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ORIGINAL RESEARCH

# Olanzapine-Associated Hepatotoxicity in Bipolar Disorder: A Multicenter Real-World Study of Prevalence, Risk Factors, and Outcomes

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**Background:** Olanzapine, an atypical antipsychotic agent, is widely used in the treatment of bipolar disorder due to its multifaceted therapeutic effects, encompassing sedation, mood stabilization, and antidepressant activity. Nevertheless, safety concerns remain a critical consideration in clinical application.

**Objects:** This real-world, multicenter retrospective cohort study aimed to investigate the prevalence, risk factors, clinical patterns, and outcomes of olanzapine-associated hepatotoxicity in bipolar disorder patients.

**Methods:** We conducted a multicenter retrospective cohort study was conducted across three tertiary hospitals, enrolling bipolar disorder patients (DSM-5 criteria) treated with olanzapine between January and December 2023. Demographics, treatment details, and laboratory data were extracted from electronic records. Univariate and multivariate logistic regression analyses identified risk factors for olanzapine-associated liver injury.

**Results:** Hepatotoxicity, defined according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria, was the primary endpoint and occurred in 118 of 487 hosptialized patients (24.2%), with the majority classified as mild (19.3%). Injury patterns were predominantly mixed in mild-to-moderate cases and hepatocellular in severe cases. Multivariate analysis identified higher daily dosage (OR: 1.070, 95%CI: 1.006–1.138, $P$=0.030) and elevated gamma-glutamyl transferase (GGT) (OR: 1.022, 95%CI: 1.006–1.139, $P$=0.007) as independent risk factors. Concomitant use of valproate (OR: 0.553, 95%CI: 0.347–0.881, $P$=0.013) was associated with a significant reduction in hepatotoxicity risk. A favorable clinical course was observed in majority of patients after olanzapine withdrawal and conservative management with hepatoprotective agents.

**Conclusion:** This real-world observational study demonstrates a significant association between olanzapine and hepatotoxicity in hospitalized bipolar disorder patients. Our findings highlight the importance of regular liver function monitoring during olanzapine treatment, particularly in patients receiving higher daily doses, and suggest that dose management strategies may play a key role in mitigating hepatotoxicity risk in routine clinical practice.

**Keywords:** bipolar disorder, olanzapine, hepatotoxicity, real-world study, risk factors



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## Introduction

Bipolar disorder (BD) is a serious mood disorder, mainly manifested by extreme emotional fluctuations and alternating episodes of depression and mania.[1] Epidemiological studies identified BD as a significant disabling mental illness, making it a major public health concern. Reported by the World Mental Health Survey Initiative, the lifetime prevalence of BD is estimated to be 2.4%, with 12-month prevalence of 1.5%, respectively.[2–4] BD characterized by significant disability, high recurrence rates, and suicidality, imposed a substantial and enduring burden both on families and society. Consequently, it constituted a critical public-health challenge that demand coordinated, multilevel interventions.[5,6]

First-line pharmacotherapy recommend for BD, including mood stabilizers (eg., lithium and valproate), atypical antipsychotics, and adjunctive antidepressants, all of which have demonstrated substantial efficacy in attenuating acute mood episodes and preventing relapse in clinic trials.[7] Olanzapine, as an atypical antipsychotic, has been widely utilized in the treatment of BD, particularly for managing symptoms of mood elevation.[8,9] Previous studies have demonstrated the efficacy of olanzapine's superiority over placebo and comparable effectiveness to lithium or valproate, with rapid symptom alleviate in acute mania.[3,10] For bipolar depression, the olanzapine-based regimen also demonstrated superior efficacy over monotherapy in alleviating depressive symptoms.[11,12] Moreover, long-term maintenance trials have demonstrated that olanzapine significantly prevent recurrence of both manic and depressive episodes, underscoring its sustained prophylactic effect across the mood spectrum.[13–15] Despite its well-documented efficacy, the clinical utility of olanzapine is substantially constrained by adverse effects, such as weight gain and dyslipidemia, highlighted the urgent need for real-world evidence to refine risk–benefit evaluations and facilitate more judicious and individualized application.

Drug-associated hepatotoxicity, also known as drug-induced hepatotoxicity or liver injury (DILI), is a spectrum of liver damage resulting from exposure to certain medications or substances.[16] It poses a significant clinical challenge due to its potential to cause serious health complications, ranging from acute liver failure to chronic liver disease.[17] In clinical practice, it is critical to distinguish between asymptomatic, self-limiting transaminase elevations and clinically meaningful liver injury that may affect treatment decisions or lead to serious outcomes. While olanzapine is widely prescribed for BD due to efficacy in managing manic and mixed episodes, its potential hepatotoxicity remains a significant safety consideration.[18] Despite olanzapine-associated hepatotoxicity has been extensively documented in schizophrenia and general psychiatric populations, the safety data specifically in BD management remain scarce.[19] Moreover, previous studies on antipsychotic-induced hepatotoxicity have primarily focused on transient transaminase elevations rather than clinically significant liver injury. Furthermore, the gap is particularly evident in limited in hospitalized BD patients, where data on risk factors and outcomes remain scarce.[20,21] Given that BD patients often receive complex, polypharmacy regimens (eg, combinations of mood stabilizers, antipsychotics, and other psychotropics), the hepatotoxic risk associated with olanzapine may be further compounded, yet real-world evidence in this specific population is lacking. Consequently, the hepatologic safety profile of olanzapine in the treatment of BD warranted systematic and prospective investigation.

This study used a multicenter, real-world inpatient cohort with BD to systematically quantify the incidence, determinants, phenotypic spectrum, and short-term prognosis of olanzapine-associated liver injury. Specifically, we hypothesized that olanzapine is associated with increased risk of clinically significant liver injury, with identifiable risk factors and generally favorable short-term prognosis. By synthesizing these findings, we derived evidence-based safety parameters to inform the rational administration of olanzapine and optimized risk-minimization strategies for BD patients.

## Methods

### Study Design and Ethics Approval

This retrospective multicenter cohort study was conducted at three tertiary hospitals in China (Renmin Hospital of Wuhan University, the First Affiliated Hospital of Nanchang University, and Guihang Guiyang Hospital) from January 2023 to December 2023. The research protocols have been approved by Ethics Committee of all institutions, Renmin Hospital of Wuhan University (no. WDRY2024-K072), First Affiliated Hospital of Nanchang University (no. IIT2025797) and Guihang Guiyang Hospital (no. GHGYYY-KXXM-2025-21). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committees. Patient data were anonymized and handled with strict confidentiality to protect patient privacy. This study was conducted in accordance with the principles of the Declaration of Helsinki.

## Patient Inclusion

Patients were diagnosed with BD independently by two experienced psychiatrists based on mini-international neuropsychiatric interview, with subsequent consensus on fulfillment on Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria.[22,23] Exclusion criteria of patients based on the following criteria: (1) Comorbidity with other psychiatric disorders, neurodevelopmental disorders or organic brain diseases. (2) Incomplete laboratory data, defined as absence of baseline liver function tests (including ALT, AST, ALP, GGT, and TBIL) within 7 days prior to olanzapine initiation, or lack of at least one follow-up liver function test during the treatment period. Patients meeting either criterion were excluded from the study to ensure completeness of primary exposure and outcome data. (3) Duplicate patients. (4) Preexisting severe liver injury at admission.[24] Comprehensive patients' data were collected, including demographic characteristics, comorbidities, olanzapine dosage and treatment duration, concomitant medications, longitudinal liver function tests, renal function and thyroid indicators, as well as baseline laboratory results. Figure 1 shows the flowchart of enrolled BD patients and the process of identifying olanzapine related-hepatotoxicity.

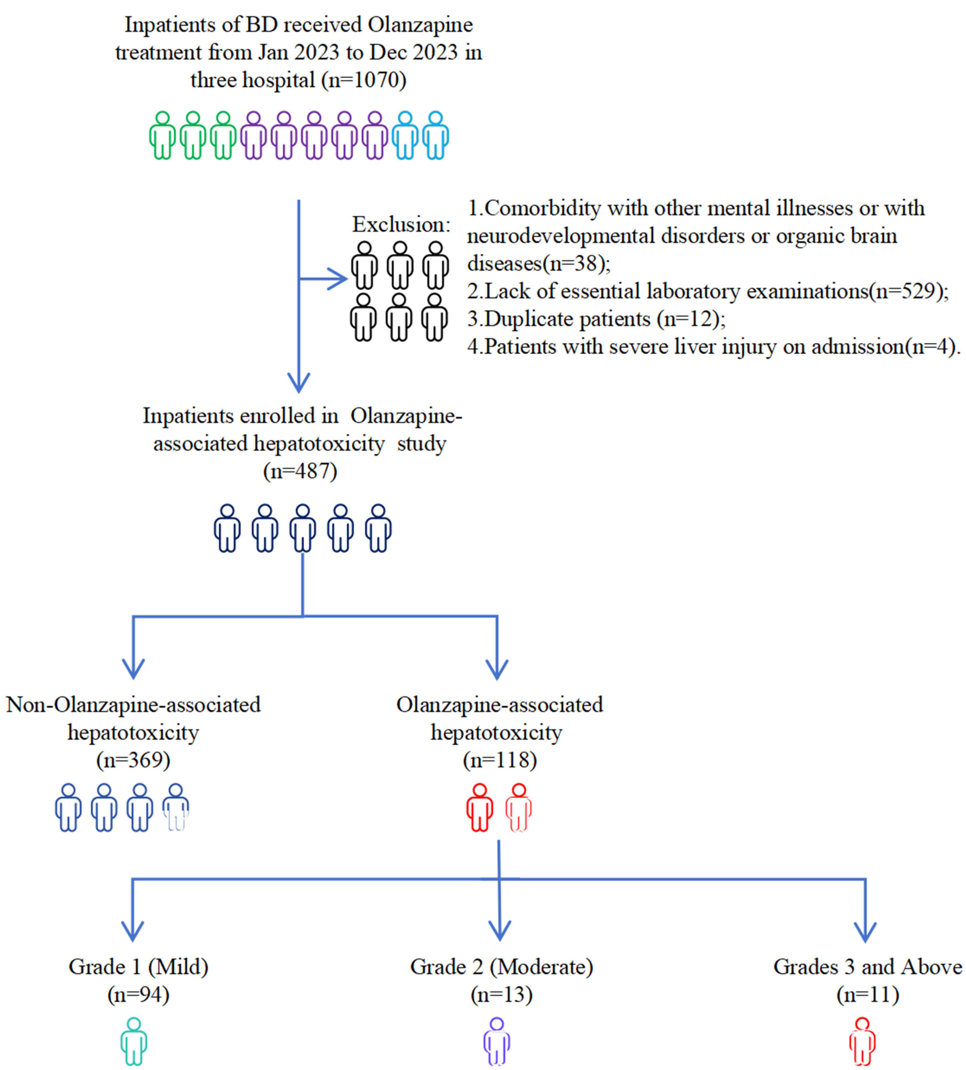


**Figure 1** Identification of Olanzapine-associated hepatotoxicity among bipolar disorder patients during the study period.

## Evaluation of Hepatotoxicity

Hepatotoxicity was characterized by clinically significant liver enzyme elevations, defined as exceeding of normalized upper limit of normal (ULN) any measured parameter: (1) alanine aminotransferase (ALT) levels above 40 U/L; (2) aspartate aminotransferase (AST) exceeding 35 U/L; (3) alkaline phosphatase (ALP) greater than 135 U/L; (4) gamma-glutamyl transferase (GGT) surpassing 45 U/L; or (5) total bilirubin(TBIL) higher than 23 μmol/L.[16] For patients with preexisting biochemical abnormalities, baseline levels were substituted as reference for the ULN prior to olanzapine initiation.[25] Participants who developed hepatotoxicity post-olanzapine administration were classified as the exposure (abnormal) cohort, whereas those with persistently normal liver function constituted the control (normal) group.

Causality assessment for olanzapine-associated hepatotoxicity was performed using the Roussel Uclaf Causality Assessment Method (RUCAM). Cases with RUCAM scores $<3$ were excluded from subsequent analyses due to insufficient evidence for establishing DILI.[26] The clinical phenotype of olanzapine-related hepatotoxicity was defined according to the R ratio, calculated as: R=(ALT/ALT ULN)/(ALP/ALP ULN). According to standard classification criteria, we identified three distinct liver injury phenotypes as follows: (1) hepatocellular ($R\geq5$), (2) cholestatic ($R\leq2$), and (3) mixed-type injury ($2<R<5$).

The severity of olanzapine-associated hepatotoxicity was categorized using the common terminology criteria for adverse events (CTCAE) v. 5.0, with reference to ULN values for key liver enzymes ALT, ALP, and GGT. The classification was defined as follows: Grade 1 (mild): ALT elevation between 1× ULN and below 3× ULN, ALP or GGT elevation between 1× ULN and below 2.5× ULN. Grade 2 (moderate): ALT elevation between 3× ULN and below 5× ULN, ALP or GGT elevation between 2.5× ULN and below 5× ULN. Grades 3 and above (severe drug-induced liver injury, DILI): ALT elevation ≥5× ULN, ALP or GGT elevation ≥5× ULN.

## Prognosis of Olanzapine-Associated Hepatotoxicity

Clinical outcomes of olanzapine-associated liver injury were classified based on post-treatment hepatic function monitoring as follows: (a) full recovery: normalization of liver enzymes (returning to levels below ULN or baseline level). (b) Partial improvement: reduction in ALT/AST to <3× ULN or ALP/GGT to <2.5× ULN. (c) Progression: further elevation of liver function markers beyond prior peak measurements. (d) Indeterminate: inadequate follow-up data to determine clinical course.

## Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, v. 26.0 (IBM Corporation, Armonk, NY, USA). To account for the inter-center variability, all laboratory values were normalized to the site-specific ULN prior to analysis. Continuous data with normal distribution were presented as mean ± standard deviation (SD), while non-normally distributed data as median (interquartile range, IQR). Group comparisons were performed using independent *t*-tests and Mann–Whitney *U*-tests, respectively. Categorical variables were analyzed using chi-squared-tests or Fisher's exact test, as appropriate. Continuous variables across groups were compared using one-way analysis of variance (ANOVA). Given the inherent limitations of the retrospective cohort design, causal inferences cannot be drawn from this study; our analyses therefore focus on identifying associations and potential risk factors rather than establishing causality. Variables with $P<0.20$ in univariate analyses were included into a multivariate logistic regression model. This conservative threshold is widely recommended for confounder selection in observational studies to avoid omitting potentially important variables that may be significant after adjusting for others. Stepwise logistic regression was employed to identify independent risk factors, with two-sided $P<0.05$ considered statistically significant for all analyses.

Sensitivity analyses were performed to evaluate the robustness and generalizability of the primary findings, in accordance with established methodological guidelines. The study involved two predefined subgroup analyses: (1) age-stratified analysis: age by treatment interaction term was incorporated into the regression model to quantify effect modification in patients older than 15 years; (2) alcohol-adjusted analysis: patients with documented history of alcohol consumption were excluded, and the primary outcomes were re-analyzed to evaluate potential confounding by medication hypersensitivity.

# Results

## Patients Enrollment

Using the electronic medical record system we initially identified 1070 hospitalized BD patients who received olanzapine therapy. According to the predefined exclusion criteria, the following patients were excluded: 38 (3.5%) due to comorbid psychiatric, neurodevelopmental disorder or organic brain disorders; 529 (49.4%) for insufficient laboratory data; 12 (1.1%) for duplicate records; and 4 (0.3%) for preexisting severe liver injury. Consequently, a total of 487 patients (44.5%) were included in the final analysis of olanzapine related hepatotoxicity (Figure 1). Subsequently, the enrolled patients were divided into two groups (normal and abnormal) according to the hepatotoxicity status. The comprehensive demographic and clinical characteristics are shown in Table 1.

**Table 1** Baseline of Patients in Olanzapine-Associated Hepatotoxicity Study

| Characteristics | Liver Tests | | | P-value |
|---|---|---|---|---|
| | Total (n=487, 100%) | Normal (n=369, 75.8%) | Abnormal (n=118, 24.2%) | |
| Demographic Characteristics | | | | |
| Gender (male), n (%) | 170(34.9) | 116(31.4) | 54(45.8) | 0.006** |
| Age, year, median (range) | 24.0(17.0–36.0) | 23.0(17.0–36.0) | 24.0(17.0–34.0) | 0.862 |
| Weight, kg, median (range) | 59.0(51.0–68.0) | 59.0(51.0–67.0) | 60.0(51.3–70.0) | 0.340 |
| Smoke, n (%) | 34(7.0) | 25(6.8) | 9(7.6) | 0.914 |
| Drink, n (%) | 10(2.1) | 7(1.9) | 3(2.5) | 0.711 |
| Allergic, n (%) | 52(10.7) | 37(10.0) | 15(12.7) | 0.515 |
| Comorbidities, n (%) | | | | |
| Liver diseases | 26(5.3) | 18(4.9) | 8(6.8) | 0.572 |
| Renal diseases | 11(2.3) | 8(2.2) | 3(2.5) | 0.732 |
| Hypertension | 20(4.1) | 15(4.1) | 5(4.2) | 1.000 |
| Hyperlipidemia | 39(8.0) | 28(7.6) | 11(9.3) | 0.682 |
| Cardiopathy | 18(3.7) | 16(4.3) | 2(1.7) | 0.265 |
| Diabetes | 16(3.7) | 11(3.0) | 5(4.2) | 0.553 |
| Infection | 27(5.5) | 24(6.5) | 3(2.5) | 0.111 |
| Olanzapine therapy | | | | |
| Daily dose, mg, median (range) | 5.0(5.0–10.0) | 5.0(5.0–7.5) | 5.0(5.0–10.0) | 0.006** |
| Treatment duration, days, median (range) | 14.0(9.0–18.0) | 13.0(8.0–17.0) | 15.0(12.0–20.8) | 0.002** |
| Concomitant medication, n (%) | | | | |
| Escitalopram/citalopram | 93(19.1) | 72(19.5) | 21(17.8) | 0.781 |
| Fluoxetine | 50(10.3) | 37(10.0) | 13(11.0) | 0.893 |
| Fluvoxamine | 76(15.6) | 54(14.6) | 22(18.6) | 0.369 |
| Sertraline | 76(15.6) | 58(15.7) | 18(15.3) | 1.000 |
| Duloxetine | 30(6.2) | 24(6.5) | 6(5.1) | 0.735 |
| Venlafaxine | 18(3.7) | 16(4.34) | 2(1.7) | 0.265 |
| Mirtazapine | 23(4.7) | 20(5.4) | 3(2.5) | 0.317 |
| Trazodone | 35(7.2) | 30(8.1) | 5(4.2) | 0.218 |
| Lithium | 192(39.4) | 143(38.8) | 49(41.5) | 0.669 |
| Valproate | 240(49.3) | 190(51.5) | 50(42.4) | 0.106 |
| Aripiprazole | 88(18.1) | 70(19.0) | 18(15.3) | 0.438 |
| Clozapine | 29(6.0) | 24(6.5) | 5(4.2) | 0.503 |
| Quetiapine | 118(24.2) | 99(26.8) | 19(16.1) | 0.025* |
| Risperidone | 39(8.0) | 28(7.6) | 11(9.3) | 0.682 |
| Benzhexol | 113(23.2) | 79(21.4) | 34(28.8) | 0.125 |
| Flupentixo and melitracen | 51(10.5) | 41(11.1) | 10(8.5) | 0.521 |

(*Continued*)


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**Table 1** (Continued).

| Characteristics | Liver Tests | | | P-value |
|---|---|---|---|---|
| | **Total (n=487, 100%)** | **Normal (n=369, 75.8%)** | **Abnormal (n=118, 24.2%)** | |
| Laboratory results | | | | |
| ALT, U/L, median (range) | 13.0(9.0–22.0) | 13.0(9.0–21.0) | 16.0(10.0–28.0) | 0.003** |
| AST, U/L, median (range) | 17.0(14.0–22.0) | 17.0(14.0–21.0) | 17.0(15.0–23.0) | 0.098 |
| ALP, U/L, median (range) | 66.1(54.0–87.3) | 66.0(54.0–86.0) | 68.5(57.0–90.8) | 0.197 |
| GGT, U/L, median (range) | 16.0(11.0–23.0) | 15.0(11.0–22.0) | 18.9(13.6–29.8) | <0.001*** |
| TB, μmol/L, median (range) | 10.6(7.1–14.8) | 10.6(7.1–14.5) | 10.8(7.3–16.1) | 0.283 |
| DB, μmol/L, median (range) | 3.6(2.4–5.2) | 3.6(2.4–5.0) | 3.9(2.5–5.5) | 0.151 |
| Total protein, g/L, median (range) | 67.0(64.0–71.0) | 66.9(64.0–70.9) | 67.5(64.5–71.5) | 0.546 |
| Albumin, g/L, median (range) | 42.4(40.3–45.0) | 42.4(40.2–44.7) | 42.9(40.4–45.4) | 0.208 |
| Urea, U/L, median (range) | 4.34(3.37–5.19) | 4.34(3.35–5.12) | 4.40(3.40–5.29) | 0.735 |
| Creatinine, U/L, median (range) | 60.0(52.0–70.0) | 59.0(51.7–68.0) | 62.0(53.0–75.0) | 0.043* |
| eGFR, mL/min, median (range) | 115.5(100.2–125.8) | 116.1(101.0–126.0) | 115.3(103.7–124.2) | 0.733 |
| FT3, pg/mL, median (range) | 3.41(3.11–3.74) | 3.38(3.10–3.71) | 3.49(3.16–3.77) | 0.203 |
| FT4, ng/dL, median (range) | 1.21(1.08–1.38) | 1.21(1.06–1.37) | 1.22(1.10–1.44) | 0.277 |
| TSH, μIU/mL, median (range) | 1.82(1.19–2.78) | 1.86(1.22–2.80) | 1.72(1.11–2.62) | 0.217 |

**Note**: *means P < 0.05. **means P < 0.01. ***means P < 0.001.

**Abbreviations**: ALT, alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, gamma–glutamyltransferase; TB, total bilirubin; DB, direct bilirubin; eGFR, estimated glomerular filtration rate; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.

## Baseline Characteristics of Olanzapine-Associated Hepatotoxicity in BD Patients

Among the 487 patients, 118 (24.2%) developed liver injury during olanzapine therapy (Table 1). A significant difference in gender distribution was observed between two groups, with a higher propensity for hepatotoxicity observed in male patients (*P*=0.006). In contrast, characteristics including age, weight, smoke and drink demonstrated no statistical difference. The distribution of concomitant diseases included liver disease (5.3%), kidney disease (2.3%), hypertension (4.1%), hyperlipidemia (8.0%), cardiopathy (8.0%), diabetes (3.7%) and infection (5.5%) were comparable between the two groups. In contrast, both the daily dose (*P*=0.006) and treatment duration of olanzapine therapy (*P*=0.002) demonstrate significant difference. Regarding concomitant medications, including valproate (49.3%), lithium (39.4%), quetiapine (24.2%), benzhexol (23.2%), escitalopram/citalopram (19.1%), aripiprazole (18.1%), fluvoxamine (15.6%), no significant difference was observed, while only quetiapine (24.1%) emerged as significant factor for prognosis of hepatotoxicity (*P*=0.025). Finally, the baseline of laboratory parameters of patients were analyzed, revealing significance predictors of ALT, GGT and creatinine between two groups (*P*<0.05).

## Univariate and Multivariate Analysis in Olanzapine-Associated Hepatotoxicity Study

We evaluated the potential risk factors for olanzapine-associated hepatotoxicity (Table 2). Univariate logistic regression analysis identified that male gender (OR: 1.840, 95%CI: 1.205–2.811, *P*=0.005) as a significantly demographic predictor. Meanwhile, no significant associations were observed for weight, smoking, and alcohol consumption. Comorbidities, such as preexisting liver disease or kidney disease, were not significantly associated with liver function abnormalities. However, both higher daily dose of olanzapine (OR: 1.074, 95%CI: 1.017–1.134, *P*=0.010) and longer treatment duration (OR: 1.030, 95%CI: 1.006–1.055, *P*=0.014) demonstrated as the strongest independent risk factors for liver injury. In terms of concomitant medication, the use of quetiapine (OR: 0.523, 95%CI: 0.304–0.900, *P*=0.019) was significantly associated with reduced risk of hepatotoxicity. Elevated baseline liver enzymes—specifically the upper ALT (OR: 1.013, 95%CI: 1.001–1.025, *P*=0.030) and GGT (OR: 1.022, 95%CI: 1.010–1.035, *P*=0.030), rather than the liver diseases, were directly associated with subsequent hepatotoxicity.

**Table 2** Results of Univariate Analysis and Multivariate Analysis in Olanzapine-Associated Hepatotoxicity Study

| **Characteristics** | **Univariate Analysis** | | **Multivariate Analysis** | |
|---|---|---|---|---|
| | **OR (95%CI)** | **P-value** | **OR (95%CI)** | **P-value** |
| Demographic Characteristics | | | | |
| Gender (male) | 1.840(1.205–2.811) | 0.005** | 1.534(0.864–2.723) | 0.144 |
| Age | 0.995(0.981–1.009) | 0.461 | | |
| Weight | 1.010(0.994–1.027) | 0.214 | | |
| Smoke | 1.137(0.515–2.509) | 0.751 | | |
| Drink | 1.304(0.332–5.124) | 0.704 | | |
| Allergic | 1.258(0.664–2.383) | 0.481 | | |
| Comorbidities | | | | |
| Liver diseases | 1.418(0.600–3.351) | 0.426 | | |
| Renal diseases | 1.177(0.307–4.511) | 0.812 | | |
| Hypertension | 1.044(0.371–2.937) | 0.934 | | |
| Hyperlipidemia | 1.252(0.603–2.600) | 0.546 | | |
| Cardiopathy | 0.381(0.086–1.680) | 0.202 | | |
| Diabetes | 1.440(0.490–4.232) | 0.507 | | |
| Infection | 0.375(0.111–1.268) | 0.115 | 0.458(0.129–1.623) | 0.226 |
| Olanzapine therapy | | | | |
| Daily dose | 1.074(1.017–1.134) | 0.010* | 1.070(1.006–1.138) | 0.030* |
| Treatment duration | 1.030(1.006–1.055) | 0.014* | 1.021(0.994–1.048) | 0.131 |
| Concomitant medication | | | | |
| Escitalopram/citalopram | 0.893(0.522–1.529) | 0.681 | | |
| Fluoxetine | 1.111(0.569–2.169) | 0.758 | | |
| Fluvoxamine | 1.338(0.775–2.308) | 0.297 | | |
| Sertraline | 0.965(0.543–1.715) | 0.904 | | |
| Duloxetine | 0.770(0.307–1.932) | 0.578 | | |
| Venlafaxine | 0.381(0.086–1.680) | 0.202 | | |
| Mirtazapine | 0.455(0.133–1.560) | 0.210 | | |
| Trazodone | 0.500(0.189–1.319) | 0.161 | 0.546(0.197–1.511) | 0.244 |
| Lithium | 1.122(0.736–1.711) | 0.591 | | |
| Valproate | 0.693(0.456–1.053) | 0.085 | 0.553(0.347–0.881) | 0.013* |
| Aripiprazole | 0.769(0.437–1.353) | 0.362 | | |
| Clozapine | 0.636(0.237–1.706) | 0.369 | | |
| Quetiapine | 0.523(0.304–0.900) | 0.019* | 0.603(0.339–1.072) | 0.085 |
| Risperidone | 1.252(0.603–2.600) | 0.546 | | |
| Benzhexol | 1.486(0.929–2.377) | 0.098 | 1.188(0.707–1.996) | 0.516 |
| Flupentixol and melitracen | 0.741(0.359–1.529) | 0.416 | | |
| Laboratory results | | | | |
| ALT | 1.013(1.001–1.025) | 0.030* | 0.998(0.982–1.014) | 0.772 |
| AST | 1.003(0.988–1.018) | 0.725 | | |
| ALP | 1.001(0.996–1.006) | 0.622 | | |
| GGT | 1.022(1.010–1.035) | <0.001*** | 1.022(1.006–1.039) | 0.007** |
| TB | 1.018(0.991–1.046) | 0.186 | 1.003(0.973–1.034) | 0.851 |
| DB | 1.816(0.896–6.405) | 0.228 | | |
| Total protein | 1.013(0.976–1.051) | 0.507 | | |
| Albumin | 1.048(0.990–1.110) | 0.108 | 1.025(0.961–1.094) | 0.451 |
| Urea | 0.964(0.863–1.076) | 0.512 | | |
| Creatinine | 1.009(0.997–1.020) | 0.142 | 0.998(0.983–1.014) | 0.839 |
| eGFR | 1.001(0.987–1.015) | 0.897 | | |
| FT3 | 1.018(0.872–5.777) | 0.934 | | |
| FT4 | 0.978(0.877–1.091) | 0.696 | | |
| TSH | 0.913(0.780–1.068) | 0.256 | | |

**Note**: *$P<0.05$. **$P<0.01$. ***$P<0.001$.

**Abbreviations**: OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, gamma–glutamyltransferase; TB, total bilirubin; DB, direct bilirubin; eGFR, estimated glomerular filtration rate; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.


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To identify risk factors associated with olanzapine-associated hepatotoxicity, we selected variables with *P* value <0.20 from the univariate analysis into the multivariate model. Multivariate logistic regression analysis identified three independent pharmacological influencing factors: high olanzapine daily dose (OR: 1.070, 95%CI: 1.006–1.138, *P*=0.030), co-use of valproate (OR: 0.553, 95%CI: 0.347–0.881, *P*=0.013) and the high value of GGT (OR: 1.022, 95%CI: 1.006–1.139, *P*=0.007). The model demonstrated acceptable discrimination, with area under the curve (AUC) of 0.706 (95%CI: 0.665–0.747, *P*<0.001), seen in Supplementary material and Figure 1).

The robustness of model was confirmed by sensitivity analyses, which yielded consistent results (Supplementary material and Table 1). All predictors were statistically significant in the original model maintained two-tailed *P*<0.05 across all sensitivity scenarios, affirming that the magnitude, direction, and significance of the observed associations remain unchanged under analytical perturbations.

## Clinical Manifestations of Olanzapine-Associated Hepatotoxicity

In our cohort, the hepatic enzymes served as objective indicators to confirm and further characterize the clinical manifestations of olanzapine-associated hepatotoxicity (see Figure 2 and Supplementary material, Table 2). Notably, the ALT and AST demonstrated a progressive increase exclusively in patients who subsequently met the formal criteria for hepatotoxicity (*P*<0.001), whereas enzyme levels in the reference subgroup remained temporally stable. Concurrently, ALP exhibited no appreciable deviation, yet GGT was markedly elevated in the hepatotoxicity subset (*P*<0.001), revealing a unique cholestatic-cytolytic hybrid profile specific to susceptible individuals. In contrast, total bilirubin (TB) declined consistently across the entire cohort, irrespective of eventual phenotype, indicating the absence of clinically relevant cholestatic or mixed injury. In summary, olanzapine-associated hepatotoxicity manifested primarily as a hepatocellular injury, characterized by coordinated ALT, AST, and GGT elevation, with minimal bilirubin participation, indicating a primary hepatocellular injury phenotype.

## Clinical Outcomes of Olanzapine-Associated Hepatotoxicity, Severity, and Treatment

The clinical features, prognosis, treatment and outcomes of olanzapine-associated hepatotoxicity were summarized in Table 3. The severity distribution of hepatotoxicity grading was as follows: mild (Grade 1) hepatotoxicity accounted for 79.7% (n=94) of cases, moderate (Grade 2) comprised 11.0% (n=13) patients, while severe (Grade 3) were observed in 9.3% (n=11) of patients. The median time to hepatoxicity onset was approximately 13 days (interquartile range: 11–18 days), with no statistically significant variations across severity groups.

The RUCAM scale was employed to assess causality of hepatotoxic effects with olanzapine, revealing a possible drug-related association (scores 3–5) in 53.4% patients (n=63), a probable association (scores 6–8) in 43.2% patients (n=51), a definite association (scores >8) in 3.4% patients (n=4), respectively, with no significant differences across severity grades. Phenotypic analysis revealed three distinct patterns of liver injury: hepatocellular damage (28.8%, 34/118), cholestatic injury (34.7%, 41/118), and mixed pattern (36.4%, 43/118), respectively. Furthermore, the severity exhibited distinct phenotypic variations: mild cases primarily manifesting as cholestatic or mixed-pattern damage, while severe presentations were predominantly hepatocellular-pattern in nature (*P*=0.021). Notably, all severity cases (reached Grade 3) exhibited the hepatocellular-pattern.

Although olanzapine was withdrawn in 27% of patients (32/118), the rate increased with severity, but without statistical significance. The prescription of hepatoprotective agents exhibited a pronounced, grade-dependent escalation: fewer than 30% of Grade 1 cases received such pharmacotherapy, whereas the proportion exceeded 80% in Grade 3 cases. Hepatocyte membrane–stabilizing agents were the most the predominant choice (24.6%, 29 cases), followed by anti-inflammatory hepatoprotectives (16.9%, 20 cases) and hepatoprotective antidotes (9.3%, 11 cases).

The overall rate of recovery or improvement was 88% (104/118), while the proportion declined to 73% (8/11) in Grade 3. Only 3.4% patients (4/118) experienced disease progression: two patients initially presented with mild liver injury (Grade 1), one with moderate liver injury (Grade 2) and one with severity (Grade 3). They demonstrated slight progression of liver injury within 1 month, yet still remaining within mild to moderate liver injury (Ggrades 1–2). The last case of Grade 3 severity, with detailed medical records presented in the following section. Subsequently, due to the patient's transfer or discontinuation treatment, further liver damage was unknown.


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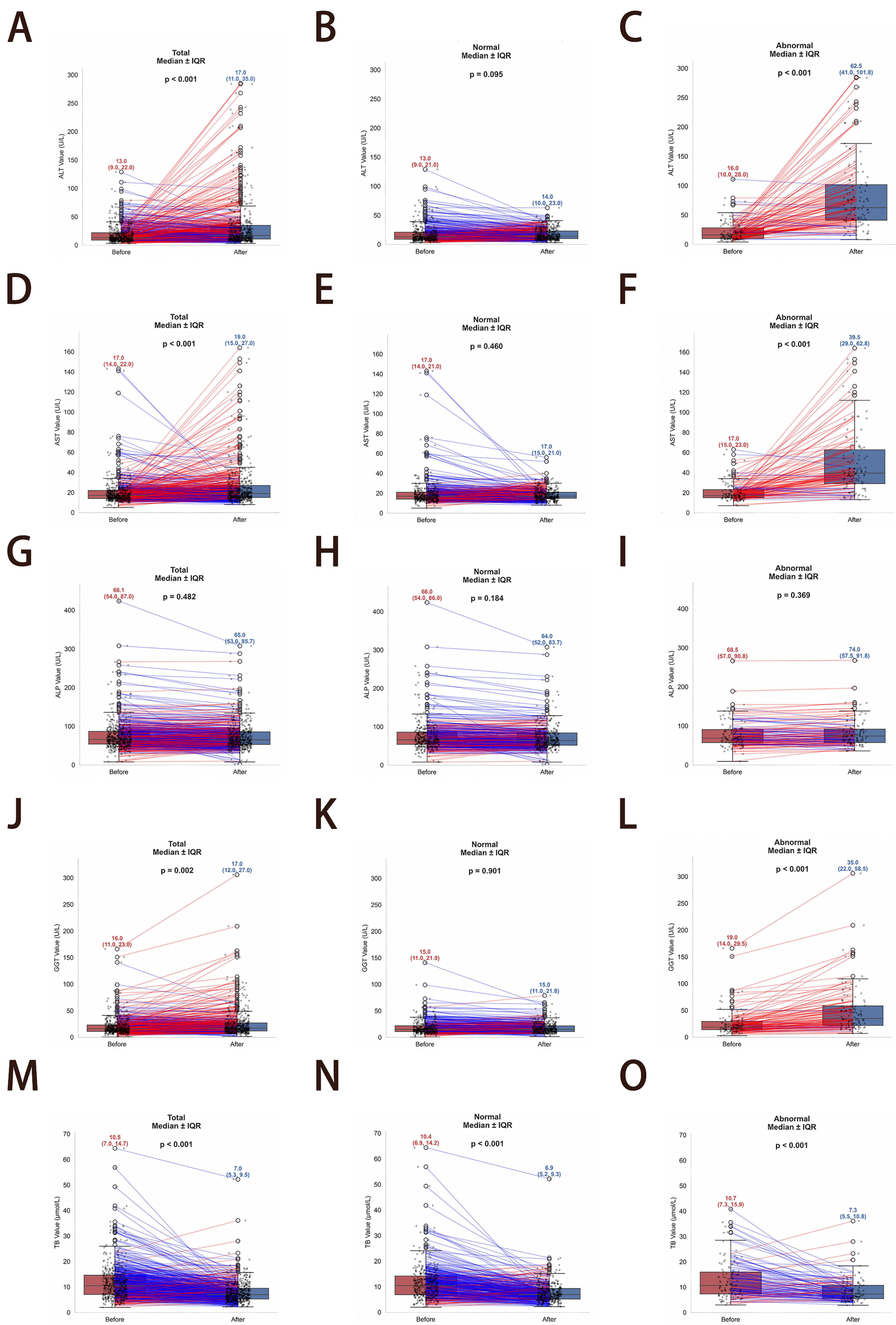


**Figure 2** Liver function test results before and after olanzapine treatment in patients with olanzapine-associated hepatotoxicity. (**A**) ALT (total), (**B**) ALT (normal), (**C**) ALT (abnormal), (**D**) AST (total), (**E**) AST (normal), (**F**) AST (abnormal), (**G**) ALP (total), (**H**) ALP (normal), (**I**) ALP (abnormal), (**J**) GGT (total), (**K**) GGT (normal), (**L**) GGT (abnormal), (**M**) TB (total), (**N**) TB (normal), (**O**) TB (abnormal). Data are presented as median (IQR).

**Table 3** Clinical Characteristics and Outcome of Olanzapine-Associated Hepatotoxicity Study

| Characteristics | | Liver Tests | | | | |
|---|---|---|---|---|---|---|
| | | Total (n=118, 100%) | Grade 1 (n=94, 79.7%) | Grade 2 (n=13, 11.0%) | Grade 3 (n=11, 9.3%) | P-value |
| Time of onset, days, median (range) | | 13.0 (11.0, 18.0) | 13.00 (11.0, 18.0) | 14.0 (13.0, 18.0) | 12.0 (9.0,23.0) | 0.471 |
| RUCAM score | Possible, 3–5 | 63(53.4) | 56(59.6) | 5(38.5) | 2(18.2) | 0.175 |
| | Probable, 6–8 | 51(43.2) | 38(40.4) | 7(53.8) | 6(54.5) | |
| | Definite, >8 | 4(3.4) | 0(3.4) | 1(7.7) | 3(27.3) | |
| Clinical classification | Hepatocyte type | 34(28.8) | 14(14.9) | 9(69.2) | 11(100.00) | 0.021* |
| | Cholestasis type | 41(34.7) | 41(43.6) | 0(0.00) | 0(0.00) | |
| | Mixed type | 43(36.4) | 39(41.5) | 4(30.8) | 0(0.00) | |
| Olanzapine therapy | Maintenance | 86(72.9) | 69(73.4) | 10(76.9) | 7(63.6) | 0.171 |
| | Withdrawal | 32(27.1) | 25(26.6) | 3(23.1) | 4(36.4) | |
| Hepatoprotective drugs | Anti-inflammatory hepatoprotectives | 20(16.9) | 10(10.6) | 4(30.8) | 6(54.5) | 0.171 |
| | Hepatoprotective antidotes | 11(9.3) | 6(6.4) | 2(15.4) | 3(27.3) | |
| | Hepatocyte membrane–stabilising agents | 29(24.6) | 16(17.0) | 8(61.5) | 5(45.5) | |
| | No treatment | 70(61.0) | 66(70.2) | 2(15.4) | 2(18.2) | |
| Clinical outcome | Recovery | 71(60.2) | 64(68.1) | 5(38.5) | 2(18.2) | 0.182 |
| | Improvement | 33(28.0) | 22(23.4) | 5(38.5) | 6(54.5) | |
| | Progression | 4(3.4) | 2(2.1) | 1(7.7) | 1(9.1) | |
| | Unknown | 10(8.5) | 6(6.4) | 2(15.4) | 2(18.2) | |

**Note**: **P*<0.05.
**Abbreviation**: RUCAM, roussel uclaf causality assessment method.

Figure 3 provided a visual summary of the patients' progression through various stages of olanzapine therapy, incorporating specific numerical data points. Each diagram used color-coded band to indicate the flow and number of patients at each stage, providing a comprehensive overview journey and the decision-making process in managing olanzapine-associated hepatotoxicity, with the numerical data points offering a precise understanding of the patient distribution across different stages.

Grade 1 cases (Figure 3A) begin with 94 patients categorized mild severity, transitioning through patterns such as hepatocellular (14 cases), cholestatic (41 cases), and mixed (39 cases), with causality assessments ranging from probable (38 cases) and possible (56 cases). The assessment result to subsequent management involving olanzapine continuation (69 cases) or withdraw (25 cases) and the use of hepatoprotective medication (28 cases), culminating in clinical outcomes like recovery (64 cases), improvement (22 cases), and progression (2 cases). The 13 patients with Grade 2 (Figure 3B) demonstrated moderate cases with hepatocellular patterns (9 cases) and mixed patterns (4 cases), associated with the causality assessment as definite (pne case), probable (7 cases) and possible (5 cases). This focused on the direct association between causality and treatment decisions, maintenance olanzapine therapy (10 cases) and combination with hepatoprotective medication (11 cases), ultimately yielding outcomes of recovery (5 cases), improvement (5 cases), and progression (1 case). Figure 3C elucidated that all Grade 3 cases revealed as hepatocellular patterns (11 cases), correlated with definite (3 cases), probable (6 cases) and possible (2 cases). This contributed treatment decisions as 7 cases for maintenance and 9 cases with co-administrated hepatoprotective drugs, tend to the recovery (2 cases), improvement (6 cases), and progression (1 case).

## Cases Presentation of Severe Olanzapine-Associated Hepatotoxicity

Typical four cases report of Grade 3 liver injury: (1) Patient 1 had no preexisting hepatic injury developed Grade 3 liver injury after 16 days of olanzapine therapy. Liver enzyme assays revealed elevated ALT (210 U/L) and AST (153 U/L), whereas ALP (47 U/L), GGT (15 U/L), total bilirubin (5.1 μmol/L) and direct bilirubin (2.0 μmol/L) levels all remained within normal limits. Upon discontinuation of olanzapine and initiation of adjunctive hepatoprotective therapy with polyene phosphatidylcholine, the patient's condition improved. (2) Patient 2 had normal liver function developed severe liver injury after 5 days therapy, with elevated ALT (285 U/L) and AST (126 U/L) levels, while GGT (59 U/L), ALP (79


**Figure 3** Characterization of olanzapine-associated hepatotoxicity among bipolar disorder patients by grade: severity, pattern, causality, and clinical outcomes. (**A**) Grade 1; (**B**) Grade 2; (**C**) Grade 3.

U/L), TB (8.1 μmol/L), and DB (3.1 μmol/L) remained within normal limits. Maintenance olanzapine therapy with combination of polyene phosphatidylcholine, the patient hepatic injury improved. (3) Patient 3 received 26 days of olanzapine treatment and developed into Grade 3 liver injury. Laboratory findings revealed ALT was 239 U/L, AST level was 93 U/L, while ALP, GGT, TB, and DB levels all remained normal at 55 U/L, 27 U/L, 13.7 μmol/L, and 5.3 μmol/L, respectively. Withdrawal of olanzapine and combined with glycyrrhizin drugs, the patient with liver injury subsequently recovered. Patient 4 had no liver injury initially but developed third-grade severity liver injury during 11 days of olanzapine treatment, characterized by elevated ALT (207 U/L) and AST (149 U/L) levels, while ALP, GGT, TB, and DB levels remained normal at 77 U/L, 58 U/L, 5.8 μmol/L, and 2.4 μmol/L, respectively. Despite the concomitant initiation of hepatoprotective pharmacotherapy (glycyrrhizin) with the current olanzapine therapy, the prognosis improved with continuously rising transaminase levels a higher ALT (212 U/L) and AST (166 U/L) at day 15), and transfer to subspecialty care.

## Discussion

While antipsychotics are the cornerstone in the management of BD, the safety profile remains a critical concern, particularly metabolic and hepatic adverse effects. Olanzapine, as a widely prescribed atypical antipsychotic, has demonstrated efficacy in clinical practice but hepatotoxic potential in real-world clinical practice remains incompletely characterized.[27] This study provided the first evaluation of olanzapine hepatotoxicity in 1070 BD patients with complex clinical features (comorbidities/ medications) in real-world analysis, offering more comprehensive evidence for clinical practices.

Long-term antipsychotic treatment in patients with BD imposes a significant metabolic burden on the liver, potentially leading to drug accumulation and subsequent liver injury. Previous studies have demonstrated that patients with severe mental illnesses, particular those with schizophrenia (1.15- to 1.27-fold) and a striking increase (2.68-fold) in BD, face a significantly higher prevalence of chronic liver disease than the general population.[28] The prevalence of antipsychotic induced liver dysfunction was approximately 32% (ranging from 5% to 78%), and the condition predominantly manifested as elevated in transaminase levels.[29] Specifically, olanzapine-associated liver injury, with a reported incidence of 9.4% to 26.9%, manifested predominantly by asymptomatic elevations in hepatic transaminases, particularly ALT and AST.[29–31] A retrospective study indicated that among 33 olanzapine-treated patients, two patients (6%) experienced a 3-fold increase in AST and ALT levels compared to baseline and necessitating treatment discontinuation.[30] In addition, seven patients with severe DILI of olanzapine have been reported.[32–34] In our study, approximately 24.2% of in-patients with BD developed olanzapine related hepatotoxicity, mostly presented as mild to moderate liver dysfunction (Grades 1–2), characterized primarily by elevations in ALT, AST and GGT, rather than TB. It is worth noting that in our study, a relatively high incidence of Grade 3 liver injury induced by olanzapine at 2.3% (11/487) necessitating heightened awareness of clinical physicians, particularly in complex polypharmacy contexts. In summary, the aggregated data from previous studies suggested that the liver damage caused by olanzapine in the context of BD should attract more clinical attention.

The precise mechanism underlying olanzapine-induced hepatotoxicity remained to be clarified.[35] Olanzapine was primarily metabolized in the liver, undergoing biotransformation into inactive derivatives via the cytochrome P450 enzyme system. Proposed mechanisms include direct metabolite toxicity, induction of non-alcoholic fatty liver disease (NAFLD), immune-mediated injury, mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum stress.[36,37] Previous studies have indicated that olanzapine can increase the activity of glutathione S-transferase (GST) in the liver,[38] suggesting that olanzapine may active intermediates through common metabolic pathways prompting a compensatory detoxification system. While this compensatory response protected the liver in the short term, the long-term metabolic burden may be involved in the pathogenesis of DILI. Using mass spectrometry-based proteomics, an investigation demonstrated that reactive intermediates of olanzapine form covalent adducts with cysteine residues on critical proteins, including GST, human serum albumin, and rat CYP enzymes.[39] These irreversible modifications may drive hepatotoxicity.[40]

Our study identified higher daily olanzapine dose as significant risk factor, which was consistent with previous literature. Given that antipsychotic-related liver injury often involves toxic metabolic intermediates, mechanism consistent with the established association between antipsychotic-induced liver injury and the generation of toxic metabolic intermediates. Pharmacokinetic studies demonstrated that olanzapine undergoes extensive metabolism prior to excretion, with urinary excretion accounting for only 9% of the administered dose recovered as parent compound, and 78% excreted as

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metabolites.[41] These indicated that the olanzapine-induced hepatotoxicity may contribute to sustained exposure to reactive metabolites, especially under condition of higher dosing or prolonged treatment duration.

Our study identified GGT as a superior discriminative biomarker than ALT for detecting olanzapine-associated hepatotoxicity. This alignment is mechanistically consistent with the predominantly low-grade, cholestatic/mixed pattern of olanzapine-related liver injury, in which GGT pathophysiological exhibits enhanced enzymatic sensitivity and earlier quantitative elevation than ALT. Implement enhanced liver function monitoring protocols in clinical trials, coupled with meticulous evaluation of abnormalities is essential for the early identification of antidepressants associated with high risk of DILI. Finally, further research is necessary to formulate rigorous and evidence-based recommendations in clinical practice.

This study identified a previously unreported association: valproic acid co-administration confers significant protective effect against olanzapine-related hepatotoxicity. This finding is based on observed associations in our cohort and should not be interpreted as proven causality. Previous pharmacokinetic studies demonstrated that valproic acid reduces peak olanzapine concentrations by inhibition UDP-glucuronosyl-transferase and competitive displacement from plasma proteins, an interaction previously regarded as merely a liability requiring therapeutic mitigation.[42,43] Our data redefine the interaction as hepatologically beneficial, the valproic-associated reduction in olanzapine cumulative exposure consequently mediates a proportionate decrease in hepatic stress. This protective effect is substantiated in our study, which revealed an inverse dose-response relationship between olanzapine cumulative daily dose and the likelihood of hepatic injury. In addition, it was demonstrated that the combination of olanzapine and sodium valproate significantly improved cognitive function, reduced inflammatory biomarkers, and lowered the incidence of adverse reactions compared to olanzapine monotherapy in patients with BD.[8] These findings suggest that the combination therapy is not only effective, but also offer superior therapeutic profile for BD patients. Further validation through larger-scale and more in-depth studies are required to fully elucidate the underlying mechanisms. However, these mechanistic and clinical hypotheses remain speculative; the protective association we observed requires confirmation in prospective, hypothesis-driven studies before any clinical recommendation regarding valproate co-administration for hepatoprotection can be made.

To our knowledge, this study provided the first comprehensively delineate of hepatotoxic potential of olanzapine in patients with BD within a real-world investigation, accounting for the concomitant influences of polypharmacy and multifactorial clinical predictors. Our data highlighted that the cumulative daily dose of olanzapine emerged as the predominant factor influencing hepatotoxicity, with a clear dose-dependent increase in risk. These findings advocated for a cautious approach in clinical practice, suggesting the adoption of low-to-moderate dosing strategies to mitigate the hepatotoxic risks associated with high-dose olanzapine therapy. Furthermore, GGT levels have attracted heightened clinical attention as a sentinel marker of hepatic function. Routine monitoring of GGT was critical to facilitate early detection and management of olanzapine-associated hepatotoxicity. The co-prescription of valproate and olanzapine represented a clinically complex scenario, necessitating a meticulous risk-benefit analysis to optimize therapeutic efficacy while minimizing hepatotoxic sequelae. Regarding prognosis, the majority of olanzapine-associated liver injuries were presented as mild and reversible liver dysfunction. However, severe cases of hepatotoxicity demanded vigilant monitoring and timely intervention to ensure patient safety and prevent potential adverse outcomes. Collectively, our research emphasized the need for a nuanced, patient-centered approach to olanzapine therapy, balancing therapeutic efficacy with vigilant hepatoprotective management.

Despite the insights revealed by our findings, several limitations should be acknowledged. First, as a retrospective cohort study, the results may be susceptible to selection bias and unmeasured confounders. Specifically, 49% of patients were excluded due to incomplete laboratory data, primarily reflecting real-world constraints such as health-care cost containment practices and the absence of routine follow-up testing when no overt clinical abnormalities were present. This high exclusion rate may introduce selection bias, as included patients might differ systematically from those excluded. Furthermore, the heterogeneity of clinical management across multiple centers—including variability in olanzapine dosing protocols, frequency of laboratory monitoring, and concomitant medication choices—could not be fully controlled for and may have influenced the observed outcomes. Second, the broad definition of hepatotoxicity (any elevation >1×ULN) was intentionally used to capture the full spectrum of olanzapine-associated liver enzyme abnormalities, including early or subclinical elevations; however, this definition differs from the more stringent criteria typically used for confirmed DILI, and readers should interpret the reported prevalence accordingly. Third, the limited follow-up data for certain laboratory indicators restricted the robustness of statistical analysis, rendering some conclusions preliminary. Future investigations should adopt prospective designs with standardized monitoring protocols to mitigate potential confounding factors and definitively establish causality. To enhance the reliability and clinical applicability of future research, we recommend structured follow-up schedules, systematic laboratory monitoring, and comprehensive documentation of concomitant medications. These methodological refinements would provide more conclusive evidence regarding the dose-dependent hepatotoxicity of olanzapine in patients with BD.

## Conclusion

This study identified a significant association between olanzapine and hepatotoxicity, with an incidence as high as 24.2%. A majority of liver injury cases were mild and proved reversible upon drug discontinuation or following hepatoprotective therapy. These findings highlight the necessity for clinicians to implement rigorous liver function monitoring during olanzapine therapy. Furthermore, olanzapine-associated hepatotoxicity exhibited a dose-dependent relationship, warranting particularly intensified surveillance in cases of high-dose regimens. Notably, co-administration of valproate was associated with a lower incidence of olanzapine-induced hepatotoxicity in this cohort, although this finding remains associative and requires confirmation in prospective studies. Special attention should be given to patients on high-dose olanzapine, as well as those on polypharmacy with other potentially hepatotoxic agents.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author, Dr Yuanguo Xiong (email: rm002397@outlook.com), on reasonable request.

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Fang Wang, Xin Lai, and Shihai Zhou are co-first authors for this study. Yuanguo Xiong and Huawei Tan are co-correspondence authors for this study. We are grateful to all the participants in this study.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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