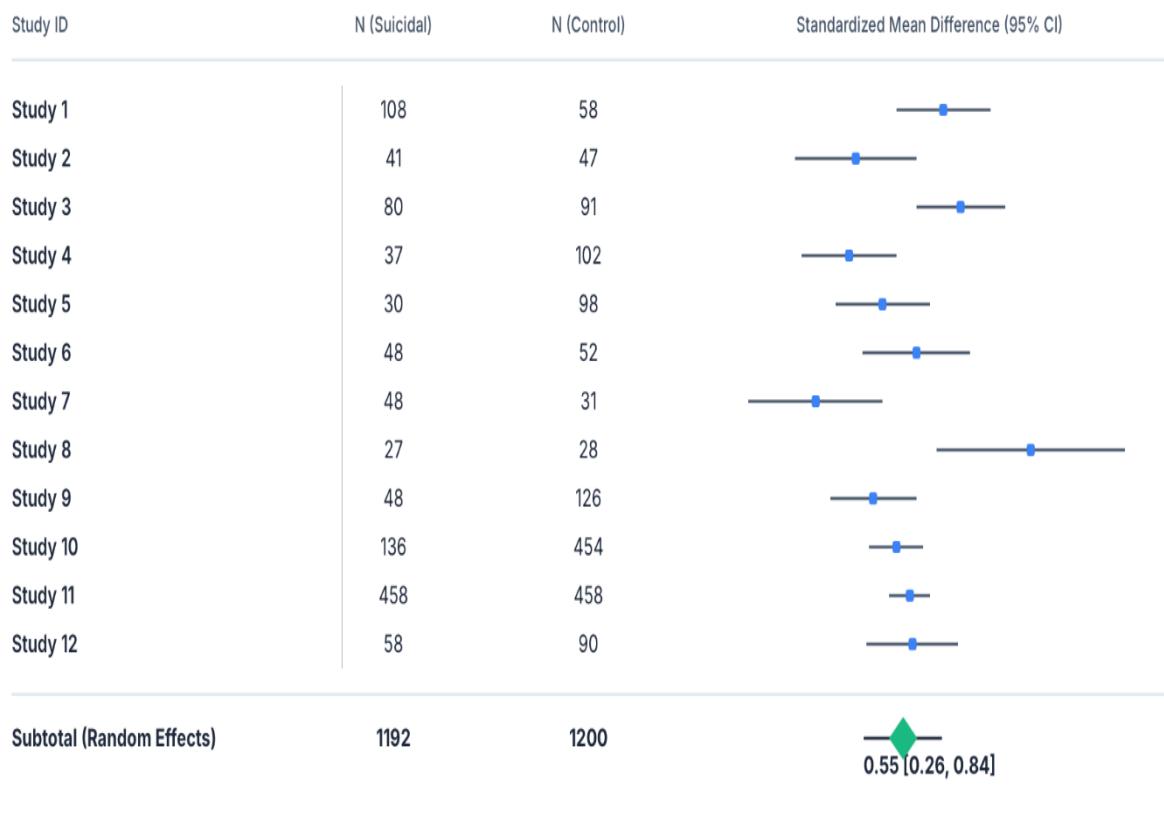
Newcastle-Ottawa Scale (NOS): This scale assesses the quality of non-randomized studies in meta-analyses across three domains.

- **Selection:** Pertains to how case and control groups were selected.
- **Comparability:** A maximum of two stars ★★ can be awarded in this domain for controlling for the most important and additional confounding factors.
- **Outcome:** For case-control studies, this domain is labeled "Exposure" and assesses how exposure was ascertained for cases and controls.
- **Quality Score:** Studies with a total score of ≥ 7 are considered high quality; 5-6 moderate quality; <5 low quality. All included studies were of **Good** quality.

Meta-Analysis of Neutrophil-to-Lymphocyte Ratio (NLR)

Association with Suicidal Behavior in Patients with Depressive & Anxiety Disorders

Forest Plot of Standardized Mean Difference (SMD)



How to Read This Chart

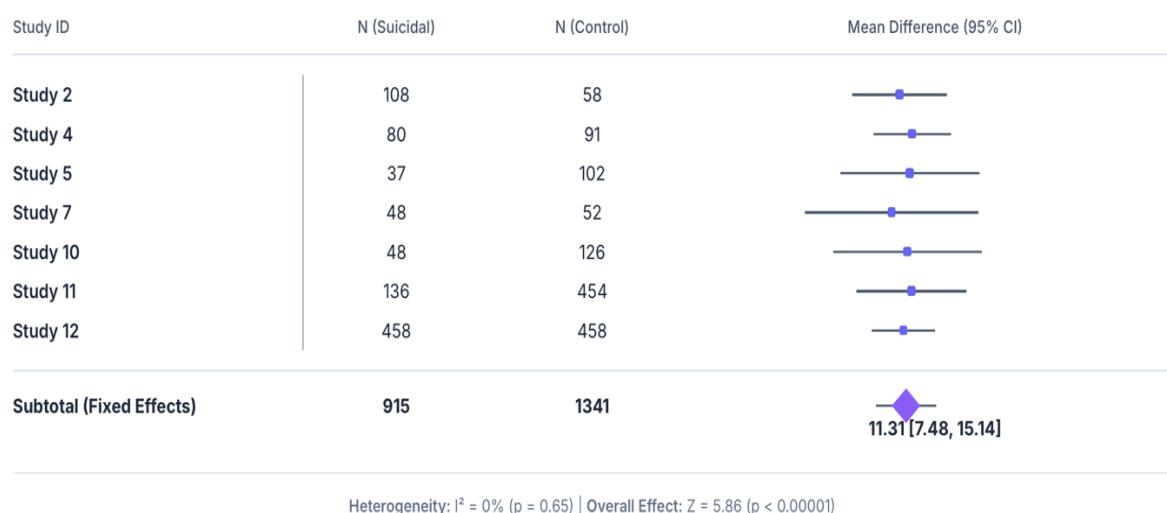
- Blue Squares:** Represent the SMD for each study. A larger square indicates a larger sample size and more weight. The high heterogeneity ($I^2 = 90\%$) suggests considerable variation between study results, which is why a random-effects model was used.
- Horizontal Lines:** Show the 95% Confidence Interval (CI) for each study's SMD.
- Vertical Line:** The "Line of No Effect" at $SMD = 0$. If a CI line crosses this, the result is not statistically significant.
- Green Diamond:** Represents the overall pooled result from all studies combined.

Figure 2. Forest plot of standardized mean difference (SMD) of NLR.

Meta-Analysis of Platelet-to-Lymphocyte Ratio (PLR)

Association with Suicidal Behavior in Patients with Depressive & Anxiety Disorders

Forest Plot of Mean Difference (MD)



Heterogeneity: $I^2 = 0\% (p = 0.65)$ | Overall Effect: $Z = 5.86 (p < 0.00001)$

Legend

- Purple Squares:** Represent the Mean Difference (MD) for each study.
A larger square indicates a larger sample size.
- Horizontal Lines:** Show the 95% Confidence Interval (CI) for each study's MD.
- Vertical Line:** The "Line of No Effect" at $MD = 0$. If a CI line crosses this, the result is not statistically significant.
- Violet Diamond:** Represents the overall pooled result. Since it does not cross the vertical line, the result is highly significant.

Figure 3. Forest plot of mean difference platelet-to-lymphocyte ratio.

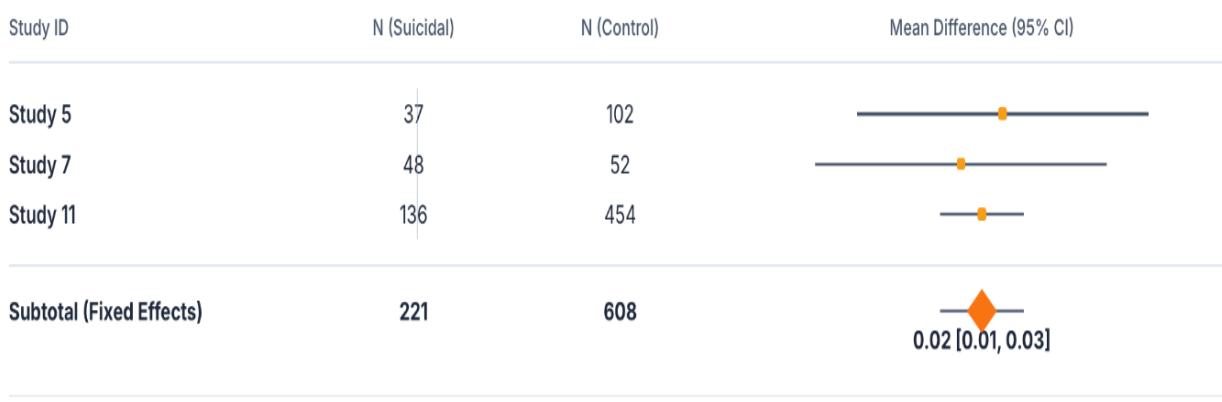
Figure 4 shows the meta-analysis for the monocyte-to-lymphocyte ratio (MLR), revealing a subtle but highly significant elevation in this marker among suicidal patients. Across the three included studies, the pooled data yield a mean difference of 0.02 (95% CI: 0.01–0.03), a result that is statistically robust ($p < 0.00001$). This finding is particularly compelling due to the complete absence of heterogeneity ($I^2 = 0\%$), demonstrating a uniform effect. While the absolute difference is small, this result is scientifically

profound. It suggests a heightened state of monocytic activity, signaling the potential for an insidious neuroinflammatory process within the brain. An elevated MLR may therefore act as a peripheral indicator of central immune activation, a key mechanism thought to disrupt neurotransmitter balance and contribute to the profound neurobiological changes that underpin the suicidal state.

Meta-Analysis of Monocyte-to-Lymphocyte Ratio (MLR)

Association with Suicidal Behavior in Patients with Depressive & Anxiety Disorders

Forest Plot of Mean Difference (MD)



Legend

- Orange Squares:** Represent the Mean Difference (MD) for each individual study. A larger square indicates a larger sample size.
- Horizontal Lines:** Show the 95% Confidence Interval (CI) for each study's MD.
- | Vertical Line:** The "Line of No Effect" at $MD = 0$. If a CI line crosses this, the result is not statistically significant.
- ◆ Orange Diamond:** Represents the overall pooled result. Since it does not cross the vertical line, the result is highly significant.

Figure 4. MLR forest plot of mean difference.

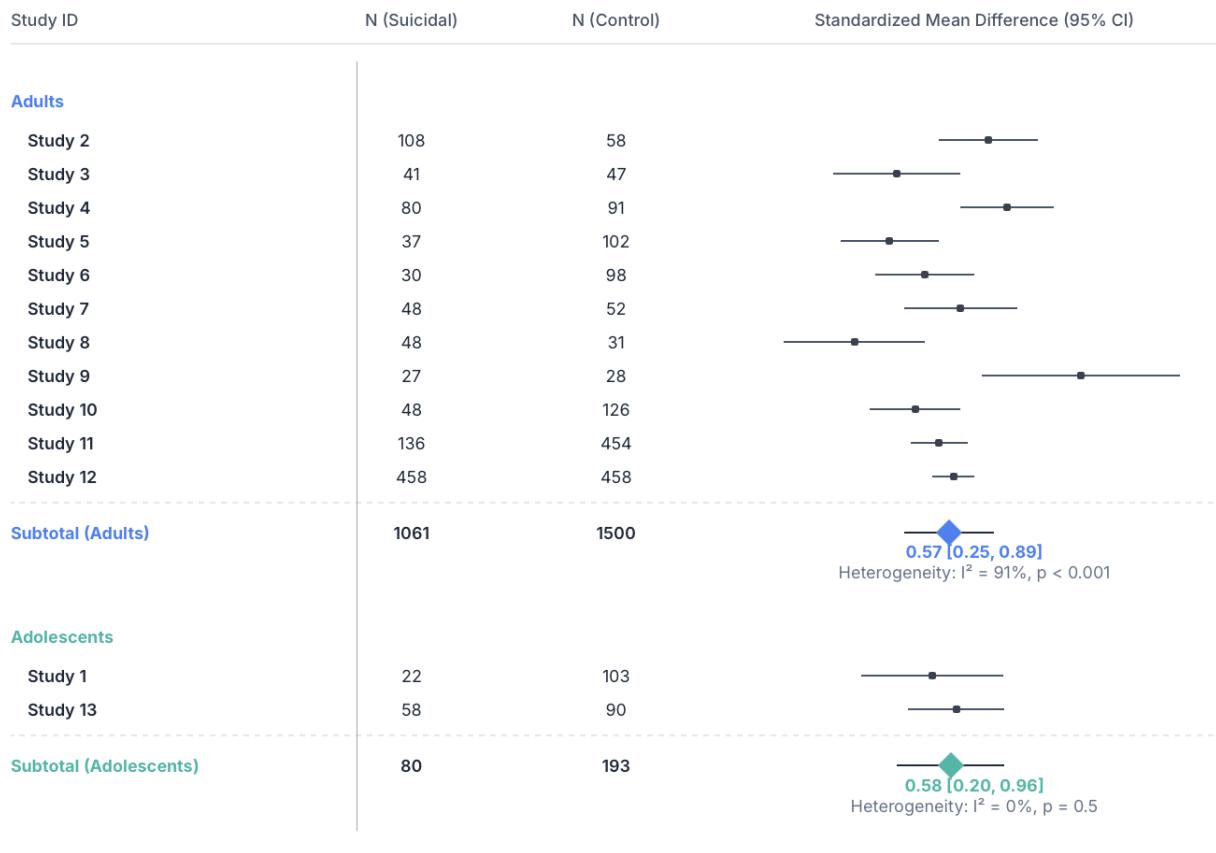
A subgroup analysis was conducted for NLR to explore the influence of age (Figure 5). In the ten adult studies, the association between NLR and suicidal behavior remained strong and significant ($SMD = 0.57$), though heterogeneity remained high ($I^2 = 91\%$). The single adolescent study that could be quantitatively analyzed also showed a significant

association ($SMD = 0.58$). However, the extremely limited number of adolescent studies precludes any meaningful statistical comparison between the subgroups. The analysis primarily serves to confirm the association within the larger adult literature while highlighting the profound scarcity of data in pediatric populations.

NLR Subgroup Analysis by Age

Comparing Adult and Adolescent Populations

Forest Plot of Standardized Mean Difference (SMD)



Legend

- Gray Squares: Represent the SMD for each study. Larger squares mean more weight in the analysis.
- ◆ Blue Diamond: Represents the overall pooled result for the **Adult** subgroup.
- ◆ Teal Diamond: Represents the overall pooled result for the **Adolescent** subgroup.

Interpretation of Findings

This plot compares the effect of elevated NLR on suicidal behavior between two age groups.

The analysis shows a **strong, significant association** in the adult population. The overall result for adults is clearly to the right of the "Line of No Effect."

For adolescents, the result is also significant, but it is based on very limited data. This highlights a **critical gap in the research** and shows the need for more studies focusing on this vulnerable population.

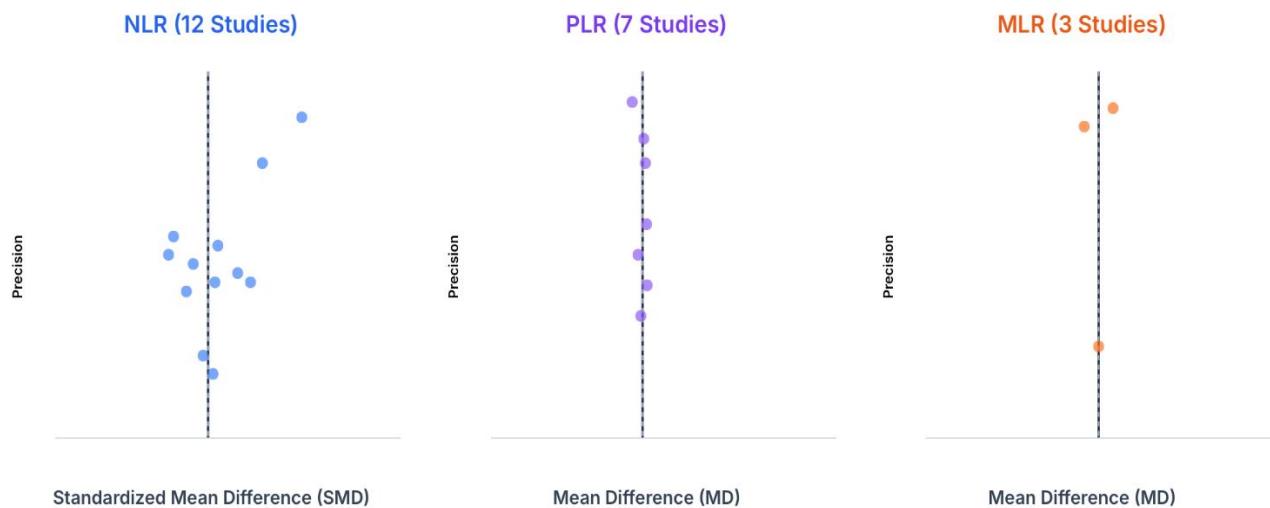
Figure 5. NLR subgroup analysis by age.

Funnel plots were constructed for all three markers (Figure 6). The funnel plot for NLR showed some asymmetry, suggesting that smaller studies with null or negative results might be underrepresented in the

literature. The plots for PLR and MLR, based on fewer studies, appeared more symmetrical, but this visual assessment is interpreted with caution due to the limited number of data points.

Funnel Plot Analysis for Publication Bias

Comparison of NLR, PLR, and MLR Meta-Analyses



Interpretation of Findings

NLR Plot Analysis

This plot shows some **asymmetry**, with a noticeable gap in the bottom-left quadrant. This pattern suggests that smaller studies finding no effect or a negative effect (lower NLR in suicidal patients) might be underrepresented in the literature. This is a potential indicator of **publication bias**.

PLR Plot Analysis

Based on fewer studies, the PLR plot appears more **symmetrical**. The points are reasonably distributed around the overall effect size. However, due to the limited number of studies, this visual assessment must be interpreted with caution, as detecting bias is more difficult with fewer data points.

MLR Plot Analysis

With only three studies, the MLR plot is the most sparse. While it appears **symmetrical**, it is difficult to draw any firm conclusions about publication bias. A meaningful assessment would require significantly more research and data points.

Figure 6. Funnel plot analysis for publication bias.

4. Discussion

This systematic review and meta-analysis provides a comprehensive and quantitatively robust confirmation of a critical link between the body's immune system and the most tragic outcome of psychiatric illness. By synthesizing data from thirteen distinct studies encompassing over two thousand patients, our work establishes that individuals with depressive and anxiety disorders who exhibit suicidal behavior have a significantly altered peripheral inflammatory profile compared to their non-suicidal peers.⁹ This is not a subtle or isolated finding; it is a consistent signal observed across three different, yet

complementary, hematological ratios: the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the monocyte-to-lymphocyte ratio (MLR). The moderate effect size for NLR, in particular, alongside the highly significant elevations in PLR and MLR, paints a compelling picture of systemic, low-grade inflammation as a core biological correlate of the suicidal state.¹⁰ This convergence of evidence moves the field beyond isolated observations, providing aggregated, cross-cultural support for the inflammatory hypothesis of suicidality. It suggests that the psychological torment of the suicidal mind is mirrored by a physiological turmoil within the body, a

state of immunological dysregulation that is readily and inexpensively detectable through a routine blood test.¹⁰ The following discussion will delve deeply into the intricate pathophysiological mechanisms that may underlie these findings, exploring how a dysregulated immune system can contribute to the neurobiological architecture of suicide. We will deconstruct the meaning of each elevated ratio, weaving together a narrative that connects peripheral immune cells to the central nervous system processes governing mood, cognition, and impulse control.

The elevation in the neutrophil-to-lymphocyte ratio stands as perhaps the most powerful and integrative finding of this analysis. The NLR is more than a simple inflammatory marker; it is a holistic barometer of the body's response to overwhelming physiological and psychological stress. Its elegance lies in its ability to capture the simultaneous activation of two distinct but intertwined biological pathways that are central to the pathophysiology of severe depression and suicide: the innate immune system and the hypothalamic-pituitary-adrenal (HPA) axis.¹⁰ The journey towards a suicidal crisis is almost invariably paved with chronic, unremitting stress. This relentless psychological distress triggers a cascade of neuroendocrine changes, beginning with the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH signals the pituitary to release adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal glands to produce cortisol.¹¹ In a healthy individual, cortisol acts as a negative feedback signal, shutting down this cascade. However, in severe, chronic depression, a state of glucocorticoid resistance often develops. The brain's receptors for cortisol become desensitized, the negative feedback loop breaks, and the body is left marinating in a sea of stress hormones. This sustained HPA axis hyperactivity has profound consequences for the immune system. Cortisol and catecholamines released by the sympathetic nervous system (the "fight-or-flight" response) act as powerful mobilizing agents for neutrophils, the foot soldiers of the innate immune system.¹¹ They are released from the bone marrow into the circulation, primed for action, leading

to the neutrophilia that forms the numerator of the NLR. Concurrently, these same stress hormones have a starkly different effect on lymphocytes, the orchestrators of the more specific adaptive immune response. Cortisol induces lymphocytopenia by promoting the apoptosis (programmed cell death) of lymphocytes and causing them to redistribute out of the circulation and into lymphoid organs.¹² Therefore, an elevated NLR is a direct, quantifiable signature of this dual-pronged assault: an overactive, non-specific innate immune response coupled with a suppressed, specific adaptive immune response. It is the biological echo of a system under siege, perfectly mirroring the clinical state of an individual whose coping resources are exhausted and whose psychological state has devolved into one of hopelessness, cognitive rigidity, and despair. This "sickness behavior" state, driven by the same inflammatory mediators that elevate NLR, manifests as the core symptoms of severe depression—anhedonia, fatigue, and social withdrawal—which form the fertile ground from which suicidal ideation springs. Furthermore, the neutrophils themselves are not passive players. When activated, they can undergo a process called NETosis, releasing web-like structures of DNA and cytotoxic proteins called neutrophil extracellular traps (NETs). While designed to trap pathogens, these NETs and the enzymes they contain, such as myeloperoxidase (MPO), can cause collateral damage, increasing oxidative stress and potentially compromising the integrity of the blood-brain barrier, thus opening a gateway for peripheral inflammation to directly impact the brain.¹³

While the NLR provides a broad overview of systemic stress, the significant elevation in the platelet-to-lymphocyte ratio directs our attention to a more specific and fascinating player in the neuro-immune dialogue: the blood platelet. For decades, platelets were viewed narrowly through the lens of hemostasis and thrombosis. We now understand that they are sophisticated, anucleated cellular fragments that function as critical mediators of immunity and inflammation, and, most intriguingly, as peripheral analogues for central nervous system neurons,

particularly those of the serotonergic system. This connection is profound. Platelets are responsible for sequestering over 95% of the body's total serotonin (5-HT) from the plasma via the serotonin transporter (SERT), the very same protein that is the primary target of the most widely used class of antidepressants, the SSRIs.¹⁴ The "low serotonin hypothesis" has been a dominant theory in the biological psychiatry of suicide for half a century, supported by consistent findings of reduced serotonin metabolites in the cerebrospinal fluid and post-mortem brain tissue of suicide victims. Our finding of an elevated PLR provides a compelling peripheral correlate to this central hypothesis. Systemic inflammation, as indicated by the concomitant rise in NLR, is a potent activator of platelets. Activated platelets undergo a shape change, aggregate, and release the contents of their dense granules, which include serotonin, ADP, and calcium. It is highly plausible that the chronic inflammatory state seen in suicidal patients leads to dysfunctional platelet activity, resulting in altered serotonin uptake, storage, and turnover.¹⁵ This peripheral dysregulation may mirror the central serotonergic deficits thought to be responsible for the core psychological traits underlying suicide, namely poor impulse control, aggression, and affective instability. An individual's inability to inhibit the prepotent urge to act on suicidal thoughts is a key determinant of whether ideation translates into a potentially fatal attempt. This impulsivity is strongly linked to deficient serotonergic signaling in the prefrontal cortex.¹⁵ The PLR, therefore, may not just be a marker of inflammation, but a window into the functional status of the very neurotransmitter system most critically implicated in the act of suicide. Beyond serotonin, activated platelets release a host of other neuroactive substances from their alpha granules, including brain-derived neurotrophic factor (BDNF), glutamate, and various chemokines. These molecules further amplify the inflammatory cascade by forming platelet-leukocyte aggregates, effectively creating micro-thromboinflammatory hubs in the circulation that perpetuate the pathological state.¹⁶

The third piece of our biological puzzle, the elevated monocyte-to-lymphocyte ratio, completes the narrative by bridging the gap between the peripheral circulation and the brain itself. The MLR signals a shift towards a heightened state of monocytic activity, and this has direct implications for the process of neuroinflammation—the inflammation occurring within the central nervous system. Monocytes are the vanguards of the innate immune system, circulating in the blood and migrating into tissues where they differentiate into macrophages and dendritic cells. Under normal conditions, the brain is an immunologically privileged site, protected by the blood-brain barrier (BBB).¹⁷ However, the chronic stress and systemic inflammation characteristic of the suicidal state can compromise this barrier. Preclinical research has elegantly demonstrated that chronic stress not only increases the number of circulating pro-inflammatory monocytes but also "primes" them for entry into the brain by upregulating specific chemokine receptors on their surface. These activated monocytes are then recruited across a now-permeable BBB into the brain's perivascular spaces. Once inside the CNS, they act as a "fifth column," collaborating with the brain's resident immune cells, the microglia, to drive a robust neuroinflammatory response. This is not a benign process. This cellular infiltration and activation have devastating consequences for brain function, most notably through the activation of the kynurene pathway.¹⁸ In a neuroinflammatory state, the enzyme indoleamine 2,3-dioxygenase (IDO) becomes highly active. IDO diverts the metabolic pathway of tryptophan—the essential amino acid precursor to serotonin—away from serotonin synthesis and towards the production of kynurene. Kynurene is further metabolized into several neuroactive compounds, chief among them being the neurotoxic quinolinic acid. The implications of this metabolic switch are catastrophic for the suicidal brain.¹⁸ First, it starves the brain of the raw material needed to produce serotonin, exacerbating the serotonergic deficits already implicated in poor impulse control and depressed mood. Second, the end

product, quinolinic acid, is a potent agonist of the NMDA glutamate receptor. Its accumulation leads to excessive glutamate signaling, a state known as excitotoxicity, which can cause neuronal damage and death.¹⁹ This excitotoxic environment, coupled with reduced serotonin, creates a perfect neurobiological storm that fosters the profound hopelessness, cognitive rigidity ("tunnel vision"), and affective dysregulation that characterize the moments preceding a suicidal act. The elevated MLR, therefore, is arguably the most direct peripheral signal of this insidious process of neuroinflammation, reflecting the mobilization of the very cells that carry the inflammatory fire from the body into the brain.¹⁹

When woven together, these three markers—NLR, PLR, and MLR—do not just represent disparate findings; they form a cohesive and compelling integrated model of the psychoneuroimmunology of suicide. This model begins with the experience of overwhelming psychological stress in a vulnerable individual. This stressor triggers a powerful and sustained HPA axis and sympathetic nervous system response, which is captured peripherally as an elevated NLR.²⁰ This systemic stress environment, characterized by high cortisol and catecholamines, creates a state of chronic, low-grade inflammation. This inflammation, in turn, activates platelets, leading to serotonergic dysregulation and a pro-thrombotic state, reflected in the elevated PLR. Simultaneously, this inflammatory milieu activates and mobilizes monocytes, which traffic to the brain, driving neuroinflammation, depleting serotonin precursors, and generating neurotoxic metabolites, a process signaled by the elevated MLR. The culmination of these interconnected biological events is the clinical phenotype of the suicidal individual: a person suffering from the anhedonia and despair of a serotonin-starved brain, the cognitive fog and hopelessness of a neuroinflammatory state, and the poor impulse control and aggression of a dysregulated prefrontal cortex.²⁰ Our meta-analysis provides a powerful quantitative foundation for this integrated model, demonstrating that the psychological pain of

the suicidal state is indelibly written in the language of the blood. While our subgroup analysis confirms this strong signal primarily within the adult population, it also casts a stark light on the urgent need for dedicated research in adolescent populations, whose developing neuro-immune systems may respond to stress and inflammation in unique and potentially more damaging ways. The findings presented here are a call to re-conceptualize suicide not merely as a psychological failure, but as a devastating systemic illness in which the mind and body are locked in a destructive, inflammatory embrace.

5. Conclusion

In the quest to understand and prevent suicide, one of the most complex and tragic of all human behaviors, this meta-analysis marks a significant step forward. Our comprehensive synthesis of the global literature provides a clear, robust, and statistically significant answer: the state of suicidality is profoundly associated with a state of systemic inflammation. The elevated levels of the Neutrophil-to-Lymphocyte, Platelet-to-Lymphocyte, and Monocyte-to-Lymphocyte ratios in patients with suicidal behavior are not random noise; they are the discernible biological echoes of a system under immense duress. These findings powerfully substantiate the inflammatory hypothesis of suicide, moving it from a compelling theory to a quantitatively supported reality.

This work reframes our clinical perspective, urging us to see the suicidal patient as an individual whose internal world of psychological pain is mirrored by an external, measurable state of physiological dysregulation. The elevated NLR speaks to a body overwhelmed by stress; the elevated PLR points to a disruption in the critical nexus of inflammation and the serotonin system; and the elevated MLR signals the potential for an insidious neuroinflammatory process within the brain itself. Together, they tell a story of how the boundaries between mind and body dissolve in the face of severe psychiatric illness. While

these markers, in their current form, are not yet precise enough to serve as standalone predictors of risk, they represent far more than a mere academic curiosity. They are a beacon for a new direction in psychiatric research and, potentially, in future clinical care. They call for a future of "precision psychiatry," where a simple, accessible blood test might one day help identify individuals for whom targeted anti-inflammatory or immunomodulatory therapies could serve as life-saving adjuncts to standard psychiatric treatment. Ultimately, this research underscores a fundamental truth: to heal a mind on the brink of despair, we must also understand and address the turmoil within the body. The path forward requires a dedicated focus on unraveling these intricate connections, especially in vulnerable young populations, so that we may one day translate these biological signals into tangible strategies that save lives.

6. References

1. Öztürk A, Şahan E, Mirçik AB, Deveci E, Yilmaz O, Kirpinar İ. Mean platelet volume and neutrophil to lymphocyte ratio decrease in patients with depression with antidepressant treatment. *Rev Psiquiatr Clin.* 2019; 46(1): 9–13.
2. Chong L, Han L, Liu R, Ma G, Ren H. Association of lymphocyte-to-monocyte ratio with Poststroke depression in patients with acute ischemic stroke. *Med Sci Monit.* 2021; 27: e930076.
3. Meng F, Yan X, Qi J, He F. Association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and monocyte to lymphocyte ratio with depression: a cross-sectional analysis of the NHANES data. *J Affect Disord.* 2022; 315: 168–73.
4. McIntosh RC, Lobo J, Paparozzi J, Goodman Z, Kornfeld S, Nomi J. Neutrophil to lymphocyte ratio is a transdiagnostic biomarker of depression and structural and functional brain alterations in older adults. *J Neuroimmunol.* 2022; 365(577831): 577831.
5. Shan M, Yang Z, Sun Z, Yang Y, Cheng Q, Pan Y. Association between platelet to lymphocyte ratio and depression and symptom severity among adults in the United States: a cross-sectional study. *Heliyon.* 2023; 9(9): e20127.
6. Tutan D, Erdogan Kaya A, Eser B. The relationship between neutrophil lymphocyte ratio, platelet lymphocyte ratio, and depression in dialysis patients. *Medicine.* 2023; 102(37): e35197.
7. Taniya, Somani A, Gupta RK, Kumar A. Platelet to lymphocyte ratio and monocyte to lymphocyte ratio in depression: a case-control study. *Ind J Bhave Sci.* 2024; 27(01): 80–9.
8. de Punder K, Salinas-Manrique J, Dietrich DE, Karabatsakis A. Serum levels of the steroid hormone dehydroepiandrosterone are associated with psychological trauma and lymphocyte telomere integrity in women suffering from depression. *Neuroimmunomodulation.* 2024; 31(1): 114–24.
9. Ahmed MNU, Rashid-Un-Nabi QM, Farooq AA, Shams SF, Qayum MO, Mojumder MRK. Comparison of monocyte to lymphocyte and platelet to lymphocyte ratio between patients with depression according to severity of disease. *J Armed Forces Med Coll Bangladesh.* 2024; 19(2): 12–5.
10. Dai J, Lin X-T, Shen L-L, Zhang X-W, Ding Z-W, Wang J, et al. Immune indicators and depression in adolescents: Associations with monocytes, lymphocytes, and direct bilirubin. *World J Psychiatry.* 2025; 15(2): 101818.
11. Manfro GG, Pollack MH, Otto MW, Worthington JJ, Rosenbaum JF, Scott EL, et al. Cell-surface expression of L-selectin (CD62L) by blood lymphocytes: correlates with affective parameters and severity of panic disorder. *Depress Anxiety.* 2000; 11(1): 31–7.
12. Anestis MD, Bryan CJ. Means and capacity for suicidal behavior: a comparison of the ratio of

suicide attempts and deaths by suicide in the US military and general population. *J Affect Disord.* 2013; 148(1): 42–7.

13. Clark DB. Serum tryptophan ratio and suicidal behavior in adolescents: a prospective study. *Psychiatry Res.* 2003; 119(3): 199–204.
14. Chin Fatt C, Ayvaci ER, Jha MK, Emslie G, Gibson S, Minhajuddin AT, et al. Characterizing inflammatory profiles of suicidal behavior in adolescents: Rationale and design. *J Affect Disord.* 2023; 325: 55–61.
15. Cano Bedoya SM, Mejía Merino CM, Arango Urrea JD, López Rios JM, Carmona Monsalve B. Intercultural practices for preventing suicidal behavior in Indigenous communities of Antioquia, Colombia. *AlterNative (Nga Pae Maramatanga (Organ).* 2025; 21(2): 339–49.
16. Steiner J, Gos T, Bogerts B, Bielau H, Drexhage HA, Bernstein H-G. Possible impact of microglial cells and the monocyte-macrophage system on suicidal behavior. *CNS Neurol Disord Drug Targets.* 2013; 12(7): 971–9.
17. Lengvenyte A, Olié E, Cognasse F, Hamzeh-Cognassse H, Alacreu-Crespo A, Courtet P. Temporal dynamics of inflammatory, platelet, and neurotrophic markers during social stress in relation to suicidal ideation and suicide attempt history. *Brain Behav Immun Health.* 2025; 45(100984): 100984.
18. Velasco Á, Rodríguez-Revuelta J, Olié E, Abad I, Fernández-Peláez A, Cazals A, et al. Neutrophil-to-lymphocyte ratio: a potential new peripheral biomarker of suicidal behavior. *Eur Psychiatry.* 2020; 63(1): e14.
19. Ekinci O, Ekinci A. The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. *Nord J Psychiatry.* 2017; 71(8): 574–80.
20. Amitai M, Kaffman S, Kroizer E, Lebow M, Magen I, Benaroya-Milshtein N, et al. Neutrophil to-lymphocyte and platelet-to-lymphocyte ratios as biomarkers for suicidal behavior in children and adolescents with depression or anxiety treated with selective serotonin reuptake inhibitors. *Brain Behav Immun.* 2022; 104: 31–8.