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Acute liver injury and acute liver failure from mushroom poisoning in North America

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Abstract

Background & Aims: Published estimates of survival associated with mushroom (amatoxin)-induced acute liver failure (ALF) and injury (ALI) with and without liver transplant (LT) are highly variable. We aimed to determine the 21-day survival associated with amatoxin-induced ALI (A-ALI) and ALF (A-ALF) and review use of targeted therapies. *Methods:* Cohort study of all A-ALI/A-ALF patients enrolled in the US ALFSG registry between 01/1998 and 12/2014. *Results:* Of the 2224 subjects in the registry, 18 (0.8%) had A-ALF (n = 13) or A-ALI (n = 5). At admission, ALF patients had higher lactate levels (5.2 vs. 2.2 mM, P = 0.06) compared to ALI patients, but INR (2.8 vs. 2.2), bilirubin (87 vs. 26 μM) and MELD scores (28 vs. 24) were similar (P > 0.2 for all). Of the 13 patients with ALF, six survived without LT (46%), five survived with LT (39%) and two died without LT (15%). Of the five patients with ALI, four (80%) recovered and one (20%) survived post-LT. Comparing those who died/received LT (non-spontaneous survivors [NSS]) with spontaneous survivors (SS), *N*-acetylcysteine was used in nearly all patients (NSS 88% vs. SS 80%); whereas, silibinin (25% vs. 50%), penicillin (50% vs. 25%) and nasobiliary drainage (0 vs. 10%) were used less frequently (P > 0.15 for all therapies). *Conclusion:* Patients with mushroom poisoning with ALI have favourable survival, while around half of those presenting with ALF may eventually require LT. Further study is needed to define optimal management (including the use of targeted therapies) to improve survival, particularly in the absence of LT.

Keywords
acute liver failure – acute liver injury – *Amanita phalloides* – fulminant hepatic failure – liver transplantation – mushroom toxicity

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Abbreviations
A-ALF, Amatoxin-induced Acute Liver Failure; A-ALI, Amatoxin-induced Acute Liver Injury; ALF, Acute Liver Failure; ALFSG, Acute Liver Failure Study Group; ALI, Acute Liver Injury; CRRT, Continuous renal replacement therapy; HE, Hepatic Encephalopathy; ICH, Intracranial hypertension; ICP, Intracranial Pressure; ICU, Intensive Care Unit; INR, International normalized ratio; IQR, Interquartile range; KCC, King's College Criteria; LT, Liver transplantation; MELD, Model for End-stage Liver Disease; MV, Mechanical ventilation; NSS, Non-spontaneous survivor (death/transplant) at day 21; RRT, Renal replacement therapy; SS, Spontaneous survivors at day 21.

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Key Points

- This is the largest North American study to assess amatoxin-induced acute liver failure (ALF) and acute liver injury (ALI).
- Patients with amatoxin-induced ALI have a favourable prognosis, even with severe coagulopathy.
- While some patients with amatoxin-induced ALF may require liver transplant, nearly half appear to recover without transplant despite the presence of organ failure.
- Further study is needed to define optimal management strategies (including the use of amatoxin-targeted therapies) associated with improved survival, even in the absence of transplant.

Mushroom poisoning is associated with significant morbidity and mortality. *Amanita phalloides*, 'death cap,' accounts for over 90% of lethal ingestions (1). From 2002 to 2005, the American Association of Poison Control Centres estimated that between 40 to 50 exposures to amatoxin-containing mushrooms occurred per year, resulting in five fatal cases in total (2).

Two types of mushroom-related toxins have been described: amatoxin and phalloidin (phallotoxin). Phallotoxin disrupts the cellular membrane of enterocytes (3), and is believed to be responsible for the gastrointestinal symptoms of mushroom poisoning (4, 5). Amatoxin, on the other hand, inhibits protein synthesis within enterocytes and hepatocytes (6), thereby resulting in hepatocellular injury and possible hepatic failure (7). The mainstays of treatment for amatoxin poisoning are: primarily supportive care (organ support), detoxification procedures (charcoal, haemoperfusion, extracorporeal liver support), chemotherapeutic agents (penicillin, silibinin), and in severe cases, liver transplantation (LT).

The prognosis of amatoxin poisoning is uncertain and the optimal treatment strategy remains unclear. Published studies to date have reported widely variable mortality rates, ranging from 0 to 100% (3, 8, 9). These differences likely arise because of significant heterogeneity between study populations – with respect to the rates of acute liver injury (ALI) and acute liver failure (ALF) – as well as potential reporting bias. Notably, few studies have specifically examined the short- and long-term outcomes of patients who developed amaxotin-induced acute liver injury (A-ALI) and amatoxin-induced acute liver failure (A-ALF) (10).

Using data from the United States Acute Liver Failure Study Group (US ALFSG) registry from 1998 to 2014, we sought:

1 To describe the characteristics of A-ALI and A-ALF in North America over a 17 year period; and,
2 To determine mortality and transplantation rates in patients with A-ALF.

Materials and methods

Study design and setting

We assembled a cohort from the United States ALF Study Group (US ALFSG), a registry of 2224 patients with acute liver failure (ALF) and acute liver injury (ALI) with enrolment between January 1998 to December 2014 (including 32 sites overall, 16 currently active; see acknowledgements). A total of 18 patients were identified as having developed severe hepatotoxicity from *Amanita phalloides* (13 ALF, five ALI). Patient consent was obtained from all patients upon inclusion into the ALFSG registry. All participating sites (California Pacific Medical Centre, University of California Davis, University of California San Francisco, Oregon Health Sciences Centre, University of Washington, University of Alberta, Northwestern University, University of Pittsburg, Virginia Commonwealth University, and Yale University Medical Center) had approval from local institutional review/ethics boards.

Participants

ALFSG registry eligibility criteria for ALF was defined by (a) the presence of hepatic encephalopathy of any degree; (b) evidence of moderately severe coagulopathy [i.e., international normalized ratio (INR) $\geq$1.5]; (c) presumed onset of acute illness of <26 weeks; and (d) the absence of cirrhosis (11). Patients with ALI were defined by (a) evidence of moderately severe coagulopathy (INR $\geq$2.0); (b) presumed onset of acute illness <26 weeks; and (c) the absence of cirrhosis (11). For our study, only patients with the primary diagnoses of A-ALF and/or A-ALI were included.

Operational definitions

Hepatic encephalopathy (HE) grade was defined using the West Haven Criteria (summarized): grade 1: any alteration in mentation; grade 2: being somnolent or obtunded but easily rousable or presence of asterixis; grade 3: being rousable with difficulty; and grade 4: unresponsive to deep pain (12). In this study, we defined 'low coma grade' as grades 1 or 2 and 'high coma grade' as grades 3 or 4. As in previous studies, we used the King's College Criteria for non-acetaminophen-ALF as a predictor of poor outcome (death/transplant), namely: (a) INR > 6.5 or (b) any three out of five of the following: patient age <10 or >40 years, serum bilirubin >300 μM (17.5 mg/dl), duration of jaundice before the onset of hepatic encephalopathy >7 days, INR >3.5, aetiology unrelated to hepatitis A/B or any drug-induced liver failure (13). The model for end-stage liver disease (MELD) was applied, as previously defined (14).

Outcomes

Our primary outcome was 21-day transplant free (spontaneous) survival (SS). Secondary outcomes included listing for and/or receipt of liver transplantation (LT). Covariates included demographics (age, gender), biochemical profile and requirement for organ support and therapies to mitigate intracranial hypertension. Data were presented comparing A-ALF (n = 13) vs. A-ALI (n = 5) patients, as well as spontaneous survivors (SS, n = 10) vs. those who died or required LT (non-spontaneous survivors, NSS, n = 8). Spontaneous survival was defined as survival at 21 days after enrolment without LT. Patients were listed for LT according to the UNOS standard (status 1; see http://optn.transplant.hrsa.gov/contentdocuments/optn_policies.pdf), provided there were no contraindications. Decisions for listing were made on a site by site basis as there was no standardized protocol through the ALFSG. For those listed for LT, the decision to proceed with LT was made locally by the surgeon and hepatologist based on the patient's clinical status. King's College Criteria (non-acetaminophen) and other clinical variables (e.g. lactate) were also used as to guide decision-making.

Data sources and collection

Data were collected prospectively as part of the US ALFSG. As a part of this registry, data were routinely collected on a daily basis for the first week after patient enrolment. Data assessed in this study included demographics (age, race, sex), biochemistry, requirement for organ support [mechanical ventilation (MV), vasopressors, continuous renal replacement therapy (CRRT)] during the first 7 days and selected clinical outcomes (LT, 21-day survival). Data were also collected on the use of amatoxin-directed therapies [*N*-acetylcysteine (NAC), silibinin, charcoal, benzyl penicillin, nasobiliary drainage, haemoperfusion, molecular adsorbent recirculating system (MARS)]. NAC was given as per institutional protocols for ALF; typically 140 mg/kg IV initial dose, then 70 mg/kg for 17 h then continued at the same concentration at the discretion of the clinician. The average duration of NAC treatment was 4 days. When given, activated charcoal was administered as 50 mg every 4 h for a total of four doses. Silibinin was administered to patients with a 5 mg/kg loading dose followed by 20 mg/kg/day via continuous infusion until recovery, death or transplant. Benzyl penicillin/penicillin G was given at doses of 300 000–1 000 000 IU/kg for up to 72 h.

Statistical analysis

Statistical analysis was performed using SPSS (Version 22.0; IBM Corp, Armonk, NY, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). For differences between groups (ALF, n = 13; ALI, n = 5; spontaneous survivors n = 10; non-spontaneous survivors n = 8), categorical variables were compared using the Fisher's exact test. For continuous variables, the Student's t-test or Wilcoxon rank–sum test were used for comparisons, where appropriate. Missing data were handled by allowing the sample size to float; missing data were uncommon. A P-value of <0.05 was considered statistically significant for all comparisons.

Systematic review

We performed a comprehensive search of MEDLINE (January 1985–May 2015) to identify all published observational studies reporting on A-ALI and A-ALF. This is presented in detail in File S2.

Results

Descriptive information

Eighteen patients presented with A-ALI/A-ALF between January 1998 and December 2014, representing 0.8% of the 2224 patients enrolled in the US ALFSG registry. Nine patients were White (50%), eight were Asian (44%) and one was a Pacific Islander (6%). Ingestions occurred throughout North America; eight were in California, three in Pennsylvania, two in Connecticut, and one each in Oregon, Illinois, Washington, Virginia and Alberta (Canada). There were 12 males (67%) and six females (33%).

Time of ingestion of mushrooms was available for 10 patients. Overall mean time from ingestion to admission to study was mean 4 days. Comparing the six spontaneous survivors against the four non-spontaneous survivors (three transplant, one death) where data on ingestion time were available, the time from ingestion to admission did not differ significantly between spontaneous survivors and those who died/required LT (3.5 vs. 4.5 days respectively; P = 0.4).

Acute liver failure vs. acute liver injury

Patient characteristics of the 13 individuals with A-ALF and five with A-ALI are summarized in Table 1. There were no statistically significant differences between A-ALF and A-ALI patients with respect to age (median 51 vs. 44 years; P = 0.7) or gender (39 vs. 20% female; P = 0.6). Individuals with A-ALF tended to have higher serum lactate levels on admission (5.2 vs. 2.2 mM respectively; P = 0.06), but other variables including INR (2.8 vs. 2.2), bilirubin (87 vs. 26 μM) and MELD scores (28 vs. 24) were not significantly different ($P > 0.2$ for all). A-ALF patients were more likely to require MV during the initial 7 days (77% vs. 0 respectively; P = 0.006) with a non-significant trend towards increased requirements for renal replacement therapy (54% vs. 0% respectively; P = 0.10). A-ALF patients were also more likely to receive fresh frozen plasma dur-

Table 1. Demographical, clinical and biochemical parameters in patients with mushroom intoxication ($N = 18$)

		Acute liver failure ($N = 13$)		Acute liver injury ($N = 5$)	
	N	Number (%) or median (IQR)	*N*	Number (%) or median (IQR)	*P*-value
Age	13	51.0 (38.0–57.0)	5	44.0 (44.0–52.0)	0.73
Sex (female)	13	5 (38.5%)	5	1 (20.0%)	0.62
Admission biochemistry					
Haemoglobin (g/dl)	13	11.9 (9.5–13.9)	5	13.0 (13.0–15.0)	0.24
White blood count ($\times 10^9$/L)	13	7.8 (4.4–11.6)	5	8.5 (8.4–9.1)	0.69
Platelet count ($\times 10^9$/L)	13	98.0 (54.0–174.0)	5	149.0 (137.0–155.0)	0.28
INR	13	2.8 (2.2–3.2)	5	2.1 (2.0–10.7)	1.0
ALT (IU/L)	13	2633.0 (1105.0–5260.0)	5	4830.0 (2728.0–5728.5)	0.32
Bilirubin (μM)	13	87 (49–201)	5	26 (12–77)	0.2
Ammonia (venous; μM)	7	61.0 (32.0–90.0)	2	32.5 (19.0–46.0)	0.30
Creatinine (mg/dL)	13	1.3 (0.9–3.0)	5	0.7 (0.6–1.0)	0.11
Lactate (mM)	9	5.2 (3.5–6.5)	3	2.2 (1.8–2.2)	0.06
Phosphate (mg/dL)	13	3.1 (2.7–4.3)	5	2.3 (2.2–2.5)	0.17
MELD (admission)	13	27.7 (21.5–34.8)	5	23.9 (22.1–35.6)	0.76
Maximum coma grade III or IV (inpatient)	13	8 (61.6%)	0		
Amatoxin therapies					
NAC	13	11 (84.6%)	5	5 (100.0%)	1.0
Silibinin	13	3 (23.1%)	5	4 (80.0%)	0.04
Charcoal	13	3 (23.1%)	5	3 (60.0%)	0.27
Penicillin	13	5 (38.5%)	5	1 (20.0%)	
Nasobiliary drainage	13	1 (7.7%)	5	0 (0.0%)	1.0
Organ support (inpatient)					
Mechanical ventilation	13	10 (76.9%)	5	0 (0.0%)	0.006
Vasopressors	13	5 (38.5%)	5	0 (0.0%)	0.25
Renal replacement therapy	13	7 (53.9%)	5	0 (0.0%)	0.10
Blood products (inpatient)					
Fresh frozen plasma	13	10 (76.9%)	5	1 (20.0%)	0.047
Platelets	13	4 (30.8%)	5	0 (0.0%)	0.28
Packed red blood cells	13	4 (30.8%)	5	1 (20.0%)	1.0
Complications (inpatient)					
Arrhythmia	13	3 (23.1%)	5	1 (20.0%)	1.0
GI bleeding	13	3 (23.1%)	5	0 (0.0%)	0.52
Abnormal brain CT or MRI	7	3 (42.9%)	0		
Tracheal infection	13	2 (15.4%)	5	0 (0.0%)	1.0
Outcomes at 21 Days					
Death	13	2 (15.4%)	5	0 (0.0%)	1.0
Waitlisted for transplant	13	6 (46.2%)	5	1 (20.0%)	0.59
Transplanted	13	5 (38.5%)	5	1 (20.0%)	0.61
Spontaneous survival	13	6 (46.2%)	5	4 (80%)	0.31

ALT, Alanine Aminotransferase; IQR, Interquartile range; INR, International normalized ratio; KCC, King's College non-acetaminophen criteria; MELD, Model for end-stage liver disease.

ing the first 7 days of observation (77% vs. 20% respectively; $P = 0.047$). Eight of the 13 A-ALF patients (61.6%) had a West Haven hepatic coma grade of III or greater.

When examining amatoxin therapies in patients with A-ALF, 85% ($n = 11$) received NAC, 23% (3) silibinin, 23% (3) charcoal, 39% (5) penicillin and one patient (8%) underwent nasobiliary drainage. Among those with A-ALI, everyone ($n = 5$) received NAC, 80% (4) received silibinin, 60% received charcoal and one patient (20%) received penicillin.

Of the 13 A-ALF patients, six patients survived spontaneously (46%), whereas five required LT (39%) and two eventually died without LT (15%), of which one was listed for potential LT. Of the five A-ALI patients, four (80%) survived spontaneously and one (20%) received liver transplantation for severe refractory coagulopathy in the absence of encephalopathy.

Spontaneous survivors vs. death/transplant

Differences between non-spontaneous survivors (NSS) ($n = 8$) and spontaneous survivors (SS) ($n = 10$) are shown in Table 2. Among the eight NSS, two patients died, one at 13 days and the other at 14 days after ingestion; one death was from *Aspergillus* pneumonia, the other from multiorgan failure (while listed for LT). Six patients (ALF = 5, ALI = 1) successfully received LT. No SS were listed for LT. NSS were more often female

Table 2. Demographical, clinical and biochemical parameters in patients with mushroom intoxication by spontaneous survival status at 21-day post-registry enrolment ($N = 18$)

	N	Non-spontaneous survival ($N = 8$) Number (%) or median (IQR)	*N*	Spontaneous survival ($N = 10$) Number (%) or median (IQR)	*P*-value
Injury type (ALF)	8	7 (87.5%)	10	6 (60.0%)	0.31
Age	8	50.0 (38.0–56.0)	10	48.5 (44.0–55.0)	0.93
Sex (female)	8	5 (62.5%)	10	1 (10.0%)	0.043
Admission biochemistry					
Haemoglobin (g/dl)	8	11.8 (10.6–15.9)	10	13.0 (9.5–13.9)	0.96
White Blood count ($\times 10^9$/L)	8	7.6 (4.1–10.0)	10	8.8 (7.8–11.6)	0.19
Platelet count ($\times 10^9$/L)	8	127.5 (54.0–169.0)	10	117.5 (66.0–174.0)	0.89
INR	8	3.0 (2.3–4.2)	10	2.2 (1.8–3.0)	0.37
ALT (IU/L)	8	3314 (1746–6041)	10	2928 (1105–5260)	0.82
Bilirubin (μM)	8	82 (51–95)	10	44 (12–243)	0.69
Ammonia (venous; μM)	6	47.5 (32.0–69.0)	3	46.0 (19.0–90.0)	0.89
Creatinine (μM)	8	80 (71–194)	10	133 (53–168)	0.89
Lactate (mM)	5	5.0 (3.5–5.2)	7	2.6 (1.8–6.5)	0.57
Phosphate (mg/dL)	8	3.1 (2.8–6.6)	10	2.6 (2.2–3.5)	0.10
MELD (admission)	8	26.7 (19.7–38.2)	10	27.3 (22.1–34.8)	0.96
Maximum coma grade III/IV (inpatient)	8	5 (62.5%)	10	3 (30.0%)	0.16
Met KCC (inpatient)	8	2 (25%)	10	2 (20.0%)	1.0
Amatoxin therapies					
NAC	8	7 (87.5%)	10	8 (80.0%)	1.0
Silibinin	8	2 (25.0%)	10	5 (50.0%)	0.37
Charcoal	8	1 (12.5%)	10	5 (50.0%)	0.15
Penicillin	8	4 (50.0%)	10	2 (20.0%)	0.32
Nasobilliary drainage	8	0 (0.0%)	10	1 (10.0%)	1.0
Organ support (inpatient)					
Mechanical ventilation	8	5 (62.5%)	10	5 (50.0%)	0.66
Vasopressors	8	3 (37.5%)	10	2 (20.0%)	0.61
Renal replacement therapy	8	5 (62.5%)	10	2 (20.0%)	0.14
Blood products (inpatient)					
Fresh frozen plasma	8	8 (100.0%)	10	3 (30.0%)	0.004
Platelets	8	3 (37.5%)	10	1 (10.0%)	0.27
RBC	8	4 (50.0%)	10	1 (10.0%)	0.12
Complications (inpatient)					
Arrhythmia	8	3 (37.5%)	10	1 (10.0%)	0.27
GI bleeding	8	3 (37.5%)	10	0 (0.0%)	0.068
Abnormal brain CT or MRI	4	2 (50.0%)	3	1 (33.3%)	1.0
Tracheal infection	8	2 (25.0%)	10	0 (0.0%)	0.18
Outcomes at 21 Days					
Waitlisted for transplant	8	7 (87.5%)	10	0 (0.0%)	0.0003
Transplanted	8	6 (75.0%)	10	0 (0.0%)	0.0015

ALF, Acute liver failure; ALT, Alanine Aminotransferase; IQR, Interquartile range; INR, International normalized ratio; KCC, King's College non-acetaminophen criteria; MELD, Model for end-stage liver disease.

(63% vs. 10%; $P = 0.043$). There were no statistically significant differences in admission biochemistry between NSS and SS except for a non-significant trend towards higher serum phosphate levels in NSS (3.1 vs. 2.6 mg/dl; $P = 0.10$).

Thirty percent ($n = 3$) of SS patients had a West Haven hepatic coma grade III or higher as compared to 63% ($n = 5$) of NSS patients ($P = 0.16$). There were no significant differences in requirements for MV, vasopressors, nor renal replacement therapy between NSS and SS during the 7 days of theis study ($P > 0.14$ for all).

Among the eight NSS, seven (88%) received NAC, two (25%) received silibinin, one (12.5%) received charcoal and four (50%) penicillin. By contrast, of the 10 individuals with SS, eight (80%) received NAC, five (50%) silibinin, two (20%) penicillin one (10%) nasobiliary drainage ($P > 0.15$ for all therapies).

When examining complications, none of the 18 patients developed bloodstream infections and only two developed positive tracheal aspirates. Gastrointestinal bleeding occurred more commonamong those with NSS (38% vs. 0%, $P = 0.07$ trend).

Systematic review

We identified 24 studies with A-ALI and A-ALF from our comprehensive search of the literature, as presented

in File S2. Mortality rates in A-ALF varied greatly, ranging from 0 to 100% (9, 15). Meta-analysis was not possible because of the rare event rate (i.e., frequently reported to be <1%).

Discussion

Summary of key results

In our study of 18 patients with amatoxin poisoning from the US ALFSG registry, we found that the overall survival in A-ALF was 85% with spontaneous survival 46%. As expected, A-ALI patients demonstrated excellent overall (100%) and spontaneous (80%) survival rates, considerably better than the A-ALF subjects. Laboratory values on admission were not significantly different between spontaneous survivors and patients who died or required LT. Liver transplantation was safely performed in 33% (six patients) among those with A-ALF. None of the amatoxin-directed therapies were observed to be associated with improved spontaneous survival; however, we were limited by sample size.

Comparisons with previous studies

Many previous studies included a much broader cohort of patients with amatoxin poisoning (e.g., even those with just gastrointestinal symptoms without ALI/ALF) (9, 16–19). Other studies have been limited by lack of important clinical data. For example, Ganzert *et al.* (3) examined the prognostic significance of various biochemical markers (i.e., prothrombin time and serum creatinine) among individuals with amatoxin poisoning, but they did not have data on how many patients developed ALI or ALF, nor did they describe the severity of hepatic encephalopathy. In contrast, we were able to identify our cohort using definitions established *a priori* for ALF (i.e., INR >1.5 with hepatic encephalopathy) and ALI (INR >2.0 without encephalopathy) (11, 13).

Other smaller case series have included only patients with A-ALF, but were limited by selection bias (20–23). For instance, Kantola (22), Faybik (20), and Sorodoc (23) primarily examined the use of MARS in A-ALF, and reported overall mortality rates of 0%, 50% and 88%, respectively. Similarly, Yardan *et al.* reported a case series of eight patients treated with Prometheus where only one patient died. The significant heterogeneity in published reports limited our ability to pool data together for meta-analysis. Nonetheless, these broad differences between studies serve to highlight the uncertainty of the short- and long-term prognosis associated with A-ALI and A-ALF to date.

Of note, however, a recent study by Escude *et al.* (10) was conducted using a well-defined cohort of seven patients with A-ALF and 15 with A-ALI. They employed similar definitions as our present study for A-ALI (i.e., INR >1.7) and A-ALF (i.e., INR >1.7 with hepatic encephalopathy), and further included criteria for LT (i.e., Clichy criteria). One of 15 patients with ALI died (7%), and five of the seven patients with ALF died (two with LT, and three without LT). There were no spontaneous survivors among those who developed ALF. In contrast, we observed a significantly better spontaneous survival rate among those with A-ALF (46%), even in the presence of coagulopathy, encephalopathy and multiorgan failure. These differences may be in part as a result of improved survival because of recent advances in critical care management, one example being the increased use of continuous renal replacement therapy (24, 25).

The decision of whether to proceed with liver transplantation in a patient with A-ALF continues to be challenging. Transplant rates have been extremely variable e.g., 0 (23) to 100%) (26). Traditionally, the decision to proceed with transplantation has been primarily based on the King's College Criteria (13) or the Clichy criteria (27). Some have broadly recommended transplantation in any individual with ALF, coagulopathy and encephalopathy (28). Others have more specifically recommended assessment for transplantation in patients with amatoxin-ALF with grade II hepatic encephalopathy (29). Still others have advocated for liver transplantation in patients with an INR >4.0 even in the absence of encephalopathy (10). Clearly, the optimal strategy in the management of A-ALF is not yet well defined. In our analysis, we found that post-LT outcomes were very favourable (i.e., all six patients receiving LT survived to the end of the 21-day follow-up). But, we were also able to identify some patients with multiorgan failure and hepatic encephalopathy that survived without LT, thus suggesting that spontaneous recovery is often possible.

Therapeutic options in amatoxin-induced ALI/ALF

A number of different detoxification procedures were tried, and they included strategies to reduce absorption (e.g., oral activated charcoal, nasobiliary drainage), as well as methods to enhance amatoxin removal (e.g., extracorporeal purification, MARS or Prometheus) (8). We did not observe any significant differences in outcome with any of the various therapies. Given the small size of our study, however, we were not adequately powered to detect small differences from these therapies.

Study limitations and strengths

This study has several limitations. First, while patients were enrolled using strict criteria and data were collected prospectively, our study was strictly observational. However, given the rarity of this condition, an experimental study would be practically infeasible. Therefore, an observational study using registry data like ours provides useful information regarding the natural history amatoxin-ALI and ALF. Second, given our small sample size, we were unable to statistically adjust for potential confounding factors. We acknowledge that

widely accepted listing criteria for amatoxin-ALF are lacking and the decision to transplant was impacted by human decisions and organ availability. Despite these limitations, our study still represents the largest North American case series of A-ALF/A-ALI (n = 13/5) ever reported. Therefore, we believe that this study provides better estimates of the true rates of transplant-free (46%) and overall (85%) survival for individuals with A-ALF than previous reports. Furthermore, within the limits of our data, amatoxin-ALI without HE appears to have a higher probability of survival than amatoxin-ALF. The presence of multiorgan failure does not necessarily imply a poor prognosis while robust liver transplant criteria are still lacking. The clinical efficacy of medical interventions (i.e., penicillin, silibinin, charcoal or NAC) remains unclear.

Conclusions

Our large series of subjects with amatoxin poisoning demonstrated that those with A-ALI have favourable survival, even in the presence of coagulopathy. While some patients with A-ALF may require LT, nearly half appear to recover even without LT. Further study is needed to define optimal management (including the use of amatoxin-targeted therapies) to improve survival, even in the absence of LT.

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Supporting information

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