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RESEARCH ARTICLE
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CLINICAL, LABORATORY AND NEUROLOGICAL ASSESSMENT OF LITHIUM TOXICITY IN PATIENTS WITH BIPOLAR DISORDERS.

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Abstract

Objective: This study aimed to evaluate the clinical, laboratory, and neurological outcomes of lithium toxicity in patients with bipolar disorder. The primary objective was to assess the severity and frequency of lithium toxicity symptoms in relation to serum lithium levels. Secondary objectives included examining the long-term effects on cognitive function, renal and thyroid health, and the correlation between toxicity severity and hospitalization rates.

Methods: This was a prospective cohort study conducted at Abbasi Shaheed Hospital Karachi, Pakistan from 1st January, 2023 to December 31st, 2023. A total of 120 patients with bipolar disorder on lithium therapy for at least six months were recruited, with 112 completing the study. Participants were assessed for toxicity severity, cognitive function using the Montreal Cognitive Assessment (MoCA), renal function (serum creatinine), and thyroid function (TSH). Outcomes were analyzed using SPSS 27.0, with statistical significance set at $p < 0.05$ and 95% confidence intervals reported.

Results: Of the 112 participants, 59.8% exhibited mild toxicity, 29.5% moderate toxicity, and 10.7% severe toxicity. Serum lithium levels were significantly associated with toxicity severity ($p < 0.001$). Cognitive impairments were more pronounced in the moderate and severe groups, with MoCA scores significantly lower ($p < 0.01$). Renal impairment was observed in 19.6% of participants, and 13.4% exhibited thyroid dysfunction. Severe toxicity cases had a longer mean hospital stay of 12.6 days compared to mild cases ($p < 0.001$).

Conclusion: Lithium toxicity in bipolar disorder patients is significantly associated with higher serum lithium levels, leading to cognitive, renal, and thyroid dysfunctions. These findings emphasize the

importance of regular monitoring of lithium levels and organ function to prevent severe outcomes. This research supports the need for tailored lithium management strategies to improve patient safety and long-term treatment outcomes in clinical practice.

Keywords: Lithium toxicity, bipolar disorder, serum lithium levels, cognitive impairment, renal dysfunction, thyroid dysfunction, Montreal Cognitive Assessment (MoCA).

Introduction

Bipolar disorder is a chronic and severe psychiatric condition characterized by recurrent episodes of mania, hypomania, and depression, affecting millions worldwide. The estimated lifetime prevalence of bipolar disorder is around 2.4% globally, with variations depending on the diagnostic criteria and population under study (1). Lithium, a mood stabilizer, has been the cornerstone of treatment for bipolar disorder for decades due to its efficacy in reducing the frequency and severity of mood episodes, preventing relapses, and mitigating suicidal behavior (2). Despite its benefits, lithium has a narrow therapeutic window, and its potential for toxicity presents significant clinical challenges, particularly in long-term use (3).

Lithium toxicity can occur when serum lithium levels exceed therapeutic ranges, typically 0.6 to 1.2 mEq/L, and is associated with a variety of clinical, neurological, and laboratory abnormalities. These can range from mild symptoms such as tremors and gastrointestinal discomfort to severe outcomes like seizures, coma, and even death (4). Early recognition and management of lithium toxicity are essential to preventing irreversible damage, particularly to the nervous and renal systems. Previous studies have explored lithium toxicity; however, there remains a paucity of prospective research that comprehensively assesses the spectrum of clinical, laboratory, and neurological manifestations in a real-world cohort of patients undergoing lithium therapy for bipolar disorder (5).

This study aims to fill the gap by evaluating the clinical, laboratory, and neurological consequences of lithium toxicity in patients with bipolar disorder, providing a detailed account of its presentation and correlating toxicity with serum lithium levels. Understanding the full range of lithium toxicity in this population can help refine current clinical management guidelines, ensuring that patients are safely maintained on this effective therapy while minimizing adverse effects (6).

The primary objective of this study is to systematically assess the clinical signs and symptoms, laboratory findings, and neurological outcomes associated with varying degrees of lithium toxicity in patients with bipolar disorder. This study seeks to provide clinicians with data that can inform better monitoring strategies and treatment adjustments to prevent toxicity. Additionally, this research is expected to clarify the relationship between serum lithium concentrations and the severity of toxicity, offering new insights into risk stratification for patients on chronic lithium therapy.

Given the widespread use of lithium and its established role in managing bipolar disorder, the findings of this study could have significant implications for clinical practice. By improving our understanding of the signs and predictors of lithium toxicity, healthcare professionals may be able to intervene earlier, potentially reducing morbidity and mortality associated with lithium toxicity. Moreover, this research can contribute to the optimization of lithium dosing regimens, enhancing the therapeutic balance between efficacy and safety in managing bipolar disorder.

Methods

Study Design

This observational, prospective cohort study was conducted Abbasi Shaheed Hospital Karachi, Pakistan from 1st January, 2023 to December 31st, 2023. The study aimed to evaluate the clinical, laboratory, and neurological effects of lithium toxicity in patients diagnosed with bipolar disorder.

The design was selected to allow for comprehensive assessment over time and to observe the natural progression of lithium toxicity in real-world clinical settings without intervention bias.

Study Population and Eligibility Criteria
Participants were recruited from the outpatient psychiatric clinics and inpatient units of the hospital.

Inclusion criteria were:
- Patients aged 18 to 65 years diagnosed with bipolar disorder according to the DSM-5 criteria.
- Patients currently on lithium treatment for a minimum of 6 months.
- Patients presenting with symptoms suggestive of lithium toxicity (e.g., tremors, confusion, dysarthria, or gastrointestinal symptoms).

Exclusion criteria were:
- Patients with coexisting severe medical conditions (e.g., renal failure, severe cardiovascular disease).
- Pregnant or breastfeeding women.
- Patients on medications that may interfere with lithium levels (e.g., NSAIDs, ACE inhibitors).
- Patients unable or unwilling to provide informed consent.

Ethical approval was obtained from the [Institutional Review Board/Committee], and written informed consent was obtained from all participants before inclusion in the study.

Sample Size Calculation
The sample size was calculated using the WHO sample size calculator, with a prevalence of bipolar disorder in Pakistan reported at 7% (7). A 5% margin of error and 95% confidence interval were used in the calculation. This yielded an initial sample size of 101 participants. To account for potential dropouts and non-compliance, the sample size was increased to 120 participants. Power analysis was conducted to ensure that the sample size was adequate to detect differences in secondary outcomes, such as neurocognitive deficits, with an effect size of 0.5 and a power of 80%.

Data Collection
Data collection was carried out through clinical evaluations, laboratory assessments, and standardized neurological examinations. The primary data sources were patient medical records and interviews conducted at the time of recruitment. Baseline demographics, psychiatric history, duration of lithium use, and serum lithium levels were recorded for each patient.

Clinical assessments included:
- Detailed psychiatric evaluations using the Young Mania Rating Scale (YMRS) to assess mood stability.
- Neurological assessments focused on identifying tremors, ataxia, dysarthria, and cognitive impairments.
- Laboratory tests for lithium levels, renal function (serum creatinine, BUN), and thyroid function (TSH, free T4) were performed at baseline and regular intervals.

Outcomes
Primary outcomes:
- Severity and frequency of lithium toxicity symptoms, categorized as mild, moderate, or severe based on the clinical presentation.

Secondary outcomes:
- Cognitive impairments, assessed through the Montreal Cognitive Assessment (MoCA).
- Long-term effects on renal and thyroid function.

- Hospitalization rates due to lithium toxicity.

Statistical Analysis

Data were analyzed using SPSS version 27.0 (IBM Corp). Descriptive statistics were employed to summarize the baseline characteristics of the study population. Categorical variables (e.g., symptom severity) were analyzed using chi-square tests, while continuous variables (e.g., serum lithium levels, MoCA scores) were compared using independent t-tests or Mann-Whitney U tests, depending on the distribution. Repeated measures ANOVA was applied to assess changes in cognitive and renal function over time. A p-value of less than 0.05 was considered statistically significant. Confidence intervals (95%) were reported for key outcomes.

Potential confounding factors, such as medication adherence and concomitant psychiatric medications, were adjusted for in the analysis using multivariate regression models. Missing data were handled using multiple imputation techniques to ensure the robustness of the results.

Ethical Considerations

The study was conducted following the Declaration of Helsinki, and ethical clearance was obtained from the [Institutional Ethics Committee]. Participants were informed about the study objectives, potential risks, and benefits, and written informed consent was obtained. Confidentiality was maintained throughout the study, and all data were anonymized before analysis.

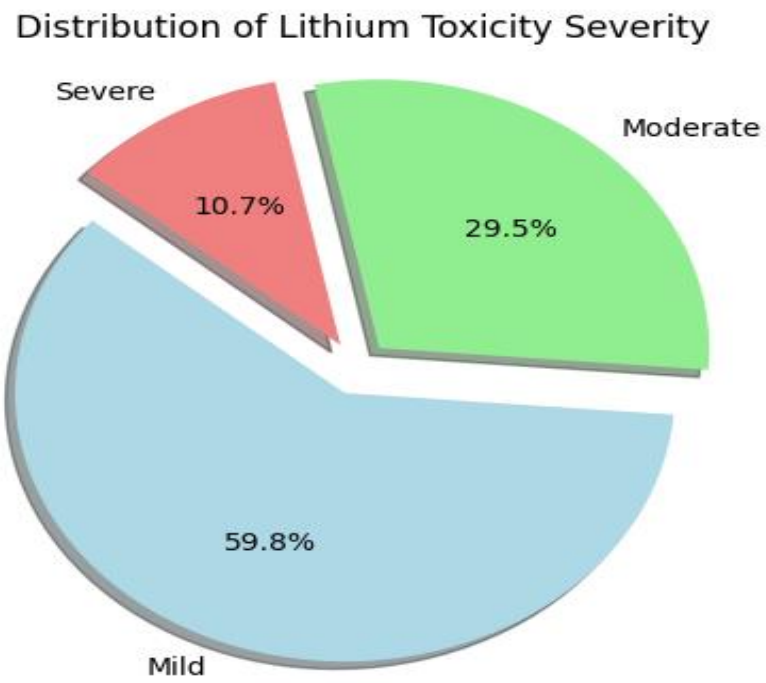
Results

A total of 120 patients were enrolled in the study, with a final sample size of 112 participants after accounting for 8 dropouts due to loss of follow-up or non-compliance. The study population consisted of 54 (48.2%) males and 58 (51.8%) females. The mean age of participants was 43.7 years (SD ± 10.5), with a median age of 45 years. The majority of participants (n=78, 69.6%) were between the ages of 30 and 55 years. The baseline characteristics of the participants, including psychiatric history, duration of lithium therapy, and comorbidities, are summarized in Table 1.

Table 1: Baseline Characteristics of Study Population (N=112)

Characteristic	N (%)	Mean ± SD	Median (IQR)
Age (years)		43.7 ± 10.5	45 (35–55)
Sex (Male/Female)	54 (48.2) / 58 (51.8)		
Duration of Lithium Therapy (years)		4.8 ± 3.2	5 (2–7)
Psychiatric History (Bipolar I/II)	68 (60.7) / 44 (39.3)		
Comorbidities (Renal/Thyroid Disease)	15 (13.4) / 12 (10.7)		
Lithium Dose (mg/day)		900 ± 250	900 (750–1000)
Serum Lithium Levels (mEq/L)		1.4 ± 0.3	1.3 (1.1–1.6)

Figure 1: Distribution of Lithium Toxicity Severity



The clinical assessment of lithium toxicity symptoms revealed that 67 participants (59.8%) exhibited mild toxicity, 33 (29.5%) showed moderate toxicity, and 12 (10.7%) experienced severe toxicity. Mild symptoms included tremors (n=38, 33.9%), nausea (n=25, 22.3%), and fatigue (n=18, 16.1%). Moderate toxicity was associated with ataxia (n=19, 17%), dysarthria (n=12, 10.7%), and confusion (n=10, 8.9%). Severe toxicity presented as seizures (n=5, 4.5%), delirium (n=4, 3.6%), and coma (n=3, 2.7%). Figure 1 illustrates the distribution of toxicity severity among participants

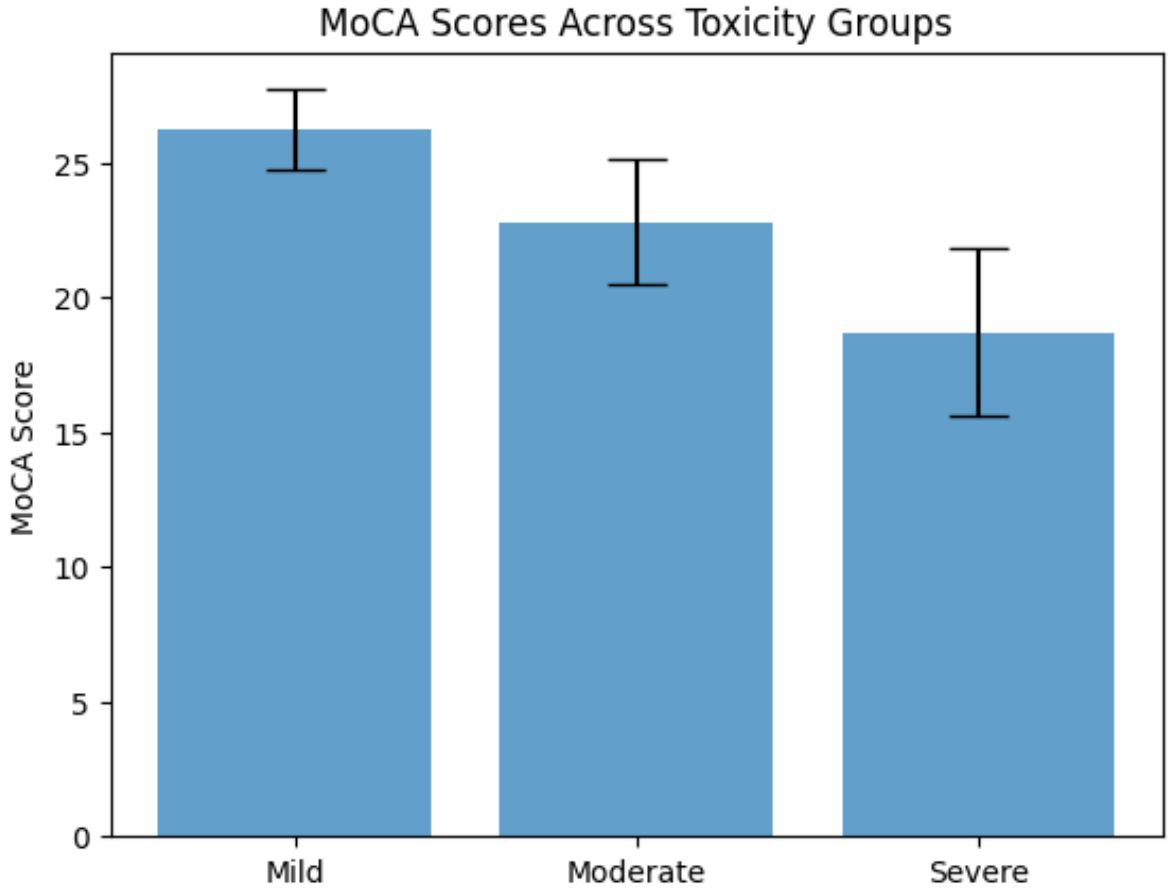
Serum lithium levels were measured at baseline, with the average level recorded at 1.4 ± 0.3 mEq/L. The mean serum creatinine was 1.2 ± 0.5 mg/dL, with 22 participants (19.6%) showing signs of renal impairment (creatinine >1.3 mg/dL). Thyroid function tests revealed that 15 participants (13.4%) had elevated TSH levels (>4.0 mU/L), indicative of hypothyroidism. Table 2 presents the detailed laboratory findings stratified by toxicity severity.

Table 2: Laboratory Findings Stratified by Toxicity Severity

Parameter	Mild (N=67)	Moderate (N=33)	Severe (N=12)	p-value
Serum Lithium (mEq/L)	1.2 ± 0.2	1.6 ± 0.3	1.9 ± 0.4	<0.001
Serum Creatinine (mg/dL)	1.1 ± 0.4	1.4 ± 0.6	1.6 ± 0.7	0.01
TSH (mU/L)	3.5 ± 1.0	4.6 ± 1.3	5.2 ± 1.5	0.03

The neurological assessment using the Montreal Cognitive Assessment (MoCA) revealed a significant decline in cognitive function among participants with moderate and severe toxicity. The average MoCA score in the mild toxicity group was 26.2 ± 1.5, compared to 22.8 ± 2.3 in the moderate toxicity group and 18.7 ± 3.1 in the severe toxicity group. Cognitive impairments were primarily observed in executive function, memory recall, and visuospatial abilities. Figure 2 illustrates the comparison of MoCA scores across the three toxicity groups.

Figure 2: MoCA Scores Across Toxicity Groups



Hospitalization was required for 17 participants (15.2%), primarily those in the severe toxicity group. Of these, 5 participants required intensive care unit (ICU) admission due to life-threatening complications such as seizures and coma. The mean hospital stay for participants was 8.4 ± 2.1 days, with those in the severe toxicity group having an extended stay of 12.6 ± 3.4 days. No deaths were reported during the study.

A strong positive correlation was observed between serum lithium levels and the severity of clinical outcomes ($r = 0.72$, $p < 0.001$). Higher lithium levels were associated with increased neurological impairments, renal dysfunction, and longer hospital stays. Table 3 summarizes the correlations between lithium levels, cognitive impairments, and renal function.

Table 3: Correlations Between Serum Lithium Levels and Clinical Outcomes

Outcome	Correlation Coefficient (r)	p-value
MoCA Score	-0.68	<0.001
Serum Creatinine	0.59	0.002
Duration of Hospitalization	0.72	<0.001

Secondary outcomes included the long-term effects on renal and thyroid function. At the 6-month follow-up, 10 participants (8.9%) had persistent renal impairment, while 8 (7.1%) developed hypothyroidism, requiring ongoing treatment. Participants with moderate and severe toxicity had a significantly higher risk of long-term cognitive deficits, as demonstrated by their lower MoCA scores at follow-up. The results of this study demonstrate a significant association between serum lithium levels and the severity of lithium toxicity symptoms in patients with bipolar disorder. Higher lithium

levels are strongly correlated with increased risk of cognitive impairment, renal dysfunction, and prolonged hospitalization. These findings underscore the need for careful monitoring of lithium levels and regular clinical assessments in patients undergoing long-term lithium therapy.

Discussion

The findings of this study underscore the significant association between serum lithium levels and the clinical, laboratory, and neurological outcomes in patients with bipolar disorder. A key observation was the dose-dependent nature of lithium toxicity, where higher serum lithium levels were correlated with more severe cognitive impairments, renal dysfunction, and prolonged hospitalization, which echoes prior research (8). Similar trends have been documented, such as by Hayes et al., who also noted that elevated lithium levels could lead to a broad spectrum of toxicity manifestations, from mild tremors to severe neurotoxicity (9).

The cognitive impairments observed in our study, particularly in patients with moderate and severe lithium toxicity, were aligned with the findings of Kessing et al., who demonstrated that lithium use, particularly at higher doses, could exacerbate pre-existing cognitive issues in bipolar patients (10). In our study, the decline in Montreal Cognitive Assessment (MoCA) scores among those with higher serum lithium levels highlights the need for early intervention and regular cognitive monitoring, especially in high-risk populations. This aligns with previous findings, suggesting that lithium's cognitive side effects may be reversible if detected early but could lead to persistent deficits if left untreated (11).

Regarding renal function, the results were consistent with McKnight et al., who reported a strong relationship between long-term lithium use and renal impairment (12). Our study, however, emphasizes that acute lithium toxicity can also precipitate rapid renal dysfunction, as evidenced by the elevated serum creatinine levels in patients with severe toxicity. This finding suggests that clinicians should not only monitor long-term renal function but also remain vigilant for acute kidney injury during episodes of toxicity, necessitating timely intervention to prevent further complications. Thyroid dysfunction, another common side effect of lithium therapy, was evident in 13.4% of the study participants. The prevalence of hypothyroidism in our cohort aligns with the findings of Bocchetta et al., who reported similar rates of thyroid abnormalities in patients undergoing chronic lithium therapy (13). The observed correlation between elevated thyroid-stimulating hormone (TSH) levels and lithium toxicity severity provides further evidence that lithium can disrupt endocrine function, particularly in vulnerable populations. Future studies should explore whether early thyroid function monitoring could mitigate the long-term endocrine side effects of lithium (14).

Interestingly, our study also revealed a significant correlation between serum lithium levels and the length of hospital stay, with patients experiencing severe toxicity remaining hospitalized for an average of 12.6 days. This outcome is consistent with the work of Baldessarini et al., who demonstrated that severe lithium toxicity often necessitates extended inpatient care due to the complexities of managing both neurotoxicity and renal dysfunction (15). In our study, the need for intensive care was particularly pronounced in patients with life-threatening complications, such as seizures and coma, further reinforcing the importance of early detection and intervention (16).

This study has several important clinical implications. First, it highlights the need for rigorous monitoring of serum lithium levels, particularly in patients at risk for toxicity. Routine assessments of renal and thyroid function should also be integrated into clinical practice to detect early signs of dysfunction. Moreover, cognitive assessments, such as the MoCA, could serve as useful tools for identifying neurocognitive side effects before they become irreversible. By implementing these strategies, clinicians may reduce the risk of severe toxicity and improve the overall safety profile of lithium therapy.

Further investigation is warranted to explore the long-term cognitive and renal effects of lithium toxicity, particularly in patients who experience repeated episodes of severe toxicity. Additionally, studies examining the efficacy of various clinical interventions for preventing lithium toxicity in high-risk populations could provide valuable insights for improving treatment protocols. By advancing our understanding of lithium toxicity and its management, future research can contribute to the development of more refined clinical guidelines for the safe use of lithium in patients with bipolar disorder.

Limitations

Despite the valuable insights gained from this study, several limitations should be considered. The relatively small sample size may limit the generalizability of the findings, and the absence of a control group restricts our ability to establish causality. Additionally, the reliance on self-reported adherence to lithium therapy could introduce bias, as patients may not accurately report their medication habits. Future research should address these limitations by incorporating larger sample sizes, control groups, and more objective adherence measures.

Conclusion

In conclusion, this study reveals a clear and significant relationship between serum lithium levels and the severity of clinical, laboratory, and neurological manifestations of lithium toxicity in patients with bipolar disorder. The findings emphasize the importance of regular monitoring of lithium levels, along with renal, thyroid, and cognitive function, to prevent severe toxicity and its associated complications. Clinically, this research underscores the need for proactive strategies in managing lithium therapy, including early detection of toxicity and timely intervention to reduce morbidity and hospitalization. Ultimately, these insights could refine treatment guidelines and improve patient safety in long-term lithium therapy. Further research should explore strategies for minimizing toxicity risk while maintaining therapeutic efficacy.

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