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Sex-Specific Links Between Peripheral Inflammation and Metabolic Risk in Bipolar Disorder: Towards Risk Stratification

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Abstract

Bipolar disorder (BD) is associated with elevated cardiometabolic morbidity and mortality, partly mediated by systemic inflammation. Sex differences in immune function and metabolic regulation are well-established, yet their impact on inflammation-related metabolic risk during pharmacotherapy remains understudied. **Objective**: To examine sex-specific associations between peripheral inflammatory indices and individual components of metabolic syndrome in patients with BD, testing the hypothesis that immuno-metabolic patterns differ between men and women. **Materials and Methods**: In this retrospective cross-sectional study 102 patients with BD (41 men, 61 women) were included. We assessed associations between inflammatory markers—including absolute cell counts, derived hematological ratios, and composite indices based on high-density lipoprotein cholesterol (HDL-C)—and individual components of metabolic syndrome (hyperglycemia, low HDL-C, hypertriglyceridemia, increased waist circumference). **Results:** Sex-specific patterns emerged: men with hyperglycemia demonstrated elevated neutrophil-to-lymphocyte ratio ($p = 0.014$) and absolute neutrophil counts (p-value = 0.044); men with hypertriglyceridemia exhibited elevated absolute lymphocytes (p-value = 0.010) and white blood cells (p-value = 0.031). In women, low HDL-C was associated with elevated neutrophil-to-HDL-C ratio (p-value = 0.031) and platelet-to-HDL-C ratio (p-value = 0.009); hypertriglyceridemia with elevated neutrophil-to-HDL-C ratio (p-value = 0.042) and lymphocyte-to-HDL-C ratio (p-value = 0.027). No associations were found for cellular inflammatory markers in women, nor for increased waist circumference in either sex. **Conclusions**: Inflammation-metabolism relationships in BD are sex-specific: men exhibit cellular inflammatory markers linked to glucose and triglyceride dysregulation, while women show lipid-dependent inflammatory indices associated with HDL-C and triglyceride abnormalities. These preliminary findings suggest that risk stratification and metabolic monitoring during BD pharmacotherapy may benefit from sex-specific approaches, though replication in prospective cohorts is required before clinical translation.

Keywords: *bipolar disorder; sex differences; metabolic syndrome; inflammatory markers; cardiometabolic risk; pharmacotherapy*

1. INTRODUCTION

Bipolar disorder (BD) is a severe, recurrent, and chronic psychiatric condition that necessitates long-term, often lifelong, pharmacotherapy. Maintenance treatment with mood stabilizers (e.g. lithium, valproate) and second-generation antipsychotics (SGAs) is the cornerstone of relapse prevention and functional recovery [1]. However, the clinical utility of these agents is frequently compromised by a substantial burden of metabolic adverse effects. SGAs, in particular, are well-documented to induce weight gain, dyslipidemia, and insulin resistance [2–4], while mood stabilizers are also associated with metabolic dysfunctions [5]. Importantly, metabolic syndrome (MetS) affects up to 40% of BD

patients—approximately double the general population rate [6,7]—contributing substantially to the 10–20-year reduced life expectancy in this population [8].

A growing body of evidence implicates systemic low-grade inflammation as a shared mechanistic substrate linking BD pathophysiology with MetS development [9,10]. Patients with BD exhibit elevated levels of pro-inflammatory cytokines and acute-phase proteins [11,12]. Concurrently, these same inflammatory mediators are critical in the pathogenesis of obesity, type 2 diabetes, and atherosclerosis [13,14]. Psychopharmacological agents can directly modulate this immune-metabolic crosstalk—certain SGAs activate macrophage infiltration in adipose tissue and alter adipokine secretion, thereby exacerbating systemic inflammation and accelerating metabolic decompensation [15,16]. Thus, inflammation in BD functions as both an intrinsic illness driver and a modifiable target—or an iatrogenic amplifier—of treatment-related morbidity.

Despite the well-established sex differences in immune system reactivity and the epidemiology of BD [17,18], the role of sex as a modulator of inflammation-related metabolic risk during pharmacotherapy remains critically understudied. Females exhibit greater innate and adaptive immune responses due to genetic factors (e.g., escape from X-inactivation in immune-related genes) and hormonal influences; estrogens tend to enhance humoral immunity, while androgens such as testosterone generally exert immunosuppressive effects [17–19]. In BD, although its lifetime prevalence is roughly equal, women experience more depressive episodes and are overrepresented in the BD-II subtype, whereas men present with more manic episodes and higher rates of substance use comorbidity [20–22]. Emerging epidemiological data on the relationship between sex and metabolic risk in BD are inconsistent: in treatment-naïve patients, male sex may confer higher MetS risk [23]; however, in treated patients, women exhibit comparable or even higher rates of metabolic disturbances [24,25]. This suggests that treatment may modify metabolic risk differently in men and women, yet the underlying mechanisms—including the role of systemic inflammation—remain poorly understood.

Peripheral blood cell ratios, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), have emerged as robust, low-cost, and easily accessible proxies of systemic inflammation [26,27]. These indices are consistently elevated in patients with BD [28] and associated with MetS both in patients with BD [29] and general medical populations [30,31]. Nevertheless, their utility in stratifying sex-specific metabolic risk in BD has never been systematically evaluated. Addressing this gap is essential for moving from "one-size-fits-all" strategy toward a more nuanced, sex-informed approach to therapeutic monitoring and adverse effect prevention. In our previous work [32], we identified sex-specific associations between hematological inflammatory indices and MetS components in BD. The present study builds on these observations by assessing their potential clinical significance for personalizing pharmacotherapy and for monitoring metabolic side effects.

2. OBJECTIVE

Our primary objective of this study was to examine the associations between peripheral inflammatory indices and individual components of MetS in male and female patients with BD. We hypothesized that the pattern of immune-metabolic associations would differ between men and women, reflecting fundamental differences in immuno-endocrine regulation and suggesting sex-specific vulnerability to treatment-related metabolic disturbances.

3. MATERIALS AND METHODS

3.1. Study Design and Participants

This retrospective, cross-sectional study was conducted at the V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology (St. Petersburg, Russia). Medical records of patients treated between January 2019 and December 2023 were systematically reviewed. Patients were eligible if they met the following inclusion criteria: (1) age ≥18 years; (2) a confirmed clinical diagnosis of BD according to ICD-10 criteria; (3) availability of complete anthropometric data (height, weight, waist circumference [WC]); (4) availability of complete blood count (CBC) results with absolute counts of neutrophils, lymphocytes, monocytes, and platelets; and (5) availability of at least one of the following biochemical parameters: high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), or fasting glucose. Exclusion criteria were as follows: (1) acute infectious or inflammatory conditions of any etiology; (2) exacerbation of chronic somatic disease; (3) pregnancy or lactation. All patients were receiving ongoing pharmacological treatment as clinically indicated; however, due to the retrospective design, detailed data on specific drug regimens, dosages, and treatment duration could not be systematically ascertained and represent a study limitation.

3.2. Clinical and Laboratory Assessments

Data were extracted from electronic and paper medical records into a dedicated research database. Collected variables included: sociodemographic characteristics (age, sex), anthropometric measurements (weight, height, WC), and clinical parameters (age at onset, illness duration, number of mood episodes). Body mass index (BMI) was calculated as weight (kg) / height (m^2).

Laboratory data were obtained from routine venous blood samples collected after an overnight fast. CBCs were performed using automated hematology analyzers. The following absolute cell counts were extracted: white blood cells (WBC, $\times 10^9$/L), neutrophils (NEU, $\times 10^9$/L), lymphocytes (LYM, $\times 10^9$/L), monocytes (MON, $\times 10^9$/L), and platelets (PLT, $\times 10^9$/L). Biochemical parameters, including fasting glucose, HDL-C, and triglycerides, were measured using standard enzymatic methods.

3.3. Definition of Metabolic Disturbances

The primary outcome was the presence of individual components of MetS, rather than a full MetS diagnosis. Although the International Diabetes Federation (IDF) criteria require the assessment of WC, blood pressure (BP), and three laboratory parameters (HDL-C, TG, fasting glucose) [33], BP data were excluded from the present analysis. This decision was based on two pragmatic considerations. First, BP recordings were available only for a minority of the medical records reviewed. Second, among available recordings, measurements were obtained using heterogeneous methods (automated oscillometric devices, aneroid sphygmomanometers) under variable conditions without standardized protocols. The lack of uniformity precluded reliable between-group comparisons or adjustment for measurement bias. Therefore, our operational definition of MetS components was restricted to the anthropometric criterion (increased WC) and the three laboratory-based criteria (hyperglycemia, low HDL-C, hypertriglyceridemia).

An additional methodological challenge was that no male patient in our sample met the full IDF criteria for MetS (mandatory abdominal obesity plus at least two of the four remaining criteria). This observation necessitated a pragmatic analytic strategy to maximize statistical power and capture clinically relevant metabolic pathology. Consequently, we analyzed "abbreviated" MetS (abdominal obesity plus at least one additional laboratory criterion) and each laboratory component of MetS separately.

Thus, the following definitions were applied:

1. Increased WC (plus one additional criterion) – WC ≥94 cm for men and ≥80 cm for women, accompanied by at least one of: elevated TG, reduced HDL-C, or elevated fasting glucose;
2. Hyperglycemia – fasting glucose ≥5.6 mmol/L or current use of antidiabetic medication;
3. Low HDL-C – <1.0 mmol/L in men, <1.3 mmol/L in women;
4. Hypertriglyceridemia – fasting TG ≥1.7 mmol/L.

Based on these definitions, patients were dichotomized according to the presence or absence of each component; separate group comparisons were then conducted within each sex stratum.

3.4. Calculation of Inflammatory Indices

From the CBC data, we extracted absolute cell counts for neutrophils, lymphocytes, monocytes, and platelets. In addition, we calculated several validated inflammatory ratios/indices that reflect the balance between innate (neutrophils, monocytes, platelets) and adaptive (lymphocytes) immune responses and have been extensively studied both in BD [28] and in metabolic disorders [30,31].

The core indices were computed as follows:

a. NLR (neutrophil-to-lymphocyte ratio) = absolute neutrophil count / absolute lymphocyte count;
b. PLR (platelet-to-lymphocyte ratio) = absolute platelet count / absolute lymphocyte count;
c. MLR (monocyte-to-lymphocyte ratio) = absolute monocyte count / absolute lymphocyte count;
d. SII (systemic immune-inflammation) index = (absolute neutrophil count × absolute platelet count) / absolute lymphocyte count [26,27].

In addition, we calculated three composite indices that incorporate both inflammatory cell counts and a key metabolic parameter (HDL-C). These indices have recently been proposed as integrative markers of cardio-metabolic inflammation [34]:

a. NHR (neutrophil-to-HDL-C ratio) = absolute neutrophil count / HDL-C ($\times 10^9$/mmol);
b. PHR (platelet-to-HDL-C ratio) = absolute platelet count / HDL-C ($\times 10^9$/mmol);
c. LHR (lymphocyte-to-HDL-C ratio) = absolute lymphocyte count / HDL-C ($\times 10^9$/mmol).

All parameters—including absolute cell counts and derived indices—were treated as continuous variables in the analysis.

3.5. Statistical Analysis

Statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) in RStudio v1.4.1717. Given the non-normal distribution of most continuous variables (assessed by Shapiro–Wilk test and visual inspection of Q–Q plots), non-parametric methods were applied throughout. Descriptive statistics are presented as median (interquartile range: Q1–Q3) and [minimum–maximum]. For each of the four metabolic components, patients were stratified by sex and then divided into two groups (present vs. absent). Between-group comparisons of absolute cell counts (WBC, neutrophils, lymphocytes, monocytes, platelets), inflammatory hematological ratios (NLR, PLR, MLR, SII), and HDL-C-based composite indices (NHR, PHR, LHR) were conducted using the Mann–Whitney U test. A two-tailed p-value < 0.05 was considered statistically significant.

4. RESULTS

4.1. Sample Characteristics

A total of 102 patients with a confirmed diagnosis of BD were included in the analysis: 41 men (40.2%) and 61 women (59.8%). The median age of the overall sample was 37.1 years (interquartile range: 27–47). Clinical and demographic characteristics, stratified by sex, are presented in **Table 1**. No significant differences between men and women were observed in age, age at onset, illness duration, or number of mood episodes (all p-value > 0.05).

Table 1. Demographic and clinical characteristics of the study sample

Variable	Men (n = 41)	Women (n = 61)
Age, years	39 (27–45) [19–69]	33 (24–47) [19–71]
Age at onset, years	21 (17–30) [11–41] (n=39)	18 (16–25) [6–60] (n=59)
Illness duration, years	12 (7–21) [1–41]	13 (7–20) [2–43] (n=60)
Number of mood episodes	6 (4–9) [2–23]	6 (5–10) [2–90]

Note: *Data are shown as median (interquartile range) [min–max].*

4.2. Waist Circumference and Metabolic Components

No statistically significant differences in any inflammatory index (NLR, PLR, MLR, SII, NHR, PHR, LHR) were found between patients with and without increased WC (plus at least one additional metabolic criterion), in either men or in women (all p-value > 0.05). Detailed data for these comparisons are provided in Supplementary **Table S1**.

4.3. Hyperglycemia

Male patients with hyperglycemia exhibited significantly higher NLR and absolute neutrophil counts compared to those with normoglycemia. No other inflammatory indices differed between the groups (**Table 2**).

No significant differences in any inflammatory marker were observed between female patients with and without hyperglycemia (all p-value > 0.05; **Table 2**).

Table 2. Inflammatory markers associated with hyperglycemia in men and women with bipolar disorder

Marker	Men			Women		
	Normoglycemia (n = 32)	Hyperglycemia (n = 8)	p-value	Normoglycemia (n = 44)	Hyperglycemia (n = 11)	p-value
NLR	1.70 (1.37–2.29)	2.97 (2.37–3.63)	0.014	2.37 (1.69–3.12)	2.46 (1.93–3.03)	0.530
NEU (×10⁹/L)	3.36 (2.70–4.30)	4.08 (3.66–5.60)	0.044	3.76 (3.06–4.68)	3.96 (3.14–4.35)	0.959

Note: *Data are shown as median (interquartile range). Only parameters demonstrating significant differences either in men or women are displayed; full data on inflammatory indices comparisons are available in Supplementary Table S2. Abbreviations: NLR - neutrophil-to-lymphocyte ratio; NEU - absolute neutrophil count.*

4.4. Low HDL-C

Female patients with reduced HDL-C demonstrated significantly higher NHR and PHR compared to those with normal HDL-C levels. LHR showed a trend toward elevation but did not reach statistical significance (**Table 3**).

No significant differences in any inflammatory index were found between male patients with and without low HDL-C (all p-value > 0.05; **Table 3**).

Table 3. Inflammatory markers associated with low HDL-C in men and women with bipolar disorder

Marker	Men			Women		
	Normal HDL-C (n = 21)	Low HDL-C (n = 6)	*p*-value	Normal HDL-C (n = 30)	Low HDL-C (n = 7)	*p*-value
NHR	2.52 (1.96–2.98)	3.12 (2.38–4.70)	0.530	2.48 (1.83–3.28)	3.75 (3.25–4.32)	**0.031**
PHR	171.37 (135.57–210.72)	266.49 (172.38–336.57)	0.062	156.96 (131.16–184.23)	235.48 (190.16–287.60)	**0.009**
LHR	1.36 (0.98–1.79)	1.79 (1.47–3.21)	0.574	1.15 (0.93–1.53)	1.77 (1.32–2.22)	0.095

Note: *Data are shown as median (interquartile range). Selected parameters of interest are displayed; full data on inflammatory indices comparisons are available in Supplementary Table S3. Abbreviations: NHR - neutrophil-to-high-density lipoprotein cholesterol ratio; PHR - platelet-to-high-density lipoprotein cholesterol ratio; LHR - lymphocyte-to-high-density lipoprotein cholesterol ratio.*

4.5. Hypertriglyceridemia

Male patients with hypertriglyceridemia had significantly higher absolute lymphocyte counts and total white blood cell counts compared to those with normal triglyceride levels. None of the calculated inflammatory ratios (NLR, PLR, MLR, SII, NHR, PHR, LHR) differed significantly between the groups in men (**Table 4**).

Female patients with hypertriglyceridemia exhibited significantly elevated NHR and LHR compared to those with normotriglyceridemia. No significant differences were observed for other inflammatory indices (**Table 4**).

Table 4. Inflammatory markers associated with hypertriglyceridemia in men and women with bipolar disorder

Marker	Men			Women		
	Normal triglycerides (n = 17)	High triglycerides (n = 12)	*p*-value	Normal triglycerides (n = 30)	High triglycerides (n = 10)	*p*-value
WBC (×10⁹/L)	5.45 (4.80 – 6.25)	6.24 (5.85 – 7.54)	**0.031**	5.74 (5.03 – 6.46)	6.58 (5.94 – 7.55)	0.249
LYM (×10⁹/L)	1.58 (1.30 – 1.80)	2.70 (1.89 – 2.96)	**0.010**	1.86 (1.61 – 2.11)	2.49 (1.99 – 2.76)	0.111
NHR	2.57 (2.10 – 3.22)	2.79 (2.18 – 3.46)	0.837	2.04 (1.56 – 2.80)	4.83 (2.14 – 5.89)	**0.042**
LHR	1.27 (1.03 – 1.51)	1.74 (1.41 – 2.07)	0.250	1.12 (0.94 – 1.37)	1.59 (1.35 – 2.00)	**0.027**

Note: *Data are shown as median (interquartile range). Only parameters demonstrating significant differences either in men or women are displayed; full data on inflammatory indices comparisons are available in Supplementary Table S4. Abbreviations: WBC - white blood cells count; LYM - absolute lymphocyte count; NHR - neutrophil-to-high-density lipoprotein cholesterol ratio; LHR - lymphocyte-to-high-density lipoprotein cholesterol ratio.*

5. DISCUSSION

The results of this retrospective cross-sectional study provide preliminary evidence of qualitative sex-specific patterns in the association between peripheral inflammatory indices and individual components of MetS in patients with BD. Our findings demonstrate distinct immuno-metabolic profiles: in men, metabolic disturbances—particularly hyperglycemia and hypertriglyceridemia—were associated with cellular inflammatory markers (elevated NLR, absolute neutrophil and lymphocyte counts); in women, metabolic abnormalities were linked exclusively to lipid-dependent inflammatory ratios (NHR, PHR, LHR), with no significant associations detected for CBC parameters or hematological indices. These results suggest that the interface between systemic inflammation and cardiometabolic risk in pharmacologically treated BD patients differs fundamentally between sexes and cannot be adequately captured by unstratified analyses.

5.1. Male Patients: Cellular Inflammatory Markers

The association between elevated NLR and hyperglycemia exclusively in men is the most clinically significant finding of this study. NLR is a robust, well-validated marker of systemic low-grade inflammation, reflecting the balance between neutrophil-mediated innate immune activation and lymphocyte-mediated adaptive immune regulation [26,28]. Previous research has demonstrated that elevated NLR independently predicts incident type 2 diabetes, cardiovascular mortality, and all-cause mortality in individuals with MetS [35,36]. Our data extend these observations to BD pharmacotherapy: men with BD and hyperglycemia exhibited significantly higher NLR and absolute neutrophil counts, whereas women with identical metabolic disturbances showed no such elevation.

This sex-specific pattern likely reflects fundamental differences in immune-metabolic regulation between males and females. Studies in untreated BD patients report both higher MetS prevalence in men [23] and sex- specific metabolic correlates [37], suggesting baseline vulnerability in male patients even without pharmacotherapy. Pharmacotherapy may act as a catalyst, unmasking and amplifying this predisposition—the metabolic stress induced by pharmacological agents may trigger the neutrophil–lymphocyte pathway in men, elevating NLR. This interpretation aligns with

pharmacovigilance data showing that men exhibit greater vulnerability to metabolic laboratory abnormalities, including hypertriglyceridemia and hyperinsulinemia [38].

Biological underpinnings of this male-specific vulnerability are further illuminated by hormonal and immunological studies. Antipsychotic-treated men with severe mental disorders show more severe cardiometabolic risk profiles, with triglyceride elevation significantly associated with alterations in multiple metabolic hormones, including leptin, insulin, cortisol, and thyroid-stimulating hormone [39]. This suggests the involvement of hormonal axes governing energy homeostasis, metabolism, and stress response. Experimental data indicate that male but not female mice develop glucose intolerance and visceral adipose tissue macrophage infiltration under metabolic stress (high-fat diet) [40]. Together, these findings are consistent with fundamental research on sexual dimorphism in immune responses showing more robust humoral and cytokine responses in females and stronger myeloid cell reactivity in males [41,42]. This sex-specific immune allocation could explain why NLR—a marker integrating the cellular component—becomes informative for metabolic risk during pharmacotherapy in men but not in women. However, direct extrapolation from animal models to clinical populations requires caution.

Thus, it appears that among male patients with BD, pharmacotherapy does not create vulnerability *ex nihilo* but rather amplifies a pre-existing predisposition, potentially forging a direct, NLR-detectable link between inflammation and metabolic disturbances.

5.2. Female Patients: Lipid-Linked Inflammation

In women with BD, metabolic abnormalities were associated with indices incorporating HDL-C. Specifically, low HDL-C was associated with higher NHR and PHR; hypertriglyceridemia was associated with higher NHR and LHR. While these associations are partially driven by mathematical coupling—HDL-C appears as both the grouping variable and the index denominator—they are unlikely to be merely artefactual. HDL particles possess intrinsic anti-inflammatory, antioxidant, and endothelial-protective properties; independently of concentration, HDL cholesterol efflux capacity inversely correlates with cardiovascular risk [43].

Notably, no associations were found between MetS components and cellular inflammatory indices (NLR, PLR, MLR, SII) in women. This absence is striking because, in treated BD populations, women exhibit metabolic disturbances at rates comparable to—and for some parameters even exceeding—men, including weight gain, obesity, and hypercholesterolemia [24,25]. This raises a critical question: if women experience metabolic abnormalities at frequencies equal to or greater than men during pharmacotherapy, why do they not show corresponding activation of the neutrophil–lymphocyte pathway?

One possible explanation is that comparable rates of metabolic disturbances in men and women may be achieved through different pathophysiological pathways. The key factor shaping this female-specific profile is likely estrogenic regulation. Estrogens are master regulators of both immune function [40,41] and lipid metabolism [44]; this axis may become the primary target under metabolic stress. Consequently, weight gain and dyslipidemia may develop without engagement of the neutrophil–lymphocyte pathway (explaining the absence of NLR elevation), but with concomitant changes in lipid-dependent indices. In other words, estrogens may transform vulnerabilities to metabolic disturbances by altering their trajectories.

Biological plausibility of this mechanism is supported by experimental data: ovariectomized female rats treated with olanzapine developed body weight gain and impaired glucose tolerance—effects reversed by estradiol replacement [45]. Notably, olanzapine-treated female but not male mice exhibited elevations in pro-inflammatory cytokines (IL-8, IL-1β) [46], consistent with the hypothesis that metabolic stress activates distinct immune compartments in females—pathways linked to humoral responses and lipid metabolism rather than the cellular arm captured by NLR.

Thus, preserved estrogenic tone in women may shield against direct neutrophil–lymphocyte pathway activation, redirecting inflammatory responses toward lipid-mediated mechanisms. This aligns with the "estrogen paradox"—the observation that heightened immunological reactivity (predisposing to autoimmunity) coexists with relative protection from cardiometabolic complications [47]. When this shielding is compromised—through menopause, antipsychotic-induced hormonal changes, or their interaction—elevations in NHR/PHR/LHR may emerge as markers of increased metabolic risk.

Our findings are partially consistent with a general population study reporting LHR as the only inflammatory marker independently associated with MetS in both sexes [48]. In our BD sample, however, LHR elevations were confined to women with dyslipidemia, with no such associations in men. This discrepancy likely reflects fundamental differences between general and psychiatric populations: the presence of BD and its treatment may substantially modify immuno-metabolic relationships. Alternatively, limited statistical power—particularly given the absence of men meeting full MetS criteria—may have precluded detection of LHR associations in males. Nevertheless, the consistent

elevation of LHR in women with dyslipidemia warrants further investigation of this index as a potential metabolic risk marker in BD.

5.3. Integration with Prior Evidence on Sex-Specific Side Effects

Our findings on sex-specific immuno-metabolic patterns align with the emerging evidence on sex differences in adverse effects of mood stabilizers and antipsychotics. A recent systematic review concluded that while women report more frequent adverse effects overall—including hypothyroidism with lithium, and weight gain and hyperprolactinemia with antipsychotics—men may exhibit greater vulnerability to certain cardiometabolic outcomes, particularly hyperglycemia and hypertriglyceridemia [24]. This apparent divergence—greater subjective weight gain in women but more severe metabolic laboratory abnormalities in men—is consistent with our results and pharmacovigilance data [38].

Several non-mutually exclusive explanations may reconcile this discrepancy. First, women may be more aware of and willing to report body image-related adverse effects, whereas men underreport. Second, body fat distribution differs by sex: women accumulate more subcutaneous adipose tissue, which is metabolically less harmful than the visceral adiposity more common in men. Third, testosterone suppression by prolactin-elevating antipsychotics may be metabolically impactful in men, contributing to insulin resistance and dyslipidemia. Fourth, pharmacokinetic differences—higher plasma drug concentrations in women due to lower body weight, higher fat proportion, and lower CYP450 activity—may lead to greater efficacy but also greater toxicity [24]. Our data suggest that NLR may serve as a readily accessible biomarker to identify men experiencing "silent" metabolic deterioration before overt clinical manifestations emerge.

5.4. Potential Clinical Implications

Our findings, while preliminary, may have implications for the clinical monitoring of patients with BD receiving pharmacotherapy. Current guidelines recommend regular metabolic assessment but do not differentiate strategies by sex [49]. Hematological ratios derived from routine complete blood counts require no additional sampling and could aid in risk stratification—but their interpretation may need to be sex-specific.

In male patients, elevated baseline NLR might signal need for closer glucose and lipid monitoring during treatment, even without overt obesity. For men with high NLR, metabolically favorable agents (aripiprazole, lurasidone, lamotrigine) could be prioritized over higher-risk options. In female patients, our data point to the particular importance of monitoring HDL-C and triglyceride levels, even when NLR and other cellular indices remain normal. A declining HDL-C level in a female patient—especially during antipsychotic treatment—may warrant attention not only as a lipid abnormality but also as a potential indicator of emerging immuno-metabolic dysregulation and possible erosion of estrogen-associated protection.

More broadly, our results suggest that sex-specific reference ranges for inflammatory biomarkers in psychiatry warrant investigation. Just as cardiology has adopted sex-specific algorithms for troponin, creatinine, and HDL-C, psychiatric populations may benefit from similar refinements: an NLR value that raises concern in a man may be within physiological variation in a woman, given her higher basal immune reactivity. Conversely, the absence of NLR elevation in a woman with metabolic disturbances should not be over-interpreted—her risk profile may be better captured by entirely different biomarkers.

5.5. Limitations

Several limitations of this study warrant acknowledgment. The retrospective, cross-sectional design precludes causal inference. The modest sample size limits statistical power and precludes multivariable adjustment for potential confounders such as age, illness duration, smoking, body mass index, and others. Lack of detailed medication data—including specific agents, doses, duration of treatment, and adherence—means we cannot definitively attribute the observed inflammation-metabolism associations to pharmacotherapy rather than illness-related factors. However, the sex-specific pattern we observed parallels experimental and pharmacovigilance data on sex-dependent antipsychotic effects, making a treatment interaction plausible.

Additionally, we could not control for menstrual cycle phase, menopausal status, or hormonal contraceptive use in women—factors modulating both inflammation and lipid metabolism. Phase of BD illness at the time of blood sampling was not systematically recorded; existing data demonstrate that NLR is significantly elevated during (hypo)mania only in men, while platelet count is elevated during (hypo)mania only in women [50]. This phase- and sex-specific variability may have introduced uncontrolled confounding into our associations. Finally, we did not assess other inflammatory markers (hsCRP, IL-6, TNF-α) that might have provided additional mechanistic insights. The pragmatic

strength of our study—its use of routine, low-cost laboratory parameters—also represents a limitation in terms of mechanistic depth.

5.6. Future Research Directions

As a hypothesis-generating study, this work suggests several directions for future investigation. Prospective longitudinal cohorts are needed to validate whether NLR predicts incident metabolic dysfunction in men initiating antipsychotic treatment and to establish optimal sex-specific risk thresholds through time-to-event analyses. Enrolling patients across illness stages—from first-episode treatment-naïve individuals to those receiving long-term treatment—would clarify how the immuno-metabolic profile evolves under pharmacotherapy and with increasing illness duration.

Studies integrating pharmacogenetics and therapeutic drug monitoring may clarify whether sex differences in NLR-metabolism associations are mediated by differential drug exposure (e.g., higher concentrations in women) or differential tissue sensitivity. Mechanistic studies should examine whether testosterone suppression by prolactin-elevating antipsychotics contributes to the NLR-hyperglycemia link in men, and explore the role of X-chromosome inactivation patterns and TLR7/IRAK1 pathway activity in modulating antipsychotic-induced metabolic inflammation.

Intervention studies testing whether switching from high-metabolic-risk agents to metabolically neutral alternatives reduce NLR and improves metabolic parameters—and whether these effects differ by sex—would provide clinically actionable evidence. Additionally, the female-specific lipid-inflammatory indices (NHR, LHR, PHR) require validation as dynamic biomarkers capable of tracking response to therapeutic interventions or lifestyle modifications.

Finally, our findings point to potential avenues for sex-specific nutritional interventions. Omega-3 polyunsaturated fatty acids (PUFAs) have shown greater antidepressant efficacy in women with major depressive disorder than in men, possibly due to higher baseline inflammation and metabolic burden in women with depression [51]. Whether similar sex differences exist in BD, and whether omega-3 PUFAs could modulate the inflammatory and metabolic pathways identified here, warrants investigation.

Thus, the primary contribution of the present study lies in informing the direction and design of future research. A mandatory component will be meticulous collection of treatment-related data (specific agents, dosages, duration), enabling not merely identification of associations but elucidation of causal relationships between exposure to specific medications, longitudinal changes in inflammatory markers, and the development of metabolic disturbances in men and women.

6. CONCLUSIONS

In summary, this study provides preliminary evidence that peripheral inflammation is linked to metabolic dysregulation in BD in sex-specific ways. In men, the association involves cellular inflammatory markers (NLR, neutrophils) and may reflect heightened vulnerability to treatment-induced metabolic stress and, by extrapolation from general medicine, increased risk of cardiovascular mortality. In women, metabolic abnormalities are associated with lipid-dependent inflammatory indices (NHR, PHR, LHR), potentially reflecting estrogenic modulation of both inflammation and lipid metabolism. These findings underscore the importance of sex-stratified analyses in psychoneuroimmunology research and suggest that personalized approaches to metabolic monitoring in BD may benefit from incorporating sex as a biological variable. However, given the exploratory nature of this study and its methodological limitations, these results require replication in larger, prospective cohorts before clinical translation can be considered.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Independent Ethics Committee of the V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology (Protocol No. 9, date of approval: 21.12.2023).

Informed Consent Statement: Patient consent was waived due to due to the retrospective, non-interventional nature of the study.

Data Availability Statement: All data supporting reported results will be provided upon request to the corresponding author.

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

SUPPLEMENTARY MATERIALS

Table S1. Inflammatory indices associated with increased waist circumference (plus at least one additional metabolic criterion) in men and women with bipolar disorder

Index	Men			Women		
	Normal waist circumference (n = 17)	Increased waist circumference (n = 2)	*p*-value	Normal waist circumference (n = 25)	Increased waist circumference (n = 6)	*p*-value
NLR	2,00	2,84	0,333	2,31	2,78	0,560
PLR	141,37	202,84	0,333	146,67	172,28	1
MLR	0,30	0,26	0,563	0,61	0,20	0,280
SII	504,71	813,38	0,333	613,02	870,98	0,560
NHR	2,60	3,07	0,749	2,58	3,14	0,129
PHR	190,04	202,89	0,749	161,66	203,58	0,093
LHR	1,45	1,15	0,556	1,22	1,33	0,447

Note: *NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio; SII = systemic immune-inflammation index; NHR = neutrophil-to-high-density lipoprotein cholesterol ratio; PHR = platelet-to-high-density lipoprotein cholesterol ratio; LHR = lymphocyte-to-high-density lipoprotein cholesterol ratio.*

Table S2. Inflammatory indices associated with hyperglycemia in men and women with bipolar disorder

Index	Men			Women		
	Normoglycemia (n = 32)	Hyperglycemia (n = 8)	*p*-value	Normoglycemia (n = 44)	Hyperglycemia (n = 11)	*p*-value
NLR	1,70	2,97	0,014	2,37	2,46	0,530
PLR	131,78	178,58	0,117	144,35	176,49	0,643
MLR	0,31	0,28	0,278	0,54	0,52	0,263
SII	437,83	740,33	0,059	622,93	791,63	0,395
NHR	2,52	3,02	0,500	2,71	2,60	0,940
PHR	193,32	186,099	0,964	163,04	198,07	0,273
LHR	1,54	1,14	0,117	1,25	1,20	0,978

Note: *NLR - neutrophil-to-lymphocyte ratio; PLR - platelet-to-lymphocyte ratio; MLR - monocyte-to-lymphocyte ratio; SII - systemic immune-inflammation index; NHR - neutrophil-to-high-density lipoprotein cholesterol ratio; PHR - platelet-to-high-density lipoprotein cholesterol ratio; LHR - lymphocyte-to-high-density lipoprotein cholesterol ratio.*

Table S3. Inflammatory indices associated with low HDL-C in men and women with bipolar disorder

Index	Men			Women		
	Normal HDL-C (n = 21)	Low HDL-C (n = 6)	*p*-value	Normal HDL-C (n = 30)	Low HDL-C (n = 7)	*p*-value
NLR	2,03	2,13	0,823	2,28	3,06	0,728
PLR	135,76	189,88	0,301	147,54	173,41	0,874
MLR	0,29	0,36	0,813	0,560	0,399	0,948
SII	509,18	585,24	0,654	612,67	937,55	0,776
NHR	2,52	3,12	0,530	2,478	3,75	0,031
PHR	171,37	266,49	0,062	156,96	235,48	0,009
LHR	1,36	1,79	0,574	1,15	1,77	0,095

Note: *NLR - neutrophil-to-lymphocyte ratio; PLR - platelet-to-lymphocyte ratio; MLR - monocyte-to-lymphocyte ratio; SII - systemic immune-inflammation index; NHR - neutrophil-to-high-density lipoprotein cholesterol ratio; PHR - platelet-to-high-density lipoprotein cholesterol ratio; LHR - lymphocyte-to-high-density lipoprotein cholesterol ratio.*

Table S4. Inflammatory indices associated with hypertriglyceridemia in men and women with bipolar disorder

Index	Men			Women		
	Normal TG (n = 17)	High TG (n = 12)	*p*-value	Normal TG (n = 30)	High TG (n = 10)	*p*-value
NLR	2,22	1,71	0,335	2,13	3,19	0,568
PLR	158,14	118,07	0,083	160,50	123,46	0,189
MLR	0,28	0,35	0,606	0,64	0,22	0,152
SII	529,35	506,88	0,820	591,36	862,24	0,376
NHR	2,57	2,79	0,837	2,04	4,83	0,042
PHR	191,04	192,01	0,902	164,08	189,65	0,288
LHR	1,27	1,74	0,250	1,12	1,59	0,027

Note: *NLR - neutrophil-to-lymphocyte ratio; PLR - platelet-to-lymphocyte ratio; MLR - monocyte-to-lymphocyte ratio; SII - systemic immune-inflammation index; NHR - neutrophil-to-high-density lipoprotein cholesterol ratio; PHR - platelet-to-high-density lipoprotein cholesterol ratio; LHR - lymphocyte-to-high-density lipoprotein cholesterol ratio, TG -triglycerides.*

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