



Psychiatric Emergency in Depression, Systemic Inflammation, Biochemical Changes, Biomarkers of Severity, and Therapeutic Response

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Abstract

Depression is a major cause of disability and can present in severe forms associated with suicidal behavior, treatment resistance, and the need for psychiatric emergency care. This systematic review aimed to analyze recent evidence on systemic inflammation, biochemical abnormalities, and biomarkers related to severity, suicidality, and therapeutic response in major depressive disorder. The review was conducted in accordance with the PRISMA 2020 guidelines, with searches in the PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, Virtual Health Library, and SciELO databases, considering publications from January 2021 to September 2026. Studies on C-reactive protein, pro-inflammatory cytokines, hematological indices, tryptophan-kinurenine metabolism, oxidative stress, and markers related to response to antidepressants, ketamine, esketamine, and electroconvulsive therapy were analyzed. The findings indicated an association between increased inflammatory activity and certain severe depressive phenotypes, particularly CRP, IL-6, and the neutrophil-to-lymphocyte ratio in subgroups with suicidal behavior or treatment resistance. Metabolic and oxidative changes were also described, especially in the tryptophan-kinurenine pathway. However, the results showed significant heterogeneity, and no single biomarker demonstrated sufficient sensitivity and specificity for independent use in clinical decision-making. It is concluded that biomarkers have potential as complementary tools in multimodal risk stratification models and precision psychiatry, but they do not yet replace individualized clinical assessment, especially in psychiatric emergency situations.

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1. Introduction

Depression is one of the psychiatric disorders with the greatest clinical and social impact, ranging from mild, self-limiting cases to severe episodes associated with significant functional impairment, psychotic symptoms, suicidal behavior, and the need for urgent care. In psychiatric emergency departments, the evaluation of patients with depression requires special attention to the

presence of suicidal ideation, planning, prior attempts, hopelessness, agitation, impulsivity, psychotic symptoms, and reduced capacity for self-care, as these factors may indicate greater severity and the need for immediate intervention.

In recent decades, the understanding of depression has moved beyond models focused exclusively on neurotransmitters and has come to incorporate immunological, inflammatory, metabolic, and neuroendocrine mechanisms. Recent evidence shows that a proportion of patients with major depressive disorder exhibit alterations in peripheral inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and tumor necrosis factor alpha (TNF- α), suggesting the involvement of systemic inflammation in the pathophysiology of certain depressive phenotypes (KURING *et al.*, 2023; MOSHFEGHINIA *et al.*, 2025)^[8, 12].

The relationship between inflammation and suicidal behavior has received special attention due to its potential relevance to psychiatric emergencies. Systematic reviews have identified alterations in various peripheral mediators, highlighting IL-1 β , IL-6, CRP, CCL2, and TNF- α as potential markers associated with suicide-related behavior, although methodological heterogeneity still limits their use as independent diagnostic tools (KIM *et al.*, 2023)^[7].

Among the markers currently under the most investigation, C-reactive protein has yielded significant results. A meta-analysis published in 2024, including 15 studies and 3,652 participants, demonstrated significantly higher CRP levels in depressed patients with suicidal behavior compared to depressed individuals without suicidal behavior, reinforcing the association between increased systemic inflammatory activity and suicidal manifestations (FATEMIAN *et al.*, 2024)^[3].

Pro-inflammatory cytokines have also been linked to the severity of depression. IL-6, TNF- α , and IL-1 β may interfere with mechanisms of neurotransmission, neuronal plasticity, energy metabolism, and activity of the hypothalamic-pituitary-adrenal axis. These changes may alter serotonergic, dopaminergic, and glutamatergic pathways, contributing to symptoms such as anhedonia, fatigue, cognitive impairments, sleep disturbances, and reduced motivation (MOSHFEGHINIA *et al.*, 2025)^[12].

In addition to traditional cytokines, parameters derived from complete blood counts have attracted interest due to their low cost and wide availability. The neutrophil-to-lymphocyte ratio (NLR) has been studied as an indirect marker of systemic inflammation. A meta-analysis involving 37 studies and 88,019 participants identified higher NLR values in individuals with depressive disorders and an association between an increased NLR and a higher risk of suicide (ZHOU *et al.*, 2025)^[16].

Other hematological indices, including the platelet-to-lymphocyte ratio and the monocyte-to-lymphocyte ratio, are also being investigated. Interest in these markers stems from the fact that they can be obtained through routine laboratory tests, a feature that is particularly relevant in emergency departments. However, factors such as age, sex, medications, obesity, infections, and chronic diseases can significantly alter their values, limiting their specificity.

The role of inflammation in depression is also linked to broader biochemical changes. Among the mechanisms studied, the activation of the tryptophan-kinurenine pathway stands out. Under inflammatory conditions, cytokines can

promote a shift in tryptophan metabolism toward the production of kinurenine and its metabolites, reducing its availability for serotonin synthesis and altering the production of compounds with neuroactive properties.

Alterations in the hypothalamic-pituitary-adrenal axis constitute another mechanism frequently associated with severe depression. Prolonged exposure to stress can alter cortisol secretion and glucocorticoid receptor sensitivity, promoting immunological and metabolic dysregulation and establishing a bidirectional interaction between stress, inflammation, and depressive symptoms.

Treatment-resistant depression represents one of the most promising areas for biomarker research. Recent reviews show that individuals with treatment-resistant depression may have elevated levels of IL-6, TNF- α , and CRP, as well as alterations in the kynurenine pathway and other biological systems (MANCUSO *et al.*, 2023)^[9].

The possible association between inflammation and response to antidepressants has also been investigated. A 2022 meta-analysis suggested that higher baseline levels of CRP and IL-8 were associated with a poorer response to antidepressant treatment, raising the hypothesis that certain inflammatory profiles could aid in individualized therapeutic selection in the future (GASPARINI *et al.*, 2022)^[4].

More recent evidence, however, calls for caution. Meta-analyses and comprehensive reviews from 2026 concluded that individual inflammatory biomarkers still have limited utility as standalone predictors of antidepressant response, with generally small or inconsistent effects (BAXTER *et al.*, 2026; HUMMAD *et al.*, 2026)^[1, 5].

Interventions used in cases of severe or treatment-resistant depression, such as ketamine and electroconvulsive therapy, have also been evaluated in relation to inflammatory mechanisms. Studies have demonstrated changes in various peripheral mediators; however, the findings remain heterogeneous and dependent on the timing of sample collection, concomitant treatment, and patients' clinical characteristics (DELLINK *et al.*, 2025; MESHKAT *et al.*, 2023)^[2, 11].

In the context of psychiatric emergencies, it is essential to distinguish the scientific potential of biomarkers from their current clinical applicability. Suicide risk assessment continues to rely primarily on the clinical interview, mental status examination, and the identification of risk and protective factors. Inflammatory and biochemical biomarkers may enhance our understanding of pathophysiology and potentially complement risk stratification models, but they do not currently replace individualized clinical assessment.

Given this scenario, the present study aims to analyze the current evidence regarding systemic inflammation, biochemical changes, and biomarkers associated with the severity of depression, suicidal behavior, and therapeutic response, discussing their potential and limitations as complementary tools in the assessment of patients treated in psychiatric emergency settings.

2. Background

Major depression poses a significant challenge for psychiatric emergency services, especially when associated with suicidal ideation, suicide attempts, psychotic symptoms, severe functional impairment, or treatment resistance. In these scenarios, clinical evaluation remains essential for identifying immediate risk and determining the therapeutic course of action. However, the multifactorial nature of

depressive disorders and the heterogeneity of their clinical presentations have spurred research into biological markers that may contribute to a better understanding of severity, suicide risk, and response to treatment.

Among the most studied mechanisms, systemic inflammation has stood out due to its association with various manifestations of depressive disorder. Fatemian *et al.* (2024)^[3], in a systematic review and meta-analysis involving 3,652 participants, identified significantly higher levels of CRP in depressed patients with suicidal behavior compared to depressed patients without suicidal behavior.

These findings suggest that immuno-inflammatory changes may contribute to the identification of certain clinical phenotypes of greater severity. However, CRP and inflammatory cytokines have low specificity and can be influenced by obesity, infection, metabolic diseases, smoking, and other clinical conditions. Therefore, it is not yet possible to use them in isolation to determine suicide risk or guide interventions in emergency situations.

Biomarker research is also relevant in the context of treatment-resistant depression. Mancuso *et al.* (2023)^[9] identified elevated levels of IL-6, TNF- α , and CRP, as well as alterations in kynurenine metabolism, in various studies involving treatment-resistant depression.

Another aspect justifying this review is the growing interest in using inflammatory markers as potential predictors of treatment response. Gasparini *et al.* (2022)^[4] observed that higher baseline levels of CRP and IL-8 were associated with a poorer response to antidepressants, while more recent evidence has shown less consistent results.

This divergence among studies highlights the need for a critical analysis of the available evidence. Although some studies suggest possible associations between inflammation, severity, and therapeutic response, others show that the effects are small or inconsistent, suggesting that no single biomarker is likely sufficient to capture the biological complexity of depressive disorder.

In the context of psychiatric emergency care, the possibility of linking clinical parameters to objective markers is particularly appealing, as it could contribute in the future to risk stratification models and therapeutic monitoring. However, current data do not yet allow for the replacement of clinical evaluation with laboratory tests.

Given the high morbidity associated with severe depression, the impact of suicidal behavior, and the existing limitations in predicting individual therapeutic response, an updated review that integrates the evidence on systemic inflammation, biochemical changes, and biomarkers of severity and treatment response is warranted.

3. Objectives

3.1. General Objective

To analyze the current scientific evidence on the relationship between major depression, systemic inflammation, biochemical changes, and biomarkers associated with clinical severity, suicidal behavior, and treatment response, considering their potential as complementary tools in the assessment of patients in psychiatric emergency settings.

3.2. Specific Objectives

- To identify the main inflammatory markers associated with major depressive disorder and symptom severity;

- To analyze the relationship between C-reactive protein, IL-6, IL-1 β , TNF- α , and other inflammatory mediators with suicidal ideation and behavior;
- To investigate the role of hematological indices, including the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio, as potential markers of severity;
- To describe the main biochemical changes associated with severe depression, including alterations in the tryptophan-kinurenine pathway, oxidative stress, energy metabolism, and the hypothalamic-pituitary-adrenal axis;
- Evaluate the association between inflammatory biomarkers and treatment-resistant depression;
- Analyze the ability of inflammatory and biochemical markers to predict response or lack of response to antidepressant treatment;
- Investigate changes in biomarkers associated with therapeutic strategies used in severe or treatment-resistant depression, including antidepressants, ketamine, and electroconvulsive therapy;
- Analyze the evidence regarding the association between biological biomarkers and suicidal behavior in patients with depression;
- To discuss the limitations of available biomarkers in terms of sensitivity, specificity, and clinical applicability;
- Evaluate the potential of these markers as complementary tools for severity stratification and therapeutic monitoring in psychiatric emergency services;
- Identify the main scientific gaps and future prospects related to the use of biomarkers in precision psychiatry.

4. Methodology

4.1. Study Design

This study was conducted as a systematic literature review of a descriptive and analytical nature, with the objective of identifying, compiling, and analyzing current scientific evidence related to systemic inflammation, biochemical changes, and biomarkers associated with severity, suicidal behavior, and therapeutic response in patients with depression, with an emphasis on psychiatric emergency situations.

The review was conducted in accordance with the recommendations of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA 2020), adopting predefined criteria for the identification, screening, eligibility, inclusion, and presentation of the selected studies (PAGE *et al.*, 2021)^[13].

4.2. Guiding Question and PICO Strategy

The review's guiding question was structured based on the PICO strategy, considering the following:

P – Population: adults with major depressive disorder, particularly those with severe depression, suicidal behavior, treatment resistance, or a need for care in a psychiatric emergency setting;

I – Intervention/Exposure: assessment of inflammatory, hematological, metabolic, neuroendocrine, and biochemical biomarkers;

C – Comparison: patients with less severe depression, patients without suicidal behavior, treatment responders versus non-responders, or healthy control subjects;

O – Outcomes: severity of depressive symptoms, suicidal ideation, suicide attempts, suicidal behavior, treatment resistance, response to treatment, and potential clinical applications of the biomarkers.

Based on this framework, we sought to answer the following question: Which inflammatory, hematological, metabolic, neuroendocrine, and biochemical biomarkers are associated with the severity of depression, suicidal behavior, treatment resistance, and response to different treatments?

4.3. Databases and Search Period

The literature search was conducted in the PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, Virtual Health Library (BVS), and SciELO databases.

Articles published between January 2021 and September 2026 were included, with the aim of incorporating the most recent scientific evidence on biomarkers associated with depression, suicidality, treatment resistance, and response to treatment.

4.4. Search Terms and Strategy

Controlled subject headings from *Medical Subject Headings* (MeSH) and the Health Sciences Descriptors (DeCS) were used, in addition to free-text terms related to the review's topic.

The main subject headings and terms used were: “Depressive Disorder, Major,” “Depression,” “Psychiatric Emergency Services,” “Suicidal Ideation,” “Suicide Attempted,” “Inflammation,” “C-Reactive Protein,” “Interleukin-6,” “Tumor Necrosis Factor-alpha,” “Interleukin-1beta,” “Neutrophil-to-Lymphocyte Ratio,” “Platelet-to-Lymphocyte Ratio,” “Monocyte-to-Lymphocyte Ratio,” “Kynurenine,” “Tryptophan,” “Oxidative Stress,” “Biomarkers,” “Treatment-Resistant Depression,” and “Treatment Response.”

The search terms were combined using the Boolean operators AND and OR, adapting the search strategy to the specific characteristics of each database consulted.

As a general strategy, the following combination was used: (“Major Depressive Disorder” OR “Depression”) AND (“Inflammation” OR “C-Reactive Protein” OR “Interleukin-6” OR “TNF-alpha” OR “Neutrophil-to-Lymphocyte Ratio” OR “Kynurenine” OR “Biomarkers”) AND (“Suicidal Ideation” OR “Suicide Attempt” OR “Severity” OR “Treatment-Resistant Depression” OR “Treatment Response” OR “Psychiatric Emergency”).

4.5. Inclusion Criteria

Studies that met the following criteria were included:

- published between January 2021 and September 2026;
- availability of the full text;
- publication in Portuguese, English, or Spanish;
- studies involving adults diagnosed with major depressive disorder or clinically significant depressive episodes;
- clinical trials, cohort studies, case-control studies, cross-sectional studies, systematic reviews, and meta-analyses;
- studies that investigated inflammatory, hematological, metabolic, neuroendocrine, or biochemical biomarkers;

- studies that assessed the relationship between these biomarkers and the severity of depression, suicidal behavior, treatment resistance, or response to treatment.

4.6. Exclusion Criteria

The following were excluded:

- isolated case reports;
- letters to the editor, editorials, and expert opinions;
- studies that were exclusively experimental or conducted in animal models;
- studies involving exclusively pediatric populations;
- studies without a clearly defined diagnosis of depression;
- studies that did not evaluate the association between biomarkers and the severity of depression, suicidal behavior, treatment resistance, or response to treatment;
- duplicate publications or those with redundant data.

4.7. Study Selection

Study selection was conducted in consecutive stages, in accordance with the PRISMA 2020 guidelines.

Initially, records obtained from various databases were identified. Subsequently, duplicates were removed. In the next step, titles and abstracts were analyzed according to the previously established inclusion and exclusion criteria.

Studies considered potentially eligible were reviewed in full. After this stage, the studies that met the review's methodological and thematic criteria were included in the final synthesis.

The selection process was organized according to the stages of identification, screening, eligibility, and inclusion established by PRISMA 2020. The numbers corresponding to the initially identified records, removed duplicates, studies excluded after reviewing titles and abstracts, articles evaluated in full text, and studies included in the final analysis were presented in the PRISMA flowchart.

4.8. Data Extraction

For each included study, the following information was extracted:

- author and year of publication;
- country where the study was conducted;
- methodological design;
- sample size;
- clinical characteristics of the population;
- biomarkers investigated;
- laboratory methods used;
- presence of suicidal ideation or behavior;
- severity of depressive symptoms;
- presence of treatment resistance;
- treatment used;
- therapeutic response;
- main results and conclusions.

The extracted data were organized into comparative tables, allowing for a joint analysis of the included studies.

4.9. Organization and Analysis of Results

The results were subjected to a narrative synthesis and organized according to the main thematic areas identified in the literature.

The analysis was structured around the following topics:

- systemic inflammation and severity of depression;
- inflammatory biomarkers and suicidal behavior;

- c. biochemical and metabolic changes related to depression;
- d. biomarkers associated with treatment-resistant depression;
- e. biomarkers related to response to antidepressants;
- f. biomarkers related to the response to ketamine and esketamine;
- g. biomarkers associated with response to electroconvulsive therapy;
- h. possible clinical applications of biomarkers in the context of psychiatric emergencies.

The interpretation of the findings took into account the consistency across studies, the characteristics of the populations analyzed, the laboratory methods used, and the magnitude of the observed associations.

4.10. Assessment of Methodological Quality

The methodological quality of the included studies was assessed according to the design of each study.

Priority was given to the critical instruments of the *Joanna Briggs Institute* (JBI), using specific tools for cross-sectional studies, case-control studies, cohort studies, clinical trials, and systematic reviews, where applicable.

The assessment considered aspects related to sample selection, diagnostic criteria, measurement of exposures and outcomes, control of confounding factors, appropriateness of statistical analysis, and methodological consistency of the studies.

4.11. Ethical Considerations

Since this is a systematic review based exclusively on previously published data available in the scientific literature, without direct human participation, clinical intervention, or access to individualized information, there was no need to submit it to the Research Ethics Committee.

5. Results

The analyzed studies demonstrated a consistent association between major depressive disorder and alterations in various biological systems, particularly in inflammatory, hematological, metabolic, and oxidative pathways. The findings were more pronounced in patients with severe symptoms, suicidal behavior, treatment-resistant depression, and a poorer response to conventional therapies. However, the magnitude of the alterations varied according to the biomarker studied, the population evaluated, the laboratory methods used, and the presence of clinical factors capable of influencing the results.

5.1. Systemic Inflammation and Severity of Depression

Peripheral inflammatory markers were among the most extensively studied biomarkers. C-reactive protein, IL-6, TNF- α , and IL-1 β were frequently analyzed in patients with major depressive disorder, with a tendency toward higher inflammatory activity observed in certain clinical subgroups. Inflammatory changes proved particularly relevant in cases of treatment-resistant depression.

Table 1: Key findings on systemic inflammation and depression

Author/year	Study type	Markers evaluated	Key findings
Mancuso <i>et al.</i> (2023) ^[9]	Review	CRP, IL-6, TNF- α , kynurenine pathway	Increased inflammatory activity in certain patients with treatment-resistant depression.
Kuring <i>et al.</i> (2023) ^[8]	Systematic review/meta-analysis	Cytokines and peripheral markers	Role of immuno-inflammatory mechanisms in the biological heterogeneity of depression.
Hummad <i>et al.</i> (2026) ^[5]	Meta-analysis; 17 studies, 1,535 participants	CRP and others	Elevated baseline inflammation associated with a higher likelihood of nonresponse to antidepressants.
Baxter <i>et al.</i> (2026) ^[11]	Umbrella review	CRP, IL-6, IL-8, TNF- α	Small and inconsistent effects for treatment prediction.

Source: Authors

5.2. Inflammatory Biomarkers and Suicidal Behavior

The relationship between inflammation and suicidality was one of the findings of greatest clinical relevance. Fatemian *et al.* (2024)^[3] demonstrated that depressed patients with suicidal behavior had significantly higher CRP concentrations than

depressed patients without suicidal behavior. Kim *et al.* (2023)^[7] identified multiple inflammatory biomarkers potentially associated with suicide-related behavior, while Moshfeghinia *et al.* (2025)^[12] observed more consistent results for IL-6 in certain comparisons.

Table 2: Key studies on inflammatory biomarkers and suicidal behavior

Author/year	Sample/design	Biomarkers	Key findings
Kim <i>et al.</i> (2023) ^[7]	Systematic review	IL-1 β , IL-6, CRP, CCL2, TNF- α	Multiple inflammatory changes associated with suicidal behavior.
Fatemian <i>et al.</i> (2024) ^[3]	Meta-analysis; 15 studies, 3,652 participants	CRP	Significantly higher CRP levels in depressed patients with suicidal behavior.
Moshfeghinia <i>et al.</i> (2025) ^[12]	Meta-analysis	IL-6, TNF- α , IL-10, and other cytokines	Higher IL-6 levels in some comparisons; other results were heterogeneous.
Zhou <i>et al.</i> (2025) ^[16]	Meta-analysis; 37 studies, 88,019 participants	NLR	Elevated NLR associated with depression and an increased risk of suicide.

Source: Authors

5.3. Hematological Indices: NLR, MLR, and PLR

Hematological indices derived from complete blood counts have emerged as particularly interesting markers due to their low cost, wide availability, and rapid acquisition. The

neutrophil-to-lymphocyte ratio was the most studied hematological marker. The monocyte-to-lymphocyte and platelet-to-lymphocyte ratios were also investigated, in addition to composite inflammatory indices.

Table 3: Hematological parameters associated with depression and suicidality

Biomarker	Main evidence	Observed association	Limitation
NLR	Meta-analysis of 37 studies/88,019 participants	Higher in patients with depression and associated with an increased risk of suicide	No universal cutoff point
MLR	Observational studies	Elevated levels reported in some patients with severe, or suicidal tendencies	Heterogeneous evidence
PLR	Observational studies	Changes in depressive subgroups	Low specificity
Composite indices	Emerging studies	Potential combination of blood count components	Lack of prospective validation

Source: Authors

5.4. Tryptophan-Kynurenine Pathway and Metabolic Alterations

The tryptophan-kinurenine pathway has been shown to be one of the metabolic alterations most consistently associated with depressive disorder. Studies have demonstrated reduced

tryptophan levels and alterations in kinurenine, kinurenic acid, and metabolic ratios related to the pathway, especially during active depressive episodes. Metabolomic analyses have also identified alterations in amino acids and metabolites involved in energy production.

Table 4: Major metabolic and kynurenine pathway alterations

Study	Sample	Main changes	Interpretation
Meta-analysis of the KYN pathway (2023)	51 studies; 7,056 participants	Decreased levels of tryptophan, KYN, KYNA, and neuroprotective ratios; increased KYN/TRP	Changes in the pathway during a depressive episode
Meta-analysis of major affective disorders (2022)	35 studies; 4,647 participants	Decrease in tryptophan and the TRP/competitive amino acids ratio	More pronounced changes in severe cases
Wang <i>et al.</i> (2024) ^[15]	Metabolomic review	Changes in tryptophan, tyrosine, phenylalanine, pyruvate, and KYNA	Involvement of multiple metabolic pathways

Source: Authors

5.5. Oxidative Stress and Biochemical Alterations

Studies have also identified an imbalance between the production of reactive oxygen species and antioxidant mechanisms in patients with depression. Changes in antioxidant enzymes, a reduction in non-enzymatic

antioxidants, and an increase in products of oxidative damage have been described, reinforcing the role of oxidative stress as a relevant component of the pathophysiology of depression.

Table 5: Main biomarkers related to oxidative stress

Class	Biomarkers	Described Change	Potential significance
Antioxidant enzymes	SOD, GPx	Changes in activity	Reduced antioxidant capacity
Non-enzymatic antioxidants	Uric acid	Reduction observed in various studies	Reduced defense against reactive oxygen species
Lipid peroxidation	Malondialdehyde	Increase	Increased lipid oxidative damage
Protein damage	Protein carbonyls	Increase	Protein oxidation
DNA damage	8-OHdG	Increase	Oxidative stress on genetic material

Source: Authors

5.6. Biomarkers and Response to Antidepressants

The association between inflammation and pharmacological response has yielded conflicting results. Hummad *et al.* (2026)^[5] observed a higher likelihood of non-response

among individuals with elevated baseline inflammation, while broader reviews demonstrated that no single biomarker consistently predicted response across all studies.

Table 6: Inflammatory biomarkers and response to antidepressants

Author/Year	Studies/sample	Marker	Result
Hummad <i>et al.</i> (2026) ^[5]	17 studies; 1,535 patients	PCR and Inflammatory Markers	Elevated inflammation is associated with a higher risk of nonresponse
Gasparini <i>et al.</i> (2022) ^[4]	Systematic review/meta-analysis	CRP, IL-8, and others	Associations between higher baseline inflammation and a weaker response in some of the studies
Baxter <i>et al.</i> (2026) ^[1]	Umbrella review	CRP, IL-8, TNF- α , and others	Small and inconsistent effects; no support for routine clinical use

Source: Authors

5.7. Biomarkers and Electroconvulsive Therapy

Electroconvulsive therapy was one of the interventions for severe depression with the largest body of data related to inflammation. Dellink *et al.* (2025) ^[2] observed that higher baseline levels of CRP and IL-6 were associated with a

greater reduction in depressive symptoms following electroconvulsive therapy. Subsequent reviews, however, highlighted the absence of a sufficiently robust marker for individual prediction.

Table 7: Inflammation and Response to Electroconvulsive Therapy

Author/Year	Sample	Findings	Interpretation
Dellink <i>et al.</i> (2025) ^[2]	14 studies; 556 patients	Higher baseline levels of CRP and IL-6 were associated with a greater reduction in symptoms	Possible prognostic value
Marcolin <i>et al.</i> (2026) ^[10]	Systematic review	IL-6, TNF- α , CRP, and other cytokines	Inconsistent results; no validated marker
Karimi <i>et al.</i> (2026) ^[6]	Systematic review	IL-10, IL-6, TNF- α , CRP	Preliminary associations with cognitive outcomes

Source: Authors

5.8. Biomarkers and response to ketamine/esketamine

Ketamine and esketamine have also been investigated from the perspective of inflammatory and molecular biomarkers. Reviews have demonstrated potential anti-inflammatory

effects and changes in genes related to glutamatergic signaling, inflammation, and neuroplasticity; however, no validated peripheral biomarker for clinical application has been identified.

Table 8: Biomarkers Related to Ketamine and Esketamine

Author/Year	Type of evidence	Key findings
Meshkat <i>et al.</i> (2023) ^[11]	Umbrella review; 108 studies, 4,912 participants	Potential anti-inflammatory effect, but no validated biomarker for clinical use
Pisanu <i>et al.</i> (2025) ^[14]	Systematic review	Changes in genes related to inflammation, glutamate, and neuroplasticity; absence of a consistent peripheral signature

Source: Authors

5.9. Applicability of Biomarkers in Psychiatric Emergency Care

A pooled analysis of the studies demonstrated that some biomarkers show significant associations with severity, suicidal behavior, and therapeutic response. CRP, IL-6, NLR,

and markers of the kynurenine pathway were those with the greatest body of supportive evidence. However, none of these measures demonstrated sufficient sensitivity and specificity to be used alone in clinical decision-making in emergency departments.

Table 9: Potential clinical applicability of the main biomarkers

Biomarker	Possible association	Current applicability
CRP	Suicidal risk, systemic inflammation, treatment resistance	Complementary marker; low specificity
IL-6	Severity, suicidality, and response to ECT	Investigational
TNF- α	Therapeutic resistance and response to treatment	Investigational
NLR	Depression and increased risk of suicide	Potential accessible biomarker; no validated cutoff point
Tryptophan/KYN/KYNA	Disease severity and status	Investigational
Oxidative markers	Severity and biological changes in depression	No standardized clinical application
Multimarker profile	Phenotype stratification	Promising strategy for future research

Source: Authors

5.10. Summary of The Main Results

The summary of the results demonstrated that major depression is associated with immunoinflammatory, metabolic, and oxidative changes, although these changes do not occur uniformly in all patients.

Suicidal behavior was primarily associated with elevated levels of CRP, IL-6, and NLR; however, the heterogeneity of the studies and the low specificity of these markers preclude their use alone for risk stratification.

The tryptophan-kinurenine pathway showed consistent alterations during active depressive episodes, with reduced tryptophan levels and changes in kinurenine-related metabolites.

Inflammatory biomarkers have shown variable associations with response to antidepressants, ketamine, and electroconvulsive therapy. Although certain profiles may contribute to precision psychiatry strategies in the future, the available studies do not yet support their use alone for individual therapeutic decision-making.

6. Discussion

The results of this review reinforce that major depression—especially in severe, treatment-resistant, or suicide-related cases—should not be understood solely in terms of monoaminergic alterations. The body of evidence points to the simultaneous involvement of immunoinflammatory, metabolic, oxidative, and neuroendocrine mechanisms, even though these alterations do not manifest uniformly in all patients. Kuring *et al.* (2023) ^[8] highlighted the presence of inflammatory changes in individuals with clinically significant depression, while Mancuso *et al.* (2023) ^[9] demonstrated that peripheral markers such as CRP, IL-6, and TNF- α are frequently elevated in studies involving treatment-resistant depression. These findings support the hypothesis that certain subgroups of patients with depression exhibit a more pronounced inflammatory phenotype, which may be relevant for prognosis and future therapeutic strategies. C-reactive protein showed one of the most consistent associations among the markers evaluated, especially in

relation to suicidal behavior. Fatemian *et al.* (2024) ^[3] identified significantly higher CRP levels in depressed patients with suicidal behavior compared to depressed patients without this outcome. This result is clinically relevant because CRP is widely available, low-cost, and routinely used in emergency departments. However, its low specificity prevents it from being interpreted as an independent marker of suicide risk, since obesity, infections, smoking, cardiovascular diseases, and other inflammatory conditions can elevate its levels. Thus, the value of CRP seems to lie more in its inclusion in clinical-biological models than in its use in isolation.

Pro-inflammatory cytokines, especially IL-6, TNF- α , and IL-1 β , have also been shown to be associated with severity and suicidality, although with greater heterogeneity across studies. Kim *et al.* (2023) ^[7] identified multiple mediators potentially associated with suicidal behavior, while Moshfeghinia *et al.* (2025) ^[12] observed more consistent results for IL-6 in certain comparisons. The discrepancy among studies may stem from differences in the timing of blood collection, clinical severity, concomitant medication use, the presence of comorbidities, and laboratory methods. This makes it difficult to define universal cutoff points and underscores the need for standardized protocols for future investigations.

Hematological indices derived from the complete blood count, particularly the neutrophil-to-lymphocyte ratio (NLR), are of interest due to their ease of measurement and low cost. Zhou *et al.* (2025) ^[16] demonstrated an association between an elevated NLR, the presence of depressive disorders, and an increased risk of suicide. In the emergency setting, this type of marker has an operational advantage over cytokines that require more complex laboratory analysis. However, its interpretation is also limited by nonspecific factors, such as acute infections, corticosteroid use, autoimmune diseases, physiological stress, and hematological abnormalities. Therefore, although the NLR shows promise as a complementary component of stratification, current evidence does not support its use as an independent diagnostic or prognostic tool.

Alterations in the tryptophan-kinurenine pathway expand our understanding of the interface between inflammation, metabolism, and neurotransmission. Inflammatory activation may promote the diversion of tryptophan toward the formation of kinurenine and neuroactive metabolites, reducing substrate availability for serotonin synthesis and interfering with glutamatergic circuits. Wang *et al.* (2024) ^[15] also described metabolomic alterations involving amino acids and energy pathways, suggesting that major depression involves broader biochemical networks. These findings help explain why patients with similar clinical manifestations may exhibit distinct therapeutic trajectories, although it remains necessary to establish which alterations have individual prognostic value.

In the field of response to antidepressants, the results were less consistent. Gasparini *et al.* (2022) ^[4] observed associations between higher baseline inflammatory activity and a poorer therapeutic response in some studies, while Hummad *et al.* (2026) ^[5] identified a higher likelihood of non-response in patients with elevated baseline inflammation. In contrast, Baxter *et al.* (2026) ^[1], in an umbrella review, emphasized that the effects of individual inflammatory biomarkers remain small and inconsistent. This divergence suggests that the inflammatory state may influence the

response in specific subgroups but is not sufficiently predictive to guide the choice of antidepressant on its own. Electroconvulsive therapy (ECT) yielded particularly interesting results. Dellink *et al.* (2025) ^[2] found an association between higher baseline levels of CRP and IL-6 and a greater reduction in symptoms after treatment, suggesting that an elevated inflammatory profile could, under certain circumstances, be related to a better response to ECT. On the other hand, Marcolin *et al.* (2026) ^[10] and Karimi *et al.* (2026) ^[6] highlighted significant inconsistencies and the absence of a validated marker for individual application. These results demonstrate that the same inflammatory change can take on different meanings depending on the treatment analyzed, the stage of the disease, and the patient's clinical characteristics.

For ketamine and esketamine, recent literature also points to effects on inflammatory pathways, gene expression, and neuroplasticity mechanisms. Meshkat *et al.* (2023) ^[11] identified possible associations between biomarkers and the antidepressant effect of ketamine, while Pisanu *et al.* (2025) ^[14] demonstrated changes in RNA expression related to inflammation, glutamatergic neurotransmission, and neuronal plasticity. Despite the mechanistic relevance, there is still no sufficiently stable peripheral signature to predict clinical response. The complexity of these treatments reinforces the hypothesis that multimarker models—combining clinical, laboratory, and possibly genomic data—are more promising than the search for a single universal marker.

The applicability of biomarkers in psychiatric emergencies requires additional caution. Suicide risk assessment should remain centered on the clinical interview, mental status examination, and evaluation of intent, planning, available means, previous attempts, impulsivity, hopelessness, psychotic symptoms, substance use, and protective factors. Biomarkers may, in the future, contribute to refining risk stratification, but their current use should be interpreted only as complementary. None of the evidence reviewed supports the use of CRP, IL-6, NLR, or any other marker to replace clinical assessment or to determine, on its own, hospitalization, discharge, or therapeutic intervention.

Another relevant aspect is the methodological heterogeneity of the included studies. Differences in diagnostic criteria, study populations, concomitant treatments, clinical comorbidities, sample collection times, laboratory techniques, and definitions of therapeutic response reduce the comparability of the results. Furthermore, much of the evidence stems from observational studies, systematic reviews, and meta-analyses of studies with relatively small sample sizes. This limitation may favor statistically significant associations that do not always translate into actual clinical utility.

A synthesis of the results suggests that the main future direction lies not in the search for a single biomarker, but in the development of multi-marker panels linked to clinical and sociodemographic variables. Profiles combining CRP, cytokines, hematological indices, kynurenine pathway metabolites, oxidative markers, and clinical information may offer greater discriminatory power. This approach is consistent with the principles of precision psychiatry; however, it requires prospective, multicenter validation in diverse populations before it can be incorporated into routine clinical care.

Thus, the findings of this review support the biological relevance of inflammation and biochemical changes in major depression, but they also demonstrate the gap between scientific association and clinical application. The biomarkers analyzed should be understood as tools still under development, useful for deepening our understanding of pathophysiology, identifying subphenotypes, and guiding future research, but still insufficient to replace the clinical pillars of psychiatric assessment and decision-making in emergency situations.

7. Conclusion

The evidence reviewed demonstrates that major depression is associated with complex biological changes involving inflammatory, hematological, metabolic, oxidative, and neuroendocrine mechanisms. Among the most extensively studied biomarkers are C-reactive protein, IL-6, TNF- α , the neutrophil-to-lymphocyte ratio, and metabolites related to the tryptophan-kinurenine pathway, although the magnitude and consistency of these changes vary among different patient subgroups.

The association between systemic inflammation and suicidal behavior is one of the most significant findings. Depressed patients with suicidal behavior have shown, in various studies, increased inflammatory activity, particularly elevated C-reactive protein and, in certain analyses, elevated IL-6 and neutrophil-to-lymphocyte ratio. However, the low specificity of these markers, the influence of comorbid conditions, and the heterogeneity of the studies preclude their use alone to determine suicide risk.

The alterations observed in the tryptophan-kinurenine pathway reinforce the existence of an interaction between the immune system, metabolism, and neurotransmission in the pathophysiology of depression. Reduced tryptophan levels, changes in kinurenine metabolites, and alterations in pathways related to energy production and oxidative stress appear to occur more frequently during active depressive episodes and in more severe clinical presentations.

In the context of therapeutic response, the results remain heterogeneous. Elevated levels of inflammatory markers have been associated with a poorer response to antidepressants in some studies, while other analyses have failed to identify biomarkers capable of consistently distinguishing responders from non-responders. These results indicate that individual markers have limited predictive power and that models involving multiple clinical and biological parameters may be more suitable for future precision medicine strategies.

Regarding electroconvulsive therapy, elevated baseline levels of CRP and IL-6 were associated with greater symptom reduction in some studies; however, these associations are not yet sufficiently consistent for individual application in therapeutic decision-making. Similarly, studies involving ketamine and esketamine have demonstrated changes in inflammatory, glutamatergic, and neuroplasticity-related pathways; however, a sufficiently validated biological signature to predict treatment response has not yet been established.

The use of parameters derived from complete blood counts, particularly the neutrophil-to-lymphocyte ratio, is of additional interest due to their ease of acquisition, low cost,

and availability in emergency departments. However, the absence of specific cutoff points and the influence of various clinical conditions have, to date, limited their use as an independent tool for stratifying severity or suicide risk.

In the context of psychiatric emergencies, therefore, biomarkers should be interpreted as potential complementary tools. The identification of suicidal ideation, planning, previous attempts, hopelessness, impulsivity, psychotic symptoms, substance use, behavioral changes, and availability of means remains fundamental for the immediate assessment of patients with severe depression.

It is concluded that systemic inflammation, biochemical changes, and various biomarkers are related to relevant aspects of depression, including severity, suicidality, and therapeutic response. However, no single laboratory measure currently performs well enough to replace clinical assessment or independently determine the course of action in psychiatric emergencies. Prospective, multicenter, and standardized studies involving large samples and a multi-biomarker approach are needed to establish cut-off points, assess prognostic value, and determine whether these changes can be safely and effectively incorporated into clinical practice and precision psychiatry.

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