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ORIGINAL RESEARCH

Acetaminophen toxicity: Patterns of liver injury, effects on hospital length of stay, and the need for inpatient psychiatric care

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Highlights & Insights

- **Scientific Gap:** The effects of overdose intent and psychiatric comorbidities on LT evaluation and psychiatric care needs remain unclear.
- **Key Finding:** In 165 patients, 67.9% had psychiatric comorbidities and 58.2% intentional overdose. ALF occurred in 43.0%. Psychiatric factors did not affect LT listing, transplantation, or mortality.
- **Clinical Impact:** Early hepatology–psychiatry collaboration may improve care planning and ensure objective LT decisions in acetaminophen overdose.

ABSTRACT

Background and Aim: Acetaminophen toxicity is the most common cause of acute liver failure (ALF) in the United States. Among patients with acetaminophen toxicity, a vast majority have intentional overdose and concurrent psychiatric comorbidities. We aimed to analyze patient characteristics, patterns of overdose, and outcomes in patients with acetaminophen overdose at our liver transplantation (LT) center.

Materials and Methods: Patients ≥18 years of age with acetaminophen overdose between 2011 and 2020 at our institution were identified. Patient demographics, clinical and laboratory data, patterns of overdose (intentional vs. unintentional), psychiatric comorbidities, need for admission to inpatient psychiatry service, transplant wait listing, need for transplantation, and death were assessed. Categorical variables are presented as counts with percentages, continuous variables as median with interquartile range IQR (Q1-Q3), and $p<0.05$ was considered significant.

Results: A total of 165 (118 female, 47 male) patients were admitted with acetaminophen toxicity. Seventy-one (43.0%) patients met criteria for ALF. The median age was 32 years (IQR 25–49), and 112 (67.9%) patients had concurrent psychiatric comorbidities. Ninety-six (58.2%) patients had intentional overdose, while 69 (41.8%) patients had unintentional overdose. Twenty-three (13.9%) patients were listed for LT, and seven (4.2%) patients underwent LT. Eighty-one (49.1%) patients were subsequently admitted to the inpatient psychiatry service. Eleven (6.7%) patients died, five of whom were on the LT list. There was no significant difference in LT listing between patients with and without psychiatric comorbidities.

Conclusion: The majority of the patients with acetaminophen overdose survived to discharge. Most cases of acetaminophen overdose were intentional and were significantly associated with the presence of a psychiatric comorbidity. Intentional and unintentional overdoses had similar rates of ALF. Inpatient psychiatric hospitalization was frequently required, particularly for patients with intentional overdose.

Keywords: Acetaminophen, acute liver failure, acute liver injury.

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Introduction

Acetaminophen toxicity is the most common cause of acute liver failure (ALF) in the United States.[1–3] Approximately half of the acetaminophen overdoses are intentional for purposes of self-harm, and the remainder occur as unintentional for purposes of pain control with excessive intake over several days to weeks ("therapeutic misadventure").[3,4] ALF due to acetaminophen usually carries a favorable outcome, with approximately two-thirds of the patients recovering without liver transplantation (LT).[5–7] Early identification of patients with acetaminophen overdose, coupled with timely initiation of treatment with N-acetylcysteine (NAC), significantly improves outcomes.[8]

Psychiatric comorbidities are more prevalent in patients with ALF due to acetaminophen overdose compared to other etiologies of ALF, and may lead to concerns regarding LT listing, particularly due to challenges with psychosocial assessment in the setting of hepatic encephalopathy (HE) and intentional overdose.[6,9] Several registry studies have reported that patients with ALF due to acetaminophen were less commonly listed for LT compared to non-acetaminophen drug-induced liver injury, autoimmune hepatitis, and hepatitis B virus.[10] However, for patients with ALF due to acetaminophen toxicity, there are limited data on patterns of acetaminophen overdose and psychiatric comorbidities in patients being listed for or undergoing LT. In addition, there are limited data regarding the utilization of inpatient psychiatric services after an acetaminophen overdose. The goal of our study was to describe acetaminophen overdose patterns and assess the effects of psychiatric comorbidities and overdose intent on LT listing and final disposition at a large LT center.

Materials and Methods

Patients ≥18 years of age admitted with acetaminophen overdose at our institution between 2011 and 2020 were identified using an electronic medical record search. Patients with pre-existing liver disease were excluded. Patient demographics, clinical and laboratory data, pattern of overdose, concurrent overdoses, psychiatric comorbidities, LT listing, and disposition were obtained from electronic medical records. Acute liver injury was defined when the international normalized ratio (INR) ≥2, alanine aminotransferase (ALT) >=10xULN, and onset of illness <2 weeks without preexisting liver disease; ALF was defined when INR ≥1.5 with any grade of HE and onset of illness <26 weeks without preexisting liver disease. Intentional and unintentional overdoses were determined based on evaluation of a psychiatrist or transplant hepatologist. All patients underwent a rigorous psychosocial evaluation by experienced transplant social workers and psychiatrists. Assessments were completed through discussion with family members when necessary for confirmation of psychiatric comorbidities per DSM-5 criteria. In addition, the presence of a psychiatric comorbidity and prior hospitalizations related to psychiatric comorbidities were determined by clinical social workers or psychiatrists through review of available outside medical records. A history of previous psychiatric hospitalization did not necessarily indicate an active psychiatric diagnosis during the index hospitalization and was analyzed separately from current psychiatric comorbidity. Patients were transferred to inpatient psychiatry care once intensive care unit (ICU) or general medical care was no longer required, following psychiatric evaluation and clearance by the medical team. All tests were two-tailed, and p<0.05 was considered significant. Ethics approval was obtained from the Miller Transplantation Institutional Review Board (Approval No. IRB-19-02876; January 13, 2020), and the study was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board due to the retrospective design of the study.

Statistical Analysis

Statistical analyses were performed using Prism, version 9 (San Diego, CA, USA). Categorical variables are presented as counts with percentages, and continuous variables as median with interquartile range (IQR). Chi-square, analysis of variance, and Kruskal–Wallis tests were used for statistical analysis.

Results

A total of 165 (118 female, 47 male) patients were included in the study. Seventy-one (43.0%) patients had ALF, and 15 (9.1%) patients had acute liver injury. The median age was 32 years (IQR 25–49). Of all patients, 112 (67.9%) patients had concurrent psychiatric comorbidities, and 96 (58.2%) patients had intentional overdose. Acetaminophen co-ingestion with alcohol was present in 27 (16.4%) patients, opioids in 28 (17.0%), and benzodiazepines in 20 (12.1%) patients. All patients received NAC, which was administered for a median duration of 48 h (IQR 24–72). Seventeen (10.3%) patients required renal replacement therapy (RRT). Twenty-three (13.9%) patients were listed for LT, and seven (4.2%) patients underwent LT within a median of 3 days (IQR 1–6). All patients who were listed for LT and all patients who underwent LT had ALF. Eighty-one (49.1%) patients were admitted to the inpatient psychiatry service after initial medical management. The median length of stay in the ICU or general medicine services was 4 days (IQR 3–7), and subsequently in the inpatient psychiatry service was 9 days (IQR 4–19.5). The median length of stay was 12 days (IQR 5–24) in patients with ALF, compared with 7 days (IQR 2.8-16) in those without ALF (p=0.4736). A total of 11 (6.7%) patients died, five of whom were on the LT list, and six patients who were not considered candidates for LT.

Table 1 shows the characteristics of patients with intentional versus unintentional acetaminophen overdose. Patients with intentional overdose were younger (p<0.005), more commonly had previous inpatient psychiatry admissions (p<0.0005), and had longer total length of stay (p<0.05) compared to patients with unintentional overdose. The great majority of the patients (90%) with unintentional overdose who had inpatient psychiatry admission had a history of a psychiatric comorbidity. Table 2 shows the comparison between patients with and without psychiatric comorbidities. Table 3 shows individual psychiatric comorbidities, with major depressive disorder (MDD) being the most common, followed by MDD and generalized anxiety disorder.

Table 1. Clinical and laboratory characteristics of patients with intentional and unintentional acetaminophen overdose

	Intentional overdose (n=96)	Unintentional overdose (n=69)	p
Acute liver failure	42 (43.8%)	29 (42.0%)	0.8270
Acute liver injury	9 (9.4%)	6 (8.7%)	0.8819
Female gender	67 (69.8%)	51 (73.9%)	0.5657
Age (years)	29.0 (23.3–45.0)	41.0 (27.0–56.5)	**0.0019**
Body mass index (kg/m^2)	26.2 (22.1–32.3)	25.9 (22.1–29.9)	0.5487
Alcohol co-ingestion	19 (19.79%)	8 (11.59%)	0.1623
iAST (IU/L)	151 (24.5–4954)	1443 (37.5–5253)	0.1626
iALT (IU/L)	147 (21.0–5373)	2150 (39.0–5469)	0.7411
iINR	1.30 (1.10–2.90)	1.90 (1.20–3.93)	0.5617
iTotal bilirubin (mg/dL)	0.90 (0.50–3.20)	1.40 (0.60–3.45)	0.3890
pAST (IU/L)	809 (32.3–6333)	2218 (66.0–7772)	0.2927
pALT (IU/L)	947 (30.8–7528)	3092 (48.5–6019)	0.9556
pINR	1.60 (1.20–3.20)	2.00 (1.20–4.10)	0.8874
pTotal bilirubin (mg/dL)	1.40 (0.82–4.05)	1.80 (0.80–4.05)	0.4461
Renal replacement therapy	10 (10.4%)	7 (10.1%)	0.9552
Listed for liver transplantation	13 (13.5%)	10 (14.5%)	0.8629
Liver transplantation	4 (4.2%)	3 (4.3%)	0.9549
Inpatient psychiatric admission	71 (74.0%)	10 (14.5%)	**0.0001**
Length of stay (medical, days)	4 (3–7)	5 (2–9.5)	0.2095
Length of stay (total, days)	9.0 (4.0–19.5)	5.0 (2.0–11.5)	**0.0278**
Death	5 (5.20%)	6 (8.69%)	0.3788

'i' indicates initial values at admission, 'p' indicates peak values during hospitalization. Categorical variables are presented as numbers and percentages, and continuous variables as medians with interquartile ranges (Q1–Q3). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio. Reference values: ALT: 0–40 IU/L; AST: 0–40 IU/L; INR: 0.8–1.2, total bilirubin: 0.2–1.0 mg/dL

Discussion

Acetaminophen overdose is the leading cause of ALF in the USA, remaining one of the leading causes of LT.[1,11] As ALF requires emergent consideration of LT, a comprehensive assessment of psychiatric comorbidities or substance-use disorder sometimes can be challenging. Given the presence of HE in ALF, a comprehensive psychosocial evaluation often cannot be completed. Our study describes the characteristics of patients with acetaminophen overdose with a special emphasis on the patterns of overdose, psychiatric comorbidities, and utilization of inpatient psychiatric services, LT listing, and transplantation at a tertiary transplant center.

In our patient cohort, the vast majority of the patients had one or more psychiatric comorbidities (67.9%) and had intentional overdose (58.2%). Patients with intentional overdose were significantly younger than those with unintentional overdose and, as expected, were more frequently admitted to an inpatient psychiatry service, and ultimately had a significantly longer total length of stay. In addition, intentional overdose was significantly more common in patients with underlying psychiatric comorbidities compared to those without. A multicenter cohort study by the ALF Study Group (ALFSG) analyzed 1190 patients with ALF due to acetaminophen overdose between 1998 and 2018 and reported that 41.9% of patients presented with intentional overdose, and 53.9% had psychiatric comorbidity.[12] In this study, 23.0% of the patients were listed for LT, 8.4% of the patients received LT, and LT listing was not affected by the presence of psychiatric comorbidity, similar to our large tertiary center results.[12] Another study from 2019, including 207 patients with acetaminophen overdose, the LT rate was 1.5%, and death was <1%.[13] The same study also reported that 76.3% of the overdoses were intentional, and that MDD was the most common psychiatric diagnosis, followed by alcohol-use disorder.[13] Similarly, another study using ALFSG data, including 93 patients with acetaminophen overdose (50 with unintentional overdose, 43 with intentional overdose), reported that psychiatric comorbidities were more common in patients with intentional overdose, with MDD being the most common comorbidity, aligning with the findings of our study.[3]

Need for inpatient psychiatric hospitalization should be anticipated in these patients, whether they are expected to medically improve or go on to require LT. This planning ahead may ultimately help to decrease the length of stay, and for patients who may need LT, ap-

Table 2. Comparison of patients with and without psychiatric comorbidities

Variables	Psychiatric comorbidity present (n=112)	No psychiatric comorbidity (n=53)	p
Acute liver failure	51 (45.5%)	20 (37.7%)	0.3477
Acute liver injury	9 (8.0%)	6 (11.3%)	0.4961
Female gender	78 (69.7%)	40 (75.5%)	0.4416
Age (years)	32.0 (24.3–47.8)	38.0 (26.0–51.5)	0.2036
Body mass index (kg/m^2)	25.7 (22.0–29.9)	26.7 (22.6–32.8)	0.0753
Intentional overdose	76 (67.9%)	20 (37.7%)	**0.0002**
Alcohol co-ingestion	16 (14.3%)	11 (20.8%)	0.2971
iAST (IU/L)	306 (29.3–4527)	977 (22.5–5751)	0.5715
iALT (IU/L)	293 (24.3–475)	1442 (20.0–5952)	0.4917
iINR	1.5 (1.10–3.40)	1.70 (1.20–3.10)	0.6328
iTotal bilirubin (mg/dL)	1.0 (0.50–3.20)	1.30 (0.60–3.90)	0.7138
pAST (IU/L)	871 (37.0–6333)	2724 (66.0–7135)	0.5705
pALT (IU/L)	1065 (35.3–6001)	2771 (47.5–6582)	0.8592
pINR	1.70 (1.20–4.00)	1.90 (1.30–3.15)	0.5185
Renal replacement therapy	13 (11.6%)	4 (7.5%)	0.4262
Listed for liver transplantation	18 (16.1%)	5 (9.4%)	0.2504
Liver transplantation	6 (5.4%)	1 (1.9%)	0.3046
Previous inpatient psychiatric admission	67 (59.8%)	14 (26.4%)	**0.0001**
Length of stay (medical, days)	5.0 (3.0–7.75)	4.0 (2.0–7.0)	0.2274
Length of stay (total, days)	11.0 (5.0–21.0)	5.0 (2.0–15.0)	0.2339

'i' indicates initial values at admission, 'p' indicates peak values during hospitalization. Numbers are given with percentage and continuous variables with median and IQR (Q1-Q3). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio. Reference values: ALT: 0–40 IU/L; AST: 0–40 IU/L; INR: 0.8–1.2, total bilirubin: 0.2–1.0 mg/dL.

propriate and timely psychiatric treatments with patient engagement in care could help in LT listing. Patients who recover from the ALF, when out of the ICU, often require a bedside sitter (with the associated costs) while recovering on the medical floor, awaiting the improvement of their liver tests or insurance clearance for inpatient psychiatric services. While on the medical floor, the patients may not receive the timely psychiatric care they require, so earlier transfer to the inpatient psychiatry service is essential.

In the current study, the LT listing rate was 13.9%, the LT rate was 4.2%, and death was 6.7%. Consistent with other reports, our data show that the disease severity of ALF due to acetaminophen was the main consideration for LT listing, and the presence of intentional overdose or presence of psychiatric comorbidity did not preclude patients from listing. Interestingly, the medical and total length of stay was not statistically significant in patients with ALF compared to those without ALF in our study, which may reflect the relatively small sample size and limited statistical power to detect differences between the groups. Another ALFSG study of 910 patients with ALF due to acetaminophen toxicity reported that 88% of the patients had psychiatric comorbidity.[6] The same study also reported that there was no difference in LT listing, and in those undergoing LT, and overall death among patients with and without psychiatric comorbidity were similar to our study.[6]

Simkin et al.,[14] reported that one-third of the patients with acetaminophen overdose had concurrent alcohol intake. Another large study reported that patients with unintentional overdoses more commonly had concurrent alcohol intake before the presentation of ALF compared to patients with intentional acetaminophen overdose.[15] The same study also reported that concurrent use of alcohol was present in 44.7% of the patients, and a psychiatric comorbidity was present in 42.3% of patients.[15] In our study, 16.4% of the patients had concurrent alcohol co-ingestion, opioids in 17.0% of the patients, and benzodiazepines in 12.1% of the patients; the presence of alcohol co-ingestion was not statistically significant in patients with intentional overdose compared to unintentional overdose.

In our study, patients listed for LT were more likely to require RRT and had a longer duration of NAC treatment and total length of stay. As expected, admission laboratory values, including ALT, INR, white blood cells, and lactic acid, were significantly higher in listed patients compared to those who were not listed. Similarly, peak values of aspartate aminotransferase, ALT, INR, and total bilirubin were significantly elevated in the listed patients compared to those who were not listed. Correspondingly, another study reported that the patients listed for LT received more interventions, including prolonged NAC treatment, extended use of RRT, longer vasopressor support, increased use of

Table 3. Psychiatric comorbidities (n=112)

	n (%)
MDD	46 (41.1)
MDD and GAD	14 (12.5)
Schizophrenia	11 (9.8)
Bipolar disorder	7 (6.3)
GAD	6 (5.4)
BPD and MDD	4 (3.6)
BPD	3 (2.7)
PTSD and MDD	3 (2.7)
Bipolar disorder, GAD and MDD	2 (1.8)
Bipolar disorder and MDD	2 (1.8)
Bipolar disorder and schizophrenia	2 (1.8)
Bipolar disorder, MDD and BPD	2 (1.8)
Bipolar disorder and GAD	1 (0.9)
BPD and bipolar disorder	1 (0.9)
BPD, MDD and GAD	1 (0.9)
Eating disorder and GAD	1 (0.9)
Impulse control disorder	1 (0.9)
Eating disorder and MDD	1 (0.9)
Panic disorder	1 (0.9)
PTSD and BPD	1 (0.9)
PTSD, BPD, and MDD	1 (0.9)
MDD and schizophrenia	1 (0.9)

BPD: Borderline personality disorder; MDD: Major depressive disorder; PTSD: Post-traumatic stress disorder; GAD: Generalized anxiety disorder.

ICP monitors, and the presence of intentional overdose or psychiatric comorbidities did not differ significantly between listed and non-listed patients, aligning with our findings.[6] Although some studies have reported that intentional acetaminophen overdose is associated with worse outcomes, morbidity, and mortality, our study found that patients with intentional overdose were significantly younger, with no differences in rates of ALF, LT, or death.[16]

Limitations of our study include its retrospective and single-center nature and potential selection bias. For most patients, the exact time of acetaminophen ingestion was not clear. Intentional/unintentional overdose information was obtained based on the transplant hepatologist or psychiatrist's assessments. Patient demographics, patterns of overdose, utilization of psychiatry services, LT listing and transplantation, and mortality may differ from centers with no transplant services or community hospitals. Strengths of our study include having a large number of patients with acetaminophen overdose and ALF, and analyzing specifically the overdose patterns, psychiatric comorbidities, and identifying the patient characteristics for LT listing and transplantation.

Conclusion

The majority of the patients with acetaminophen overdose in the current study recovered during index hospitalization, although inpatient psychiatric care was frequently required, particularly after intentional overdose. Rates of acute liver injury, ALF, LT listing and transplantation, and mortality did not differ significantly between intentional and unintentional overdoses. Future prospective and multicenter studies with long-term follow-up are needed to validate these findings and further characterize the prevalence and outcomes of psychiatric comorbidities in patients with acetaminophen overdose, with or without ALF.

Ethics Committee Approval: Ethics approval was obtained from the Miller Transplantation Institutional Review Board (Approval No. IRB-19-02876; January 13, 2020), and the study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: The requirement for informed consent was waived by the Institutional Review Board due to the retrospective design of the study.

Conflict of Interest: The authors declare no conflict of interest.

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