ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
In press.

Prominent Role of T Cells and Inflammasome in Bipolar Disorder

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Received: 21 November2025; Received in revised form: 12 May 2026; Accepted: 21 May 2026

ABSTRACT

This study investigated the gene expression of t-bet, interferon-γ (IFN-γ), GATA3, interleukin-4 (IL-4), RoRγt, IL-17, Foxp3, IL-10, and transforming growth factor-β (TGF-β) as transcription factors and associated cytokines of T-cell subsets, and nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3), P2X7R, IL-1β, and IL-18 as inflammasome complex-related factors in bipolar disorder (BD) cases compared to healthy controls (HCs).

Whole blood was collected from 48 BD patients and 48 HCs. RNA was then extracted, cDNA was synthesized, and gene expression was assessed using SYBR® Green real-time polymerase chain reaction (PCR) with specific primers.

P2X7R expression was significantly higher in BD patients than in HCs. Additionally, GATA3 and Foxp3 expression levels were significantly lower, and IL-17 expression levels were significantly higher in BD patients than in HCs.

In conclusion, higher levels of inflammation-associated factors and a deregulated balance of T-cell subsets toward a pro-inflammatory status could highlight the importance and involvement of inflammation in the immunopathogenesis of BD.

Keywords: Bipolar disorder; Immune response; Inflammation; Inflammasome; T-lymphocyte subsets

INTRODUCTION

Psychiatric disorders are defined as a loss of mood control and a history of experiencing mental distress. Bipolar disorder (BD), the 17th most disabling disease worldwide, is a complex mental disorder characterized by recurrent mood swings between manic and depressive episodes, which significantly affects the

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Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

overall quality of life because of its chronic, progressive course.[1–3] In the manic phase, patients develop high activity levels, rapid speech, a decreased need for sleep, and increased self-confidence and grandiose beliefs, while in the depressive phase, patients show decreased energy levels, hopelessness, sadness, anorexia, guilty feelings, and suicidal behavior.[4] Although the exact pathogenesis of BD is unknown, genetic predisposition, environmental factors, and biological elements are considered risk factors that impact the occurrence and severity of the disease.[5,6] Multiple lines of evidence have emphasized the involvement of immunologic and inflammatory pathways in the pathogenesis of BD and evidence of low-grade inflammation.[1] In addition, recent reports have highlighted elevated serum C-reactive protein (CRP), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) levels as inflammatory mediators, along with deregulated gene expression of both pro- and anti-inflammatory mediators in manic or depressive phases of patients with BD.[7–10]

The inflammasome is a multiprotein complex activated during innate immune responses that induces caspase-1 activation and the production of IL-1β and IL-18. The *P2X7R* gene belongs to the P2 purine signaling receptor family and is crucial in neurotransmission regulation by inducing NLRP3 inflammasome activation.[11] A recent study reported that *P2X7R*, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3), IL-1β, and IL-18 expression levels were significantly increased in the peripheral blood mononuclear cells (PBMCs) of patients with schizophrenia, highlighting systemic inflammation and the involvement of this inflammasome pathway in psychiatric disorders.[12] T lymphocytes are also important in the formation of immunologic synapses between immune cells and neurons by expressing various types of noradrenergic, cholinergic, and peptidergic receptors.[13] Studies have shown that imbalances in T-cell subsets, i.e., helper T (T_H) cells, including T_H1, T_H2, T_H17, and regulatory T (Treg) cells, are associated with chronic inflammation in patients with BD.[14,15] Reduced numbers of Tregs and imbalanced populations of T_H1, T_H2, and T_H17 cells were correlated with elevated inflammatory mediators and reduced expression of anti-inflammatory cytokines.[14,15]

In the present study, we evaluated the gene expression of *t-bet*, interferon-γ (IFN-γ), *GATA3*, IL-4, *RoRγt*, IL-17, *Foxp3*, IL-10, and transforming growth factor-β (TGF-β) as T-cell subset-specific transcription factors and related cytokines, as well as NLRP3, *P2X7R*, IL-1β, and IL-18 as inflammasome complex-related factors in patients with BD and healthy controls (HCs).

MATERIALS AND METHODS

Ethics Approval

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.IRH.REC.1402.016). We utilized the −80 °C stored RNA bank of a previous study entitled "Evaluating the gene expressions of *CCL2*, *CCL3*, and *CXCL8* chemokines in patients with bipolar disorder," which was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1394.494) and the resulting article was published in 2019.[1]

Participants

Forty-eight patients with diagnosed BD and 48 age- and sex-matched HCs were recruited for the study. Patients were enrolled from Ibn-Sina Psychiatric Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. They had no history of autoimmune disease or malignancy and were screened for BD using the Structured Clinical Interview for DSM-IV-Axis I disorders (SCID-I). In addition, the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS) (using a score of 7 as the cutoff point) were used to assess the severity of manic and depressive symptoms, respectively. The HCs were recruited from the local population and screened to ensure that they were not pregnant and had no history of psychiatric disorders (SCID-I rating), inflammatory, autoimmune, or infectious diseases, and malignancy.

RNA Extraction and cDNA Synthesis

Whole blood samples (5 mL) were collected from all participants, total RNA was extracted using the Total RNA Purification Mini Kit (FavorPrep; Yekta Tajhiz Azma [YTA], Tehran, Iran), and cDNA was synthesized using a cDNA synthesis kit (Ana Cell, Tehran, Iran) according to the manufacturers' protocols.

SYBR Green Real-Time Polymerase Chain Reaction

The SYBR Green real-time PCR was used to assess the gene expression of *t-bet*, *IFN-γ*, *GATA3*, *IL-4*, *RoRγt*, *IL-17*, *Foxp3*, *IL-10*, *TGF-β*, *P2X7R*, *NLRP3*, *IL-1β*, and

IL-18. PCR reactions were conducted in a total volume of 20 µL containing 8 µL cDNA, 10 µL SYBR® Green Master Mix, 0.8 µL forward primer (10 pmol/µL), 0.8 µL reverse primer (10 pmol/µL), and 0.4 µL distilled water. Additionally, an ABI Thermal Cycler (Applied Biosystems Inc, CA, USA) was used for amplification under the following conditions: for *GAPDH*, *t-bet*, *IFN-γ*, *GATA3*, *IL-4*, *RoRγt*, *IL-17*, *IL-10*, and *TGF-β*, 95°C for 15 minutes for initial denaturation, followed by 40 three-step cycles of 95°C for 10 seconds, 60 °C for 30 seconds, and 72°C for 20 seconds; for *P2X7R*, *NLRP3*, *IL-1β*, and *IL-18*, 95°C for 15 minutes for initial denaturation, followed by 40 three-step cycles of 95°C for 10 seconds, 58°C for 30 seconds, and 72°C for 20 seconds; and for *Foxp3*, 95°C for 10 minutes for initial denaturation, followed by 40 three-step cycles of 95°C for 15 seconds, 60 °C for 15 seconds, and 72°C for 20 seconds. The sequences of the in-house-designed primers are provided in Supplementary Table 1. All samples were run in duplicate, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a housekeeping gene to normalize the expression of target genes, and data were analyzed by the $2^{-\Delta\Delta C_T}$ method.

Statistical Analysis

GraphPad Prism, version 9 (GraphPad Software, San Diego, CA), was used for statistical analysis and graphing. The Shapiro-Wilk test was used to assess the normality of distribution, and an unpaired *t* test or Mann-Whitney test was applied to compare expression levels between BD patients and HCs. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Demographic Characteristics of BD Patients and HCs

The 48 BD patients included 24 females (50%) and 24 males (50%), while the 48 HCs had the same female-to-male ratio. The mean±SD of age in BD subjects and HCs was 35.95±12.32 and 34±12.37 years, respectively. In addition, the mean±SD of HDRS and YMRS parameters in BD patients were 6.54±2.04 and 31.22±5.26, respectively.

Relative Expression of Inflammasome-related Genes

As shown in Figure 1, the relative expression levels of inflammasome-associated genes were compared between patients with BD and HCs. Although the expression levels of all four candidate genes, including *IL-1β*, *IL-18*, *P2X7R*, and *NLRP3*, were higher in patients with BD, only *P2X7R* expression was significantly different ($p = 0.02$) between the BD and HC groups, and the differences in *NLRP3* ($p = 0.27$), *IL-1β* ($p = 0.33$), and *IL-18* ($p = 0.60$) expression levels were not statistically significant.

Relative Expression of T_H1-, T_H2-, and T_H17-related Genes

As shown in Figure 2, the gene expression levels of *t-bet* and *IFN-γ*, as the transcription factor and cytokine, respectively, of the T_H1 pro-inflammatory subset, were higher in BD patients than in HCs ($p = 0.34$ and $p = 0.34$, respectively). In the case of T_H2-associated transcription factors and cytokines, the gene expression level of *GATA3* was significantly lower in BD patients than in HCs ($p = 0.001$), while the level of *IL-4* was lower, but the difference was not statistically significant, in BD patients than in HCs ($p = 0.86$). Evaluation of T_H17-associated factors revealed that both *RoRγt* and *IL-17* expression levels were higher in patients with BD than in HCs, but the difference in the case of *IL-17* was statistically significant ($p = 0.02$), while that of *RoRγt* was not statistically significant ($p = 0.35$).

Relative Expression of Treg-related Genes

As shown in Figure 3, the expression levels of *Foxp3*, a Treg-specific transcription factor, were lower in patients with BD than in HCs, and the difference was statistically significant ($p<0.001$). In addition, *IL-10* ($p=0.53$) and *TGF-β* ($p=0.28$) expression levels were lower in BD patients than in HCs; however, the differences were not statistically significant.

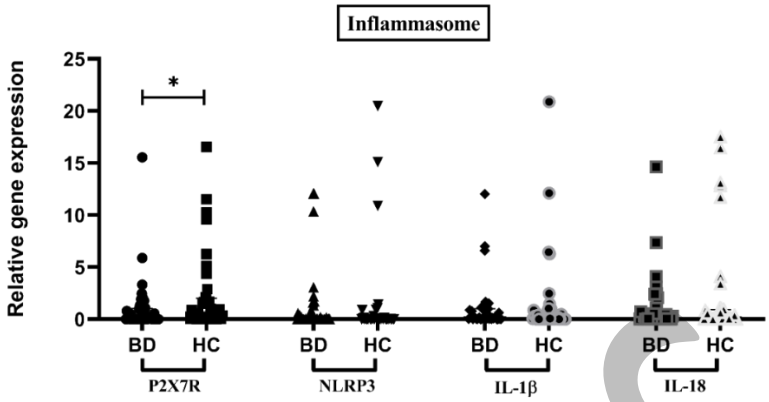

Figure 1. Relative expression levels of *IL-1β*, *IL-18*, *NLRP3*, and *P2X7R* in BD patients compared to HCs. The Shapiro-Wilk test was used to assess normality; an unpaired *t* test or Mann-Whitney test was used to compare the BD and HC groups for normally and nonnormally distributed data, respectively. Data are presented as individual points with median and quartile lines; $p \leq 0.05$ was considered statistically significant, and * represents $p \leq 0.05$.

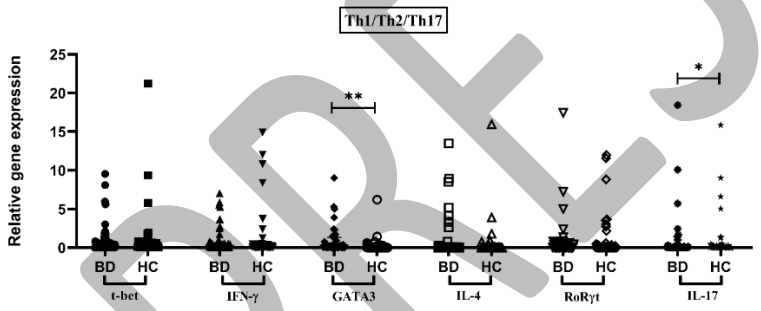

Figure 2. Relative gene expression of *t-bet*, *IFN-γ*, *GATA3*, *IL-4*, *RoRγt*, and *IL-17* as transcription factors and cytokines associated with T_H1, T_H2, and T_H17 subsets in BD patients compared to HCs. The Shapiro-Wilk test was used to assess normality; an unpaired *t* test or Mann-Whitney test was used to compare the BD and HC groups for normally and nonnormally distributed data, respectively. Data are presented as individual points with median and quartile lines; $p \leq 0.05$ was considered statistically significant, and * represents $p \leq 0.05$, ** represents $p \leq 0.01$.

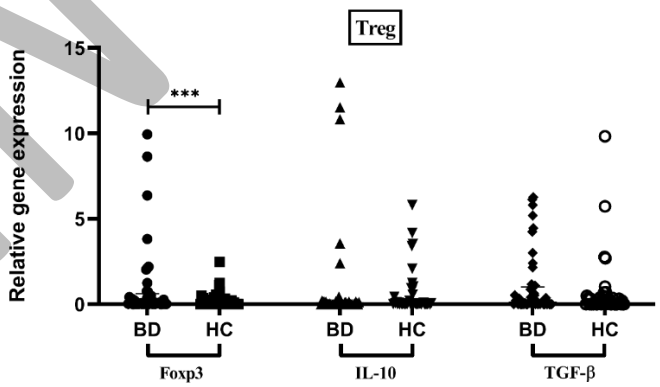

Figure 3. Relative expression levels of *Foxp3*, *IL-10*, and *TGF-β* as transcription factors and cytokines associated with Tregs in BD patients compared to HCs. The Shapiro-Wilk test was used to assess normality; an unpaired *t* test or Mann-Whitney test was used to compare the BD and HC groups for normally and nonnormally distributed data, respectively. Data are presented as individual points with median and quartile lines; $p \leq 0.05$ was considered statistically significant, and * represents $p \leq 0.001$.**

DISCUSSION

The current study evaluated the gene expression levels of *P2X7R*, *NLRP3*, *IL-1β*, and *IL-18* as components of the inflammasome pathway, as well as T-cell subset-associated transcription factors and cytokines, including *t-bet*, *IFN-γ*, *GATA3*, *IL-4*, *RoRγt*, *IL-17*, *Foxp3*, *IL-10*, and *TGF-β*, in peripheral blood samples of BD patients compared to HCs. The results indicated significantly higher *P2X7R* and *IL-17* expression levels and significantly lower *GATA3* and *Foxp3* expression levels, implying increased inflammatory responses and a deregulated balance of T-cell subsets toward a pro-inflammatory status in BD patients.

Interactions between inflammatory and immune responses and the central nervous system (CNS) have been reported in several psychiatric disorders, including BD.[16–18] In the manic phase, patients develop high activity levels, rapid speech, a decreased need for sleep, and increased self-confidence and grandiose beliefs, while in the depressive phase, patients show decreased energy levels, hopelessness, sadness, anorexia, guilty feelings, and suicidal behavior.[4] Although the exact pathogenesis of BD is unknown, genetic predisposition, environmental factors, and biological elements are considered risk factors that influence the occurrence and severity of the disease.[5,6] Multiple lines of evidence have emphasized the involvement of the immune system and inflammation in the immunopathogenesis of BD.[1] In addition, recent reports have highlighted elevated serum C-reactive protein (CRP), IL-1β, and TNF-α levels as inflammatory mediators, along with deregulated gene expression of both pro- and anti-inflammatory mediators in manic or depressive phases of patients with BD.[7–10]

The inflammasome is a multiprotein complex that is activated during innate immune responses and induces caspase-1 activation to produce IL-1β and IL-18 cytokines. The *P2X7R* gene belongs to the P2 purine signaling receptor family and is crucial in neurotransmission regulation by inducing NLRP3 inflammasome activation.[11] A recent study reported that *P2X7R*, NLRP3, IL-1β, and IL-18 expression levels were significantly higher in the PBMCs of patients with schizophrenia, highlighting systemic inflammation and the involvement of this inflammasome pathway in psychiatric disorders.[12] T lymphocytes are also important in the formation of immunologic synapses between immune cells and neurons by expressing various types of noradrenergic, cholinergic, and peptidergic receptors.[13] Studies have shown that imbalances in T-cell subsets, ie, T_H cells, including T_H1, T_H2, T_H17, and regulatory T (Treg) cells, are associated with chronic inflammation in patients with BD.[14,15] Reduced numbers of Tregs and imbalanced populations of T_H1, T_H2, and T_H17 cells were correlated with elevated inflammatory mediators and reduced expression of anti-inflammatory cytokines.[14,15]

Although reports on the direction and patterns of inflammatory changes in BD are inconsistent, our comparison of the *NLRP3* inflammasome-related factors between patients with BD and HCs showed significantly higher *P2X7R* expression and no significant between-group differences in *NLRP3*, *IL-1β*, and *IL-18* expression. *NLRP3* is expressed by neurons, microglia, astrocytes, and CNS-infiltrating lymphocytes, and its activation and overexpression in peripheral blood imply systemic inflammation.[23] The increased expression of *P2X7R*, which is an important participant in the inflammasome pathway, triggers *NLRP3* complex assembly after sensing ATP released during stress and exposure to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[24,25] Postmortem analysis of the human frontal cortex from BD patients showed similar results, with elevated levels of caspase-1 and IL-1β, as well as other inflammatory mediators, such as IL-6 and TNF-α.[28] Interestingly, similar observations have been reported in other psychiatric disorders, such as schizophrenia (SCZ). In this case, Unal et al reported a significant elevation of *NLRP3*, *P2X7R*, *IL-1β*, and *IL-18* expression levels in patients with schizophrenia compared with HCs.[12]

Fluctuations in immune cell numbers and function, including imbalances in T-cell subsets, are commonly reported in patients with BD and other manic disorders.[29–31] In the present study, we observed a significant increase in the expression of the *IL-17* pro-inflammatory cytokine as a signature of the T_H17 subset, whereas RoRγt expression did not differ significantly between groups. Additionally, *GATA3* and *Foxp3* expression levels were significantly lower in BD cases than in HCs. These results suggest a deregulated balance of T_H1/T_H2 and T_H17/Treg cells toward T_H1 and T_H17 pro-inflammatory responses and a suppressed anti-inflammatory and immunoregulatory function of Tregs. These observations are in line with various previous studies regarding the frequency and ratio of T_H1, T_H2,

T_H17, and Treg subpopulations in BD patients,[32–36] some of which reported a reduced percentage of IL-10-producing Tregs, which could be involved in the abnormal levels of other subsets.[15,37] This imbalance can lead to decreased production of their associated immunomodulatory cytokines, including IL-10 and TGF-β, as well as pro-inflammatory cytokines. do Prado et al[33] and Wu et al[38] reported significantly elevated serum concentrations of IL-6, IL-17, IFN-γ, and TNF-α due to deregulated T-cell subsets in BD subjects compared with HC subjects. Interestingly, similar findings were reported by another study, highlighting another aspect of immune-inflammatory responses in BD patients that may fluctuate during different phases of the disease.[39] This dysregulation of T-cell subsets can contribute to the chronic low-grade inflammation observed in BD.[14,40]

The present study showed a significant increase in the expression levels of P2X7R and IL-17 as pro-inflammatory factors and a significant decrease in the expression levels of GATA3 and Foxp3 as anti-inflammatory transcription factors in BD patients compared to healthy controls, suggesting the role of deregulated T-cell subsets in these patients. However, the whole blood samples include heterogeneous leukocyte populations and further investigation may be helpful for designing diagnostic biomarkers and novel therapeutic strategies by targeting the immune system.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.IRH.REC.1402.016) and all participants provided written informed consent.

FUNDING

This research was financially supported by the Vice Chancellor for Research, Mashhad University of Medical Sciences, Mashhad, Iran (Grant No. 4012135).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this manuscript.

AI ASSISTANCE DISCLOSURE

The authors declare that they have not used AI-generated work in this manuscript.

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