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The Natural History of Severe Acute Liver Injury

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CONFLICT OF INTEREST

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Abstract

OBJECTIVES—Acute liver failure (ALF) is classically defined by coagulopathy and hepatic encephalopathy (HE); however, acute liver injury (ALI), i.e., severe acute hepatocyte necrosis without HE, has not been carefully defined nor studied. Our aim is to describe the clinical course of specifically defined ALI, including the risk and clinical predictors of poor outcomes, namely progression to ALF, the need for liver transplantation (LT) and death.

METHODS—386 subjects prospectively enrolled in the Acute Liver Failure Study Group registry between 1 September 2008 through 25 October 2013, met criteria for ALI: International Normalized Ratio (INR)≥2.0 and alanine aminotransferase (ALT)≥10× elevated (irrespective of bilirubin level) for acetaminophen (*N*-acetyl-p-aminophenol, APAP) ALI, or INR≥2.0, ALT≥10× elevated, and bilirubin≥3.0 mg/dl for non-APAP ALI, both groups without any discernible HE. Subjects who progressed to poor outcomes (ALF, death, LT) were compared, by univariate analysis, with those who recovered. A model to predict poor outcome was developed using the random forest (RF) procedure.

RESULTS—Progression to a poor outcome occurred in 90/386 (23%), primarily in non-APAP (71/179, 40%) vs. only 14/194 (7.2%) in APAP patients comprising 52% of all cases (13 cases did not have an etiology assigned; 5 of whom had a poor outcome). Of 82 variables entered into the RF procedure: etiology, bilirubin, INR, APAP level and duration of jaundice were the most predictive of progression to ALF, LT, or death.

CONCLUSIONS—A majority of ALI cases are due to APAP, 93% of whom will improve rapidly and fully recover, while non-APAP patients have a far greater risk of poor outcome and should be targeted for early referral to a liver transplant center.

INTRODUCTION

Patients who develop severe acute liver injury (ALI) without preexisting chronic liver disease, oft en demonstrate significant liver dysfunction marked by coagulopathy (defined as an International normalized ratio (INR)≥1.5), and are classically designated as acute liver failure (ALF) when any degree of hepatic encephalopathy (HE) is present (1–3). However, little is known about the earlier stages of ALI where there may be significant coagulopathy, but no discernible HE (4). We explored this apparently milder stage of liver injury, its causes and the relative risk of poor outcomes, namely, progressing to ALF, receiving a liver transplant (LT) or dying within 3 weeks from admission to the study. To describe the clinical features and natural history of ALI, and to identify patients most at risk for poor outcomes, we proposed a new strictly defined category of ALI, specifically to capture additional information about subjects with severe liver injury without HE. Beginning in 2008, we adopted the same multicenter registry design, study sites and forms for enrolling patients with ALF by our Acute Liver Failure Study Group (ALFSG) to prospectively collect data from ALI patients in parallel to the data already being collected from classic ALF patients. The current report describes this newly defined ALI cohort. Using these data, we applied random forest (RF), to identify those with ALI at risk of progression to ALF and other poor outcomes.

METHODS

Study population

We prospectively studied 386 consecutive subjects who were considered to have ALI and who were enrolled into the NIH-funded ALFSG registry from 1 September 2008 through 25 October 2013. After an ALFSG workshop to define ALI in the ALFSG registry, criteria were agreed upon and enrollment of subjects with ALI began in September 2008, from up to 23 academic centers in the United States. ALI was defined as follows: absence of HE and, either:

Acetaminophen (n-acetyl-p-aminophenol, APAP) ALI:

INR≥2.0 and ALT≥10×upper limit of normal

Or

Non-acetaminophen (non-APAP) ALI:

INR≥2.0, ALT≥10×upper limit of normal, and bilirubin≥3.0 mg/dl

According to the study protocol, patients were eligible if the peak INR was>2.0 within 48 h of enrollment. Only patients without pre-existing chronic liver disease were eligible for enrollment. Etiology was determined by each study center's principal investigator, based on historical, clinical, laboratory, and radiographic data, as well as liver histopathologic results, when available. Diagnoses of etiology (APAP/non-APAP) were established using standard

criteria: for APAP, a history of any acetaminophen ingestion and/or parent compound (acetaminophen blood level) positive, plus alanine aminotransferase “ALT”, or aspartate aminotransferase (AST) levels≥1,000 IU/l with bilirubin<10 mg/dl; for non-APAP, patients in whom acetaminophen toxicity could be reasonably excluded. If an extensive search for the cause of ALI was inconclusive, the etiology was recorded as Indeterminate. HE, defined as the presence of disorientation or asterixis, was assessed by the study site principal investigator at the time of enrollment and on each subsequent day that the subject was enrolled in the registry. If present, HE severity was classified according to the West-Haven criteria (5).

Data management and integrity

Written informed consent was obtained from the enrolled subjects, as they were not encephalopathic. Patient demographics, medical history, clinical features, and laboratory values were collected prospectively at study enrollment, and clinical status and laboratory results were also recorded serially for up to 7 days, or until discharge, death, or transplant if prior to 7 days. All data are managed and housed on a central server by the ALFSG Statistical and Data Management Center at the Medical University of South Carolina. Each center’s Institutional Review Board approved the study.

Statistical Analyses

Data from the 386 subjects on the day of enrollment into the study were used for the analyses and included the following: subject demographics (age, gender, and race), calendar year of enrollment and center where enrollment occurred, dates of first symptom, and onset of jaundice and encephalopathy, etiology of the acute illness, use of *N*-acetylcysteine (NAC), blood product transfusion, measures of systemic distress (blood pressure, heart rate, temperature, pH, serum lactate levels, and need for vasopressor support, mechanical ventilation, or renal replacement therapy), and laboratory data, including measures of liver injury and dysfunction (serum bilirubin, aminotransferases, albumin, and INR). Descriptive statistics were performed and results expressed as medians (and interquartile ranges) and *n* (%) for continuous and categorical variables, respectively. Wilcoxon rank sum and χ^2 tests were used as appropriate, and subjects with missing data were not included in the univariate analyses of the variables for which data were missing. Our primary outcome was the composite occurrence within 21 days of enrollment of either progression to ALF, receiving a LT, or dying. In some instances, ALI alone led to liver transplantation or death without an apparent phase of ALF. Associations with a $P<0.05$ were considered statistically significant. Univariate analyses were performed using SAS (v 9.1.03 Cary, NC).

A model to predict poor outcome, i.e., ALF, LT, or death, was developed using the RF procedure first developed by Breiman in 2001 (6). The resulting model was then applied to the validation dataset of 163 subjects enrolled from November 2013 to September 2015. RF is a statistical method that iteratively develops decision trees, or models, using binary splits on predictor variables, thus providing a mechanism for estimating the probability that each individual ALI patient will have a poor outcome. In addition, the RF procedure provides information about which input variables are most important for the prediction of poor outcome, referred to as importance measures(7). The procedure is an alternative approach to

more common prediction models such as logistic regression and can be used to overcome the statistical obstacles of correlated predictors, non-normality of predictor variables and missing data(6,8,9). The method has been used previously to determine etiology in the ALF population using the ALFSG registry(9). RF modeling was performed using R soft ware version 2.15.1(8). See the Supplementary Material online for a detailed description of the RF procedure.

RESULTS

Patient demographics

All 386 subjects with defined ALI enrolled in the ALFSG registry during the initial study period were included in the analysis. Of these 386 subjects, several had an INR<2.0 at the time of enrollment into the study. However, they were eligible for entry into the registry since their peak INR was>2.0 within 48 h of enrollment. The majority were women (61%) and Caucasian (72%) with a median age of 38.0 (interquartile range 28.0–49.0) years (Table 1). APAP toxicity was the most common cause of ALI, accounting for 194 (50%) cases, followed by 46 (12%) due to autoimmune hepatitis, and 42 (11%) considered as Indeterminate cases. There were 13 subjects who had not received an etiologic diagnosis at the time of the data analysis. On average, subjects had marked elevations of aminotransferase levels, with median AST 2,270 U/l (929–5,219 U/l) and ALT 2,784 U/l (942–5,713 U/l). Serum bilirubin (5.1 mg/dl, 2.6–15.6 mg/dl) and INR (2.4, 2.1–3.4) were moderately elevated as was venous ammonia (65.5 μmol/dl, 41.0–94.0 μmol/dl). Subjects developed symptoms on average 5 days prior (2.0–14.0 days) and the onset of jaundice on average 4 days prior (1.0–10.0 days), to enrolling in the study. The most common symptoms reported include nausea and vomiting (290/383, 76%), abdominal pain (272/383, 71%), joint pain (55/383, 14%), and peripheral edema (37/367, 10%). Kidney injury requiring renal replacement therapy was rare, occurring in only 8 subjects (2%). Overall, 68% of the subjects were treated with NAC at some time during hospitalization. The majority (90%) of APAP cases received NAC compared to 30% of the non-APAP cases. Forty-three subjects (11%) were transfused blood products, particularly fresh frozen plasma (FFP) that accounted for 88% of the transfusions.

Comparing APAP to the other ALI etiologies, there was no gender difference, but APAP ALI subjects were younger, 34.5 years (27 years—46 years) vs. 44 years (33 years—55 years, $P<0.001$) and more frequently Caucasian than the non-APAP subjects (79 vs. 64%, $P<0.001$, Table 2). Aminotransferase levels were nearly 4-fold higher in APAP compared to non-APAP ALI subjects, but both bilirubin (3.2 mg/dl, 1.9–4.6 mg/dl vs. 15.7 mg/dl, 8.1–23.4 mg/dl, $P<0.001$) and phosphate (2.2 mmol/l, 1.6–3.0 mmol/l vs. 3.3 mmol/l, 2.7–4.2 mmol/l, $P<0.001$) were lower. Subjects with APAP toxicity also had a shorter duration of symptoms (3 days, 2.0–4.0 days vs. 11 days, 6.0–24.0 days, $P<0.001$) and jaundice (1 day, 1.0–2.0 days vs. 8 days, 3.0–16.0 days, $P<0.001$) prior to enrollment.

Outcomes

During the study period, 90/386 (23%) subjects developed one or more of the three primary outcomes, not all of which involved ALF (Table 3). Of these, 72/386 (19%) subjects

progressed to ALF, 19/386 (5%) subjects died and 44/386 (11%) underwent LT. Non-Caucasians had a greater risk of poor outcome than whites (31 vs. 20%, P=0.026) as did older subjects, but there was no difference between men and women (Table 3). Those with disease progression also had a more protracted clinical course with a longer duration of symptoms (11 days vs. 4 days, P<0.001) and jaundice (8 days vs. 3 days, P<0.001) before admission to the study. Those who were destined for a poor outcome were significantly more likely to have non-APAP liver injury (40% non-APAP vs. 7.2% APAP, P<0.001). The worse outcomes for non-APAP ALI was primarily due to their greater risk of developing ALF (56/179, 31% non-APAP cases developed ALF compared to 11/194, 6% of APAP cases, P<0.001). Accordingly, bilirubin (17.5 mg/dl vs. 4.0 mg/dl, P<0.001), INR (2.8 vs. 2.3, P<0.001), and lactate (3.0 mmol/l, vs. 2.0 mmol/l, P<0.001) levels were higher in subjects with poor outcomes, but aminotransferase levels were lower (ALT: 1,165.0 U/l vs. 3,330.0 U/l, P<0.001; and AST: 1,450.0 U/l vs. 2,642.0 U/l, P<0.001). Subjects who progressed to ALF, death or LT were also more likely to be transfused blood products than those in whom ALI resolved (27 vs. 8%, respectively, P<0.001). Finally, 261 (68%) of subjects were treated with NAC during the study period; the majority (81%) were APAP cases. Overall, fewer patients treated with NAC progressed to ALF, died or underwent LT compared to subjects who did not receive NAC (19 vs. 32%, P=0.005); however, this was primarily driven by the large number of APAP cases nearly all of whom were given NAC, and their very low overall risk of doing poorly. For the non-APAP cases, there was no association between NAC use and outcome (Table 3).

Overall, 19/386 (5%) subjects died and 45/386 (12%) underwent LT. Of the subjects who died, 10/19 (53%) had progressed to ALF (Table 3) including one who underwent LT, dying postoperatively. Additionally, not all patients who died appeared to progress to ALF (Table 4). Although the small number of deaths precludes detailed analysis, it did not appear that a specific ALI etiology was over-represented among the deaths. The deaths recorded were as follows: APAP toxicity (4), indeterminate (4), autoimmune hepatitis (5), hepatitis B (3), ischemia (2), and DILI (1). The commonest causes of death mentioned were multisystem organ failure (4) and progressive liver failure (4). The number of patients (by etiology) who underwent liver transplantation included APAP toxicity (3), autoimmune hepatitis (15), DILI (2), hepatitis A (2), hepatitis B (3), mushroom intoxication (2), Wilson disease (2), and indeterminate (13). Two transplant patients had missing etiologies.

Modeling the risk of having a poor outcome

A RF model was created to determine the risk for the primary composite outcome to occur, namely progressing to ALF, having a LT, or dying within 21 days of enrolling into the study (see the Supplementary Material for a detailed description of the RF procedure). Eighty-two variables were considered based on results from the univariate analyses. For calculations used in model building, non-APAP cases were assigned an APAP blood level of zero. To simplify the model without compromising predictability, a variable selection procedure identified the most predictive variables for inclusion in the final model: etiology, admission values of bilirubin, INR, acetaminophen level, and duration of jaundice prior to enrollment. The most important variable for determining risk of poor outcome was etiology, followed in order by the reported duration from onset of jaundice to study admission, acetaminophen

level, bilirubin, and INR. The final model yielded an overall prediction accuracy of 81% and an area under the receiver operating curve of 0.84, indicating overall good model performance. Correct predictions were made for 83% (245/296) of ALI patients who had resolution of their underlying liver injury and for 76% (68/90) of the ALI patients who did progress to ALF, received LT, or died.

The RF model was applied to the validation cohort of 163 ALI subjects. There were no clinical differences between the training and validation datasets (Supplementary Table 1). Overall accuracy for the validation dataset was 75%, with accurate predictions for 67% (95/141) of ALI patients who did not progress to ALF, death or LT and 88% (28/32) of ALI patients who did progress to ALF, death or LT. Thus, the model generally made conservative predictions.

Partial dependence plots allowed for analysis of the relationship between outcome and variables included in the RF model (data not shown). Etiologies more associated with a higher chance of poor outcomes than other causes were pregnancy-associated liver injury, autoimmune hepatitis, infection with hepatitis A or B, mushroom intoxication, Wilson disease, Indeterminate diagnoses, and other viruses. Aside from etiology, thresholds that were derived from the remaining variables and that identified the at risk subjects included jaundice for greater than 3 days, bilirubin level greater than 3 mg/dl, APAP level greater than 60 mg/l or INR greater than 1.7.

DISCUSSION

The original definition of ALF, sometimes termed fulminant hepatic failure, derived from a review article in 1970 by Trey and Davidson (1), included the presence of HE and coagulopathy in patients without pre-existing liver disease. While HE is a useful clinical marker (10), it is also a subjective one. Our knowledge of severe liver injury has been derived primarily from patients with HE, whereas, to-date, there have only been a few studies of the outcome of severe liver injury that falls short of ALF (11–18). The current study satisfies that unmet need. Therefore, in an effort to further understand and expand the repertoire of patients with severe hepatocyte necrosis and its sequelae, we developed criteria for ALI without HE to include patients with advanced disease by using a higher INR threshold (>2.0), eliminating to some extent those who might have a milder, non-progressive condition. We intended to provide some unique insights into the causes and natural progression of a cohort of ALI patients in whom HE had not yet occurred, to better determine what might trigger progression to ALF, need for LT, or death within 21 days of study enrollment. This analysis could aid clinicians' assessment and management of patients with severe liver injury who lack the crucial feature of HE.

As with ALF, the majority of ALI cases occurred in Caucasian women and was due to APAP toxicity. This contrasts with the 25% APAP prevalence reported recently from King's College Hospital (KCH) in London UK, in a more severe version of ALI than defined here, as the KCH cases included both HE and non-HE patients who required Intensive Care Unit admission(19). Among the ALI etiologies, APAP toxicity stands out as being considered 'hyperacute(20),' characterized by very short duration of symptoms (<3 days), marked

elevation of aminotransferases and only mildly abnormal bilirubin levels. Despite the severity of laboratory abnormalities, these cases appear self-limited, as recovery of ALI due to APAP toxicity is nearly universal—here only 7% progressed to ALF, died, or needed LT. Conversely, non-APAP ALI patients tend to have a longer duration of symptoms and jaundice with more marked elevation of bilirubin and worse overall outcomes. Accordingly, the probability of progressing to ALF is greater with autoimmune hepatitis, DILI, and indeterminate etiologies, accounting for 61% of the cases. Additionally, treating non-APAP ALI patients with NAC did not appear to reduce the risk of developing ALF in our population. Death was also not confined to those ALI patients who progressed to ALF since half of the patients who died did not appear to pass through that stage as shown in Table 3; many were listed as dying of multi-organ failure or central nervous system or other conditions that were specific and not necessarily associated with encephalopathy. However, it is possible that case report form data did not reflect the exact details of disease progression, and some of these cases may have actually developed ALF. Notwithstanding, transfer to a liver transplant center is important in all forms of ALI, but particularly so for non-APAP cases (of whom 40% had with poor outcomes, compared to only 7.2% of APAP subjects), to permit early evaluation for liver transplantation.

Using a novel, multivariable RF modeling system, we identified clinical variables associated with progression to ALF, need for LT, or death and created a tool to estimate this probability of disease progression to a poor outcome. We opted for this statistical analysis rather than the more conventional logistic regression modeling since RF is able to account for missing data and is not affected adversely by interactions in the data. The result was a model that provides an estimate for the probability of poor outcome with an accuracy of 81%. Several variables were examined: the most influential within the RF model were ALI etiology, duration of symptoms, and study admission blood levels of bilirubin, APAP (which is zero in non-APAP cases), and INR. Each of these should be readily available to clinicians, allowing for estimation of the risk in any hospital setting. Although the overall accuracy of the model in the validation set was lower than in the model creation set, the model actually performed better for those subjects with a poor outcome compared to those who recovered.

An added benefit of RF analysis is the ability to dichotomize the predictive variables into thresholds that predict the outcome, allowing for quick assessment at the bedside. These include jaundice for greater than 3 days, bilirubin greater than 3 mg/dl, acetaminophen level greater than 60 mg/l, and INR greater than 1.7 (See Supplementary Material).

Of interest is the potential risk that transfusion of blood products, particularly FFP, appeared to have for patients with ALI. Although having a transfusion was not determined to be a predictive variable for disease progression for any of the three outcomes outlined in the RF model, 42% of the subjects who received FFP had a poor outcome as compared to 58% of those who did not. The clinical justification for transfusion in each subject was not available. The association between FFP use and progression to ALF or other outcomes does not necessarily indicate that FFP is contributing to worse liver injury since it may be that the presence of worse liver disease prompted the clinician to use FFP. However, there is evidence that ALF is a hypercoagulable state and it is possible that administration of clotting factors enhanced intrahepatic thrombosis that contributed to impairment in liver function

(21,22). Further studies would be needed to determine if there is inherent risk with transfusion in these subjects, but prudence should be exercised with regard to transfusion, especially given the growing awareness that the standard hematologic and coagulation indices (such as the INR and platelet count) do not necessarily predict bleeding risk either in patients with acute (21,23–26) or chronic (23,27,28) liver diseases.

CONCLUSION

In this in-depth analysis of the natural history of ALI, according to the specific criteria we defined, the likelihood and risk factors for poor outcome directly or indirectly related to liver disease were determined. APAP toxicity (52%) was the most common cause of ALI, while non-APAP causes were observed to have a greater risk of poor outcome, particularly when compared to APAP-induced liver injury. Patients at risk of a poor prognosis were identified with 81% accuracy using a multivariable RF predictive model.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Patients with acute liver failure have coagulopathy and encephalopathy.
- ✓ Acute liver failure is associated with high mortality.

WHAT IS NEW HERE

- ✓ A detailed natural history study of patients with less severe acute liver injury prior to developing encephalopthy.
- ✓ Patients with acute liver injury at risk for a poor outcome can be identified using our prognostic score.
- ✓ Death in patients with acute liver injury can occur even without progression to acute liver failure.

Table 1

Clinical variables of enrolled subjects with acute liver injury

Admission variables	Overall population (*N*=386)
Age (years)	38.0 (28.0–49.0)
Gender	
Male	151 (39%)
Female	235 (61%)
Race	
Caucasian	276 (72%)
African American	70 (18%)
Other	40 (10%)
Etiology of ALI[a]	
APAP toxicity	194 (50%)
Autoimmune hepatitis	46 (12%)
Indeterminate	42 (11%)
Hepatitis A	25 (6%)
Drug-induced liver injury	23 (6%)
Ischemia	12 (3%)
Other	31 (8%)
Duration of symptoms (days)	5.0 (2.0–14.0)
Duration of jaundice (days)	4.0 (1.0–10.0)
Bilirubin (mg/dl)	5.1 (2.6–15.6)
Creatinine (mg/dl)	0.9 (0.6–1.4)
AST (U/l)	2,269.5 (929.0–5,219.0)
ALT (U/l)	2,784.0 (942.0–5,713.0)
Alkaline Phosphatase (IU/ml)	117.0 (87.0–161.5)
Albumin (mg/dl)	2.9 (2.5–3.2)
INR	2.4 (2.1–3.4)
Phosphate (mmol/l)	2.7 (1.9–3.6)
Venous ammonia (μmol/dl)	65.5 (41.0–94.0)

ALI, acute liver injury; ALT, alanine aminotransferase; APAP, *N*-acetyl-p-amino-phenol; AST, aspartate aminotransferase; INR, International normalized ratio.

[a]Etiology not recorded for 13 subjects.

Table 2

Clinical variables according to ALI etiology[a]

Admission variables	APAP ALI (*N*=194)	Non-APAP ALI (*N*=179)	*P* value[b]
Age (years)	34.5 (27–46)	44 (33–55)	<0.001
Gender			0.14
Male	69 (36%)	77 (43%)	
Female	125 (64%)	102 (57%)	
Race			<0.001
Caucasian	154 (79%)	114 (64%)	
African American	31 (16%)	38 (21%)	
Other	9 (5%)	27 (15%)	
Duration of symptoms (days)	3.0 (2.0–4.0)	11.0 (6.0–24.0)	<0.001
Duration of jaundice (days)	1.0 (1.0–2.0)	8.0 (3.0–16.0)	<0.001
Bilirubin (mg/dl)[c]	3.2 (1.9–4.6)	15.7 (8.1–23.4)	<0.001
Creatinine (mg/dl)	0.9 (0.7–1.7)	0.9 (0.6–1.3)	0.20
AST (U/l)	4,506.0 (2,110.0–8,048.0)	1,331.0 (561.0–2,293.0)	<0.001
ALT (U/l)	4,837.0 (2,489.0–7,880.0)	1,135.0 (653.0–2,813.0)	<0.001
Alkaline phosphatase (IU/ml)	98.0 (74.0–124.0)	143.0 (110.0–193.0)	<0.001
Albumin (mg/dl)	3.1 (2.7–3.3)	2.6 (2.2–2.9)	<0.001
INR	2.6 (2.1–4.0)	2.3 (2.2–2.9)	0.03
Phosphate (mmol/l)	2.2 (1.6–3.0)	3.3 (2.7–4.2)	<0.001
Venous ammonia (μmol/dl)	68.0 (42.0–96.0)	63.0 (41.0–83.0)	0.54
Primary outcome			<0.001
Progressed to ALF only	7 (4%)	16 (9%)	
Transplant only	0 (0%)	10 (6%)	
Death only	3 (2%)	7 (4%)	
More than one of the above	4 (2%)	40 (22%)	
Alive/no transplant/no progression to ALF	180 (93%)	106 (59%)	

ALI, acute liver injury; ALF, acute liver failure; ALT, alanine aminotransferase; APAP, *N*-acetyl-p-aminophenol; AST, aspartate aminotransferase; INR, International normalized ratio.

[a] Etiology not recorded for 13 subjects.

[b] Univariate Comparisons between APAP ALI and non-APAP ALI.

[c] The definition of APAP ALI included any bilirubin level, whereas for non-APAP ALI, bilirubin>3 mg/dl was the threshold for inclusion.

Table 3

Clinical measures and ALI outcome

	N	Liver recovered (*N*=296)	Poor outcome[a] (*N*=90)	*P* value
Age (years)	386	37.0 (28.0–48.0)	44.5 (32.0–56.0)	0.002
Gender	386			0.30
Male		120 (41%)	31 (34%)	
Female		176 (59%)	59 (66%)	
Race	386			0.062
Caucasian		220 (74%)	56 (62%)	
African American		50 (17%)	20 (22%)	
Other		26 (9%)	14 (16%)	
Etiology[†]	373			<0.001
APAP		180 (63%)	14 (16%)	
Non-APAP		108 (37%)	71 (84%)	
Duration of symptoms (days)	376	4.0 (2.0–9.0)	11.0 (5.0–21.0)	<0.001
Duration of jaundice (days)	230	3.0 (1.0–8.0)	8.0 (2.0–16.0)	<0.001
Bilirubin (mg/dl)	378	4.0 (2.2–9.5)	17.5 (8.2–24.4)	<0.001
AST (U/l)	382	2,642.0 (1,038.0–6,127.0)	1,450.0 (669.0–2,584.0)	<0.001
ALT (U/l)	382	3,330.0 (1,250.0–6,227.0)	1,165.0 (660.0–3,061.0)	<0.001
Alkaline Phosphatase (IU/ml)	380	112.0 (81.0–148.0)	139.0 (105.0–183.0)	<0.001
Albumin (mg/dl)	350	3.0 (2.6–3.3)	2.6 (2.3–2.9)	<0.001
INR	368	2.3 (2.0–3.1)	2.8 (2.2–4.4)	<0.001
Creatinine (mg/dl)	380	0.9 (0.6–1.4)	1.0 (0.7–1.3)	0.465
Phosphate (mmol/l)	310	2.5 (1.8–3.4)	3.1 (2.3–4.3)	<0.001
Venous ammonia (μmol/dl)	112	65.5 (41.0–88.)	65.0 (41.0–114.0)	0.591
Transfusion	386			<0.001
No		273 (92%)	66 (73%)	
Yes		23 (8%)	24 (27%)	
FFP transfusion	386	16 (5%)	22 (24%)	<0.001
NAC use				
Overall	386	211 (71%)	50 (56%)	0.005
Non-APAP ALI	179	42 (39%)	33 (46%)	0.314

ALF, acute liver failure; ALI, acute liver injury; ALT, alanine aminotransferase; APAP, *N*-acetyl-p-aminophenol; AST, aspartate aminotransferase; FFP, fresh frozen plasma; IQR, interquartile range; LT, liver transplantation.
Categorical data presented as *n* (%) and continuous data as median (IQR).

[†]Etiology not recorded for 13 subjects.

[a]Poor outcome includes ALF and/or LT and/or death.

Table 4

Characteristics of 19 ALI subjects who died within 21 days of enrollment

ALI etiology	Progression to ALF	Time from enrollment to death (days)	Cause of death
1. APAP	No	2	Cardiac arrest
2. Hepatitis B	Yes	3	Multisystem organ Failure/sepsis
3. Shock/ischemia	Yes	11	Unknown
4. Autoimmune hepatitis	Yes	16	Unknown
5. DILI	Yes	8	Multisystem organ failure
6. APAP	Yes	8	Neurological (cerebral edema)
7. Indeterminate	No	1	Unknown
8. Indeterminate	Yes	11	Neurological (cerebral edema)
9. APAP	No	8	Pulmonary embolism
10. Autoimmune hepatitis	Yes	7	Liver failure
11. Indeterminate	Yes	4	Multisystem organ failure/sepsis
12. Autoimmune hepatitis	No	13	Multisystem organ Failure
13. Autoimmune hepatitis	Yes	4	PEA arrest
14. Shock/ischemia	No	14	Multisystem organ failure
15. APAP	No	10	Liver failure
16. Hepatitis B	No	9	Liver failure
17. Indeterminate	No	18	Unknown
18. Hepatitis B	No	20	Liver failure
19. Autoimmune hepatitis[a]	Yes	17	Intracardiac thrombosis

ALI, acute liver injury; ALF, acute liver failure; APAP, *N*-acetyl-p-aminophenol; DILI, drug-induced liver injury; PEA, pulseless electrical activity.

[a]Patient died shortly after liver transplant.