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Research Article

Liver Transplantation Outcomes in Acetaminophen-Induced Acute Liver Failure: A Systematic Review

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ABSTRACT

Background: Acetaminophen-induced Acute Liver Failure (ALF) is a leading cause of liver transplantation globally. Despite its widespread use as an over-the-counter analgesic, overdose both intentional and unintentional can result in severe hepatotoxicity. Early identification of patients who may benefit from liver transplantation is critical for improving outcomes.

Objective: This systematic review aims to analyze the role of liver transplantation in patients with acetaminophen-induced ALF, evaluating transplantation rates, patient outcomes, prognostic factors, and clinical considerations to inform practice and guide future research.

Methods: A comprehensive literature search was conducted, reviewing cohort studies, prospective and retrospective analyses, and systematic reviews that focused on liver transplantation outcomes in acetaminophen-induced ALF patients. Key prognostic models and biomarkers were also evaluated.

Results: Liver transplantation offers a significant survival benefit for patients with acetaminophen-induced ALF, with post-transplant survival rates comparable to those transplanted for other etiologies. The rapid progression of acetaminophen-induced ALF necessitates swift decision-making, yet current prognostic models like the King's College Criteria (KCC) have limitations in sensitivity and early detection. Alternative scoring systems such as the Sequential Organ Failure Assessment (SOFA) and APACHE II scores demonstrate improved predictive accuracy. Emerging biomarkers, including arterial lactate show promise in enhancing early identification of high-risk patients. Underlying psychiatric conditions are prevalent in this patient population, indicating a need for integrated psychiatric support pre- and post-transplantation.

Conclusion: Optimizing outcomes for acetaminophen-induced ALF requires a multifaceted approach that includes timely liver transplantation, utilization of improved prognostic tools, and comprehensive patient care addressing both medical and psychosocial factors. Future research should focus on refining prognostic models, exploring novel therapies, and implementing effective public health strategies to reduce the incidence of acetaminophen overdose.

Keywords: Acetaminophen; Acute liver failure; Liver transplantation; Prognostic models; King's college criteria; SOFA score; Biomarkers; Psychiatric support

INTRODUCTION

Acetaminophen (paracetamol) is one of the most commonly used over-the-counter analgesic and antipyretic medications worldwide due to its effectiveness and general safety at therapeutic doses. However, it is also the leading cause of Acute Liver Failure (ALF) in many countries, primarily resulting from overdose both intentional and unintentional which poses significant challenges for healthcare systems globally [1].

The hepatotoxicity associated with acetaminophen overdose is attributed to the accumulation of its toxic metabolite, N-acetyl-p-

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benzoquinone imine (NAPQI). In normal doses, NAPQI is detoxified by hepatic glutathione, but in overdoses, glutathione stores become depleted, leading to oxidative stress and hepatocellular injury. Early administration of N-acetylcysteine (NAC) is the standard antidotal therapy and is most effective when initiated within 8 hours of ingestion. Despite prompt NAC treatment, a subset of patients progresses to ALF, characterized by coagulopathy and encephalopathy, necessitating consideration for liver transplantation. Liver transplantation remains the only definitive treatment for patients with acetaminophen-induced ALF who are unlikely to recover with medical management alone [2].

The decision to proceed with transplantation is complex and relies on prognostic models to predict outcomes. The King's College Criteria, developed specifically for acetaminophen-induced ALF, are widely used to identify patients who may benefit from transplantation. However, these criteria have limitations in sensitivity and specificity, leading to ongoing research to refine prognostic tools and incorporate novel biomarkers. Epidemiological studies highlight the significant burden of acetaminophen-induced ALF on healthcare systems. In the United States and the United Kingdom, acetaminophen overdose accounts for approximately half of all ALF cases. The outcomes following liver transplantation for acetaminophen-induced ALF are generally favorable, However, transplantation is associated with considerable risks, including perioperative complications, graft rejection, infections due to immunosuppression, and the psychological impact of a life-altering procedure [3].

Moreover, many patients who experience acetaminophen-induced ALF have underlying psychiatric conditions or psychosocial stressors contributing to overdose, such as depression, substance abuse, or intentional self-harm. These factors complicate post-transplant care and underscore the necessity for integrated psychiatric support alongside medical treatment to improve long-term outcomes and reduce the risk of recurrence. Advancements in critical care and liver support therapies have improved the management of patients with ALF. Novel interventions, such as extracorporeal liver support systems and stem cell therapies, are being investigated as potential bridges to recovery or transplantation. Additionally, research into genetic and molecular biomarkers aims to enhance the accuracy of prognosis and personalize treatment strategies. Public health initiatives play a crucial role in mitigating the incidence of acetaminophen-induced hepatotoxicity. Regulatory measures, such as limiting the maximum single-dose packaging of acetaminophen and increasing public awareness about the risks of overdose, have been implemented in several countries, resulting in a decrease in severe overdose cases. These interventions highlight the importance of a multifaceted approach combining clinical management with preventative strategies [4].

Despite these efforts, the global burden of acetaminophen-induced ALF remains substantial, and the demand for liver transplantation exceeds the supply of available organs. This disparity emphasizes the need for optimizing donor organ allocation and exploring alternative therapies. It also reinforces the importance of conducting systematic reviews to synthesize existing evidence, identify gaps in knowledge, and guide future research and policy development [5].

This systematic review aims to provide a comprehensive analysis of liver transplantation in patients poisoned with acetaminophen. By examining transplantation rates, patient outcomes, prognostic factors, and clinical considerations across multiple studies, we seek to inform clinical practice, enhance patient care, and contribute to the development of evidence-based guidelines for managing this critical condition [6].

MATERIALS AND METHODS

Study design

This systematic review aimed to evaluate the outcomes of liver transplantation in patients with acetaminophen (paracetamol) poisoning. The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7].

Search strategy

A comprehensive literature search was performed across four electronic databases: PubMed, Embase, Scopus, and the Cochrane Library. The search aimed to identify relevant studies published up to September 2024. The keywords and search strategies were tailored to each database to maximize sensitivity.

For PubMed, the following search strategy was used:

(("liver transplantation"[Title/Abstract] OR "liver transplant"[Title/Abstract] OR "hepatic transplant"[Title/Abstract] OR "orthotopic liver transplantation"[Title/Abstract] OR "liver grafting"[Title/Abstract])

AND

(("acetaminophen"[Title/Abstract] AND "poisoning"[Title/Abstract]) OR "acetaminophen toxicity"[Title/Abstract] OR "paracetamol overdose"[Title/Abstract] OR "APAP poisoning"[Title/Abstract] OR "acetaminophen hepatotoxicity"[Title/Abstract] OR "paracetamol toxicity"[Title/Abstract] OR "paracetamol poisoning"[Title/Abstract]))

This search yielded 227 results.

For Embase, the search terms included:

('liver transplantation'/exp OR 'liver transplant' OR 'hepatic transplant' OR 'orthotopic liver transplantation')

AND

(('acetaminophen'/exp AND 'poisoning'/exp) OR 'acetaminophen toxicity' OR 'paracetamol overdose' OR 'APAP poisoning')

AND

('survival rate'/exp OR 'mortality'/exp OR 'complications'/exp OR 'adverse event'/exp OR 'liver failure'/exp OR 'graft survival' OR 'prognosis'/exp OR 'prognosis' OR 'outcomes' OR 'benefits' OR 'advantages' OR 'treatment benefits')

AND

[humans]/lim

AND

[article]/lim

This search resulted in 323 articles.

For Scopus, the search strategy was:

(TITLE-ABS-KEY("liver transplantation" OR "liver transplant" OR "hepatic transplant" OR "orthotopic liver transplantation"))

AND

(TITLE-ABS-KEY("acetaminophen" AND "poisoning") OR TITLE-ABS-KEY("acetaminophen toxicity") OR TITLE-ABS-KEY("paracetamol overdose") OR TITLE-ABS-KEY("APAP poisoning"))

AND

(TITLE-ABS-KEY("survival rate" OR "mortality" OR "complications" OR "adverse event" OR "liver failure" OR "graft survival" OR "prognosis" OR "outcomes" OR "benefits" OR "advantages" OR "treatment benefits"))

AND

DOCTYPE(ar)

AND

SUBJAREA(medi)

This search identified 164 results.

In the Cochrane Library, a search was conducted using similar keywords. We found 4 systematic reviews and 13 trials. One systematic review 2018 updated was relevant to our topic. We included the un-updated version in our analysis.

Eligibility criteria

Studies were included if they met the following criteria:

- **Population:** Patients undergoing liver transplantation due to acetaminophen poisoning.
- **Intervention:** Liver transplantation.
- **Outcomes:** Reporting on survival rates, mortality, graft survival, complications, adverse events, prognosis, or treatment benefits or evaluating criteria.
- **Study design:** Reviews and Original research articles, including randomized controlled trials, cohort studies, case-control studies, and case series.
- **Language:** Articles published in English.
- **Participants:** Human subjects.

Exclusion criteria were:

- Non-original articles such as editorials, commentaries, and conference abstracts without full texts.
- Animal studies.
- Studies not reporting relevant outcomes or lacking sufficient data.
- Studies with less than 5 acetaminophen poisoned patients which underwent liver transplant

Study selection

A total of 715 records were identified from the database searches:

- **PubMed:** 227 articles
- **Embase:** 323 articles
- **Scopus:** 164 articles
- **Cochrane library:** 13 articles and 4 reviews

After removing duplicates, 300 unique articles remained. Two independent reviewers screened the titles and abstracts of these articles for relevance. Any disagreements were resolved through discussion or consultation with a third reviewer [8].

During the title and abstract screening, 250 articles were excluded for the following reasons:

- Irrelevant to the research question.
- Studies on animal models.
- Articles not in English.
- Not reporting outcome or reporting death and liver transplant without segregation.

The full texts of the remaining 50 articles were retrieved and assessed for eligibility. After full-text review, 34 articles were excluded due to:

- Lack of relevant outcome data.
- Insufficient methodological quality.
- Population not meeting inclusion criteria.
- Not reporting outcome or reporting death and liver transplant without segregation.

Consequently, 16 studies 10 reporting outcome and 6 evaluating critera were included in the final systematic review [9].

Data extraction

Data were extracted independently by two reviewers using a standardized data extraction form. The extracted information included:

- **Study characteristics:** Authors, year of publication, country, study design.
- **Participant details:** Sample size, age, gender distribution.
- **Clinical information:** Indications for transplantation, severity of poisoning, time from ingestion to transplantation.
- **Outcomes:** Survival rates, graft survival, mortality, complications, adverse events, length of hospital stay, and any reported prognostic factors.

Discrepancies in data extraction were resolved by consensus or by involving a third reviewer.

Quality assessment

- **Overall quality:** The majority of the included studies were of moderate to high quality. They provided valuable insights into the outcomes of liver transplantation in patients with acetaminophen-induced acute liver failure.
- **Strengths:** Most studies had well-defined patient populations, clear outcome measures, and appropriate statistical analyses. The observational studies often controlled for key confounding variables, enhancing the reliability of their findings.

- **Limitations:** Some studies had limitations such as small sample sizes, single-center designs, or lack of long-term follow-up data. In addition, the observational nature of many studies means that causality cannot be firmly established.

Implications

The generally acceptable quality of the included studies supports the validity of the systematic review's conclusions. However, the noted limitations suggest that findings should be interpreted with some caution. Future research with more robust designs, larger sample sizes, and longer follow-up periods would strengthen the evidence base.

Data synthesis

Due to the heterogeneity of the study designs, populations, and outcome measures, a narrative synthesis was performed. Key findings from each study were summarized in text and tables. Where appropriate, results were grouped by outcome measures such as survival rates and complications.

A meta-analysis was not conducted because of the variability in study methodologies and outcomes, which precluded meaningful statistical pooling.

Ethical considerations

Ethical approval was not required for this study as it involved the analysis of previously published data without any direct involvement of human participants.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

RESULTS

This systematic review included 16 studies that evaluated the outcomes of Liver Transplantation (LT) in patients with acetaminophen-induced Acute Liver Failure (ALF). The studies comprised cohort analyses, retrospective reviews, and systematic overviews, providing a comprehensive assessment of LT efficacy, patient survival rates, prognostic factors, and the utility of predictive models in this patient population (Table 1).

Table 1: Summary of outcomes. Mortality rate after transplant reports mortality of patients fulfill transplant criteria but did not transplanted.

Acute liver failure 1,691 (2022)	1691	756	436	-	107 (25%) at one year 211 (52%) at five years
Paracetamol (Acetaminophen) poisoning (2015) (systematic review of Bernal et al. 1998 article and another systematic review of 2007)	-	-	-	20/24 (83%) in Bernal et al. study and 121/180 (67%) in one systematic review	11 (25%) before discharge and 15 (34%) overall in Bernal et al. study and 121/180 (67%) in one systematic review
Acute liver failure in Scotland (2012)	949	-	53	134/151 (89%)	15 (28%)
Long-term outcome following liver transplantation for paracetamol overdose (2010)	608	68	44	-	13 (30%) during index admission 5 (11%) during follow-up: 45.5% at 5 years
Medical and psychiatric outcomes for patients transplanted for acetaminophen-induced acute liver failure: A case-control study (2010)	52	-	36	-	5 (13%) at 1 year, 9 (25%) at 5 years
Paracetamol (Acetaminophen) poisoning (2007) (systematic review)	-	-	-	Reports different statistics: 0-60%, 83%, 75-80% for one year survival	Reports different statistics: 25%, 30-40% for one year survival

Acetaminophen-induced acute liver failure: Results of a United States multicenter. Prospective study (2005)	275	-	23	-	5 (22%)
Interventions for paracetamol overdose (2003) (systematic review)	-	-	61	33/46 (72%)	17 (28%) (during hospitalization)
Serious paracetamol poisoning and the results of liver transplantation (1994)	92	17	10	6/7 (86%)	3 (30%)
Use and outcome of liver transplantation in acetaminophen-induced acute liver failure (1998)	548	68	44	20/24 (83%)	11 (25%) before discharge and 15 (34%) overall
Study title	Total patients assessed	Patients listed for transplantation	Underwent transplantation	Supportive treatment mortality	Mortality after transplantation

Patient demographics and survival rates

Wong et al. analyzed a cohort of 1,691 patients listed for LT between 2002 and 2019, identifying 765 cases (45.2%) of acetaminophen (APAP)-induced ALF. These patients had the shortest median time from hospital admission to LT waitlisting (≤ 2 days in 94% of cases), reflecting the rapid progression of APAP-related ALF. Waitlist mortality was highest among APAP patients (22.8%) compared to those with Hepatitis B Virus (HBV) (13.0%), Autoimmune Hepatitis (AIH) (10.2%), and Drug-Induced Liver Injury (DILI) (15.2%). Post-transplant mortality showed no significant differences across etiologies, with an overall rate of 24.5%.

Park et al. conducted a systematic review incorporating data from observational studies on LT outcomes in APAP poisoning. The pooled data indicated a hospital discharge survival rate of 75% for LT recipients, with mortality primarily due to cerebral edema, multi-organ failure, sepsis, and acute rejection. Comparatively, mortality was 28% in transplanted patients versus 67% in non-transplanted patients who met similar criteria but did not receive LT.

A large prospective study in Scotland assessed 949 patients admitted with ALF over 17 years, finding that 73.9% had APAP overdose-related ALF. Among those meeting King's College Hospital Poor Prognostic Criteria for emergency LT, 48.7% of APAP patients survived following transplantation. Mortality among transplant candidates who did not receive LT was 97.2%, underscoring the critical need for transplantation in severe cases.

Khan et al. retrospectively reviewed outcomes of 44 patients who underwent Orthotopic Liver Transplantation (OLT) for APAP overdose. The post-transplant mortality rate during the initial hospital admission was 30%, and the 5-year actuarial survival rate was 54.5%. Re-transplantation was necessary in 13.6% of cases due to complications such as primary non-function and hepatic artery thrombosis.

A retrospective case-control study compared outcomes of patients undergoing OLT for APAP-induced ALF with those transplanted for non-APAP ALF and Chronic Liver Disease (CLD). Despite greater pre-transplant illness severity and higher prevalence of psychiatric comorbidities, APAP-ALF patients had comparable survival rates to other groups, with 1-year survival at 87% and 5-year survival at 75%.

Larson et al. conducted a multicenter prospective study of 662 patients with ALF, identifying 275 cases (42%) of APAP-induced ALF. Among these, 65% survived without transplantation, 27% died without transplantation, and 8% underwent LT with a 71% survival rate at three weeks post-transplant.

Prognostic models and biomarkers

Several studies evaluated prognostic models used to identify patients unlikely to survive without LT. The King's College Criteria (KCC) remained the most widely used but demonstrated limited sensitivity (~58%) and reliance on late-stage clinical parameters. Alternative models like the Sequential Organ Failure Assessment (SOFA) score showed improved predictive accuracy (Area Under the Curve (AUC) of 0.79-0.84) by assessing multi-organ dysfunction.

Emerging biomarkers such as arterial lactate levels and serum phosphate were investigated for their prognostic value. Elevated arterial lactate levels (>4.7 mmol/L) measured within 12 hours

of admission were associated with high mortality risk, offering a sensitivity of 98%. Hypophosphatemia (<2.5 mg/dL) indicated spontaneous recovery potential due to active liver regeneration.

DISCUSSION

The collective findings emphasize the critical role of liver transplantation in managing patients with acetaminophen-induced ALF. APAP overdose leads to rapid disease progression and high waitlist mortality, necessitating swift evaluation and listing for transplantation. Despite the severity of their condition, post-transplant survival rates for APAP-ALF patients are comparable to those with other etiologies, affirming the efficacy of LT in this context.

The studies underscore the importance of timely transplantation. Wong et al. highlighted that APAP patients had the shortest time from admission to LT waitlisting, reflecting the urgency required in these cases. The high spontaneous survival rates in APAP-related ALF also suggest a need for careful patient selection to optimize outcomes and resource utilization.

Psychiatric comorbidities present additional challenges in managing APAP-ALF patients. The retrospective case-control study revealed a significant prevalence of psychiatric disorders and previous suicide attempts among APAP-ALF patients. Post-transplant, these patients required ongoing psychiatric support, and some exhibited lower compliance with medical follow-up. This highlights the necessity for integrated psychiatric evaluation and support services as part of the transplantation process.

The evaluation of prognostic models reveals that while KCC provides a specific framework, its limited sensitivity and reliance on advanced clinical signs reduce its utility for early prediction. Alternative models like the SOFA score offer improved accuracy by assessing multiple organ systems but require more resources and repeated measurements. Biomarkers such as arterial lactate levels show promise for early risk stratification due to their high sensitivity and ease of measurement. However, combining these biomarkers with existing criteria has not significantly enhanced predictive power, indicating that they may be more effective as standalone tools.

The integration of dynamic prognostic models and biomarkers into clinical practice could enhance the early identification of patients who would benefit most from LT. This approach may improve survival outcomes by facilitating timely decision-making and optimizing resource allocation.

CONCLUSION

Liver transplantation remains a vital intervention for patients with acetaminophen-induced acute liver failure. The studies reviewed demonstrate that, despite rapid disease progression and high mortality rates without transplantation, post-transplant survival is favorable and comparable to other causes of ALF. Incorporating dynamic prognostic models like the SOFA score and monitoring biomarkers such as arterial lactate levels can improve early identification of high-risk patients, enabling timely intervention.

Addressing psychiatric comorbidities is essential for optimizing long-term outcomes, emphasizing the need for comprehensive care that includes mental health support. Continued research into refining prognostic tools and integrating them into clinical protocols will enhance patient selection processes and improve overall outcomes in this critical patient population.

REFERENCES

1. Lee WM. Acetaminophen (APAP) hepatotoxicity-Isn't it time for APAP to go away? J Hepatol. 2017;67(6):1324-1331.
2. Hinson JA, Roberts DW, James LP. Mechanisms of acetaminophen-induced liver necrosis. Handb Exp Pharmacol. 2010;(196):369-405.
3. Heard KJ. Acetylcysteine for acetaminophen poisoning. N Engl J Med. 2008;359(3):285-292.
4. Fernandez J, Bassegoda O, Toapanta D, Bernal W. Acute liver failure: A practical update. JHEP Rep Innov Hepatol. 2024;6(9): 101131.
5. McPhail MJW, Farne H, Senvar N, Wendon JA, Bernal W. Ability of King's College criteria and model for end-stage liver disease scores to predict mortality of patients with acute liver failure: A meta-analysis. Clin Gastroenterol Hepatol. 2016;14(4):516-525.
6. Hawton K, Bergen H, Simkin S, Wells C, Kapur N, Gunnell D. Six-year follow-up of impact of co-proxamol withdrawal in England and Wales on prescribing and deaths: Time-series study. PLoS Med. 2012;9(5):e1001213.
7. Reuben A, Tillman H, Fontana RJ, Davern T, McGuire B, Stravitz RT, et al. Outcomes in adults with acute liver failure between 1998 and 2013: An observational cohort study. Ann Intern Med. 2016;164(11):724–732.
8. Koch DG, Speiser JL, Durkalski V, Fontana RJ, Davern T, McGuire B, et al. The natural history of severe acute liver injury. Am J Gastroenterol. 2017;112(9):1389-1396.
9. McDowell Torres D, Stevens RD, Gurakar A. Acute liver failure: A management challenge for the practicing gastroenterologist. Gastroenterol Hepatol. 2010;6(7):444-450.