Review

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Posted Date: 15 May 2026

doi: 10.20944/preprints202605.1077.v1

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 doi:10.20944/preprints202605.1077.v1

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Peripheral Inflammatory Biomarkers in First-Episode, Drug-Naïve Major Depressive Disorder: A Systematic Review

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Abstract

Major depressive disorder (MDD) is clinically heterogeneous, and peripheral inflammatory biomarkers may help clarify early biological mechanisms before illness chronicity or pharmacologic treatment confound interpretation. This systematic review synthesized evidence on peripheral inflammatory biomarkers in first-episode, drug-naïve major depressive disorder (FEDN-MDD) compared with healthy controls and examined associations with clinical severity. Following PRISMA 2020, searches of PubMed/MEDLINE, Embase, PsycINFO, and Scopus from inception to March 19, 2026 identified 313 records; after screening, 16 publications were included in qualitative synthesis. Studies varied in age group, biological matrix, assay platform, and statistical reporting, precluding meta-analysis. The most frequently assessed biomarkers were IL-1β, TNF-α, IL-6, and CRP/hs-CRP. IL-6 showed the clearest recurrent tendency toward elevation in FEDN-MDD, whereas CRP/hs-CRP findings were partially positive but methodologically limited. TNF-α and IL-1β findings were mixed, and clinical correlations with depressive severity were sparse and inconsistent. Overall, the evidence supports heterogeneous early immune dysregulation in a subset of patients with FEDN-MDD rather than a single reproducible inflammatory signature. Peripheral inflammatory biomarkers should currently be considered research tools for biological stratification and mechanistic hypothesis generation, pending larger standardized longitudinal studies.

Keywords: major depressive disorder; first-episode depression; drug-naïve patients; peripheral inflammation; inflammatory biomarkers; interleukin-6; C-reactive protein; cytokines; systematic review

1. Introduction

Major depressive disorder (MDD) remains one of the leading causes of disability worldwide, yet its diagnosis continues to rely primarily on clinical symptoms rather than validated biological measures that could improve prognosis, stratification, or treatment selection. This limitation is particularly relevant for a condition as prevalent, heterogeneous, and clinically consequential as MDD. Accordingly, increasing attention has been directed toward identifying measurable biological signals that may reflect clinically meaningful disease mechanisms [1,2].

Among the candidate systems implicated in MDD, immune and inflammatory pathways have drawn sustained attention. Over the past two decades, peripheral inflammatory biomarkers—including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and

 doi:10.20944/preprints202605.1077.v1

interleukin-1β (IL-1β)—have been repeatedly associated with depressive states, lending support to the broader inflammatory hypothesis of depression [3–5].

Importantly, the field has moved beyond the question of simple cross-sectional association. Longitudinal studies suggest that inflammatory dysregulation may precede at least some later depressive outcomes, particularly for IL-6, while more recent meta-analytic and symptom-level work indicates that inflammation may be linked more closely to specific depressive phenotypes—such as fatigue, sleep and appetite disturbance, and anhedonia—than to depression as a unitary construct [6–9].

These findings have strengthened the biological plausibility of inflammatory models of depression, while also underscoring the likelihood that inflammation is relevant to some patients and some symptom dimensions more than others. Yet a central limitation of this literature is clinical heterogeneity. Much of the biomarker evidence has been derived from mixed samples that combine first and recurrent episodes, variable illness duration, prior antidepressant exposure, and medical or psychiatric comorbidity.

Each of these factors may influence inflammatory signaling independently of early depressive pathophysiology. As a result, the biological signal present near illness onset may be diluted by chronicity, treatment effects, and accumulated disease burden. The more precise question, therefore, is not simply whether inflammation is associated with MDD in general, but whether peripheral immune alterations are already detectable at the first clinically identifiable stage of the disorder [4,5,7].

First-episode, drug-naïve major depressive disorder (FEDN-MDD) offers a particularly informative model in which to address that question. By focusing on patients close to illness onset and before pharmacologic exposure, studies of FEDN-MDD may provide a clearer view of inflammatory alterations that are more closely related to early disease expression rather than to its downstream consequences. In this setting, peripheral biomarkers are especially appealing because they are accessible, clinically scalable, and biologically plausible as translational tools for early stratification and mechanistic subtyping. At the same time, the FEDN-MDD literature remains fragmented, with substantial variation in diagnostic definitions, sample composition, biological matrices, laboratory platforms, and biomarker panels, limiting direct comparison across studies [4,5,7,9].

Accordingly, a focused synthesis of this evidence is needed. The present systematic review aimed to identify, evaluate, and synthesize the available literature on peripheral inflammatory biomarkers in first-episode MDD, with particular attention to drug-naïve patients, cross-study biomarker patterns, clinical correlates, methodological quality, and the extent to which these markers may reflect biologically meaningful processes relevant to early depressive illness.

2. Materials and Methods

2.1. Study Design and Reporting Standards

This systematic review was designed to identify, appraise, and synthesize evidence on peripheral inflammatory biomarkers in FEDN-MDD. The review was conducted in accordance with the PRISMA 2020 statement.

2.2. Protocol Registration

The review protocol was registered in an international database of systematic reviews PROSPERO prior to study selection with the next ID: CRD420261347590. Any deviations from the registered protocol will be transparently reported and justified in the final manuscript.

 doi:10.20944/preprints202605.1077.v1

2.3. Research Question

This review is guided by the following research question: which peripheral inflammatory biomarkers differ between patients with first-episode, drug-naïve major depressive disorder and healthy controls, and how are these biomarkers associated with clinical severity and early-stage illness characteristics? This question is structured according to the PECO framework. The population of interest consists of individuals diagnosed with first-episode, drug-naïve major depressive disorder. The exposure examined is the presence and levels of peripheral inflammatory biomarkers, while the comparator group is composed of healthy control subjects. The outcomes of interest include between-group differences in biomarker levels, as well as the associations between these biomarkers and relevant clinical variables.

2.4. Eligibility Criteria

Studies will be considered eligible for inclusion if they are original peer-reviewed research articles published in English and include participants who met standardized diagnostic criteria for major depressive disorder. The depressive sample must be explicitly described as first-episode and drug-naïve or medication-naïve at the time of biomarker assessment. Eligible studies must also include a healthy control group and report quantitative data on peripheral inflammatory biomarkers, measured in blood-derived or other peripheral biological matrices, such as serum, plasma, saliva, or peripheral blood-derived material. In addition, baseline data must be available for extraction.

Studies will be excluded if they include recurrent, chronic, previously treated, or mixed samples of major depressive disorder without separately extractable data for first-episode, drug-naïve MDD. Studies without a healthy control group, those that do not report extractable quantitative biomarker data, or those focused exclusively on central biomarkers, such as cerebrospinal fluid, without peripheral measurements will also be excluded. In addition, studies including major psychiatric or severe medical comorbidities likely to compromise the interpretation of inflammatory markers will be excluded unless these factors are clearly controlled for and separately analyzable. Reviews, meta-analyses, editorials, letters, case reports, and conference abstracts without full extractable data will not be considered eligible.

Importantly, the review will not assume that terms such as untreated, unmedicated, first diagnosis, or washout are automatically equivalent to drug-naïve or first-episode status unless this is clearly supported by the full study report.

2.5. Information Sources and Search Strategy

A systematic search was conducted in PubMed/MEDLINE, Embase, PsycINFO, and Scopus. The search covered records from database inception to March 19, 2026, and combined controlled vocabulary with free-text terms related to major depressive disorder, first-episode status, drug-naïve or medication-naïve samples, inflammation, cytokines, and biomarkers. The full database-specific search strategies will be reported in Supplementary Appendix Table S1. In addition, the reference lists of included studies and relevant reviews were screened to identify any further eligible records.

2.6. Study Selection

All records were imported into a reference management and screening platform, and duplicates were removed before screening. Study selection was then performed in two stages: first, title and abstract screening, followed by full-text review.

Eligibility was assessed according to the predefined criteria for first-episode, drug-naïve major depressive disorder. Particular attention was given to explicit confirmation of first-episode status, drug-naïve or medication-naïve status at the time of biomarker assessment, measurement of peripheral biomarkers, and the inclusion of a healthy control group.

 doi:10.20944/preprints202605.1077.v1

2.7. Data Extraction

Data were extracted using a standardized form. The following items were collected:

- Study characteristics: authors, year, country, and study design
- Sample characteristics: sample size, age, and sex distribution
- Diagnostic criteria
- Operational definition of first-episode status
- Treatment status at baseline
- Biological matrix: serum, plasma, saliva, whole blood, or other peripheral material
- Inflammatory biomarkers assessed
- Laboratory methods
- Main biomarker findings
- Clinical severity measures
- Correlations between biomarkers and clinical variables
- Methodological notes relevant to interpretation

When values were missing, they were recorded as "Not reported". Original reporting formats were preserved. Medians were not converted to means, SEM values were not converted to SD, and original units were retained. Any important differences in unit format, data presentation, or transformation were documented in extraction notes.

2.8. Handling of Overlapping Publications

When multiple eligible publications appeared to arise from the same or partially overlapping cohort, all such publications were retained if they contributed distinct biomarker or analytic information relevant to the review question. However, these reports were not treated as fully independent samples when interpreting cumulative participant totals or the overall weight of evidence. Explicit cohort reuse was documented when stated in the article, and probable overlap was flagged when strongly suggested by recruitment setting, time frame, authorship, and sample characteristics.

2.9. Risk of Bias Assessment

The methodological quality and risk of bias of included studies was independently assessed by two reviewers using appropriate validated tools such as Joanna Briggs Institute (JBI) checklists depending on study design.

2.10. Data Synthesis

A formal meta-analysis was not performed because the included studies showed substantial heterogeneity in biological matrices, assay methods, biomarker units, statistical reporting formats, age composition, and potential cohort overlap. Instead, the direction of reported between-group findings was summarized descriptively at the publication level for biomarkers assessed in multiple studies. Biomarkers most frequently assessed across studies were summarized narratively, with particular attention to CRP, IL-6, TNF-α, and IL-1β as recurrent core inflammatory markers. Additional peripheral biomarkers were retained and described as secondary or exploratory findings when relevant. Findings were synthesized only within the FEDN-MDD framework and were not generalized to major depressive disorder more broadly.

2.11. Generative AI Use for Figure Preparation

During the preparation of this manuscript, the authors used Google Gemini 3 Flash Image, internally referred to as Nano Banana 2, for the purpose of generating the initial visual draft of the mechanistic hypothesis figure (Figure 4). The figure was used only as a graphical representation of the hypothesis-generating mechanistic model described in the Discussion. The authors reviewed,

 doi:10.20944/preprints202605.1077.v1

edited, and critically assessed the generated output and take full responsibility for the content of this publication.

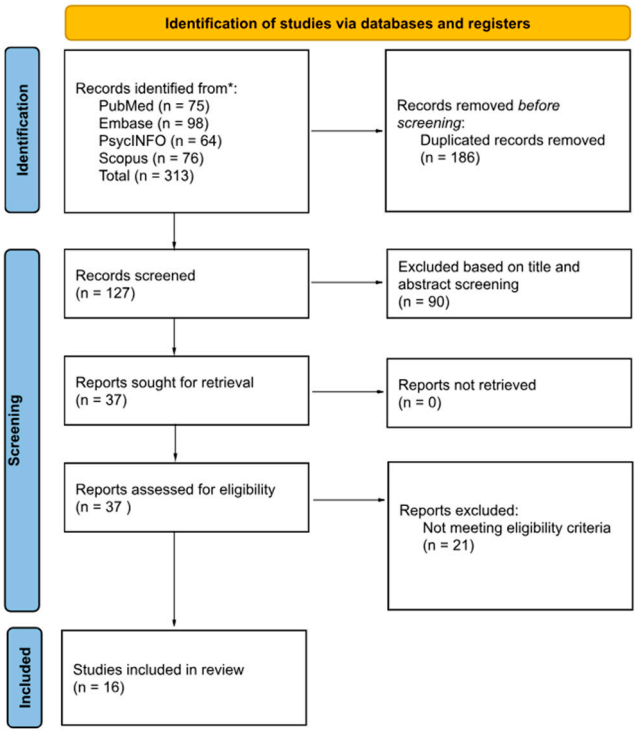

Figure 1. PRISMA-flow diagram for the studies included in this review.

Figure 2. Risk of bias assessment of cross-sectional/case-control studies using the JBI Analytical Cross-Sectional Studies Checklist.

 doi:10.20944/preprints202605.1077.v1

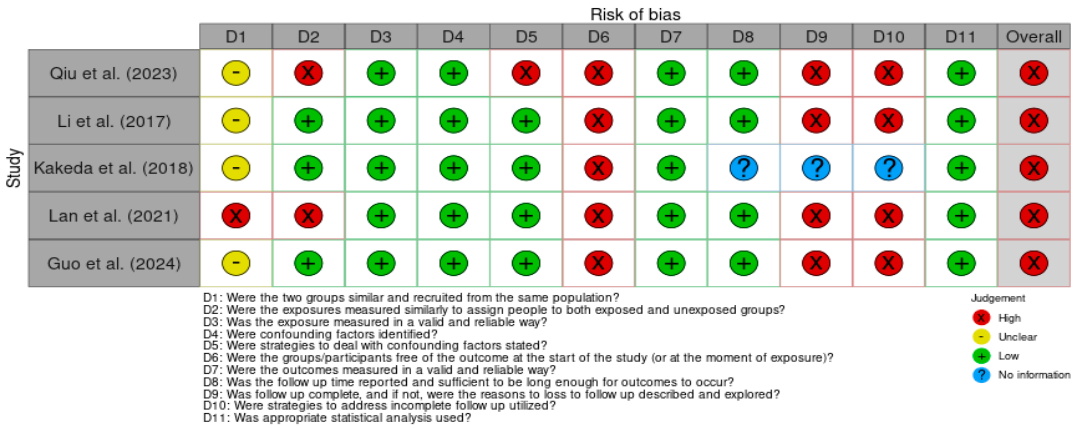

Figure 3. Risk of bias assessment of prospective/longitudinal studies using the JBI Cohort Studies Checklist.

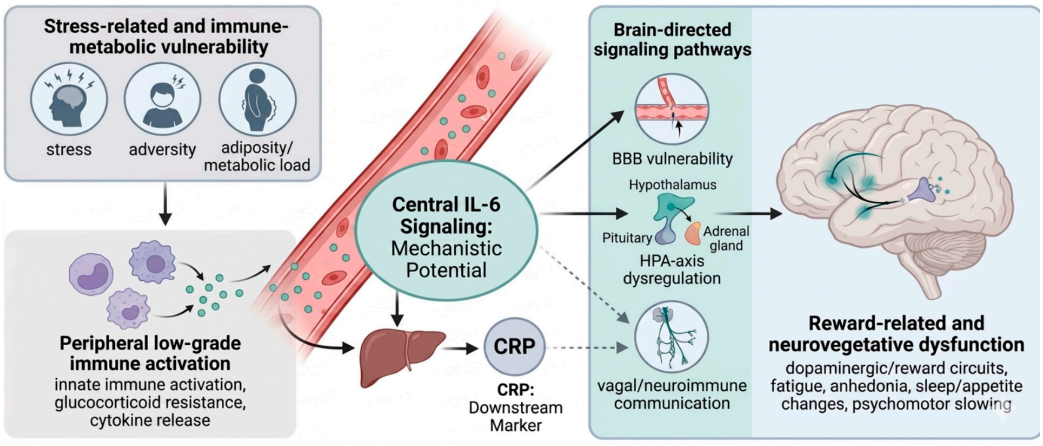

Figure 4. Hypothetical multistep inflammatory model involving IL-6-related signaling in FEDN-MDD.

3. Results

3.1. Study Selection

A total of 313 records were identified through database searching: PubMed (*n* = 75), Embase (*n* = 98), PsycINFO (*n* = 64), and Scopus (*n* = 76). After removal of 186 duplicate records, 127 records remained for title and abstract screening. At this stage, 90 records were excluded because they did not meet the predefined eligibility criteria based on the information available in the title and abstract. The remaining 37 reports were sought for full-text retrieval, successfully retrieved, and assessed for eligibility. Following full-text review, 21 reports were excluded because they did not meet the predefined FEDN-MDD eligibility criteria. Ultimately, 16 publications met the inclusion criteria and were included in the final qualitative synthesis. All included publications examined patients with FEDN-MDD in comparison with a healthy control group.

3.2. Study Characteristics

The 16 included publications were distributed across six countries: China (n = 9), Japan (n = 3), Poland (n = 1), the Slovak Republic (n = 1), Taiwan (n = 1), and Turkey (n = 1). Study designs included cross-sectional or case-control studies (n = 11) and prospective or longitudinal case-control studies (n = 5). Most publications were in adults; four focused exclusively on adolescent samples (Liu et al., 2025; Ferencova et al., 2022; Qiu et al., 2023; Guo et al., 2024). The predominant severity instrument was the HDRS/HAMD family, used in 14 publications; the MADRS was used in one study (Yang et

 doi:10.20944/preprints202605.1077.v1

al., 2021), and the Children's Depression Inventory (CDI) was used in another study (Ferencova et al., 2022).

Biological matrices were heterogeneous, although serum and plasma were the most frequently used. Laboratory methods also varied across studies, with ELISA-based approaches being the most common, followed by multiplex-based platforms and other mixed analytic methods. Participant denominators were extractable for most included publications. Li Z. et al. used a three-sample-set design and was therefore retained in the qualitative synthesis but not included in the cumulative participant count, because the publication could not be reduced to a single non-overlapping MDD and control denominator. Among the 15 publications with directly summable sample sizes, the review included approximately 935 FEDN-MDD participants and 833 healthy controls. These totals should be interpreted cautiously, because three Japanese publications (Kakeda et al., 2018; Kakeda et al., 2020; Sugimoto et al., 2018) arose from confirmed or probable overlapping cohorts and were therefore not treated as fully independent samples for participant-counting or evidence-weighting purposes.

Table 2. Characteristics of the included studies on peripheral inflammatory biomarkers in first-episode, drug-naïve major depressive disorder.

Study	Country	Design	MDD (N)	Health Control (N)	Age group	Diagnostic criteria	Sample type	Core biomarker finding against healthy control	Assay Method
Xueer Liu et al., 2025 [10].	China	Cross-sectional/case-control	46	44	Adolescent (~15.9 y)	DSM-5	Plasma	CRP, IL-6, TNF-α higher	ELISA
Kakeda et al., 2020** [11].	Japan	Cross-sectional/case-control	45	38	Adult (~47.2 y)	DSM-IV-TR (SCID-I/NP)	Serum	TNF-α higher	V-PLEX multiplex ELISA (MSD)
Guan et al., 2026 [12].	China	Cross-sectional/case-control	31	31	Adult	DSM-5	Serum	TNF-α and IL-1β not significantly different	ELISA
Cubała & Landowski, 2014 [13].	Poland	Cross-sectional/case-control	20	20	Adult (<median 30.5 y)	DSM-IV (SCID)	Saliva + plasma	Salivary CRP not significantly different	ELISA / CMIA
Ferencova et al., 2022 [14].	Slovak Republic	Cross-sectional/case-control	100	60	Adolescent (~15.4 y)	DSM-5	Plasma	TNF-α higher; IL-6 and IL-1β not significantly different	Multiplex (Randox Biochip)
Liu P. et al., 2022 [15].	China	Cross-sectional/case-control	66	43	Adult (~24.2 y)	DSM-IV (MINI)	Plasma + stool	hs-CRP higher; IL-6, TNF-α, IL-1β not significantly different	ELISA (cytokines); 16S rRNA (microbiota)

 doi:10.20944/preprints202605.1077.v1

Yang et al., 2021 [16].	Taiwan	Cross-sectional/case-control	34	34	Adult (~43.7 y)	DSM_IV-TR	Plasma	IL-1β lower	ELISA
Qiu et al., 2023 [17].	China	Prospective/longitudinal case-control	40	30	Adolescent (~15.7 y)	DSM-5 (SCID-I/P)	Serum	IL-6 higher; IL-1β not significantly different	ELISA
Li Z. et al., 2017** [18].	China	Prospective/longitudinal case-control	Not directly summable	Not directly summable	Adult (~31–34 y)	DSM-IV-TR (SCID-I/P)	Plasma + peripheral blood lymphocytes	ENA78 findings; no core cytokine panel directly comparable	Microarray; RT-qPCR; ELISA
Kakeda et al., 2018** [19].	Japan	Prospective/longitudinal case-control	40	47	Adult (~46.6 y)	DSM-IV-TR (SCID-I/NP)	Serum	IL-6 higher; TNF-α and IL-1β not significantly different	V-PLEX multiplex ELISA (MSD)
Sugimoto et al., 2018** [20].	Japan	Cross-sectional/case-control	35	35	Adult (~46.3 y)	DSM-IV-TR(SCID-I/NP)	Serum	IL-6, TNF-α, IL-1β not significantly different	V-PLEX multiplex ELISA (MSD)
Hursitoglu et al., 2023 [21].	Turkey	Cross-sectional/case-control	50	50	Adult (~31.1 y)	DSM-5 (SCID)	Serum	Exploratory inflammatory proteins associated with severity	Sandwich ELISA
Wang et al., 2026 [22].	China	Cross-sectional/case-control	236	207	Adult (median 31 y)	DSM-5	Whole/peripheral blood	CRP internally inconsistent; blood-derived inflammatory indices reported	Hematology analyzer (Sysmex)
Wu et al., 2026 [23].	China	Cross-sectional/case-control	90	104	Adult (~28.6 y)	DSM-5 (SCID-RV)	Plasma	CRP, IL-6, and IL-1β higher; TNF-α not significantly different	ELISA (CRP, Claudin-5); Luminex (IL-6, IL-1β, TNF-α)
Lan et al., 2021 [24].	China	Prospective/longitudinal case-control	54	60	Adult (~30.7 y)	DSM-5 (SCID)	Plasma	IL-6, TNF-α, and IL-1β higher	MILLIPLEX MAP (Luminex-based)
Guo et al., 2024 [25].	China	Prospective/longitudinal case-control	48	30	Adolescent (~15.75 y)	DSM-5	Serum	IL-1β not significantly different; exploratory inflammasome/lipid	ELISA

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					mediator findings

**Li Z. et al. was retained in the qualitative synthesis but was not included in cumulative participant totals because its three-sample-set design could not be reduced to a single non-overlapping participant denominator. The Japanese publications by Kakeda et al. and Sugimoto et al. were considered confirmed or probable overlapping cohorts and were therefore not treated as fully independent samples for participant-counting purposes. .

3.3. Biomarkers Assessed

The most frequently assessed core peripheral inflammatory biomarkers across included publications were IL-1β (n = 10 publications), TNF-α (n = 9), IL-6 (n = 8), and CRP or hs-CRP (n = 5). These constituted the primary basis of the narrative synthesis and are shown in Table 3. In addition, several publications evaluated secondary or exploratory markers, including IFN-γ (n = 4), IL-8 (n = 4), IL-4 (n = 3), and single-study markers such as Claudin-5, ENA78/CXCL5, NOX1, Raftlin, AISI, RvD1, Maresin-1, Zonulin, FABP, LPS, and NLRP3M; but their biological interpretation and comparability across studies were more limited. All biomarkers are shown in appendix section.

Table 3. Descriptive direction of reported between-group findings for the most frequently assessed peripheral inflammatory biomarkers in FEDN-MDD compared with healthy controls.

Biomarker	Assessed in n publications	Higher in FEDN-MDD	No significant difference	Lower in FEDN-MDD	Unclear / internally inconsistent
IL-6	8	5	3	0	0
CRP / hs-CRP	5	3	1	0	1
TNF-α	9	4	5	0	0
IL-1β	10	2	7	1	0

Note: This table summarizes the reported direction of between-group findings at the publication level and should not be interpreted as a vote-counting analysis or as a pooled estimate of effect. Because included studies differed substantially in biological matrix, assay platform, statistical reporting format, biomarker units, age composition, and potential cohort overlap, no formal meta-analysis was undertaken. The table is intended to support the narrative synthesis by showing the descriptive pattern of reported findings across studies.

3.4. Main Findings by Biomarker

TNF-α. Findings for TNF-α were mixed. Of nine publications assessing TNF-α, four reported elevated levels in FEDN-MDD (Liu et al., 2025; Kakeda et al., 2020; Ferencova et al., 2022; Lan et al., 2021) and five found no significant difference (Guan et al.; Liu P. et al., 2022; Kakeda et al., 2018; Sugimoto et al., 2018; Wu et al., 2026). The available evidence does not support describing TNF-α as consistently elevated in FEDN-MDD [10,11,14,19,20,23,24].

IL-1β. Results for IL-1β were similarly heterogeneous. Ten publications assessed IL-1β: two reported elevation in FEDN-MDD (Lan et al., 2021; Wu et al., 2026), seven found no significant between-group difference, and one study (Yang et al., 2021) reported IL-1β levels that were significantly lower in FEDN-MDD than in healthy controls ($p = 0.001$). This directional reversal substantially limits any claim of elevated IL-1β in FEDN-MDD. Taken across all included publications, the evidence does not support a consistent IL-1β alteration in this population [16,23,24].

CRP/hs-CRP. Findings for CRP and hs-CRP were also variable. Five publications assessed CRP or hs-CRP: three reported higher levels in FEDN-MDD (Liu et al., 2025; Liu P. et al., 2022; Wu et al., 2026), one found no significant difference (Cubała & Landowski, 2014, using salivary CRP), and one was classified as internally inconsistent (Wang et al., 2026, where Table 1 reported $p = 0.558$ while the

 doi:10.20944/preprints202605.1077.v1

discussion text stated p = 0.028). Additional limitations include nonstandardized units across studies and the use of a salivary rather than blood-derived CRP matrix in one publication. These factors limit cross-study interpretation of CRP findings [10,13,15,22,23,26].

IL-6. Findings for IL-6 also were mixed. Of eight publications assessing IL-6, five reported elevated levels in FEDN-MDD (Liu et al., 2025; Qiu et al., 2023; Kakeda et al., 2018; Wu et al., 2026; Lan et al., 2021), whereas three found no significant difference (Ferencova et al., 2022; Liu P. et al., 2022; Sugimoto et al., 2018). Overall, the available evidence suggests that IL-6 may be elevated in FEDN-MDD, although findings are not fully consistent across studies [10,14,15,17,19,20,23,24].

Exploratory biomarkers. Several publications reported findings for markers not assessed in other included studies. NOX1 and Raftlin were both significantly elevated in FEDN-MDD in one Turkish study, with large correlations with depression severity (Hursitoglu et al., 2023); however, these findings require independent replication. AISI, a hematologic inflammatory index, was elevated in one large Chinese sample (Wang et al., 2026). ENA78/CXCL5 was reduced in FEDN-MDD across multiple sample sets in one study (Li Z. et al.). Pro-resolving mediators (RvD1, Maresin-1) showed opposing patterns in adolescent samples. Gut-related markers (Claudin-5, Zonulin, FABP, LPS) were elevated in one study (Liu et al., 2025). Because each of these markers was assessed in only one or two publications, no cross-study patterns can be established for them [18,21,22,27]

To facilitate interpretation of these mixed findings, Table 3 provides a descriptive publication-level summary of the direction of reported between-group differences for the most frequently assessed biomarkers. This summary was not used as a formal statistical test of consistency or effect size, but rather as a structured aid to the narrative synthesis.

3.5. Clinical Correlations

Clinical associations involving core peripheral inflammatory biomarkers were reported in a limited subset of studies, most commonly using the HDRS/HAMD family of scales. The MADRS was used in one adult study, and the CDI was used in one adolescent study. Although CDI was used in one adolescent study, no additional extractable CDI-based association involving the predefined core biomarkers was available for inclusion in Table 4. In keeping with the focus of the present synthesis, this section summarizes only extractable associations involving IL-6, CRP/hs-CRP, TNF-α, and IL-1β. Associations involving secondary or exploratory biomarkers are described in the Appendix A.

Table 4. Clinical associations reported for core peripheral inflammatory biomarkers included FEDN-MDD publications.

Author	Year	Biomarker(s)	Clinical scale	Association reported
Kakeda S. et al.	2020	TNF-α	HAMD-17	TNF-α was negatively correlated with total HAMD-17 score in MDD (r = -0.350, p = 0.01).
Yang K.-C. et al.	2021	IL-1β	MADRS	IL-1β concentration was negatively associated with MADRS score (r = -0.36, p = 0.048).
Qiu T. et al.	2023	IL-6; IL-1β	HDRS-17	Both IL-6 and IL-1β were significantly associated with HDRS-17 scores. In multiple linear regression, IL-6 (β = 0.162, p < 0.05) and IL-1β (β = 0.173, p < 0.05) emerged as independent positive predictors of depressive severity.
Kakeda S. et al.	2018	IL-6; TNF-α; IL-1β	HAMD-17	None of the measured serum cytokine levels were associated with total HAMD-17 score or duration of depressive episode.

 doi:10.20944/preprints202605.1077.v1

Guo et al.	2024	IL-1β	HDRS	Across pre- and post-treatment assessments, HDRS scores showed a significant positive correlation with IL-1β (r = 0.286, p = 0.008). This reflected a longitudinal/pre-post analytic context rather than baseline-only severity.

Overall, the available evidence was sparse and heterogeneous. Qiu et al. (2023) reported that both IL-6 and IL-1β were positively associated with HDRS-17 scores and emerged as independent positive predictors of depressive severity. In contrast, Kakeda et al. (2018) found no association between serum cytokines, including IL-6, TNF-α, and IL-1β, and total HAMD-17 score or duration of depressive episode [17].

Directionality was also inconsistent across studies. Yang et al. (2021) reported a negative association between IL-1β and MADRS score, whereas Kakeda et al. (2020) found a negative correlation between TNF-α and HAMD-17 score. In a different analytic context, Guo et al. (2024) observed a positive correlation between IL-1β and HDRS across pre- and post-treatment assessments rather than at baseline alone. No clear or recurrent clinical correlation pattern was identified for CRP/hs-CRP in the included studies [11,16,25].

Taken together, the current evidence does not support a consistent relationship between any individual core peripheral inflammatory biomarker and depressive severity in FEDN-MDD. Although isolated associations were reported for IL-6, IL-1β, and TNF-α, these findings were not uniform across studies and varied according to clinical scale, analytic framework, and timing of assessment. Correlations involving secondary or exploratory biomarkers are presented separately in the Appendix A.

3.6. Methodological Remarks

Several methodological features limited direct comparability across publications. These included variation in the operational definition of first-episode status, differences in biological matrices, heterogeneity in assay methods, and non-uniform statistical reporting formats, including mean ± SD, median with interquartile range, SEM, and transformed values. In addition, the scope of biomarker panels varied considerably, ranging from classical cytokines to exploratory inflammatory, oxidative, hematologic, and barrier-related markers.

The dataset also identified a subgroup of Japanese publications with confirmed or probable cohort overlap. These publications were retained because they contributed distinct biomarker and imaging-related information relevant to the review question. However, they were not interpreted as fully independent sources of evidence, and this was taken into account when considering cumulative participant counts and the overall weight of the literature. In addition, these studies included first-episode samples with relatively high mean ages compared with other included FEDN-MDD cohorts. This feature may reflect differences in ascertainment, timing of first clinical presentation, or operational definitions of first-episode status, but it also limits direct comparability with younger adult and adolescent samples. The interpretation of this subgroup is further complicated by the fact that partly overlapping cohorts did not yield fully homogeneous biomarker findings across publications.

3.7. Narrative Synthesis

Taken together, the 16 included publications support a heterogeneous pattern of peripheral inflammatory alterations in FEDN-MDD rather than a single robust inflammatory signature. Within this framework, IL-6 showed the most reproducible tendency toward elevation compared with healthy controls, though this pattern was not observed in all studies assessing it. CRP/hsCRP findings were also partially positive but were confounded by unit inconsistencies, nonstandard matrices, and one internally inconsistent result. Findings for TNF-α and IL-1β were predominantly mixed, and IL-

 doi:10.20944/preprints202605.1077.v1

1β showed directional reversal in one study. Exploratory and secondary biomarkers were too diverse in biological meaning and study-level reporting to support cross-study patterning.

The evidence is compatible with early peripheral immune dysregulation in at least a subset of patients with FEDN-MDD. However, the substantial methodological heterogeneity across publications — in assay platforms, biological matrices, reporting formats, first-episode definitions, and age-group composition — precludes strong or uniform conclusions. The findings should be interpreted as hypothesis-generating evidence for the role of peripheral inflammation in early-stage depression rather than as proof of a specific or stable biomarker profile.

3.8. Assessments of Risk of Bias

Eleven cross-sectional/case-control studies were evaluated with the JBI Analytical Cross-Sectional Studies Checklist, and five prospective/longitudinal case-control studies were evaluated with the JBI Cohort Studies Checklist. Overall, the cross-sectional evidence showed predominantly low to moderate methodological concern, although several studies were limited by incomplete identification or management of confounding factors and, in some cases, insufficiently detailed reporting of statistical handling. By contrast, the longitudinal/cohort-style studies showed greater methodological vulnerability overall, mainly because of concerns related to comparability of groups, management of confounding, follow-up design and reporting, and outcome assessment over time.

Among the cross-sectional studies, most were judged as having low risk of bias overall, while a smaller number were rated as unclear or high risk. In the cohort group, all included studies showed at least some important methodological limitations, resulting in a less favorable overall risk-of-bias profile than that observed for the cross-sectional evidence. These findings should be considered when interpreting the consistency and strength of the biomarker patterns identified in this review, particularly for associations derived from longitudinal analyses.

4. Discussion

4.1. Principal Findings

This systematic review synthesized the available evidence on peripheral inflammatory biomarkers in FEDN-MDD. The findings support early but heterogeneous peripheral immune alterations rather than a single reproducible inflammatory profile. Among the core biomarkers most frequently studied, IL-6 showed the clearest recurrent tendency toward elevation, whereas CRP/hs-CRP, TNF-α, and IL-1β yielded less consistent results. Associations between inflammatory biomarkers and depressive severity were also mixed, with no stable cross-study pattern.

These findings are important because the review was restricted to first-episode, drug-naïve or medication-naïve samples. By limiting confounding from recurrence, chronicity, and prior treatment exposure, this approach offers a more informative view of inflammatory alterations near illness onset than is often possible in the broader MDD literature. The relative consistency of IL-6 in this setting is notable and aligns with prior meta-analytic evidence in depression more broadly. At the same time, the marked heterogeneity across studies indicates that peripheral inflammation in FEDN-MDD should not be interpreted as a uniform trait. Rather, the current evidence is more consistent with immune dysregulation in a subset of patients than with a single biomarker-defined inflammatory phenotype [4,5,7,28].

4.2. Why the FEDN-MDD Focus Matters

A major strength of this review is its exclusive focus on FED-MDD. Much of the broader inflammation literature in depression has been derived from clinically heterogeneous samples that combine first and recurrent episodes, variable illness duration, prior treatment exposure, and medical or psychiatric comorbidity. Such factors may influence inflammatory signaling independently of early depressive pathophysiology and can make it difficult to determine whether observed

 doi:10.20944/preprints202605.1077.v1

biomarker alterations reflect illness onset, chronic disease burden, or treatment-related effects [4,28–30].

By restricting the synthesis to FEDN-MDD, the present review was better positioned to examine whether peripheral inflammatory alterations are already detectable near the earliest clinically identifiable stage of illness and before substantial pharmacologic exposure. This distinction is important because prior meta-analytic work in broader MDD populations has suggested reproducible inflammatory abnormalities—particularly for IL-6 and, in some analyses, CRP—while also showing substantial between-study heterogeneity. The FEDN-MDD framework therefore provides a more informative setting in which to examine early immune dysregulation than mixed-sample designs, even if it does not fully eliminate interpretive uncertainty [4,28–30].

At the same time, restricting the review to FEDN-MDD did not remove heterogeneity within the evidence base itself. Substantial differences remained across studies in the operational definition of first-episode status, biological matrices, assay platforms, biomarker panels, and clinical severity instruments. These differences may also partly reflect variation in clinical practice, cultural context, and the ways in which depressive symptoms are assessed and conceptualized across settings. Accordingly, the present findings are better interpreted as evidence of possible early immune dysregulation in FEDN-MDD than as proof of a single reproducible inflammatory signature [28–30].

4.3. Possible Pathophysiological Explanations for the Observed Positive Trends

A more mechanistically oriented interpretation of the present findings is that, in a biologically susceptible subgroup of patients with FEDN-MDD, early low-grade immune activation may be driven by stress-related neuroendocrine dysregulation and broader immune-metabolic perturbation, with IL-6 signaling representing one potentially proximal component of this broader inflammatory cascade. Within this framework, IL-6 may be more informative than CRP because pathogenic effects appear to be linked not only to circulating IL-6 concentration but also to IL-6 trans-signalling/activity, whereas CRP is better understood as a downstream acute-phase readout of systemic inflammation. This interpretation is supported by recent work showing that IL-6 activity/bioavailability is associated with somatic symptoms, fatigue, psychomotor slowing, and overall depression severity, as well as by longitudinal evidence that higher baseline IL-6 is associated with worse depressive symptom trajectories across the life course [31,32] .

One plausible initiating pathway is chronic stress-related immune priming. Recent neuroimmune models indicate that psychological stress activates the HPA axis and sympathetic output, but that persistent stress may lead to glucocorticoid resistance, impaired negative feedback, immune-cell mobilization, and sustained increases in pro-inflammatory cytokines such as IL-6 and TNF-α. These effects are not confined to the circulation alone, but extend to peripheral organs including the gut, liver, and adipose tissue, thereby linking systemic inflammation with immune-metabolic dysregulation. In this context, IL-6 may reflect a more proximal inflammatory signal, whereas CRP may index the broader downstream systemic response that emerges from it [33,34].

A second mechanistic step may involve peripheral-to-central immune communication. Human and translational data increasingly support the idea that stress-related inflammatory states may affect barrier integrity and facilitate the central impact of peripheral cytokine signaling. In particular, genetic evidence in humans supports an interaction among recent stress, IL6-related variation, and CLDN5, suggesting that blood-brain barrier vulnerability may be one pathway through which peripheral inflammatory signals gain greater relevance for depressive symptom formation. Within the brain, these signals may converge less on a unitary “depression pathway” than on specific systems regulating motivation, reward, energy balance, and neurovegetative function [35,36].

A third and especially relevant downstream mechanism may involve dopaminergic and reward-circuit dysfunction. Recent experimental work showed that IL-6 can directly impair human dopaminergic neurons through the kynurenine pathway, reducing dopamine release and neuronal firing, thereby providing a biologically plausible link between inflammation and motivational impairment. In parallel, contemporary clinical studies indicate that inflammation and metabolic

 doi:10.20944/preprints202605.1077.v1

dysregulation cluster preferentially with anhedonia and atypical/energy-related symptoms, and that patients with higher CRP together with dyslipidemia may show greater reward-circuit and symptomatic response to inflammation-targeted or dopamine-enhancing interventions. This may help explain why inflammatory biomarkers may be more closely linked to selected behavioral and neurovegetative dimensions than to global depressive severity alone [37–40].

Taken together, the current evidence supports a hypothetical multistep inflammatory model in which stress-linked and partly immune-metabolic low-grade inflammation may emerge early in a subset of FEDN-MDD patients, promote downstream CRP elevation, and influence the brain through neuroendocrine, barrier-related, and reward-circuit pathways. Within this framework, CRP is best interpreted as a downstream systemic marker, whereas IL-6 may represent a relatively proximal and biologically informative inflammatory signal. However, because most mechanistic evidence derives from broader MDD and inflammatory-depression research rather than FEDN-MDD specifically, this framework should be regarded as biologically plausible and hypothesis-generating, not as an established causal model of early depressive illness [41–44].

4.4. Interpretation of the Biomarker Pattern

Taken together, the present findings suggest that IL-6 is the clearest biomarker signal within the current FEDN-MDD literature. This interpretation does not rest on uniform elevation across all studies, but rather on the relative consistency of the direction of effect in a field otherwise marked by substantial heterogeneity. That pattern is broadly aligned with the wider depression literature, in which IL-6 has repeatedly emerged as one of the more reproducible peripheral inflammatory correlates of major depressive disorder, whereas evidence for TNF-α and IL-1β has been less stable across studies [4,5].

By contrast, the current evidence does not support describing CRP/hs-CRP, TNF-α, or IL-1β as consistently altered in FEDN-MDD. In the present review, findings for CRP/hs-CRP were only partially positive and were further limited by matrix-related and reporting inconsistencies, while TNF-α and IL-1β showed mixed or contradictory results. This heterogeneity may reflect true biological variation across patients, but it may also arise from differences in age group, sampling procedures, assay platforms, and statistical handling. Accordingly, inflammatory biomarkers in FEDN-MDD should be interpreted cautiously as indicators of possible early immune dysregulation rather than as stable trait markers of early-stage depression.

The pattern observed for IL-6 and CRP may also be biologically informative. Prior longitudinal and genetic work suggests that IL-6 may be closer to the active inflammatory pathway, whereas CRP may function more as a downstream and less specific index of low-grade immune-metabolic activation. This distinction may help explain why IL-6 appears somewhat more coherent across studies, while CRP often shows directionally similar but less stable associations that are more vulnerable to metabolic and methodological confounding [6,7,45]

The inclusion of both adult and adolescent samples is also relevant to interpretation. In this context, adolescent, young adult, and later-adult first-episode samples may not represent biologically interchangeable populations. They may differ in developmental stage, cumulative exposure to inflammatory or metabolic stressors, timing of first clinical presentation, and the phase of the stress–immune cascade captured at biomarker assessment. These differences may partly contribute to inconsistent or even directionally divergent biomarker findings across studies. More broadly, MDD, like other psychiatric disorders, is a heterogeneous and multifactorial syndrome that may arise through different etiological pathways rather than a single biological mechanism. Consistent with this view, recent symptom-level work suggests that inflammatory markers may map more closely onto selected depressive dimensions than onto depression as a single uniform construct. This may partly explain why convergence across biomarkers remained incomplete even in this clinically restricted population [8].

Overall, the biomarker pattern identified here is more consistent with heterogeneous early immune involvement in a subset of patients with FEDN-MDD than with a single reproducible

 doi:10.20944/preprints202605.1077.v1

inflammatory signature. From that perspective, IL-6 may be the most informative candidate biomarker currently available in this literature, whereas the remaining core markers are better interpreted as variable or context-dependent signals that require further standardization and replication before stronger conclusions can be drawn.

4.5. Clinical Correlations and Potential Relevance

Clinical correlations in the present review were limited and inconsistent, which argues against a simple linear model in which greater peripheral inflammation maps directly onto greater depressive severity in FEDN-MDD. Rather than functioning as general cross-sectional severity markers, peripheral inflammatory biomarkers may have clinical relevance only in a subset of patients or within specific symptom dimensions. This interpretation is consistent with the broader depression literature, in which associations between inflammation and depression are typically modest and heterogeneous, and are partly shaped by metabolic and other confounding factors [3,7].

A more plausible interpretation is that inflammatory biomarkers may be most informative for identifying biologically meaningful subgroups or phenotypes rather than for indexing overall depressive burden. In large cohort and genetic analyses, IL-6 and CRP have shown stronger associations with selected symptom dimensions, including fatigue, sleep disturbance, appetite change, and anhedonia, than with depression considered as a single uniform construct. Similarly, genetic work suggests overlap between inflammatory and metabolic dysregulation and selected depressive symptoms, with the IL-6 pathway appearing more mechanistically informative than CRP in some phenotypes [8,45].

This framework also helps explain why clinical-correlation findings in FEDN-MDD remain difficult to interpret. If inflammation is linked preferentially to particular symptom domains rather than to total score severity, then inconsistent results across studies using different scales, analytic strategies, and timepoints would be expected. Longitudinal meta-analytic evidence further suggests that associations between depressive symptoms and inflammatory markers are bidirectional and small in magnitude, which makes a single baseline biomarker unlikely to perform as a robust severity marker across all patients [7,46].

Taken together, the current evidence suggests that the clinical value of peripheral inflammatory biomarkers in FEDN-MDD may lie less in measuring overall symptom severity and more in supporting biological stratification. At present, however, the literature remains too limited and methodologically heterogeneous to define reliable inflammatory subgroups or to support clinical application. These markers should therefore be regarded as hypothesis-generating tools for phenotyping and mechanistic research rather than as established clinical severity indicators [7,8,45].

4.6. Methodological Considerations

Several methodological issues shape the interpretation of this review. First, although all included studies met the overall FEDN-MDD framework, the operational definition of first-episode and drug-naïve status was not fully uniform across publications. In a literature focused on early-stage illness, even small differences in how illness onset, prior treatment exposure, or episode status are defined may materially affect biological comparability.

Second, substantial methodological heterogeneity remained in biomarker assessment itself. Studies differed in biological matrix, assay platform, and statistical reporting, with some reporting means and standard deviations, others medians and interquartile ranges, and others transformed or otherwise non-directly comparable values. These differences are not trivial, because they complicate cross-study interpretation even when nominally similar biomarkers are being measured. This is particularly relevant for markers such as CRP, for which matrix-related and reporting inconsistencies may partly account for variable findings.

Third, the biomarker landscape was broad but uneven. Although the present review prioritized core markers—IL-6, CRP/hs-CRP, TNF-α, and IL-1β—many included studies also examined secondary or exploratory inflammatory, oxidative, hematologic, or barrier-related markers. This

 doi:10.20944/preprints202605.1077.v1

broadens the biological scope of the literature but reduces comparability across studies and limits the ability to distinguish replicated signals from study-specific findings. In that sense, heterogeneity was present not only in methods but also in the underlying biological targets being sampled.

A further consideration is the presence of confirmed or probable cohort overlap among a subgroup of Japanese publications. These studies were retained because they contributed distinct biomarker or imaging-related information relevant to the review question, but they should not be interpreted as fully independent sources of evidence. Accordingly, cumulative sample counts and the apparent weight of repeated findings should be interpreted with caution. This subgroup also requires careful interpretation because the reported mean ages were relatively high for samples described as first-episode MDD, which may reflect differences in illness ascertainment, timing of first clinical contact, or operational definitions of first-episode status. Moreover, despite probable cohort overlap, biomarker findings were not fully homogeneous across these publications. Taken together with their less favorable risk-of-bias profile, these issues limit the extent to which this subgroup can be used to support robust conclusions about early inflammatory alterations in FEDN-MDD.

Taken together, these methodological considerations suggest that the current literature is better suited to hypothesis generation and biological signal detection than to definitive biomarker validation.

4.7. Clinical and Translational Implications

The present findings support continued interest in peripheral inflammatory biomarkers as tools for biological stratification in early-stage depression. The observation that inflammatory alterations may already be detectable in FEDN-MDD raises the possibility that immune-related mechanisms are relevant from illness onset rather than emerging only as a consequence of chronicity or treatment exposure. In that respect, the relative consistency of IL-6 across the present evidence base is notable and aligns with broader work suggesting that inflammatory dysregulation may characterize a biologically meaningful subset of depressive illness rather than depression as a whole.

At the same time, the current evidence remains insufficient for direct clinical translation. The heterogeneity of findings, the lack of standardized thresholds, and the limited reproducibility of several markers argue against the use of peripheral inflammatory measures as established diagnostic or severity tools in FEDN-MDD at present. Moreover, the included studies did not provide sufficiently consistent or detailed symptom-level data to support reliable conclusions about specific clinical presentations associated with inflammatory biomarker patterns. More plausibly, their near-term value may lie in enrichment and stratification: identifying patients with a greater likelihood of immune-metabolic involvement, refining phenotypic subgroups, and informing the design of longitudinal or mechanism-based studies.

Accordingly, peripheral inflammatory biomarkers in FEDN-MDD should still be regarded primarily as research tools. Their greatest translational value at present is likely to lie in helping refine biological models of early depression, generate hypotheses about clinically relevant subtypes, and support the development of more targeted prospective studies. Whether such markers will ultimately prove useful for prognosis, treatment selection, or intervention targeting will require larger, methodologically standardized, and longitudinally designed investigations.

4.8. Future Directions

Future work in FEDN-MDD should move beyond asking whether inflammation is present and toward clarifying in whom, when, and in what form it is most clinically relevant. Greater methodological standardization will be essential, including clearer operational definitions of first-episode and drug-naïve status, harmonized sampling procedures, and more consistent use of core biomarker panels spanning inflammatory, metabolic, and stress-related systems. Without greater comparability in study design and biomarker measurement, it will remain difficult to distinguish true biological heterogeneity from methodological noise [47–49].

 doi:10.20944/preprints202605.1077.v1

Future studies should also examine age and developmental stage as potential moderators of inflammatory biomarker findings in FEDN-MDD. Comparisons between adolescent, young adult, and later-adult first-episode samples may be particularly informative, because these groups may differ in neurodevelopmental context, cumulative inflammatory exposures, metabolic risk, and the timing at which stress-related immune changes are captured. However, the current evidence base remains too small and methodologically heterogeneous to support robust age-stratified conclusions.

Longitudinal designs should be prioritized. Repeated biomarker assessments beginning near illness onset and extending through early treatment would help determine whether inflammatory alterations are stable, state-dependent, or dynamically related to clinical course. Such designs are particularly important given growing evidence that inflammatory signals may be small in magnitude, context-dependent, and more informative at the symptom level than at the level of overall case status alone [50,51].

An additional priority will be to test whether the relevant biological signal in FEDN-MDD is better captured within an allostatic load framework than by isolated abnormalities in single biomarkers. Recent work conceptualizes allostatic load as a composite, multisystem index of cumulative physiological dysregulation, and studies in broader MDD samples suggest that allostatic load is elevated even in unmedicated patients and may prospectively predict risk for depression. Taken together, these findings suggest that future FEDN-MDD studies should examine biomarker constellations—using composite indices, latent-factor approaches, and network-level relationships among inflammatory, metabolic, cardiovascular, and neuroendocrine markers—rather than relying exclusively on single analytes measured in isolation [47,48,52–54].

Future studies should also place greater emphasis on phenotype refinement. Emerging evidence suggests that inflammatory biomarkers may map more closely onto selected symptom dimensions—notably fatigue, sleep or appetite disturbance, anhedonia, and other neurovegetative features—than onto overall depressive severity. Accordingly, FEDN-MDD research may benefit from more detailed symptom-level characterization, rather than relying primarily on total scale scores, as well as from efforts to identify potential inflammatory or immune-metabolic subgroups within early-stage depression [51,55–57].

Finally, progress will likely depend on multimodal approaches. Integrating peripheral inflammatory biomarkers with neuroimaging, genetics, stress biology, and detailed clinical phenotyping may provide a more informative framework for understanding whether inflammatory dysregulation is mechanistically relevant in a subset of patients with FEDN-MDD. Recent work in recent-onset depression and transdiagnostic depression samples supports the value of multivariate brain-blood and multi-omics models for identifying biologically meaningful subgroups, and IL-6-related signaling remains a particularly relevant pathway for further mechanistic investigation [50,51,58,59].

5. Conclusions

This systematic review supports the presence of heterogeneous peripheral inflammatory alterations in first-episode, drug-naïve major depressive disorder. Among the core biomarkers most frequently assessed, IL-6 showed the clearest recurrent tendency toward elevation, whereas findings for CRP/hs-CRP, TNF-α, and IL-1β were more variable and less reproducible. Taken together, the available literature is more consistent with early immune dysregulation in a subset of patients with FEDN-MDD than with a single uniform inflammatory signature.

The current evidence does not support immediate clinical use of peripheral inflammatory biomarkers as diagnostic or severity markers in FEDN-MDD. Their most plausible value at present lies in biological stratification, mechanistic hypothesis generation, and the identification of potentially meaningful subgroups or symptom dimensions within early-stage depression. More rigorous, standardized, and longitudinally designed studies will be required before these biomarkers can be translated into clinically useful tools.

 doi:10.20944/preprints202605.1077.v1

Author Contributions: Conceptualization, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; methodology, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; software, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; validation, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; formal analysis, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; investigation, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; resources, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; data curation, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; writing—original draft preparation, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; writing—review and editing, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; visualization, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; supervision, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; project administration, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F.; funding acquisition, L.G.H.-J., R.M.-G., S.A.-C., J.M.-J., E.Z.-M. and J.M.C.-F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: During the preparation of this manuscript, the authors used Google Gemini 3 Flash Image, internally referred to as Nano Banana 2, for the purpose of generating the Figure 4. The authors reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AISI	Aggregate index of systemic inflammation
CDI	Children's Depression Inventory
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
FEDN-MDD	First-episode, drug-naïve major depressive disorder
HAMD	Hamilton Depression Rating Scale
HAMD-17	17-item Hamilton Depression Rating Scale
HDRS	Hamilton Depression Rating Scale
HDRS-17	17-item Hamilton Depression Rating Scale
HPA	Hypothalamic–pituitary–adrenal
JBI	Joanna Briggs Institute
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	Major depressive disorder

Appendix A

Appendix A.1

Table A1. Search strategy used in this review.

Database	Keywords	Strategy	Filters applied to the database	Number of possible items to select

 doi:10.20944/preprints202605.1077.v1

PubMed / MEDLINE	"major depressive disorder", "first episode", "inflammation", "cytokines", "biomarkers"	(Depressive Disorder, Major[Mesh] OR "major depressive disorder"[ti] OR "first episode depression"[ti] OR "first-episode depression"[ti] OR "first-episode MDD"[ti] OR ("major depressive disorder"[tiab] AND "first episode"[tiab]) OR ("major depression"[tiab] AND "first episode"[tiab])) AND ("first episode"[tiab] OR "first-episode"[tiab] OR "first lifetime episode"[tiab] OR "first diagnosis"[tiab] OR "drug naive"[tiab] OR "drug-naive"[tiab] OR "drug-naïve"[tiab] OR "treatment naive"[tiab] OR "treatment-naive"[tiab] OR "medication naive"[tiab] OR "antidepressant naive"[tiab] OR "psychotropic naive"[tiab] OR "drug free"[tiab]) AND (C-Reactive Protein[Mesh] OR Interleukins[Mesh] OR Tumor Necrosis Factor-alpha[Mesh] OR Acute-Phase Proteins[Mesh] OR Cytokines[Mesh] OR "C-reactive protein"[tiab] OR "CRP"[tiab] OR "interleukin"[tiab] OR "interleukin-1"[tiab] OR "IL-1"[tiab] OR "IL-1beta"[tiab] OR "interleukin-6"[tiab] OR "IL-6"[tiab] OR "interleukin-10"[tiab] OR "IL-10"[tiab] OR "interleukin-17"[tiab] OR "IL-17"[tiab] OR "interleukin-18"[tiab] OR "IL-18"[tiab] OR "tumor necrosis factor"[tiab] OR "TNF"[tiab] OR "TNF-alpha"[tiab] OR "TNF alpha"[tiab] OR "neopterin"[tiab] OR "pentraxin"[tiab] OR "inflammatory marker"[tiab] OR "inflammatory biomarker"[tiab] OR "pro-inflammatory"[tiab] OR "proinflammatory"[tiab] OR "systemic inflammation"[tiab] OR "low-grade inflammation"[tiab] OR "immune activation"[tiab] OR "acute phase protein"[tiab]) AND ("serum"[tiab] OR "plasma"[tiab] OR "peripheral blood"[tiab] OR "whole blood"[tiab] OR "blood sample"[tiab] OR "venous blood"[tiab] OR "peripheral"[tiab]) NOT ("hepatitis C"[tiab] OR "hepatitis B"[tiab] OR "HCV"[tiab] OR "HBV"[tiab] OR "peginterferon"[tiab] OR "interferon therapy"[tiab] OR "antiviral therapy"[tiab] OR "chronic hepatitis"[tiab] OR "schizophrenia"[ti] OR "schizoaffective"[ti] OR "bipolar disorder"[ti] OR "bipolar I"[ti] OR "bipolar II"[ti] OR "autism"[ti] OR "ADHD"[ti] OR "attention deficit"[ti] OR "alzheimer"[ti] OR "dementia"[ti] OR "multiple sclerosis"[ti] OR	Humans; English; No date restriction	75

 doi:10.20944/preprints202605.1077.v1

		"rheumatoid arthritis"[ti] OR "lupus"[ti] OR "inflammatory bowel"[ti] OR "crohn"[ti] OR "review"[pt] OR "editorial"[pt] OR "letter"[pt] OR "comment"[pt] OR "case reports"[pt] OR "systematic review"[pt] OR "meta-analysis"[pt])		
Embase	'major depressive disorder', 'first episode', 'inflammation', 'cytokines', 'biomarkers'	('major depressive disorder'/exp OR ('major depressive disorder':ti OR 'first episode depression':ti OR 'first-episode MDD':ti OR 'unipolar depression':ti OR 'MDD':ti) OR ('major depressive disorder':ab AND 'first episode':ab) OR ('major depression':ab AND 'first episode':ab)) AND ('first episode':ti,ab OR 'first-episode':ti,ab OR 'first episode depression':ti,ab OR 'first lifetime episode':ti,ab OR 'first diagnosis':ti,ab OR 'drug naive':ti,ab OR 'drug-naive':ti,ab OR 'drug-naïve':ti,ab OR 'treatment naive':ti,ab OR 'treatment-naive':ti,ab OR 'medication naive':ti,ab OR 'antidepressant naive':ti,ab OR 'psychotropic naive':ti,ab OR 'drug free':ti,ab) AND ('C reactive protein'/exp OR 'interleukin'/exp OR 'tumor necrosis factor'/exp OR 'acute phase protein'/exp OR 'interferon'/exp OR 'C-reactive protein':ti,ab OR 'CRP':ti,ab OR 'interleukin':ti,ab OR 'interleukin-1':ti,ab OR 'IL-1':ti,ab OR 'IL-1beta':ti,ab OR 'interleukin-6':ti,ab OR 'IL-6':ti,ab OR 'interleukin-10':ti,ab OR 'IL-10':ti,ab OR 'interleukin-17':ti,ab OR 'IL-17':ti,ab OR 'interleukin-18':ti,ab OR 'IL-18':ti,ab OR 'tumor necrosis factor':ti,ab OR 'TNF':ti,ab OR 'TNF-alpha':ti,ab OR 'TNF alpha':ti,ab OR 'neopterin':ti,ab OR 'pentraxin':ti,ab OR 'inflammatory marker':ti,ab OR 'inflammatory biomarker':ti,ab OR 'pro-inflammatory':ti,ab OR 'proinflammatory':ti,ab OR 'systemic inflammation':ti,ab OR 'low-grade inflammation':ti,ab OR 'immune activation':ti,ab) AND ('serum':ti,ab OR 'plasma':ti,ab OR 'peripheral blood':ti,ab OR 'whole blood':ti,ab OR 'blood sample':ti,ab OR 'venous blood':ti,ab OR 'peripheral':ti,ab) NOT ('hepatitis C':ti,ab OR 'hepatitis B':ti,ab OR 'HCV':ti,ab OR 'HBV':ti,ab OR 'peginterferon':ti,ab OR 'interferon therapy':ti,ab OR 'antiviral therapy':ti,ab OR 'chronic hepatitis':ti,ab OR 'schizophrenia':ti OR 'schizoaffective':ti OR 'bipolar disorder':ti OR 'bipolar I':ti OR 'bipolar II':ti OR 'autism':ti OR 'ADHD':ti OR	Humans; English language; Article; No date restriction	98

 doi:10.20944/preprints202605.1077.v1

		'attention deficit':ti OR 'alzheimer':ti OR 'dementia':ti OR 'multiple sclerosis':ti OR 'rheumatoid arthritis':ti OR 'lupus':ti OR 'inflammatory bowel':ti OR 'crohn':ti)	
PsycINFO	"major depressive disorder", "first episode", "inflammation", "cytokines", "biomarkers"	("major depressive disorder".ti. OR "first episode depression".ti. OR "first-episode depression".ti. OR "first-episode MDD".ti. OR ("major depressive disorder" AND "first episode").ti,ab. OR ("major depression" AND "first episode").ti,ab. OR exp Major Depression/) AND ("first episode".ti,ab. OR "first-episode".ti,ab. OR "first lifetime episode".ti,ab. OR "first diagnosis".ti,ab. OR "drug naive".ti,ab. OR "drug-naive".ti,ab. OR "treatment naive".ti,ab. OR "treatment-naive".ti,ab. OR "medication naive".ti,ab. OR "antidepressant naive".ti,ab. OR "psychotropic naive".ti,ab. OR "drug free".ti,ab.) AND ("C-reactive protein".ti,ab. OR CRP.ti,ab. OR interleukin.ti,ab. OR "interleukin-1".ti,ab. OR "IL-1".ti,ab. OR "IL-1beta".ti,ab. OR "interleukin-6".ti,ab. OR "IL-6".ti,ab. OR "interleukin-10".ti,ab. OR "IL-10".ti,ab. OR "interleukin-17".ti,ab. OR "IL-17".ti,ab. OR "interleukin-18".ti,ab. OR "IL-18".ti,ab. OR "tumor necrosis factor".ti,ab. OR TNF.ti,ab. OR "TNF-alpha".ti,ab. OR "TNF alpha".ti,ab. OR neopterin.ti,ab. OR pentraxin.ti,ab. OR "inflammatory marker".ti,ab. OR "inflammatory biomarker".ti,ab. OR "pro-inflammatory".ti,ab. OR proinflammatory.ti,ab. OR "systemic inflammation".ti,ab. OR "low-grade inflammation".ti,ab. OR "immune activation".ti,ab. OR "acute phase protein".ti,ab. OR exp Inflammation/ OR exp Cytokines/) AND (serum.ti,ab. OR plasma.ti,ab. OR "peripheral blood".ti,ab. OR "whole blood".ti,ab. OR "blood sample".ti,ab. OR "venous blood".ti,ab. OR peripheral.ti,ab.) NOT ("hepatitis C".ti,ab. OR "hepatitis B".ti,ab. OR HCV.ti,ab. OR HBV.ti,ab. OR peginterferon.ti,ab. OR "interferon therapy".ti,ab. OR "antiviral therapy".ti,ab. OR "chronic hepatitis".ti,ab. OR schizophrenia.ti. OR schizoaffective.ti. OR "bipolar disorder".ti. OR "bipolar I".ti. OR "bipolar II".ti. OR autism.ti. OR ADHD.ti. OR "attention deficit".ti. OR alzheimer.ti. OR dementia.ti. OR	Peer-reviewed articles; English; Human

 doi:10.20944/preprints202605.1077.v1

		"multiple sclerosis".ti. OR "rheumatoid arthritis".ti. OR lupus.ti. OR "inflammatory bowel".ti. OR crohn.ti.)		
Scopus	"major depressive disorder", "first episode", "inflammation", "cytokines", "biomarkers"	(TITLE("major depressive disorder") OR TITLE("first episode depression") OR TITLE("first-episode depression") OR TITLE("first-episode MDD") OR (ABS("major depressive disorder") AND ABS("first episode")) OR (ABS("major depression") AND ABS("first episode"))) AND (TITLE-ABS-KEY("first episode") OR TITLE-ABS-KEY("first-episode") OR TITLE-ABS-KEY("first lifetime episode") OR TITLE-ABS-KEY("first diagnosis") OR TITLE-ABS-KEY("drug naive") OR TITLE-ABS-KEY("drug-naive") OR TITLE-ABS-KEY("drug-naïve") OR TITLE-ABS-KEY("treatment naive") OR TITLE-ABS-KEY("treatment-naive") OR TITLE-ABS-KEY("medication naive") OR TITLE-ABS-KEY("antidepressant naive") OR TITLE-ABS-KEY("psychotropic naive") OR TITLE-ABS-KEY("drug free")) AND (TITLE-ABS-KEY("C-reactive protein") OR TITLE-ABS-KEY("CRP") OR TITLE-ABS-KEY("interleukin") OR TITLE-ABS-KEY("interleukin-1") OR TITLE-ABS-KEY("IL-1") OR TITLE-ABS-KEY("IL-1beta") OR TITLE-ABS-KEY("IL-1β") OR TITLE-ABS-KEY("interleukin-6") OR TITLE-ABS-KEY("IL-6") OR TITLE-ABS-KEY("interleukin-10") OR TITLE-ABS-KEY("IL-10") OR TITLE-ABS-KEY("interleukin-17") OR TITLE-ABS-KEY("IL-17") OR TITLE-ABS-KEY("interleukin-18") OR TITLE-ABS-KEY("IL-18") OR TITLE-ABS-KEY("tumor necrosis factor") OR TITLE-ABS-KEY("TNF") OR TITLE-ABS-KEY("TNF-alpha") OR TITLE-ABS-KEY("TNF-α") OR TITLE-ABS-KEY("interferon gamma") OR TITLE-ABS-KEY("IFN-γ") OR TITLE-ABS-KEY("neopterin") OR TITLE-ABS-KEY("pentraxin") OR TITLE-ABS-KEY("inflammatory marker") OR TITLE-ABS-KEY("inflammatory biomarker") OR TITLE-ABS-KEY("pro-inflammatory") OR TITLE-ABS-KEY("proinflammatory") OR TITLE-ABS-KEY("systemic inflammation") OR TITLE-ABS-KEY("low-grade inflammation") OR TITLE-ABS-KEY("immune activation") OR TITLE-ABS-KEY("acute phase protein")) AND (TITLE-ABS-KEY("serum") OR	Article; English; Human studies	76

 doi:10.20944/preprints202605.1077.v1

	TITLE-ABS-KEY("plasma") OR TITLE-ABS-KEY("peripheral blood") OR TITLE-ABS-KEY("whole blood") OR TITLE-ABS-KEY("blood sample") OR TITLE-ABS-KEY("venous blood") OR TITLE-ABS-KEY("peripheral")) AND NOT (TITLE-ABS-KEY("hepatitis C") OR TITLE-ABS-KEY("hepatitis B") OR TITLE-ABS-KEY("HCV") OR TITLE-ABS-KEY("HBV") OR TITLE-ABS-KEY("peginterferon") OR TITLE-ABS-KEY("interferon therapy") OR TITLE-ABS-KEY("antiviral therapy") OR TITLE-ABS-KEY("chronic hepatitis") OR TITLE("schizophrenia") OR TITLE("schizoaffective") OR TITLE("bipolar disorder") OR TITLE("bipolar I") OR TITLE("bipolar II") OR TITLE("autism") OR TITLE("ADHD") OR TITLE("attention deficit") OR TITLE("alzheimer") OR TITLE("dementia") OR TITLE("multiple sclerosis") OR TITLE("rheumatoid arthritis") OR TITLE("lupus") OR TITLE("inflammatory bowel") OR TITLE("crohn"))

Table A2. Biomarkers assessed across included studies.

Biomarker	Studies assessing it (N)	Higher in FEDN-MDD	No significant difference	Lower in FEDN-MDD	Unclear / internally inconsistent	Overall direction	Notes on heterogeneity
IL-6	8	5	3	0	0	Tends toward elevation	Most consistent signal; values not numerically comparable (ELISA vs multiplex; log-transformed in Lan 2021; adolescent vs adult cohorts).

 doi:10.20944/preprints202605.1077.v1

TNF-α	9	4	5	0	0	Mixed; no consistent elevation	Nearly even split (4 vs 5); Kakeda 2018 and 2020 show divergent results within overlapping cohort.
IL-1β	10	2	7	1	0	No consistent pattern; majority NS	Only study reporting significant difference in Yang 2021 shows LOWER (not higher) IL-1β; heterogeneous assay platforms.
CRP / hs-CRP	5	3	1	0	1	Possible elevation in subset; less stable	CRP in Wang 2026 internally inconsistent (p=0.558 Table vs p=0.028 text); Cubała 2014 uses salivary CRP.
IL-8	4	1	2	1	0	Heterogeneous; no consistent direction	Opposite directions: 1 higher (adolescent), 1 lower (adult); too few studies for interpretation.
IFN-γ	4	1	3	0	0	Predominantly NS	Insufficient evidence for directional conclusion.

 doi:10.20944/preprints202605.1077.v1

IL-4	3	2	0	1	0	Directionally inconsistent	Adolescent studies show elevation; adult study shows reduction; possible age-group moderator.
Claudin-5	2	2	0	0	0	Both studies show elevation	Tight junction / BBB marker; not a classical cytokine; very few studies.
ENA78 / CXCL5	1	0	0	1	0	Reduced (single study)	Exploratory chemokine; multi-sample study (Li Z., year NR).
NOX1	1	1	0	0	0	Elevated (single study)	Novel oxidative marker; strong severity correlation (r=0.847); requires replication.
Raftlin	1	1	0	0	0	Elevated (single study)	Novel marker; same study as NOX1.
AISI	1	1	0	0	0	Elevated (single study)	Hematologic index from blood routine; not comparable to cytokine assays.

 doi:10.20944/preprints202605.1077.v1

RvD1	1	1	0	0	0	Elevated (single adolescent study)	Pro-resolving lipid mediator; elevation is biologically atypical.
Maresin-1	1	0	1	0	0	Reduced (single adolescent study)	Pro-resolving mediator; reduction may indicate impaired inflammation resolution.
Zonulin	1	1	0	0	0	Elevated (single study)	Gut permeability marker; adolescent only.
FABP	1	1	0	0	0	Elevated (single study)	Barrier protein; adolescent only.
LPS	1	1	0	0	0	Elevated (single study)	Gut translocation marker; adolescent only.
NLRP3	1	0	1	0	0	NS at baseline	Inflammasome component; single adolescent study; severity correlation present.

Table A3. Clinical associations reported in included FEDN-MDD publications for exploratory biomarkers.

Author	Year	Biomarker(s)	Clinical scale	Association reported
Kakeda S. et al.	2020	TNF-α	HAMD-17	TNF-α was associated with the total HAMD-17 score in MDD (reported as negative correlation: r = -0.350, p = 0.01).

 doi:10.20944/preprints202605.1077.v1

Guan H. et al.	2026	IL-4	HAMD-17; QIDS-SR16	Higher serum levels of IL-4 associated significantly with increased severity of symptoms as measured by the HAMD-17 (p=0.03) and QIDS-SR 16 (p=0.009) scales; while IL-17 was positively associated with QIDS-SR16 (p=0.04)
Ferencova N. et al.	2022	sIL-6R; IL-10	CDI	Correlation analysis across the entire cohort (depressed and control groups) revealed significant positive associations between CDI scores and both IL-10 (r=0.167, p=0.041) and sIL-6R (r=0.163, p=0.050). Notably, this relationship with IL-10 remained significant among adolescent males (r=0.306, p=0.017), whereas no significant correlations were observed within the adolescent female subgroup.
Yang K.-C. et al.	2021	IL-1β	MADRS	IL-1β concentration was negatively associated with MADRS score (r = − 0.36, t = − 2.07, p = 0.048).
Qiu T. et al.	2023	Maresin-1; IL-1β; IL-4; IL-6	HDRS-17	Maresin-1, IL-1β, IL-4, and IL-6 significantly correlated with HDRS-17 scores. Subsequent multiple linear regression revealed that the HDRS-17 score was independently and negatively associated with serum Maresin-1 levels (standardized beta = -0.618, p < 0.001). Conversely, both IL-6 (beta = 0.162, p < 0.05) and IL-1β (beta = 0.173, p < 0.05) emerged as independent positive predictors of the HDRS-17 score.
Li Z. et al.	2017	ENA78/CXCL5	HRSD-17	No significant association was found between ENA78 and HRSD-17 severity. Change in plasma ENA78 was also not associated with reduction rate of HRSD-17 after treatment.
Kakeda S. et al.	2018	Serum cytokines (including IL-6, TNF-α, IL-1β, IFN-γ)	HAMD-17	None of the measured serum cytokine levels were associated with total HAMD-17 score or duration of depressive episode.
Hursitoglu et al.	2023	NOX1; Raftlin	HAM-D	In the MDD group, serum NOX1 (r = 0.847, p < 0.001) and Raftlin (r = 0.774, p < 0.001) levels both demonstrated significant positive correlations with HAM-D scores.
Wang et al.	2026	AISI	HAMD-24; SHAPS	AISI correlated with HAMD-24 total score, HAMD-24 subdomains, SHAPS score, and disease duration; mediation analyses also linked AISI and anhedonia with depression severity.
Wu et al.	2026	Claudin-5	HAMD-17; HAMA	No significant correlations were observed between plasma Claudin-5 levels and either HAMD-17 (r = -0.002, p = 0.985) or HAMA scores (r = -0.007, p = 0.949).

 doi:10.20944/preprints202605.1077.v1

Lan et al.	2021	ITAC	HAMD-17 reduction after 4 weeks	Baseline ITAC was negatively correlated with reduction in HAMD-17 score after treatment; this reflected treatment-response association rather than baseline severity.
Guo et al.	2024	RvD1; NLRP3; IL-1β; IL-18; IL-4	HDRS	Across pre- and post-treatment assessments, HDRS scores demonstrated significant positive correlations with levels of RvD1 (r=0.310, p=0.002), NLRP3 (r=0.271, p=0.008), IL-18 (r=0.257, p=0.012), and IL-1β (r=0.286, p=0.008). In contrast, a significant negative correlation was observed between HDRS scores and IL-4 levels (r = -0.331, p=0.002). Furthermore, significant inter-correlations were found among NLRP3, IL-1β, and IL-4.

Table A4. Duplicate and probable overlap studies.

Study	Possible duplicate/overlap with	Reason	Which record retained as primary
Kakeda S. et al., 2020	Kakeda S. et al., 2018	Same Japanese research group; overlapping recruitment setting, time frame, authorship, sample sizes, and assay platform. Authors share all principal investigators. Confirmed by overlap flag in database.	Both retained. Kakeda 2018 = primary for IL-6 data; Kakeda 2020 = primary for TNF-α and imaging data. Neither counted as independent cohort for participant totals.
Kakeda S. et al., 2018	Kakeda S. et al., 2020	See above.	See above.
Sugimoto et al., 2018	Kakeda S. et al., 2018 + 2020	Same research institution; identical assay platform (V-PLEX MSD); similar age range and sample size; overlapping publication period. Overlap not confirmed but considered probable.	Sugimoto 2018 retained. Participant total flagged as probable overlap; counts not added independently.

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