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Association of Serum Uric Acid Levels with Manic Episodes, Effect on Symptom Severity: A Case-Control Study

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Article Details

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ABSTRACT

Background: Bipolar disorder is marked by alternating depressive and manic episodes. Recent studies suggest a correlation between serum uric acid levels and manic symptoms, yet limited research exists in Pakistan. Objectives: This study aims to investigate the association between serum uric acid levels and manic episodes, and to evaluate the impact of elevated uric acid on symptom severity in patients with bipolar disorder. Methods: A case-control study was conducted at Khyber Teaching Hospital, Peshawar, involving 110 participants (55 with manic episodes and 55 controls). Serum uric acid levels were measured, and manic symptom severity was assessed using the Young Mania Rating Scale (YMRS). Results: Patients with manic episodes exhibited significantly higher serum uric acid levels (6.84 ± 1.42 mg/dL) compared to controls (5.36 ± 1.18 mg/dL, $p<0.001$). Hyperuricemia prevalence was 63.6% in manic patients versus 25.5% in controls. A strong positive correlation was found between uric acid levels and YMRS scores ($r=0.583$, $p<0.001$), indicating increased severity of manic symptoms with higher uric acid levels. Conclusion: Elevated serum uric acid levels are associated with manic episodes and the severity of symptoms in bipolar disorder. These findings suggest that serum uric acid may serve as a potential biomarker for manic episodes, warranting further investigation into therapeutic interventions targeting the purinergic system.

INTRODUCTION

Bipolar disorder is characterized by alternating periods of depression and manic symptoms. Manic symptoms comprise euphoria or irritability, increased activity or energy, and other symptoms such as increased talkativeness, racing thoughts, heightened self-esteem, decreased need for sleep, distractibility, and impulsive, potentially dangerous behavior. Globally, 40 million people suffered from bipolar disorder in 2019. (1)

Emil Kraepelin was the first to hypothesize that the purinergic system might be indirectly involved in the pathogenesis of mood disorders; his findings revealed that uric acid excretion was reduced during altered mood states, especially during manic episodes in Bipolar disorder. (2) The concept that purines may have a role in neurotransmission and neuromodulation and that ATP acts as a neurotransmitter was proposed in 1972. (3) ATP is produced from nerves as a neurotransmitter to function as an extracellular signaling molecule on both pre-and postjunctional membranes at neuroeffector junctions and synapses; this process is known as purinergic neurotransmission. Numerous brain regions incorporate this purinergic system, including the cerebral cortex, hypothalamus, basal ganglia, hippocampus, and other limbic areas. (4) Sleep, motor activity, cognition, memory, aggressive behavior, and social interaction—all processes involved in the mood dysfunction in a manic episode—are among the activities that are affected by the modulation of second messenger systems by ATP and its breakdown product in the purinergic system, adenosine. (5)

The question of whether there is a connection between mood disorders and plasma uric acid levels has gained more attention recently. Recent studies carried out in the past two decades have demonstrated elevated levels of uric acid in individuals suffering from mood disorders, especially those experiencing manic episodes.(6,7) This idea is supported by the finding of a study showing bipolar disorder patients had higher rates of gout development than the general population. (8) The severity of manic symptoms was also significantly correlated with uric acid levels. (7) In neurocognitive domains, patients with Bipolar disorder have been shown to perform worse than healthy controls, and this has been correlated with increased serum uric acid levels in these patients. (9)

There have been several studies worldwide assessing increased serum uric acid levels in patients with bipolar disorder and its effects on symptom profile and severity. (10,11) Serum uric acid levels have been linked to an increased risk of developing bipolar disorder from major depressive illness. Hence, the purinergic system may hold the key to discovering biomarkers for the likelihood that unipolar depression will turn into bipolar disorder. (12)

There are no studies on this subject available in Pakistan. Considering this, our research attempts to be the first in Pakistan to establish a relationship between serum uric acid levels and manic episodes, as well as to investigate the impact of elevated uric acid levels on the severity of bipolar affective disorder symptoms.

OBJECTIVES

- To determine the association between a manic episode and serum uric acid levels
- To study the effects of increased serum uric acid levels on symptom severity in a manic episode.

OPERATIONAL DEFINITIONS

MANIC EPISODE: As per the International Classification of Diseases-10 Diagnostic Criteria for Research criteria. (13)

MATERIALS AND METHODS

STUDY DESIGN: Case-Control Study

STUDY SETTING: Department of Psychiatry, Khyber Teaching Hospital, Peshawar.

DURATION OF STUDY: A minimum of 6 months after the approval of the research proposal is required.

SAMPLE SIZE: Taking the approximate exposure of raised serum uric acid levels in the controls as the prevalence of hyperuricemia in the general population, i.e., 39 percent (14), 95 percent confidence intervals, with a power of 80 percent and the assumption of odds ratio to be 3.00, the sample size for unmatched case-controls turns out to be 110 in total, with 55 cases and 55 controls. (15)

SAMPLING TECHNIQUE: Consecutive (Non-probability) Sampling.

SAMPLE SELECTION

INCLUSION CRITERIA

FOR CASES

1. Patients with Manic Episode, as diagnosed by a qualified Psychiatrist as per International Classification of Diseases-10 Diagnostic Criteria for Research Criteria.
2. Young Mania Rating Scale (YMRS)>=13 (16)
3. Patient age not less than 14 years.
4. Both genders.
5. Both admitted and outdoor patients.

FOR CONTROLS

1. Matched by gender, age, and BMI with cases.
2. GHQ-28 (Urdu Transliteration) Score <23 (17)

EXCLUSION CRITERIA

1. If they are taking oral contraceptives, beta-blockers, or another pharmacological agent is known to influence uric acid homeostasis.
2. If they have consumed alcohol or another psychoactive substance within the last one month (except for nicotine and tea/coffee).
3. If they are over 65 years of age.

DATA COLLECTION PROCEDURE

The study was conducted after the approval of the institutional ethical review board. Patients fulfilling the inclusion criteria was approached and informed about the purpose of the study. Those who agree to participate were enrolled in the study after informed consent.

Exclusion criteria was applied to limit the effect of confounding variables. In these cases, the patients were assessed for the presence of a manic episode by a qualified psychiatrist. Once diagnosed, demographic parameters like age and gender and other variables like inpatient and outpatient status were recorded on a structured proforma. Serum samples were collected and analyzed for uric acid levels at the central hospital laboratory to assess a potential link between uric acid levels and the study objectives. On the same day, the Young Mania Rating Scale (YMRS) was applied. For controls, individuals were matched with the cases, and the Kessler Psychological Distress Scale (K10) and Mood Disorder Questionnaire (MDQ) were applied to screen for psychiatric co-morbidities as well as Bipolar Affective Their serum uric acid levels will be collected and analyzed similarly, and data was recorded.

DATA ANALYSIS PROCEDURE

Data was entered into EpiData version 3.1 for collection, and analysis was done using

Statistical Package for Social Sciences (SPSS), version 21. The data obtained was tested for normal distribution using the Kolmogorov–Smirnov test. The control and case groups were compared using independent sample T-tests for continuous variables, specifically the uric acid levels, and Chi-Square for categorical variables. Bivariate correlations were calculated using the Pearson correlation coefficient between the variables of interest, specifically serum uric acid levels in cases of manic episodes in cases was calculated, and co-variates were controlled as necessary. Significant correlations were further analyzed through linear regression. The odds ratio of manic episodes to serum uric acid levels was calculated. For this study, a p-value of less than or equal to 0.05 indicate statistical significance.

DATA ANALYSIS

The research executed its data collection within six months at the Department of Psychiatry, Khyber Teaching Hospital located in Peshawar. One hundred ten participants were enrolled in the study because they matched the inclusion criteria for manic episodes and control groups based on age demographics, gender matches, and body mass index.

DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

The demographic evaluation demonstrated similar features between cases and controls because the research design utilized matched group selection. Both ethnographic groups undergo demographic profiling, as shown in Table 1.

TABLE 1: DEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS

Characteristic	Cases (n=55)	Controls (n=55)	p-value
Age (years), mean ± SD	32.7 ± 9.8	32.3 ± 9.5	0.832
Gender, n (%)			1.000
- Male	31 (56.4%)	31 (56.4%)	
- Female	24 (43.6%)	24 (43.6%)	
BMI (kg/m²), mean ± SD	24.9 ± 3.2	24.7 ± 3.1	0.739
Education, n (%)			0.047*
- Below Secondary	24 (43.6%)	14 (25.5%)	
- Secondary	19 (34.5%)	21 (38.2%)	
- Graduate or higher	12 (21.8%)	20 (36.4%)	
Marital Status, n (%)			0.184
- Single	27 (49.1%)	20 (36.4%)	
- Married	23 (41.8%)	31 (56.4%)	
- Divorced/Widowed	5 (9.1%)	4 (7.3%)	

*Statistically significant ($p<0.05$)

Table 1 demonstrates that the research participants from both groups shared equivalent age, gender, and BMI values because of all matched criteria ($p>0.05$). The patients in the case and control groups had similar mean ages recorded at 32.7 ± 9.8 years and 32.3 ± 9.5 years, respectively. The participant compositions matched exactly between groups regarding gender composition at 56.4% male and 43.6% female. Cases and controls had equivalent BMI average values, of 24.9 ± 3.2 kg/m² and 24.7 ± 3.1 kg/m² respectively. The results demonstrated that controlled subjects achieved better education levels than manic patients ($p=0.047$).

CLINICAL CHARACTERISTICS OF PATIENTS WITH MANIC EPISODES

A complete set of clinical markers was used to analyze the depth and types of manic episodes

among tested subjects. Table 2 summarizes these clinical characteristics.

TABLE 2: CLINICAL CHARACTERISTICS OF PATIENTS WITH MANIC EPISODES (N=55)

Clinical Characteristic	Value
Duration of illness (years), mean ± SD	7.3 ± 5.4
Number of previous episodes, n (%)	
- First episode	15 (27.3%)
- 2-3 episodes	22 (40.0%)
- >3 episodes	18 (32.7%)
Family history of mood disorders, n (%)	21 (38.2%)
Current episode duration (weeks), mean ± SD	3.2 ± 1.7
YMRS score, mean ± SD	27.5 ± 6.8
YMRS severity categories, n (%)	
- Mild (13-19)	10 (18.2%)
- Moderate (20-25)	16 (29.1%)
- Severe (26-35)	22 (40.0%)
- Very severe (>35)	7 (12.7%)
Hospitalization status, n (%)	
- Inpatient	32 (58.2%)
- Outpatient	23 (41.8%)

Table 2 shows patients with manic episodes showed an illness duration of 7.3 ± 5.4 years, while 72.7% of them had recurrent manic episodes. The distribution of manic symptoms in patients ranged from moderate to severe based on YMRS assessment results, which averaged 27.5 ± 6.8. More than half of the patients (58.2%) required hospitalization for the management of their current manic episode.

SERUM URIC ACID LEVELS IN CASES AND CONTROLS

This research aimed to understand how manic episode occurrences relate to serum uric acid measurements. Based on the data in Table 3, the study examined the differences in serum uric acid between patients who experienced manic episodes and those who did not.

TABLE 3: COMPARISON OF SERUM URIC ACID LEVELS BETWEEN CASES AND CONTROLS

Group	n	Serum Uric Acid (mg/dL)	p-value
		Mean ± SD	
Cases (Manic)	55	6.84 ± 1.42	<0.001*
Controls	55	5.36 ± 1.18	
Male Cases	31	7.12 ± 1.35	<0.001*
Male Controls	31	5.64 ± 1.22	
Female Cases	24	6.48 ± 1.46	<0.001*
Female Controls	24	5.01 ± 1.05	

*Statistically significant (p<0.05)

The analysis in table 3 revealed a considerable variation between manic patients and control subjects regarding serum uric acid measurements (p<0.001). The serum uric acid concentration of patients during manic episodes reached 6.84 ± 1.42 mg/dL, which exceeded the level of healthy controls who measured 5.36 ± 1.18 mg/dL. Sex-based examination of the data showed

that men consistently displayed higher uric acid concentration than women in both cases and controls.

PREVALENCE OF HYPERURICEMIA IN CASES AND CONTROLS

We analyzed the incidence rates of hyperuricemia (defined as serum uric acid greater than 6.8 mg/dL for males and 6.0 mg/dL for females) between manic episode patients and healthy controls to explore their connection better. Table 4 displays the obtained results.

TABLE 4: PREVALENCE OF HYPERURICEMIA IN CASES AND CONTROLS

Group	Hyperuricemia	Normal Uric Acid	Total	p-value
Cases, n (%)	35 (63.6%)	20 (36.4%)	55	<0.001*
Controls, n (%)	14 (25.5%)	41 (74.5%)	55	
Odds Ratio (95% CI)	**5.13 (2.28-11.56)**			
Male Cases, n (%)	21 (67.7%)	10 (32.3%)	31	0.002*
Male Controls, n (%)	9 (29.0%)	22 (71.0%)	31	
Odds Ratio (95% CI)	**5.13 (1.75-15.06)**			
Female Cases, n (%)	14 (58.3%)	10 (41.7%)	24	0.005*
Female Controls, n (%)	5 (20.8%)	19 (79.2%)	24	
Odds Ratio (95% CI)	**5.32 (1.49-18.95)**			

*Statistically significant ($p<0.05$)

Hyperuricemia turned out to be more prevalent among patients experiencing manic episodes at a rate of 63.6%, while the control group only demonstrated a 25.5% prevalence ($p<0.001$) as stated in table 4. Data analysis showed manic episode patients had a 5.13 times higher chance of developing hyperuricemia than control subjects (OR: 5.13, 95% CI: 2.28-11.56). The research confirmed this association by evaluating manic patient associations separately by gender and recording equivalent odds ratios for males and females.

RELATIONSHIP BETWEEN SERUM URIC ACID LEVELS AND MANIC SYMPTOM SEVERITY

This study examined the relationship between serum uric acid concentrations and manic symptom severity through YMRS measurement to assess the second objective of the analysis. Serum uric acid levels provided mean data at various severity rates of YMRS (Table 5).

TABLE 5: SERUM URIC ACID LEVE
LS ACROSS YMRS SEVERITY CATEGORIES IN CASES

YMRS Severity Category	n	Serum Uric Acid (mg/dL)	ANOVA
		Mean ± SD	p-value
Mild (13-19)	10	5.87 ± 1.13	<0.001*
Moderate (20-25)	16	6.49 ± 1.31	

Severe (26-35)	22	7.18 ± 1.36
Very severe (>35)	7	7.91 ± 1.22

*Statistically significant ($p<0.05$)

The analysis found serum uric acid levels significantly different among patients grouped into different YMRS severity categories ($p<0.001$). The study revealed that patients with very severe manic symptoms showed peak serum uric acid levels at 7.91 ± 1.22 mg/dL, followed by the mild symptom group having the lowest at 5.87 ± 1.13 mg/dL.

CORRELATION BETWEEN SERUM URIC ACID LEVELS AND YMRS SCORES

This study used correlation analysis to understand how manic symptom severity relates to serum uric acid levels among manic patients during assessment. The table showing these analysis results appears in Table 6.

TABLE 6: CORRELATION BETWEEN SERUM URIC ACID LEVELS AND YMRS SCORES IN CASES

Variables	Pearson's Correlation Coefficient (r)	p-value
Serum Uric Acid (mg/dL) vs. YMRS Total Score	0.583	<0.001*
YMRS Individual Items		
Elevated mood	0.427	0.001*
Increased motor activity/energy	0.512	<0.001*
Sexual interest	0.386	0.004*
Sleep	0.462	<0.001*
Irritability	0.498	<0.001*
Speech (rate and amount)	0.523	<0.001*
Language/thought disorder	0.479	<0.001*
Content	0.405	0.002*
Disruptive/aggressive behavior	0.531	<0.001*
Appearance	0.374	0.005*
Insight	0.417	0.002*

*Statistically significant ($p<0.05$)

Healthy participants with elevated serum uric acid revealed increased manic symptoms according to The Young Manic Rating Scale scores (total YMRS scores), as shown by the strong correlation factor ($r=0.583$, $p<0.001$). Results showed that disruptive/aggressive behavior ($r=0.531$) maintained the strongest correlation to serum uric acid levels alongside speech ($r=0.523$) and increased motor activity/energy (0.512). A positive association occurred with all YMRS individual items.

LINEAR REGRESSION ANALYSIS

A linear regression was conducted using the YMRS score as the outcome to determine the connection between manic symptom intensity and serum uric acid levels. The examination adjusted for potential underlying variables. The data analysis appears in Table 7.

TABLE 7: LINEAR REGRESSION ANALYSIS WITH YMRS SCORE AS DEPENDENT VARIABLE

Independent Variables	Unstandardized Coefficients		Standardized Coefficients	t	p-value
	B	Std. Error	Beta		
(Constant)	3.865	4.714		0.820	0.416
Serum Uric Acid (mg/dL)	2.782	0.561	0.579	4.957	<0.001*
Age (years)	0.007	0.080	0.010	0.088	0.930
Gender (Male=1, Female=0)	0.841	1.531	0.062	0.549	0.585
BMI (kg/m²)	0.185	0.245	0.087	0.755	0.454
Duration of illness (years)	0.072	0.146	0.058	0.493	0.624
Number of previous episodes	0.452	0.268	0.200	1.687	0.098

$R^2 = 0.413$, Adjusted $R^2 = 0.346$, $F = 5.632$, $p<0.001$ *Statistically significant ($p<0.05$)

The linear regression produced valid results with $F=5.632$ and $p<0.001$ and accounted for 34.6% (adjusted $R^2=0.346$) of YMRS score variability. The statistical analysis controlling other variables demonstrated that uric acid levels in blood had a strong correlation with YMRS scores ($\beta=0.579$ $p<0.001$). A rise in serum uric acid by 1 mg/dL leads to a 2.782-point increase in YMRS manic symptoms intensity. The recorded variables failed to yield significant outcome predictions against YMRS scores during this model.

SUBGROUP ANALYSIS BASED ON EPISODE HISTORY

This analysis of serum uric acid levels evaluated how manic episode history impacted their relationship with serum uric acid levels through subgroup analysis. Results from the examination appear in Table 8.

TABLE 8: COMPARISON OF SERUM URIC ACID LEVELS BASED ON EPISODE HISTORY

Group	n	Serum Uric Acid (mg/dL)	p-value
		Mean ± SD	
First-episode Mania	15	6.32 ± 1.28	0.042*
Recurrent Episodes	40	7.03 ± 1.44	
- 2-3 episodes	22	6.89 ± 1.41	0.124^
- >3 episodes	18	7.21 ± 1.49	
Controls	55	5.36 ± 1.18	<0.001†

* p-value for comparison between first-episode and recurrent episodes ^p-value for comparison between 2-3 episodes and > three episodes †p-value for comparison between all cases and controls Statistically significant ($p<0.05$)

Patients diagnosed with recurrent manic episodes presented serum uric acid levels at 7.03 ± 1.44 mg/dL, which exceeded survey participants going through this condition for the first time at 6.32 ± 1.28 mg/dL ($p=0.042$). Patients who experienced four or more manic

episodes showed higher serum uric acid levels at 7.21 ± 1.49 mg/dL despite patients with 2-3 episodes remaining at 6.89 ± 1.41 mg/dL; yet, the results were not statistically significant (p=0.124). The serum uric acid levels of patients with initial mania significantly differed from those in healthy individuals (p=0.007). These results did not appear in the table.

VALIDATING THE FINDINGS

Our investigation into serum uric acid levels as a manic episode indicator was supplemented with specific clinical parameters analysis followed by treatment response examination and physiological assessments. These supplementary data tables can be found next.

TABLE 9: MULTIPLE LOGISTIC REGRESSION ANALYSIS FOR PREDICTORS OF MANIC EPISODE

Predictor Variables	Odds Ratio	95% CI	p-value
Serum Uric Acid (mg/dL)	2.27	1.58-3.26	<0.001*
Age (years)	1.01	0.97-1.06	0.624
Gender (Male vs. Female)	1.12	0.46-2.74	0.803
BMI (kg/m²)	1.03	0.89-1.19	0.678
Education Level	0.61	0.39-0.95	0.029*
Family History of Mood Disorder	2.84	1.12-7.21	0.028*
Smoking Status	1.59	0.62-4.07	0.334

*Statistically significant (p<0.05)

The analysis based on multiple logistic regression reveals essential predictors of manic episodes, as shown in Table 9. The evaluation showed that serum uric acid level served as an individual predictor of manic episodes (OR=2.27, 95% CI: 1.58-3.26, p<0.001), which remained significant after controlling for confounding variables. The data shows that elevated serum uric acid concentrations by 1 mg/dL elevated subjects' chance of manic episodes to 127% beyond other confounding variables.

The data revealed that subjects with less education, together with those with mood disorders in their family tree, showed a stronger association with manic episodes (OR=2.84, 95% CI: 1.12-7.21, p=0.028), as did decreased educational background (OR=0.61, 95% CI: 0.39-0.95, p=0.029). The results from this analysis cement the link between high serum uric acid and manic symptoms since demographic factors and clinical aspects did not affect this relationship.

TABLE 10: ANALYSIS OF SERUM URIC ACID LEVELS AND SPECIFIC MANIC SYMPTOM CLUSTERS

Symptom Cluster	Correlation with Uric Acid Levels		Multiple Regression Analysis	
	Pearson's r	p-value	Standardized β	p-value
Mood Elevation *YMRS items: Elevated mood, content*	0.456	<0.001*	0.403	0.003*
Psychomotor Activation	0.578	<0.001*	0.542	<0.001*

YMRS items: Motor activity/energy, speech, irritability				
Thought Disturbance *YMRS items: Language/thought disorder, content*	0.487	<0.001*	0.445	0.001*
Behavioral Dysregulation *YMRS items: Disruptive/aggressive behavior, sexual interest*	0.562	<0.001*	0.531	<0.001*
Sleep Disruption *YMRS item: Sleep*	0.462	<0.001*	0.428	0.002*
Impaired Judgment *YMRS items: Insight, appearance*	0.417	0.002*	0.384	0.005*

*Statistically significant ($p<0.05$)

Additional details about the connection between serum uric acid concentration and manic episode symptom clusters appear in Table 10. A clinical analysis merged YMRS symptoms into meaningful domains before studying their connection to serum uric acid concentrations. The most significant correlations existed between psychomotor activation ($r=0.578$, $p<0.001$) and behavioral dysregulation ($r=0.562$, $p<0.001$), while thought disturbance showed a correlational strength of $r=0.487$ ($p<0.001$).

The regression models applying age, gender, BMI, and illness duration adjustments showed psychomotor activation ($\beta=0.542$, $p<0.001$) and behavioral dysregulation ($\beta=0.531$, $p<0.001$) as having the most significant independent relations with serum uric acid levels. The research shows that elevated uric acid levels specifically affect pathways that regulate psychomotor functions and behavioral control in brain areas with high dopaminergic and glutamatergic systems activity.

TABLE 11: SUBGROUP ANALYSIS BASED ON COMORBIDITIES AND CLINICAL CHARACTERISTICS

Subgroup	**n**	**Serum Uric Acid (mg/dL)** Mean ± SD	**p-value**
Psychiatric Comorbidities			
With anxiety disorder	18	7.21 ± 1.53	0.148
Without anxiety disorder	37	6.66 ± 1.35	
With substance use	12	7.38 ± 1.57	0.046*

disorder			
Without substance use disorder	43	6.69 ± 1.35	
Psychotic Features			
With psychotic features	23	7.35 ± 1.39	0.010*
Without psychotic features	32	6.48 ± 1.33	
Seasonality			
Summer/spring onset	33	7.12 ± 1.46	0.032*
Fall/winter onset	22	6.42 ± 1.27	
Family History			
With family history	21	7.24 ± 1.38	0.027*
Without family history	34	6.59 ± 1.40	
Controls (for reference)	55	5.36 ± 1.18	<0.001†

*Statistically significant ($p<0.05$) †p-value for comparison between all cases and controls

The analysis of Table 11 explores clinical traits and multiple occurring health problems through different subgroups. Patients who experienced manic episodes and had substance use disorder manifested higher uric acid serum levels at 7.38 ± 1.57 mg/dL when compared with patients without substance use disorder (6.69 ± 1.35 mg/dL). This difference reached statistical significance ($p=0.046$). The data stands out because researchers have previously shown that substance use disorders, along with the purinergic system, share an established relationship in addictive behavior along with reward processing systems.

Patients who exhibited psychotic symptoms during their manic episodes had a statistically significant higher uric acid concentration in serum at 7.35 ± 1.39 mg/dL in comparison to manic patients without psychotic symptoms (uric acid level 6.48 ± 1.33 mg/dL) ($p=0.010$). The data indicates that higher uric acid concentrations link to severe manic states, which display psychotic symptoms because they demonstrate increased neurological disturbances.

The research revealed a notable seasonal difference. Patients with manic episodes starting in summer or spring had substantially higher serum uric acid levels, at 7.12 ± 1.46 mg/dL, compared to fall and winter onsets, which were at 6.42 ± 1.27 mg/dL ($p=0.032$). Previous research about purine metabolism revealed seasonal changes while supporting the idea that environmental elements shape the link between uric acid and mood disorder.

Patients with families affected by mood disorders showed increased serum uric acid measurement levels at 7.24 ± 1.38 mg/dL, which exceeded the levels found in patients without mood disorder family members (6.59 ± 1.40 mg/dL) ($p=0.027$). Therefore, this data demonstrates a genetic element in the connection between elevated uric acid and manic episode manifestation. Data that supports purinergic signaling as a possible pathophysiological mechanism adds to evidence describing the origin of bipolar disorder, specifically in family-linked cases of the illness.

The additional statistical evaluations disclose precise information about manic episode relationships with serum uric acid levels by identifying particular patient groups with extreme

uric acid elevations. Given these findings, practitioners can develop more efficient targeted interventions to manage patient risks in actual medical care.

DISCUSSION

The objective of this case-control research study was to evaluate manic episode relationships with serum uric acid levels alongside manic symptom severity effects caused by elevated uric acid numbers. The research indicated that manic patients presented higher serum uric acid amounts compared to healthy participants and showed a direct relationship between serum uric acid measurements and manic symptom severity. The study outcomes show essential findings regarding purinergic system activities that affect bipolar disorder pathogenesis during manic conditions.

ASSOCIATION BETWEEN SERUM URIC ACID LEVELS AND MANIC EPISODES

The research showed that manic episode patients demonstrated greater uric acid concentrations in their serum (6.84 ± 1.42 mg/dL) when compared to healthy subjects (5.36 ± 1.18 mg/dL) ($p<0.001$). The research findings presented here concur with earlier investigations about this subject. Machado-Vieira et al. (2008) identified that medication-free individuals displayed elevated plasma uric acid concentrations during manic episodes versus healthy controls. Likewise, Bartoli et al. (2016) utilized ten research studies totaling 1,618 participants to establish bipolar disorder's connection with higher serum uric acid concentrations, which were most extreme during manic episodes.

The results showed that manic patients had a much higher incidence of hyperuricemia at 63.6% than controls at 25.5% ($p<0.001$), which created a fivefold increased risk (OR=5.13; 95% CI: 2.28-11.56). The research demonstrates that people undergoing manic episodes demonstrate a probability over 500% higher for hyperuricemia than non-affected individuals. Albert et al. (2015) observed that bipolar disorder patients exhibited elevated levels of hyperuricemia when compared to the general population, according to their findings.

Multiple biological factors lead to the connection between elevated levels of serum uric acid and manic episode occurrences. Uric acid is the end product of purine metabolism, and the purinergic system plays a crucial role in neurotransmission and neuromodulation. Purines, particularly adenosine, and ATP, act as neurotransmitters and neuromodulators in various brain regions implicated in mood regulation, including the limbic system, basal ganglia, and cerebral cortex. During manic episodes, hyperactivity in these brain regions may lead to increased purine metabolism and, consequently, elevated uric acid levels.

Elevated uric acid tends to create a connection with oxidative stress in the body. Uric acid functions both as an antioxidant and a pro-oxidant substance, yet higher levels observed in manic episodes might indicate an inadequate response to elevated oxidative stress. Multiple investigations demonstrated raised oxidative stress indicators during these manic episodes.

The influence of uric acid on manic episodes might operate through inflammatory mechanisms. Uric acid activates the NLRP3 inflammasome by affecting inflammatory factors IL-1β and IL-18. Moreover, patients with bipolar disorder show elevated inflammatory markers during mood episodes, and inflammation plays a vital role in disorder pathophysiology. Due to these effects, patients with manic episodes experience elevated uric acid levels that increase inflammatory state symptoms.

RELATIONSHIP BETWEEN SERUM URIC ACID LEVELS AND MANIC SYMPTOM SEVERITY

Our research established that YMRS scores, along with serum uric acid measurements, had a

meaningful relationship ($r=0.583$, $p<0.001$), which showed patients with elevated serum uric acid levels generally displayed more severe manic symptoms. Scientists have verified this result throughout past studies. Machado-Vieira et al. (2008) presented evidence for a statistically significant link between plasma uric acid levels and YMRS manic symptom evaluation results ($r=0.509$, $p<0.001$). Kesebir et al. (2014) verified this connection through their study of bipolar disorder manic patients ($r=0.509$, $p<0.001$).

Research on individual YMRS components presented positive correlations between serum uric acid measurements and scores across all item sets and the disruptive/aggressive behavior item (0.531), followed by speech (0.523) and increased motor activity/energy (0.512). Elevated uric acid levels show a specific correlation with manic symptoms affecting different behavioral domains, which include behavioral hyperactivity.

Much of the interest in uric acid increases leading to higher motor activity comes from research exploring purinergic system functions in motor control. Elevated uric acid particularly affects motor activity regulation because adenosine interacts with basal ganglia dopaminergic systems to control motor function. The observed changes in uric acid levels may, therefore, explain manic episodes with increased motor activity.

The significant relationship between uric acid amounts and disruptive/aggressive conduct validates research evidence showing connections between the purinergic system and aggressive behavior. Due to their ability to influence the serotonin and dopamine neurotransmitter systems, purinergic signals regulate aggressive behavior, so elevated uric acid levels may disrupt these connections and enhance manic aggression patterns in patients.

Research data from linear regression demonstrates a direct connection between manic symptom intensity and serum uric acid concentrations. Serum uric acid level was shown as a crucial contributor to the YMRS score through a multi-factor analysis ($\beta=0.579$, $p<0.001$). The intensity of manic symptoms increases by 2.782 points when serum uric acid reaches 1 mg/dL higher. The clinical relationship between serum uric acid measurement and manic symptom severity implies its value as a diagnostic biomarker for healthcare professionals.

INFLUENCE OF EPISODE HISTORY ON SERUM URIC ACID LEVELS

The subgroup analysis showed an increased serum uric acid concentration of 7.03 ± 1.44 mg/dL in patients with recurrent manic episodes compared to patients experiencing their first manic episode, which was 6.32 ± 1.28 mg/dL ($p=0.042$). The study findings indicate that the duration of the manic episode and the number of previous episodes influence how serum uric acid levels associate with manic episodes.

This finding supports the theory of neuroprogression in bipolar disorder, showing how the illness gradually worsens and becomes less responsive to treatment through each case of episode. (26) The progressive serum uric acid level increases in patients potentially linked to neurobiological modifications caused by this progression. Expanded purinergic signaling and a stressed cellular environment produce increased inflammatory responses that add to rising serum uric acid concentrations in each successive episode.

The serum uric acid content of patients with their first manic episode surpassed that of controls, which demonstrates that increased serum uric acid begins at the preliminary stages of bipolar disorder development. Such findings can assist early detection of individuals who might develop bipolar disorder alongside presenting options for early intervention. Elevated uric acid measurement before manic disorder development offers the potential to identify high-risk candidates, mainly among relatives of bipolar disorder patients and individuals experiencing

depressive symptoms who might develop bipolar disorder in the future.

MULTIPLE PREDICTORS OF MANIC EPISODES

An analysis using multiple logistic regression in Table 9 validates the main study results and eliminates confounding effects from various variables. Serum uric acid level showed the strongest independent association with manic episodes in the analysis as an odds ratio was 2.27 (95% CI: 1.58-3.26, $p<0.001$) after controlling for demographic and clinical variables. The risk of developing manic episodes increases by more than two times, with each 1 mg/dL increase in serum uric acid after eliminating the effects of other risk factors. The result provides strong evidence to support the biological link between uric acid metabolism and mania pathophysiology.

Epidemiological evidence shows that weaker educational attainment (OR=0.61, $p=0.029$) functions as a risk factor for bipolar disorder, but the relationship between uric acid persists beyond education level adjustment. The study confirms research-supported genetic prevalence estimates of bipolar disorder by showing that family history acts as an individual risk factor (OR=2.84, $p=0.028$).

The high significance level of serum uric acid suggests that dysfunctional purinergic systems function as a distinct pathological mechanism for bipolar disorder while being independent of genetic and environmental influences. Studies linking bipolar disorder to polymorphisms in purine metabolism genes support the view that the purinergic system requires increased investigation as an important biological mechanism for bipolar disorder research.

SYMPTOM-SPECIFIC ASSOCIATIONS

Detailed analysis performed on particular symptom clusters in Table 10 identifies the potential neurological pathways that alterations in purinergic signaling create. The research connection between manic symptoms and serum uric acid reached its highest point for psychomotor activation ($r=0.578$, $p<0.001$) and behavioral dysregulation ($r=0.562$, $p<0.001$) and then reached a second peak for thought disturbance ($r=0.487$, $p<0.001$). Statistical models with multiple regression analysis proved significant for these connections even when controlling factors that could affect the results.

Neurobiological insights can be best derived from the strong correlations between psychomotor activation and biochemical measures. The regulation of motor activity involves complex interactions between dopaminergic, glutamatergic, and purinergic systems, particularly in the basal ganglia and motor cortex. Adenosine, a breakdown product of ATP in the purinergic system, acts as an endogenous inhibitor of dopaminergic neurotransmission through A2A receptors in the striatum. Elevated uric acid levels may reflect decreased adenosine activity, resulting in disinhibition of dopaminergic transmission and consequently increased motor activity characteristic of mania.

Purinergic signaling shows an equivalent relationship to behavioral dyscontrol and remains fundamental for the regulation of impulsiveness when making decisions. The prefrontal cortex expresses P2X7 receptors, which belong to the purinergic receptor family, to regulate emotional regulation processes, and these receptors play a role in impulsive behaviors. This supports the findings of elevated uric acid levels demonstrating impaired judgment ($r=0.417$, $p=0.002$) since purinergic signaling contributes to executive functions such as decision-making and impulse control.

While purinergic abnormalities impact euphoria and mood elevation in manic patients ($r=0.456$,

p<0.001), the strength of association remains weaker than other neurotransmitter system involvement, including serotonergic and noradrenergic pathways. These connections between symptoms and purinergic dysfunction form an essential basis for developing targeted medication methods that treat the strongest purinergic symptoms.

The data from Table 11 identifies distinct clinical patterns that healthcare providers could use to create personalized treatment strategies. Subjects diagnosed with manic episodes linked to substance abuse had increased serum uric acid measures in their blood tests (7.38 ± 1.57 vs 6.69 ± 1.35 mg/dL) compared to manic patients without substance abuse (p=0.046). This finding is particularly relevant given the growing evidence for overlapping neurobiological mechanisms between substance use disorders and bipolar disorder, with the purinergic system implicated in both conditions. The P2X7 receptor, which plays a key role in purinergic signaling, has been associated with both substance use vulnerability and mood regulation. Our findings suggest that patients with this dual diagnosis might represent a distinct neurobiological subtype with more pronounced purinergic abnormalities, potentially benefiting from targeted interventions addressing this system.

Laboratory results identify psychotic manic patients as having an average serum uric acid value of 7.35 ± 1.39 mg/dL, significantly above the 6.48 ± 1.33 mg/dL measured in patients without psychotic symptoms (p=0.010), which supports the association between purinergic dysfunction and symptom severity. Psychotic symptoms represent a more severe manifestation of bipolar disorder and are associated with poorer prognosis and treatment response. The association with elevated uric acid levels suggests that purinergic abnormalities may contribute to the neurobiological substrate of psychotic symptoms in mania, potentially through interactions with glutamatergic and dopaminergic systems that are implicated in psychosis. This finding has important treatment implications, as targeting the purinergic system might provide a novel approach to managing psychotic symptoms in bipolar disorder, which often respond inadequately to conventional mood stabilizers.

Observations indicate that patients with manic episodes starting in summer or spring show higher uric acid serum levels at 7.12 ± 1.46 vs 6.42 ± 1.27 mg/dL (p=0.032), which contributes to the understanding of purinergic mechanisms in bipolar disorders. Multiple scientific studies of mood conditions report increased manic episode occurrences during spring and summer periods, thus supporting the hypothesis that seasonal purine metabolism changes contribute to these seasonal patterns. Ultraviolet radiation detected during spring and summer causes modifications to purine metabolism and produces uric acid, while changing seasonal diets and physical activities influence uric acid levels in the bloodstream. The pathophysiology of bipolar disorder demands environmental factor evaluation since seasonal risk profiles should influence preventive strategy development and implementation.

The 0.027 statistically significant difference (7.24 ± 1.38 vs 6.59 ± 1.40 mg/dL) between serum uric acid levels of patients with a mood disorder family history enhances our understanding of predisposing genetic factors in bipolar disorder and dysregulation of purinergic systems. Previous scientific studies connected bipolar disorder risk with polymorphisms in genes that regulate purine metabolism, including adenosine deaminase and purine nucleoside phosphorylase. Our research supports the genetic basis of inherited purinergic dysfunction as a bipolar disorder factor affecting developmental neuro processes, optic plasticity mechanisms, and immune system responses. Current theories of bipolar disorder match the evidence that shows this mental disorder follows neurodevelopmental patterns and

exhibits sophisticated genetic components and variable manifestations.

These analyses—in conjunction with the integration of our primary findings in Tables 1 through 8—introduce the reader to the relationship between serum uric acid levels and manic episodes in a more complete manner that encompasses these additional analyses. The multivariate prediction model reasserts that there is an association between elevated uric acid and mania that is not due to demographic factors, comorbidities, or other clinical characteristics. The correlational finding between symptom domains and uric acid levels points to psychomotor activation and behavioral dysregulation as being the most symptomatic domains that purinergic abnormalities could impact during neurobiological pathways. Specific patient populations (psychotic features, substance use comorbidity, positive family history, and summer/spring onset) are then identified that are characterized by particularly pronounced elevations in uric acid levels.

Taken together, these findings suggest that serum uric acid is consistently high in manic episodes but that the extent of this elevating and its clinical implications may differ among several patient subgroups and symptom profiles. As such, BP illustrates the necessity for a personalized medicine approach to combating the disorder with similarly diverse treatments. For example, patients with severely high uric acid levels, particularly those with a predominantly psychomotor and behavior-dominant picture, might benefit from adjunctive purinergic system targeting treatments, such as allopurinol, which has preliminarily proven beneficial.

Finally, we did not test other biological markers involved with the purinergic system or in the inflammatory process which would have given a more comprehensive understanding of the involved mechanisms. In future studies it will be useful to consider a more extensive panel of biomarkers which would allow to better elucidate the pathophysiological processes.

CONCLUSION

The researchers show conclusive evidence of an association between serum uric acid and manic episodes in bipolar disorder. Moreover, serum uric acid levels in patients with manic episodes were significantly higher than in those in healthy controls, and the odds of having hyperuricemia were 5.13 times higher. Moreover, serum uric acid levels showed a significant positive correlation with the severity of manic symptoms, and higher levels were correlated with greater severity in all areas of manic psychopathology. In addition, these associations were significant when potential confounding variables were controlled.

This study findings are important in the following ways. From a pathophysiological point of view, they strengthen the involvement of the purinergic system in bipolar disorder neurobiology during manic episodes. Raised uric acid levels in patients with manic disorder might be due to altered purinergic signaling, increased oxidative stress, or involvement of inflammatory processes that contribute to the development of manic symptoms. The increase of serum uric acid, according to the increasing number of episodes, indicates that these biochemical changes may worsen over time during the course of the illness, that is, neuro progression in bipolar disorder.

These findings may have clinical implications, given that serum uric acid level would be a biomarker for the occurrence of mania, which may help to diagnose, monitor the disease process, and possibly identify subjects at risk of developing bipolar disorder or manic relapse. It appears that serum uric acid testing could offer objective information on the severity of a manic episode, as it shows a very strong correlation with how severe patients' symptoms are.

Furthermore, our results bring into focus the possibility of developing the purinergic system as a target for the treatment of bipolar disorder. Given that purinergic signaling is modulated by medications that reduce uric acid levels (allopurinol) and that uric acid levels are relatively high in bipolar disorder, these medications may represent new treatments for this patient population. While these approaches can shift depressed patients towards recovery, more research is needed to see if they will help alleviate the severity of manic symptoms or prevent episodes.

In addition, this study suggests the potential worth of a personalized medicine route in bipolar disorder. Since the variability in serum uric acid levels among patients with manic episodes is considerable, it appears that different pathophysiological processes predominate in different individuals. Selecting patients with elevated uric acid levels may assist in picking out these patients, which would maximize the advantage of interventions that objective the purinergic gadget and, additionally, grow remedy outcomes.

First, it is important to recognize that although our study sets an association between high serum uric acid and manic episodes, it does not prove causality. To determine whether elevated uric acid levels predate the onset of manic episodes, rise during episodes, and decrease during remission, or whether they represent a trait marker that remains elevated through all the mood states, the urine acid levels need to be investigated by using longitudinal studies. Future research should also determine if similar associations exist in other phases of bipolar disorder (e.g., depression and euthymia) and in other psychiatric disorders in which mood and behavior are altered.

Further analyses considerably reinforce the evidence for a significant relationship between serum uric acid levels and episodes of mania in bipolar disorder. An elevated serum uric acid proves to be an independent risk marker for manic episodes such that with each 1 mg/dL increase in uric acid, the odds of mania are more than doubled after adjusting for demographic and clinical factors. These findings offer the potential utility of serum uric acid as a biomarker in clinical practice for manic vulnerability.

Detailed analysis of symptom correlations indicates that the strongest links between uric acid and symptoms of psychomotor activation, behavioral dysregulation, and grandiosity suggest specific neurobiological pathways by which purinergic abnormalities may lead to the clinical presentation of mania. The correlations of these symptom domains with known P2RX7 targets provide a rational basis for targeting purinergic system modulation to assist in ameliorating these symptom domains specifically.

Subgroup analyses show that several groups of patients experience unusually high levels of serum uric acid, including patients with psychotic features on top of bipolar depression, comorbid substance use disorders, spring or summer onset of mood episodes, and positive family history of mood disorders. These data further suggest this purinergic dysfunction might be particularly relevant in some clinical presentations of bipolar disorder that could typify biologically distinct subtypes requiring unique treatment.

Overall, our data provide another line of evidence for the increasing number of studies linking the purinergic system to the pathophysiology of bipolar disorder. Elevated serum uric acid levels were associated with manic episodes, and such an association was correlated with an increase in symptom severity, which can serve as a basis for further research relating to the neurobiology of bipolar disorder and new therapeutic approaches. Integrating serum uric acid into clinical practice may improve our capability to diagnose, monitor, and treat this complex and disabling disorder, thereby offering better clinical outcomes for patients affected with

bipolar disorder.

CLINICAL IMPLICATIONS

This study delivers multiple vital healthcare recommendations for medical practice. The research indicates that measuring uric acid levels in the blood could represent a useful biological marker to assess manic states in bipolar disorder individuals. The research indicates that serum uric acid measurements could help diagnose manic episodes because they show distinct levels between manic patients and healthy controls while correlating with client symptom intensity. Specialized psychiatric assessments become much easier to access by employing serum uric acid testing as a diagnostic tool in areas with limited psychiatric resources.

The data support investigating purinergic system intervention as a therapeutic method for bipolar disorder, especially during manic stages. Patients with bipolar disorder might benefit from medication treatments that influence purinergic signaling functions while lowering their uric acid amounts. Preliminary research demonstrates that allopurinol, which decreases uric acid through xanthine oxidase inhibition, shows potential as an additional mania treatment. Our study adds weight to this investigative direction.

Uric acid level monitoring in bipolar disorder patients, especially those with mania risks, provides a tool to detect individuals at risk of experiencing manic episodes. Early intervention access for the prevention of manic episodes would become possible through this approach.

Research findings demonstrate that patients with first-episode mania possess elevated uric acid levels above those measured in controls, thus establishing potential biomarker qualities for bipolar disorder risk assessment. Medical practitioners can use this discovery to find unipolar depression patients who may develop bipolar disorder so they can receive proper treatment.

The connection between elevated uric acid levels and higher manic episode frequency demonstrates that treating uric acid through lifestyle changes such as nutritional adjustments could benefit bipolar disorder patients. More studies need to evaluate how much such therapeutic interventions succeed at decreasing the likelihood or decreasing the intensity of manic episode occurrence.

STRENGTHS AND LIMITATIONS

The study incorporates several advantageous methodological aspects that utilize case-control assessments using well-matched controls that help reduce confounding factors. The researchers executed strict control procedures on patient enrollment to exclude variables affecting serum uric acid measurements through medication intake and alcohol use as well as metabolic diseases within participants. The team used validated manic assessment tools in addition to running complete statistical procedures to examine manic episode connections with serum uric acid concentrations.

Several restrictions stand in the way of recognizing the findings in our research. The case-control design of this study allows only the establishment of associations while having no ability to prove causality. The connection between increased serum uric acid levels and manic episodes remains unclear because it might stem from either direction of influence or from another common factor. Time-series data collection will help define the exact sequence of change between uric acid fluctuations and bipolar manic outbreaks.

The research examined solely manic patients while omitting bipolar disorder patients who were in depression or euthymic states. The observed increases in serum uric acid levels during manic

episodes do not establish whether this pattern is manic-specific since it could apply to bipolar disorder during all states of mood. Alternative research should study patients who are in various stages of bipolar disorder to resolve this issue.

Our study sample provided sufficient power for main research associations yet failed to adequately assess certain group examination relationships. More comprehensive research, including additional subjects, should replicate and advance findings regarding serum uric acid level sensitivity to prior manic events.

The assessment did not include measurements of lifestyle factors and health conditions which might have an influence on serum uric acid measurements during this study. The research needs to implement methods of controlling external influences to demonstrate the direct connection between uric acid levels and manic episode occurrences.

This study took place at one center in Pakistan, which might limit how broadly the research findings can be applied to populations that differ in terms of genetic inheritance, consumption methods, and environmental influences. Research spanning multiple centers needs to verify whether the results from this study can apply to populations worldwide.

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