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Clinical characteristics of bipolar 1 disorder in relation to interleukin-6: a cross-sectional study among Egyptian patients

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Abstract

Background Strong evidence in the literature points to the role of pro-inflammatory cytokines in bipolar disorder (BD) pathophysiology. Interleukin-6 (IL-6) is a pro and anti-inflammatory cytokine that was repeatedly found higher in bipolar patients than in healthy controls. However, studies on the phasic differences of IL-6 in bipolar type I (BP-I) were limited. This study aims to explore the phasic differences of serum IL-6 levels in BP-I during euthymia, depression, and mania and their association with the disease's clinical characteristics in a sample of Egyptian BP-I patients. Thirty currently euthymic, 24 currently depressed, 29 currently manic BP-I patients, and 20 healthy subjects were recruited. Serum IL-6 levels were compared among BP-I groups and then between each group and a group of 20 healthy controls. Serum IL-6 levels (pg/ml) were measured with a sandwich enzyme-linked immunosorbent assay (ELISA). Depression and mania symptoms were assessed using the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS), respectively. Clinical characteristics were evaluated through a semi-structured clinical psychiatric interview, and cognitive status was tested using the Montreal Cognitive Assessment (MoCA).

Results Serum IL-6 levels were significantly higher in each bipolar phase than in healthy subjects. In the BP-I patients, IL-6 levels were lower in patients with a current manic episode than in patients with a current depressive episode ($P < 0.05$) or who were currently euthymic ($P < 0.001$). Moreover, IL-6 levels correlated inversely with the YMRS score ($r_s = -0.29$; $P < 0.05$). Compared to patients without psychotic features, patients with psychotic features had decreased serum IL-6. Moreover, IL-6 levels were lower in inpatients compared to outpatients.

Conclusions BP-I disorder is associated with an inflammatory state. The decreased levels of IL-6 during manic episodes, affective episodes with psychotic features, and their inverse correlation with the severity of mania symptoms indicate a possible anti-inflammatory role of IL-6 in mania and psychotic symptoms pathogenesis.

Keywords Bipolar 1 disorder, Interleukin-6, Biochemical markers, Cytokines, Neuroinflammation, Psychoneuroimmunology

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Background

Bipolar disorder (BD) is a chronic disorder of mood encompassing alternating periods of elevated and depressed emotions, rendering patients unable to function. The presentation of mood abnormalities is episodic, with residual symptoms that usually persist during remission [1]. According to the WHO, BD is the sixth most common disease-causing disability worldwide [2], with the prevalence of bipolar type 1 (BP-I) is estimated up to 0.6%, affecting both men and women equally [3], and the peak age of onset is late teen and early 20 s [4]. In Egypt, 6.43% is affected with mood disorders [5], and more than half of patients affected with BD were misdiagnosed as major depressive disorder [6].

BP-I is diagnosed in patients with a distinct period of mania which causes impairment of function in the absence of secondary causes such as other medical conditions or drugs. The duration of symptoms must last for 1 week unless hospitalization is needed or psychotic features were present [7].

Inflammation appears to play a role in the pathophysiology of bipolar disease. When bipolar patients were compared to healthy controls, both pro-inflammatory (e.g., tumor necrosis factor alpha [TNF-α], interleukin-6 [IL-6]), and anti-inflammatory (e.g., interleukin-10 [IL-10]) cytokines were elevated. Moreover, several cytokines, such as TNF-α and IL-6, were reported to have mood state-dependent elevation [8] and demonstrated enhanced gene expression [9]. Furthermore, exploring the status of pro-inflammatory cytokines in bipolar patients showed that their levels correlated with the feature of the illness. For instance, IL-6 was linked to illness duration, whereas TNF-α was linked to the number of suicide attempts [10].

IL-6 is a pro- and anti-inflammatory cytokine. It acts through two distinct signaling pathways, depending on the form of the activated IL-6 receptor. The classical pathway involves binding to membrane-bound IL-6 receptors found on macrophages, neutrophils, certain T-lymphocytes, and hepatocytes. The trans-signaling pathway starts with soluble IL-6 receptors. These receptors then interact with glycoprotein 130 (gp130), a universally present signal transducer on many cell types such as neurons, endothelial cells, and oligodendrocytes, to exert their effects [11, 12].

IL-6 is integral to the acute phase response of the innate immunity and aids the transition from innate to adaptive immune response [13]. In CNS, IL-6 functions as a neuropoietin. Experimental studies showed a proliferative effect of IL-6 on astroglia and oligodendrocytes [14]. Moreover, IL-6 secreted by astrocytes salvaged neuronal cells from inflammation-mediated injury [15].

In BD, a strong association between neurobiological alterations that appear as mood dysregulation or cognitive impairment and IL-6 has been documented in the literature. For instance, the absent G allele in the promoter region of IL-6 has been linked to an earlier onset of BD [16]. Moreover, IL-6 was found to shift tryptophan (Trp) metabolism away from serotonin and towards the kynurenine (Kyn) pathway through upregulation of the indoleamine 2,3-dioxygenase (IDO) activity, resulting in an increase in Kyn/Trp ratio [17]. Furthermore, IL-6 upregulated the activity of the hypothalamic–pituitary–adrenal axis, leading to increased production of cortisol [18]. Increased cortisol levels were associated with manic episodes [19], and antipsychotic drugs were shown to reduce both IL-6 and cortisol levels to physiologic range [20]. Additionally, resting-state functional magnetic resonance imaging showed abnormally reduced functional connectivity in the insula of bipolar patients. That finding was associated with an increased level of IL-6, suggesting the role of IL-6 in the deterioration of cognitive and emotional function in bipolar patients [21].

Moreover, IL-6 was further associated with bipolar comorbidities such as cardiovascular diseases, which are highly prevalent among the patients and manifest at an earlier age than in people without bipolar illness [22, 23].

Of note, serum levels of IL-6 were reported to be higher during the mood episodes of BP-I when compared to healthy subjects [24, 25]. Moreover, in a sample of Egyptian bipolar patients, the serum levels of IL-6 were elevated during the euthymic phase of BD (types 1 & 2) when compared to healthy controls, and those levels correlated negatively with the patients' cognitive function [26]. However, fewer studies focused on the phasic differences of IL-6 in BP-I and on assessing its association with the clinical characteristics of the diseases.

Therefore, the current work postulates that IL-6 levels tend to be higher in BP-I patients than in healthy subjects. Moreover, those levels rise more during mania than in depression and in euthymia, and they are related to the severity of mood episodes, degree of cognitive impairment, and clinical features of BP-I.

Aim of the study

This study aims to assess the phasic difference of serum IL-6 levels in three phases of BP-I: euthymia, depression, and mania and to evaluate their relation to the clinical features, mood symptoms severity, and cognitive function of BP-I.

Methods

Subjects

This is a cross-sectional study. BP-I patients attending the outpatient clinic or admitted to the inpatient

of Mansoura University Hospitals were consecutively enrolled from April 2021 to May 2022. Two senior psychiatric consultants validated the diagnosis in independent evaluation settings. Clinical assessment was done through a semi-structured clinical psychiatric interview that was designed for this study according to the diagnostic criteria of *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) with particular concern on the following: demographic data, illness duration, the presentation of a current mood episode, number of previous mood episodes, need for hospitalization, and suicide history. Psychometric assessment of patients' mania and depression symptoms was done using the 11 items YMRS [27] and HDRS-17 (Arabic version) [28], respectively. The patients' cognition status was evaluated using the paper-based Arabic version 7.1 of the Montreal Cognitive Assessment test full. The test is sensitive for detection of mild cognitive impairment. It assesses various domains of cognition, including short-term and working memory, visuospatial and executive function, attention span and concentration, language, and orientation. Total score is 30 points, and scores less than 26 indicate cognitive impairment [29].

BP-I patients of both sexes, ranging in age from 18 to 55, were enrolled in the study if at least one of the patient's first-degree relatives was available. Patients with bipolar type 2 or other psychiatric or medical comorbidities were excluded. Patients who refused to participate after receiving a complete description of the procedures and giving consent were also excluded.

The study aimed to recruit 30 euthymic, 30 depressed, and 30 manic BP-I patients. Eighty-three patients who met the inclusion and exclusion criteria were included in the study. Seven were excluded for the following reasons: after giving consent, 1 patient refused to participate in the study, 2 samples were insufficient, and 1 sample exceeded the test's detection limit. Moreover, to avoid potential interference with the ELISA assay, 2 samples showing lipemic turbidity and 1 sample showing evident hemolysis on visual inspection were excluded.

The selected patients who fulfilled the previous inclusion and exclusion criteria were further assigned to the corresponding group according to their HDRS and YMRS scores: BP-I patients currently euthymic ($HDRS \leq 7$; $YMRS \leq 12$), BP-I patients with current depressive episode ($HDRS \geq 7$; $YMRS \leq 12$), and BP-I patients with current manic episodes ($HDRS \leq 7$; $YMRS \geq 12$).

Twenty healthy controls were recruited from blood donors attending to Mansoura University Hospitals. Healthy controls aged between 18 and 55 years old. They were free from any past or present major medical illness as well as personal or family history of psychiatric disorder.

Samples

A total of 3 ml of venous blood was withdrawn from each subject with venipuncture, collected into an anticoagulant-free vacuum tube, and allowed to stand for 20 min to colt. The clot is removed by centrifuging at 2000–3000 rpm for 20 min. The resulting serum was frozen at − 20 °C for later analysis.

Serum IL-6 was measured using a sandwich-ELISA immunoassay kit (INNOVA Biotech Co Limited., China), and procedures were performed according to the manufacturer's instructions and expressed in pg/ml. Serum samples showing evidence of hemolysis or lipemic cloudiness on visual inspection were avoided. The assay range of the test was 1–70 pg/ml with inter-assay variation coefficients < 12% and intra-assay variation coefficients of < 10%.

Known concentrations of human IL-6 standard and its corresponding reading OD are plotted on the log scale (x-axis) and the log scale (y-axis), respectively. The concentration of human IL-6 in the sample is determined by plotting the sample's OD on the Y-axis. The actual concentration is calculated by multiplying the dilution factor.

Statistical analysis

All statistical analysis was done using SPSS 28.0 for Macintosh (IBM Corporation, NY, USA). The normality of data was first tested with Shapiro–Wilk test. Qualitative data were described using number and percent. The association between categorical variables was tested using the chi-square test. As regards continuous variables, they were presented as mean ± SD for parametric data and median for non-parametric data. The two groups were compared with Student t-test (parametric data) and the Mann–Whitney test (non-parametric data). For more than 2 groups comparison, the one-way ANOVA test with post hoc Bonferroni test (parametric data) and Kruskal–Wallis test with pairwise comparison test (non-parametric data) were used. Pearson correlation is used to correlate continuous parametric data, while Spearman correlation is used to correlate continuous non-parametric variables. Studied variables with P-value < 0.05 were considered as potential predictors and entered a stepwise multivariable linear regression model. Categorical variables included in the linear regression model were coded as dummy variables.

Results

Demographics and clinical characteristics

Table 1 shows the demographic of 20 healthy subjects and 83 BP-I patients. There was no statistically significant difference in age, gender, and marital status across the healthy and patients' groups. However, full-time

Table 1 Demographic characteristics of the studied groups

	Euthymia *n* = 30	Depression *n* = 24	Mania *n* = 29	Healthy subjects *n* = 20	Test value	*p*-value
Age, mean (SD)	34.7 (8.9)	39 (10)	34.4 (9.8)	38.6 (8.3)	$F = 1.75$	0.16
Male gender, *n* (%)	20 (66.7)	11 (45.8)	20 (69)	12 (60)	$\chi^2 = 3.51$	0.32
Years of education, med. (min–max)	13 (6–18)	13 (3–18)	13 (0–17)	15 (8–18)	K-W test $\chi^2 = 6.85$	0.08
Marital status, *n* (%)					$\chi^2 = 10.59$	0.31
Single	13 (43.3)	4 (16.7)	14 (48.3)	7 (35)		
Married	14 (46.7)	15 (62.5)	10 (34.5)	11 (55)		
Divorced	3 (10)	4 (16.7)	5 (17.2)	2 (10)		
Widowed	0 (0)	1 (4.2)	0 (0)	0 (0)		
Employment, *n* (%)					$\chi^2 = 27$	**0.001***
Unemployed	8 (26.7)	12 (50)	11 (37.9)	4 (20)		
Part time	9 (30)	11 (45.8)	13 (44.8)	2 (10)		
Full time	13 (43)	1 (4.2)	5 (17.2)	14 (70)		

F: one-way ANOVA; χ^2 :chi-square test; *K-W test* χ^2 :Kruskal–Wallis test chi-square

* Healthy subject vs depression and mania are statistically significant in terms of part time and full-time employment; euthymia vs depression and mania are statistically significant in terms of full-time employment

employment was less frequent in mania and depression groups in comparison with euthymia or healthy groups. Moreover, part-time employment was more frequent in mania and depression groups than in healthy subjects.

The clinical characteristics of the three BP-I groups are summarized in Table 2. The three groups were not different as regards the family history of BP-I, duration of illness, number of previous manic and depressive episodes, number of previous hospitalizations, and history of suicide attempts. On the other hand, the MoCA test scores in the mania and depression groups were significantly lower, and the frequencies of current hospitalization and current psychotic features were significantly higher when compared to the euthymia group.

As regards the scores of YMRS and HDRS in the three BP-I groups, the median and range of YMRS were 17 (13–34) in the mania group, 4 (0–12) in the euthymia group, and 0 (0–9) in the depression group. The HDRS score had median and range of 12 (9–25) in the depression group and 0 (0–7) in the euthymia and mania groups (not tabulated).

Serum IL-6 levels

There was a statistically significant difference in the median levels of serum IL-6 (pg/ml) among the healthy (median = 6, range = 0.7–17.5), euthymia (median = 15, range = 9.6–28.2), depression (median = 14, range = 5.8–35.3), and mania (median = 10, range = 6.5–22.9) groups (Kruskal–Wallis chi-square = 42.96, $P < 0.001$).

Table 2 Clinical characteristics of the BP-I groups

	Euthymia	Depression	Mania	Test value	*p*-value
Family history of BP-I (yes), *n* (%)	6 (20)	10 (41.7)	9 (31)	$\chi^2 = 2.99$	0.22
Duration of illness in years, med (min–max)	13 (0.25–35)	10 (1–25)	10 (0.25–37)	K-W test $\chi^2 = 1.31$	0.52
Number of previous manic episodes, med (min–max)	9 (1–20)	9 (1–20)	7 (1–30)	K-W test $\chi^2 = 0.6$	0.74
Number of previous depressive episodes, med (min–max)	4 (0–15)	7 (0–18)	3 (0–20)	K-W test $\chi^2 = 3.03$	0.22
History of suicide attempts (yes), *n* (%)	7 (23.3)	9 (37.5)	4 (13.3)	$\chi^2 = 4.05$	0.13
Number of previous hospitalizations, med (min–max)	1 (0–14)	1 (0–10)	2 (0–7)	K-W test $\chi^2 = 1.46$	0.48
MoCA, med (min–max)	21 (3–27)	16 (5–23)	15 (1–24)	K-W test $\chi^2 = 10.33$	**0.006***
Current psychotic features (yes), n (%)	0 (0)	7 (29.2)	18 (62.1)	$\chi^2 = 27$	**< 0.001***
Current hospitalization (yes), *n* (%)	1 (3.3)	7 (29.2)	13 (14.8)	$\chi^2 = 13.7$	**0.001***

HDRS: Hamilton Depression Rating Scale; *MoCA:* Montreal Cognitive Assessment; *YMRS:* Young Mania Rating Scale; χ^2 :chi-square test; *K-W test* χ^2:Kruskal–Wallis test chi-square

* Euthymia vs depression and euthymia vs mania are statistically significant

Further pairwise comparison detected that IL-6 levels were statistically significantly lower in the healthy subjects than in euthymia ($P<0.001$), depression ($P<0.001$), and mania groups ($P=0.006$). Moreover, in BP-I, IL-6 was statistically significantly lower during a current manic episode than in patients with a current depressive episode or currently euthymic ($P=0.01$; $P=<0.001$, respectively). No statistically significant difference was found between depression and euthymia ($P=0.34$) (Fig. 1).

Association of serum levels of IL-6 with the clinical characteristics of BP-I patients

Comparison of serum levels of IL-6 according to the clinical features of the total BP-I patients showed that IL-6 levels were significantly lower in patients with psychotic features than in patients without these features ($P<0.001$). Moreover, current inpatients had lower IL-6 levels than the outpatients ($P<0.05$) (Table 3). No statistically significant difference in IL-6 levels was found based on the patients' sex, family history of BP-I, or past suicide attempts.

The correlation analysis was statistically significant and negative between serum IL-6 levels and YMRS score ($r_s=-0.29$; $P<0.05$). Patients' age, illness duration, number of manic and depressive episodes, number of prior hospitalizations, YMRS, HDRS, and MoCA test scores did not significantly correlate with IL-6 (Table 4).

Regression analysis to predict IL-6

Stepwise multiple linear regression was done to predict IL-6 levels in BP-I patients. Variables that were significantly associated with IL-6 were used as predictors (current manic episode, current depressive episode, current psychotics features, current hospitalization, YMRS score). The resultant model was statistically significant, explaining 17% of variance in IL-6 levels ($R2=0.17$; $F=16.19$; $P<0.001$). Having a current manic episode was the only significant predictor of serum IL-6, with predicted decrease in IL-6 levels by 5.56 pg/ml ($B=-5.56$; $P=<0.001$) from being currently euthymic (constant = 16.51) (Table 5).

Table 3 Comparison of serum IL-6 levels according to the BP-I patients clinical characteristics

	IL-6, med (min–max)	*U*-test	*p*-value
Gender			
Male	12 (6–31)	777	0.72
Female	13 (8–35)		
Family history of BP-I			
Yes	13 (8–31)	638	0.39
No	12 (6–35)		
Previous suicide attempts			
Yes	13 (6–35)	534	0.31
No	12 (7–33)		
Current psychotic features			
Yes	10 (7–35)	302	**<0.001**
No	14 (6–33)		
Current hospitalization			
Yes	10 (6–31)	357	**0.002**
No	13 (7–35)		

U-test: Mann–Whitney test

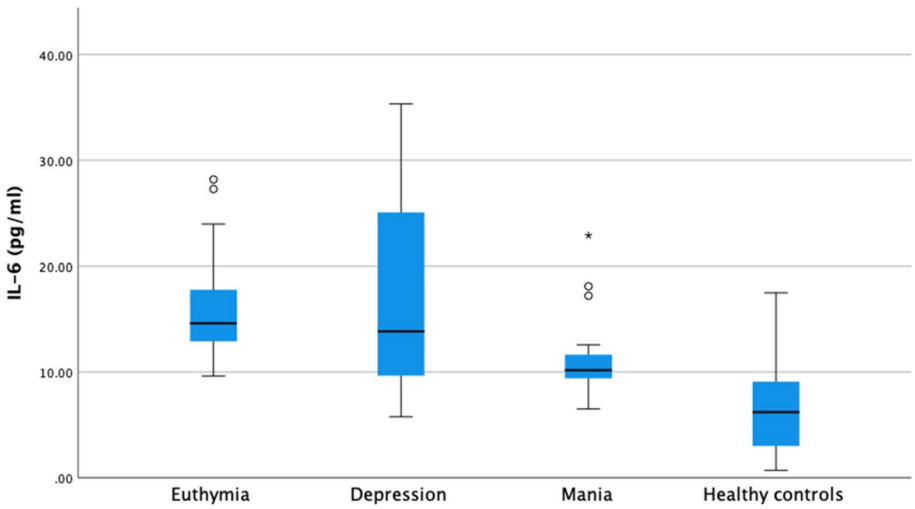

Fig. 1 Boxplot of serum IL-6 levels among studied groups. The pairwise comparison shows that median levels of IL-6 are significantly higher in each BP-I group than in healthy group. Moreover, IL-6 is significantly lower in mania than in euthymia. Also, IL-6 was lower in mania than in depression with statistically significant difference. Circles are mild outliers; asterisks are the extreme outliers

Table 4 Correlation of IL-6 with the clinical characteristics of BP-I patients

	r_s	*p*-value
Age	−0.04	0.69
Duration of illness	0.07	0.56
Number of previous maniac episodes	−0.01	0.92
Number of previous depressive episodes	0.01	0.89
Number of previous hospitalizations	−0.02	0.89
YMRS	−0.29	**0.01**
HDRS	0.2	0.08
MoCA	0.1	0.36

r_s :Spearman correlation; *HDRS:* Hamilton Depression Rating Scale; *MoCA:* Montreal Cognitive Assessment; *YMRS:* Young Mania Rating Scale

Table 5 Stepwise multiple linear regression analysis for prediction of serum IL-6 levels in BP-I

	B	*t*	*p*-value	95% *CI*	
Predictors				Upper	lower
Current manic episode	−5.56	−4.02	**<0.001**	−8.3	−2.81
#Current depressive episode	0.01	0.95	0.34	–	–
#Current psychotic features	−0.08	−0.64	0.52	–	–
#Current hospitalization	−0.07	−0.64	0.52	–	–
#Young Mania Rating Scale	−0.004	−0.02	0.98	–	–
Constant = α	16.51				
Model R2	0.17				
Model F	16.19				
Model *P*-value	**<0.001**				

Outcome, serum IL-6 level

B: unstandardized beta (slope) coefficient; *t*: test of significance of B; *R2*: the proportion of variation in the dependent variable that is predicted by the statistical model; *F*: test of significance of R2; *CI*: confidence interval of unstandardized B; #excluded variables from the model

Discussion

High pro-inflammatory cytokines have been repeatedly found in BD, and IL-6 has been proposed as a biomarker for mood episodes. Examining IL-6 phasic differences in BP-I and evaluating how it interacts with the clinical characteristics of BP-I patients can give a basis for understanding its role in the disease's pathophysiology.

The present study showed that serum levels of IL-6 during euthymia, depression, and mania were significantly higher in each phase than in healthy subjects. This is further supporting the inflammatory hypothesis in bipolar disorders and consistent with the outcome of a meta-analysis examining difference in IL-6 levels across the mood spectrum of BD compared to healthy subjects [30].

Moreover, comparison of IL-6 levels according to the disease phase in the present study showed lower levels of IL-6 during mania than in depression and euthymia; no difference was detected between the depression and euthymia groups.

Results on IL-6 phasic differences have been discordant. Jacoby et al. did not detect any difference between the different phases of BP-I. However, earlier work by the same team had shown higher IL-6 levels in mania than in euthymia and bipolar depression. The authors' rationale for this discrepancy was based on the variation among studies in duration of studied phases, illness stage, patients' medication status, and the number and dosage of medications used [31, 32].

The current finding in mania group is in line with the early work of Ortiz-Domínguez et al., who found decreased IL-6 levels in manic patients compared to bipolar depression and healthy subjects. Since mania is thought to be a highly catabolic condition, the authors hypothesized that IL-6 breakdown may explain its reduction [33]. The altered sleep patterns that occur during manic episodes, which include longer nighttime awakening periods and less exposure to daylight, may also be responsible for the lower levels of IL-6 that have been observed in mania [34]. Furthermore, a suggested mechanism of how the decrease in IL-6 during mania in comparison with depression can affect mood might be through its effect on midbrain serotonin transporters (SERT). The SERT density correlated with CNS serotonin availability [35], and it was noted to be higher in mania and lower in depression [36]. Moreover, it inversely correlated with IL-6 in bipolar patients [37]. Therefore, we can conclude that low levels identified in the current mania group contributed to an increase in SERT availability in the midbrain, whereas high levels in the current depression group resulted in a decrease in SERT availability. However, more research is required to solidify this association.

In line with the findings of this study, levels of IL-6 did not differ between euthymia and depression [32]. Additionally, monitoring the IL-6 serum levels in the same patients throughout depressive episodes and euthymia revealed no changes between these two states [38]. The comparable levels of IL-6 in both depression and euthymia groups could be explained in the light of the immune-inflammatory response system/compensatory immune-regulatory reflex system model in the pathophysiology of mood disorders. According to that theory, the production of pro-inflammatory cytokines causes the mood episode, and the release of anti-inflammatory molecules is responsible for its resolution. Interestingly, IL-6 increased in both reactions, and the pro-inflammatory effect was only dictated by the availability of soluble IL-6

receptors. Therefore, it was proposed that the change from an acute mood into the remission phase was mediated by a decrease in soluble IL-6 receptors rather than IL-6 serum levels [39].

In contrast to our findings in the euthymia group, previous research showed that IL-6 levels fall to normal levels of healthy control during euthymia. However, authors also postulated that IL-6 levels in euthymia may be altered by the duration of euthymia and residual effect of prior mood episodes [40]. If the assumption holds, increased IL-6 levels during euthymia in the current study could be a compensation for the decrease in IL-6 in mania or a lag in the decrease of high serum levels from a previous depressive episode.

The current results of psychometric assessment showed a negative correlation of IL-6 with the severity of mania symptoms, while no correlation was found with the severity of depression symptoms or degree of cognitive impairment. The current results are consistent with the observation that IL-6 had no correlation with the severity of depression symptoms [32]. However, positive correlation was previously found between HDRS and IL-6 in bipolar patients [24]. Moreover, to our knowledge, this study is the first to find a negative correlation between IL-6 and YMRS score in BP-I. Previous research had reported the correlation to be either absent [32] or positive [24, 41]. However, similar results were observed with the soluble vascular cell adhesion molecule-1 (sVCAM-1), a cytokine-dependent molecule which inversely correlated with YMRS scores during BP-I mania [42]. The disagreement among the results of IL-6 correlation with symptoms severity could be attributed to the inclusion of patients with different range of symptoms severity in those studies. Moreover, previous research pointed that comparison of patients with and without subthreshold symptoms may show different patterns of cytokine profiles [43]. Hence, stratification of patients according to the severity of the mood episodes as well as the presence or absence of residual symptoms during euthymia or mild symptoms of opposite polarity during the mood episodes can eliminate their effect on correlation studies.

Furthermore, the lack of correlation between the IL-6 levels and the MoCA test score in the current study contrasts with the findings of positive correlation between IL-6 and the deterioration of cognitive performance in bipolar patients [26, 44, 45]. Nevertheless, it is consistent with reports from other studies, including one study that had only BP-I patients [46–48]. This discrepancy was suggested to be a result of differences in patients' clinical characteristics, current treatment, and mood state [48]. Moreover, the cognitive deterioration linked to IL-6 and seen in bipolar patients is suggested to be a result of a chronic and progressive immune process rather than being a result of acute variation in immune biomarkers [49].

In the current sample of patients with psychotic features, IL-6 levels were decreased compared to patients without psychotic features. In agreement with the current results, previous research showed that psychotic symptoms were associated with higher IL-6 levels in comparison with healthy controls [50]. Moreover, the decrease in IL-6 levels in patients with psychotic illness was associated with increased positive psychotic symptoms severity [51] with comparable results in CSF analysis [52]. The psychotic symptoms associated with low IL-6 can be explained by the absence of its dopamine-reducing impact, as IL-6 was shown to reduce BH4, a cofactor required in dopamine synthetics pathway [53].

The currently hospitalized patients in this sample had lower IL-6 than the outpatients. This result could be explained by the confounding effect of hospitalization. Hospitalization is a proxy for the severity of manic episodes and the presence of psychotic features [54], both of which were associated with decreased IL-6 levels in the current sample.

As regards BD patients who attempted suicide, the current study is in line with the finding that IL-6 was not significantly linked with suicidality in BD patients [55]. However, IL-6 levels were found higher in bipolar patients with suicide attempts than in patients without these attempts [56]. This disagreement could be due to the small number of patients in the current study who attempted suicide.

The absence of association between IL-6 and patients' gender in the current study further supports the previous results of Shams-Alizadeh et al. in BP-I patients [41]. Although IL-6 was previously reported higher among bipolar men than in healthy subjects [57], comparison among bipolar patients was in line with the current study's result [25]. Moreover, for several cytokines in bipolar and schizophrenic patients, such as IL-6, TNF-α, and IL-10, stratification of results according to gender did not change the study outcome [58].

In agreement with previous studies, the association between IL-6 and duration of illness was also absent in the present work [24, 42]. Moreover, this is consistent with the finding that, after controlling for confounders, only brain-derived neurotrophic factor, rather than IL-6, significantly correlated with illness duration [59].

Furthermore, the current results showed no association between IL-6 and positive family history of BP-I. This is consistent with previous results reporting no difference in IL-6 levels between studied subjects with and without a bipolar diagnosis and had positive family history of BP-I [60].

Strengths and limitations

This work is one of the few studies that compared the three phases of BP-I disorder as regards IL-6. However, the limitations of this study should be taken into account when interpreting this study's results, such as the cross-sectional design which does not establish causality, the small sample size which increases the probability of type 2 error, and the heterogeneity of the sample due to inclusion of both outpatient and hospitalized patients. Finally, current medications used are one of the confounders present in the current study. Although all the enrolled patients were on medications at the time of the study, we did not investigate the effect of different medications on IL-6.

Conclusions

IL-6 is a potential biomarker for BP-I and for the manic phase. Increased levels of IL-6 in BP-I favor the immune dysregulation hypothesis in the pathogenesis of the disease. IL-6 may have an anti-inflammatory role in reducing the severity of mania symptoms in BP-I patients and in psychotic symptoms pathogenesis. Longitudinal studies are needed to confirm whether the difference in IL-6 is attributed to mood-related changes. Moreover, investigations that assess the dominant signaling cascade, such as evaluating the mRNA expression of soluble and membrane-bound IL-6 receptors, as well as serum IL-6 levels, could explain the effect of IL-6 during different phases. Furthermore, psychotic symptoms are a common presentation in acute episodes of mania, schizophrenia, and schizoaffective disorders; thus, comparing IL-6 levels in these groups could provide insight into whether these illnesses are caused by shared or independent pathophysiologic mechanisms.

Abbreviations

BD	Bipolar disorder
BH4	Tetrahydrobiopterin
BP-I	Bipolar type 1
DSM-V	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
CNS	Central nervous system
ECT	Electroconvulsive therapy
ELISA	Enzyme-linked immunosorbent assay
gp130	Glycoprotein 130
HDRS	Hamilton Depression Rating Scale
IDO	Indoleamine2,3-dioxygenase
IL	Interleukin
Kyn	Kynurenine
MoCA	Montreal Cognitive Assessment
OD	Optical density
SERT	Serotonin transporter
TNF-α	Tumor necrosis factor alpha
Trp	Tryptophan
YMRS	Young Mania Rating Scale

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Not applicable

Authors' contributions

MM, conceptualized the study. YM and ME designed the study. ME and IE have interviewed patients at different time points and performed participant assessments. MH collected the data. All co-authors made substantial contributions to the interpretation of the data. RE and MH drafted the first manuscript. All co-authors contributed with substantial revisions and critical review of the manuscript and accepted its final form. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Mansoura Faculty of Medicine Institutional Research Board under proposal code number MS/17.01.59.
Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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