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Risk Factors and Outcomes of Acute Kidney Injury in Patients With Acute Liver Failure

Shannan R. Tujios^{*}, Linda S. Hynan[‡], Miguel A. Vazquez[§], Anne M. Larson^{||}, Emmanuel Seremba[¶], Corron M. Sanders^{*}, William M. Lee^{*,#}, and Acute Liver Failure Study Group

^{*}Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas [‡]Division of Biostatistics, University of Texas Southwestern Medical Center, Dallas, Texas [§]Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, Texas ^{||}Swedish Liver Center, Seattle, Washington [¶]Makerere University, Kampala, Uganda [#]Division of Gastroenterology, Hepatology and Nutrition, The Wexner Medical Center, The Ohio State University, Columbus, Ohio

Abstract

BACKGROUND & AIMS—Patients with acute liver failure (ALF) frequently develop renal dysfunction, yet its overall incidence and outcomes have not been fully assessed. We investigated the incidence of acute kidney injury (AKI) among patients with ALF, using defined criteria to identify risk factors and to evaluate its effect on overall outcomes.

METHODS—We performed a retrospective review of data from 1604 patients enrolled in the Acute Liver Failure Study Group, from 1998 through 2010. Patients were classified by the Acute Kidney Injury Network criteria, as well as for etiology of liver failure (acetaminophen-based, ischemic, and all others).

RESULTS—Seventy percent of patients with ALF developed AKI, and 30% received renal replacement therapy (RRT). Patients with severe AKI had higher international normalized ratio values than those without renal dysfunction ($P < .001$), and a higher proportion had advanced-grade coma (coma grades 3 or 4; $P < .001$) or presented with hypotension requiring vasopressor therapy ($P < .001$). A greater proportion of patients with acetaminophen-induced ALF had severe kidney injury than of patients with other etiologies of ALF; 34% required RRT, compared with 25% of patients with ALF not associated with acetaminophen or ischemia ($P < .002$). Of the patients with ALF who were alive at 3 weeks after study entry, significantly fewer with AKI survived for 1 year. Although AKI reduced the overall survival time, more than 50% of patients with acetaminophen-associated or ischemic ALF survived without liver transplantation (even with

Address requests for reprints to: William M. Lee, MD, Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center at Dallas, 5959 Harry Hines Boulevard, Suite 420, Dallas, Texas 75390-8887. william.lee@utsouthwestern.edu; fax: (214) 645-6114.

Conflicts of interest

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RRT), compared with 19% of patients with ALF attribute to other causes ($P < .001$). Only 4% of patients requiring RRT became dependent on dialysis.

CONCLUSIONS—Based on a retrospective analysis of data from more than 1600 patients, AKI is common in patients with ALF and affects short- and long-term outcomes, but rarely results in chronic kidney disease. Acetaminophen-induced kidney injury is frequent, but patients have better outcomes than those with other forms of ALF.

Keywords

Nephrotoxicity; Rhabdomyolysis; Acute Liver Failure; Acute Kidney Injury

Acute liver failure (ALF) is a rare condition characterized by the abrupt onset of hepatic dysfunction, coagulopathy, and encephalopathy in the absence of pre-existing liver disease.¹ Approximately 2000 patients are affected each year in the United States.^{2,3} Acute kidney injury (AKI) is common in ALF. Early reports have suggested that 79% of patients with grades III/IV encephalopathy had evidence of renal dysfunction.⁴ A decline of renal function has been recognized as a poor prognostic factor, with serum creatinine (Cr) levels higher than 300 $\mu\text{mol/L}$ being one of the King's College Hospital criteria for transplant in relation to acetaminophen (APAP)-induced ALF.⁵ However, disparate definitions have been used to identify acute renal failure, making analysis difficult. To better characterize and define AKI, criteria corresponding to risk, injury, failure, loss, and end-stage renal disease (ie, RIFLE criteria) were created, validated, and later modified.⁶ Recently, it has become clear that even minor degrees of AKI can have a major impact on patient outcomes. In general intensive care units, up to 25% of patients develop AKI, with in-hospital mortality rates of 40% to 80%.⁷ Even those who survive the initial hospitalization have a 28-fold risk of developing long-term chronic kidney disease and increased mortality.⁸ Although renal function has been studied extensively in end-stage liver disease and is a recognized predictor of mortality, the occurrence and consequences of AKI in ALF are less well known.

A specific aim of this study was to determine the incidence and outcomes of AKI in ALF patients using standardized criteria, by examining the Acute Liver Failure Study Group registry of more than 1600 patients. We were interested in APAP-induced ALF because reports of acute renal failure have varied from 1% of overdoses to more than 20% in more severely poisoned patients.⁹ Case studies described APAP-induced renal failure independent of dosage and degree of hepatotoxicity, suggesting that APAP may have a direct nephrotoxic effect.^{10–14} We hypothesized that the incidence, characteristics, and outcomes of APAP and ischemic ALF would differ from other etiologies of ALF.

Methods

Subjects

From 1998 to 2010, there were 1604 patients enrolled at 23 US Acute Liver Failure Study Group sites using standard ALF criteria.² By definition, eligible patients had an international normalized ratio of 1.5 or higher, hepatic encephalopathy, and presented within 26 weeks of illness onset without a known history of liver disease. After informed consent was obtained from their legal next of kin, demographic, clinical, laboratory, and outcome information

were recorded prospectively. All centers were in compliance with their local institutional review board. Case report forms were reviewed by investigators at the central site, the sites responded to questions about missing values or discrepancies, and the data were double-entered into a database maintained at the University of Texas Southwestern Medical Center.

We examined the database for AKI as defined by the Acute Kidney Injury Network using the ratio of admission and maximum Cr level.⁶ Baseline renal function information was unavailable but we presumed normality because the study population was relatively young (mean age $\pm$ SD, 40.9 $\pm$ 14.5 y) and generally without comorbidities. AKI categories included no AKI (Cr $\leq$ 1.3 mg/dL at all times); intermediate (Cr > 1.3 mg/dL but improved or did not meet definition of AKI); stage 1 AKI (maximum Cr 1.5- to 2-fold higher than admission Cr), corresponding to risk; stage 2 AKI (maximum Cr 2- to 3-fold higher than admission Cr), representing injury; stage 3 AKI (maximum Cr 3-fold greater than admission Cr); and need for renal replacement therapy (RRT) at any time, representing failure. Placement of patients on RRT was at the discretion of the treating physician. In 31 patients (6.3%), RRT was used with a maximum Cr level of 1.3 or less, typically because of concern for fluid overload, presence of anuria, or severe hyperammonemia. Patients were grouped by etiology of ALF as well as degree of renal impairment. The frequency of AKI in APAP-related ALF was compared with the rates observed in patients with ischemia-related ALF and with ALF caused by all other etiologies. Ischemia is the cause of ALF in nearly 5% of patients and AKI is common in this setting with a mean Cr level of 2.9 mg/dL and 25% already receiving RRT at enrollment.¹⁵ Accordingly, we analyzed patients with ischemic hepatic injury separately.

Statistics

Demographics, clinical parameters, and outcomes were compared between etiologies and degree of renal impairment. Data are reported as medians, ranges, and percentages unless otherwise noted. The chi-square test or the Fisher exact test, as appropriate, was used to analyze categorical measures, and the Kruskal–Wallis test was used for continuous measures. Log-rank tests (Kaplan–Meier) examined 1-year transplant-free survival (hospital discharge or 21 days after study admission [whichever came first] to 1 year after discharge) for renal impairment groups for all etiologies combined and for APAP and non-APAP groups separately. All analyses were 2-tailed, with *P* values less than .05 indicating statistical significance.

Results

Study Cohort Characteristics

Of the 1604 patients, 738 had ALF caused by APAP, 84 had ALF caused by shock/ischemia (shock), and 783 had ALF secondary to nonischemic, non-APAP causes (other) (Table 1). APAP patients were, on average, younger, with a mean age of 37 vs 53 years for shock, and 42 years for the other group (*P* < .001). The APAP group also was predominantly female compared with the shock or other groups (75.5% vs 61% vs 63.5%, respectively; *P* < .001). The median alanine aminotransferase levels were higher in the APAP cases compared with the shock and other etiology cases (3846 vs 2300 vs 756 IU/L; *P* < .001). More APAP and

shock patients presented with grade IV encephalopathy (31.6% and 31.75% vs 21.5%; $P < .001$), and these groups tended to have a higher percentage of grade IV as the maximum coma grade (49.1% and 49.4% vs 43.9%; $P = .019$).

Acute Kidney Injury in Acute Liver Failure

Seventy percent of ALF patients showed some degree of kidney injury (Table 2). AKI appeared more frequently and with greater severity in APAP cases; 34% required RRT compared with 25% in the other 2 groups ($P < .0002$). The median maximum serum Cr level was higher for APAP-related ALF across all AKI categories compared with shock and other ALF causes combined (2.7 vs 2.1 mg/dL; $P < .001$). Older age and history of chronic kidney disease were associated with AKI in the other cases, but a previous history of renal disease was not a predictor of AKI in APAP cases (Tables 3 and 4). Among those with APAP-related ALF, the development of AKI was not associated with dose ingested, type of ingestion (unintentional vs suicidal cases), or the use of the antidote N-acetylcysteine (NAC). There was a higher prevalence of alcohol use in APAP-related AKI: 60% compared with 40% in those with no AKI ($P = .001$). In all cases of ALF, AKI was observed more frequently in the most critically ill patients as shown by coma grades of III/IV ($P < .001$) and requirement of vasopressors ($P < .001$). However, approximately 15% of APAP-related ALF patients requiring RRT had low coma grades and a low international normalized ratio, suggesting that the kidney injury was out of proportion to the degree of liver injury.

Acute Kidney Injury and Increased Creatine Kinase Levels

Renal injury in association with muscle injury would be expected in patients with certain presentations, such as shock or in relation to drugs associated with muscle injury. We evaluated whether muscle injury was observed in our patients, and whether it might contribute to kidney injury. Although creatine kinase (CK) values were not obtained routinely as standard of care, values available for 509 patients (32%) ranged from 1 to 152,856 IU/L, with a median of 330 IU/L. CK levels were available for 266 (36%) APAP cases, 57 (57.9%) shock cases, and 186 (23.8%) other cases. Increased CK levels were associated with poorer renal function, with those who required RRT having higher CK levels than those without AKI (median RRT, 528.5 IU/L vs no AKI 112.5 IU/L; $P < .001$). A total of 110 patients (59.1%) on renal replacement therapy had values greater than 400 IU/L, and 35 (18.8%) showed CK values greater than 5000 IU/L compared with 25 (27.8%) and 2 (2.2%) patients without renal injury ($P < .001$). Patients with shock-related ALF showed the highest median CK levels when compared with APAP and ALF cases resulting from other causes (622 IU/L vs 376.5 IU/L vs 176 IU/L; $P < .001$). Shock-related and APAP-related ALF cases had a higher percentage of CK values greater than 400 IU/L compared with the other etiologies (61.4% vs 48.1% vs 33.3%; $P < .001$). CK values greater than 5000 IU/L also were more frequent in the ischemic and APAP patients (15.8% vs 10.5% vs 6.5%), but this was not statistically significant ($P = .087$). By using logistic regression analysis, sex, APAP dose, suicidal intention, or alcohol use did not predict CK levels.

Acute Kidney Injury and Outcome

Patients who required RRT had poorer survival rates across all etiologies of ALF (Table 5). APAP and shock had the most favorable 3-week outcomes, with 66.9% and 66.7% surviving

without transplant, respectively, compared with a 28.9% spontaneous survival rate of non-APAP, nonshock cases ($P < .001$). After adjusting for etiology and coma grade, AKI remained a significant risk factor, decreasing the rate of spontaneous survival ($P < .001$). Across all etiologies, patients requiring RRT with high CK levels had a higher proportion of death ($P = .029$). In APAP-induced ALF, CK values greater than 400 were more common in those requiring transplant or dying compared with those spontaneously surviving (61.5% vs 58.1% vs 36.7%; $P = .009$). Despite the high frequency of severe AKI in APAP and shock cases, more than 50% of those on RRT spontaneously survived compared with 17% of those with other causes of ALF ($P < .0001$).

Long-Term Follow-up Evaluation

In 911 patients (81%) who survived for at least 3 weeks, 12- and/or 24-month long-term follow-up data were available for analysis. Patients with shock-related ALF were most likely to require RRT after discharge (13%) compared with APAP (9%) and other causes (10%). Of patients with severe AKI (stage 3 or need for RRT), only 27% reported requiring dialysis after discharge. Only 10 patients (4%) reported requiring dialysis over 3 months after ALF admission: 7 patients with APAP-related ALF and 3 patients with liver injury owing to other causes. Of the patients with severe AKI who received a liver transplant, only 2 of 24 APAP and 1 of 65 other ALF patients required dialysis over 3 months, indicating that renal injury in both categories is largely reversible.

One year after hospital discharge we compared transplant-free survival in AKI groups for 305 (39.3%) of the 776 cases surviving for at least 3 weeks without a transplant (Figures 1 and 2). The mean survival days were significantly different (log-rank, $P = .028$); for those with AKI it was 276.8 days (95% CI, 254.6–299.0) and for those with no AKI it was 314.6 (95% CI, 291.9–337.2). In the APAP group, the mean survival days also were significantly different (log-rank, $P = .023$); for those with AKI it was 309.6 days (95% CI, 285.6–333.6) and with no AKI it was 349.3 (95% CI, 333.2–365.4). Although the mean survival times for the no AKI group were higher than those of the AKI group in the survival analysis for the combined etiologies of shock and other causes (247.3 vs 222.8 d), these results were nonsignificant (log-rank, $P = .464$).

Discussion

The principal finding of this study was a high incidence of AKI in ALF patients that was most evident in those with APAP-induced toxicity. AKI is expected in ALF, but particularly so when ischemia or APAP causes the liver necrosis.¹⁵ Kidney injury observed in ischemic ALF is presumed to result from acute tubular necrosis as a result of hypoperfusion, but the mechanism of AKI observed with APAP remains unknown. A unique direct toxic injury to the kidney recently was postulated.¹⁶ Although AKI rarely has been reported with mild APAP toxicity, recent single tertiary referral center data have shown that renal impairment ($\text{Cr} > 1.36 \text{ mg/dL}$) was present in nearly half and that a Cr level on admission of 1.39 mg/dL or higher portended a poor prognosis.¹⁷ Indeed, our study showed that APAP-induced ALF was associated with an increase in Cr levels in more than 70%. Although any patient who develops encephalopathy owing to ALF is likely to show vasodilatation, hypoperfusion, and

features resembling hepatorenal syndrome, a direct nephrotoxic effect is supported by the higher proportion of the AKI observed in APAP-overdose patients,¹⁸ despite the fact that severity measures of ALF as indicated by the proportion of coma grades III/IV and degree of coagulopathy were similar between the APAP and nonischemic, non-APAP groups. Anecdotally, patients with slowly evolving ALF (typically resulting from idiosyncratic drug reactions) are those most likely to develop ascites and hepatorenal physiology when compared with APAP-related ALF. Because the non-APAP ALF patients were older, and had more comorbidities, the finding of more frequent and more severe AKI in the APAP-related ALF patients also supports a direct toxic effect rather than hepatorenal physiology in these settings. Our findings are similar to a recent report in which 79% of 302 patients admitted with APAP hepatotoxicity showed AKI. However, the investigators reported that more than half received RRT (even though approximately 90% had recovery of renal function by hospital discharge), which was a more frequent use of RRT in this single-center study vs 34% RRT use in APAP patients in our study.¹⁶ Although Acute Liver Failure Study Group lacks a defined AKI management protocol, the current study provides a snapshot of practice across 23 US liver centers over a 13-year period, including ALF across all etiologies. Despite AKI occurring with increased frequency and severity in the APAP and shock patients, the transplant-free survival rate remained greater than 50%, supporting the use of aggressive management, including RRT, in this setting.

The presence of AKI impacted the long-term outcome in patients with ALF, both for APAP and for the overall group, regardless of the low likelihood of long-term dialysis dependence (Figures 1 and 2). For the non-APAP group (n = 113 with known outcomes), AKI was associated with a lower but nonsignificant survival rate, compared with those without AKI (data not shown). The reasons for the poorer outcomes for this group are unclear. It does not seem that AKI severity is associated with more severe APAP hepatotoxicity; we observed striking examples of early hepatic recovery with lingering kidney failure.

With the exception of the earlier-mentioned study, reports of kidney injury caused by APAP have been limited primarily to small case series and experimental animal models. Clinically, APAP-induced renal injury manifests as acute tubular necrosis, with oliguric renal injury occurring 24 to 48 hours from ingestion and peaking over 7 to 10 days.^{17,18} APAP-related AKI can be distinguished from prerenal azotemia and hepatorenal syndrome by patients having active urine sediment, a urine sodium level greater than 20 $\mu\text{mol/L}$, and a urine osmolality similar to plasma osmolality.¹⁹ Given the retrospective nature of our study, detailed sequential urine measurements and kidney histology were not available so we could not definitely exclude alternative etiologies of AKI. In some cases, APAP-induced renal injury has been attributed to the use of concomitant nephrotoxic drugs, alcohol, dehydration, chronic overuse, pre-existing renal or liver disease, and age older than 70 years.^{20–23} We could find no evidence supporting these or similar associations other than a trend toward more alcohol use in the AKI group. The occurrence of nephrotoxicity in some milder APAP cases (15% of those with low coma grades) out of proportion to the liver injury may indicate a genetic predisposition for this form of AKI. The persistence of kidney injury for several weeks after resolution of the liver injury also suggests a unique but recoverable tubular insult. It is reassuring that even patients requiring RRT virtually always recover kidney

function within 4 weeks, unless multiorgan failure is present. Thus, there is minimal impact on long-term kidney function in patients requiring liver transplantation.^{13,24}

The role of muscle injury in the setting of ALF remains to be elucidated. There have been case reports of APAP-associated rhabdomyolysis,^{25,26} with renal injury occurring when CK levels are greater than 5000 IU/L.²⁷ In our cohort, increased CK levels occurred quite frequently in shock as well as during APAP-related ALF, although very high levels were quite rare. Increased CK levels were associated with AKI and poorer outcomes, suggesting that muscle injury caused by hypoperfusion is part of multiorgan damage, including kidney and liver. There is likely a role for rhabdomyolysis in causing AKI in certain patients in addition to direct effects of APAP or hypoperfusion of the kidney. However, less than 10% of patients with CK measurements available had levels greater than 5000 IU/L and there appeared to be no independent effect of increased CK values on overall outcome, either for the total group or for the APAP group separately. Although rhabdomyolysis may contribute to a proportion of APAP-induced kidney injury and to some degree in other ALF settings (heat stroke, ischemia), it is unlikely to be a primary cause except in rare instances.

NAC replenishes glutathione and serves as an effective antidote to APAP hepatotoxicity but may be less useful in reversing kidney injury. Renal cells are unable to generate glutathione locally from precursors and must obtain glutathione from plasma, perhaps lessening the protective effect of NAC in the kidney.²⁸ In our study, the use of NAC did not appear to have any impact on renal function; however, more than 90% of APAP-related ALF patients received NAC, so an adequate comparison with patients not receiving NAC could not be made. Potential limitations of our study included the lack of information on kidney status before admission to the study and the lack of urinary volume or sediment data to confirm the presence or absence of tubular damage.

In conclusion, ALF frequently is complicated by AKI, with more than 70% showing evidence of renal impairment. ALF cases owing to shock or APAP are especially susceptible to renal injury, with more patients in these groups requiring RRT. Increased CK levels are common and should be measured routinely in ALF patients to assess for the occurrence of rhabdomyolysis. AKI in ALF may have been underappreciated as a significant complication because it is an independent risk factor negatively impacting spontaneous short- and long-term survival in patients with ALF. Despite the high incidence of AKI in APAP-related ALF, overall survival remains favorable, renal recovery is common, and aggressive supportive treatment should be encouraged. There remains a need for specific biomarkers to identify and manage AKI cases early in the disease process.

Abbreviations used in this paper

AKI	acute kidney injury
ALF	acute liver failure
APAP	acetaminophen
CK	creatinine kinase

Cr	serum creatinine
NAC	N-acetylcysteine
RRT	renal replacement therapy

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Figure 1.

Kaplan–Meier survival curves for patients with transplant-free survival for all etiologies (APAP, shock, and other groups) by AKI status (no AKI vs AKI). AKI groups were significantly different (log-rank $\chi^2(1) = 4.81$; $P = .028$). The mean survival time from hospital discharge (or 21 days after study admission, whichever came first) to 1 year for the AKI group was significantly lower (276.8 d; 95% CI, 254.6–299.0) than for the no-AKI group (314.6 d; 95% CI, 291.9–337.2). Of note, 14.5% (17 of 117) of the no-AKI patients died in the interval between hospital discharge and 1 year after discharge, whereas 24.5% (46 of 188) of the AKI patients died during the same interval.

Figure 2.

Kaplan–Meier survival curves for patients with transplant-free survival for APAP patients by AKI status (no AKI vs AKI). AKI groups were significantly different (log-rank $\chi^2(1) = 5.15$; $P = .023$). The mean survival time from hospital discharge (or 21 days after study admission, whichever came first) to 1 year for the AKI group was significantly lower (309.6 d; 95% CI, 285.6–333.6) than for the no-AKI group (349.3 d; 95% CI, 333.2–365.4). A total of 5.3% (4 of 75) of the no-AKI patients died in the interval between hospital discharge and 1 year after discharge; 15.4% (18 of 117) of the AKI patients died during the same interval.

Table 1

Presenting Characteristics of ALF Patients (N = 1605) by Etiology

Etiology	APAP (n = 738)	Shock (n = 84)	Other (n = 783)	P value ^a
Age, y	37 (17–81)	53 (18–84)	42 (16–87)	<.001
Sex, female	557 (75.5%)	51 (60.7%)	497 (63.5%)	<.001
Race				
White	637 (86.3%)	69 (82.1%)	525 (67.0%)	
African American	59 (8.0%)	9 (10.7%)	155 (19.8%)	
Asian	15 (2.0%)	2 (2.4%)	59 (7.5%)	
Native Hawaiian	2 (0.3%)	0	7 (0.9%)	
Native American	10 (1.4%)	0	6 (0.8%)	
Other	15 (2.0%)	4 (4.8%)	31 (4.0%)	
Serum ALT level, IU/L	3846 (32–26,600)	2300 (123–12,533)	756 (3–13,100)	<.001
International normalized ratio	2.8 (0.9–27.1)	2.4 (1.4–10.8)	2.6 (1.0–26.1)	.005
Maximum Cr level, mg/dL	2.7 (0.4–15.4)	3.2 (0.6–10.0)	2.0 (0.5–17.9)	<.001
Hepatic coma grade at admission				<.001
1	200 (27.1%)	16 (19.5%)	211 (27.1%)	
2	148 (20.1%)	22 (26.8%)	236 (30.3%)	
3	156 (21.2%)	18 (22.0%)	165 (21.2%)	
4	233 (31.6%)	26 (31.7%)	168 (21.5%)	
Maximum hepatic coma grade				.019
1	131 (17.8%)	12 (14.5%)	115 (14.7%)	
2	126 (17.1%)	21 (25.3%)	177 (22.7%)	
3	118 (16.0%)	9 (10.8%)	146 (18.7%)	
4	362 (49.1%)	41 (49.4%)	343 (43.9%)	
Overall survival	550 (74.5%)	58 (69.0%)	518 (66.2%)	.002
Spontaneous survival	494 (66.9%)	56 (66.7%)	226 (28.9%)	<.001
Transplanted	65 (8.8%)	3 (3.6%)	320 (40.9%)	<.001

^aThe Kruskal–Wallis test was used for continuous measures, and the chi-square test was used for categoric measures.

Table 2

AKI in ALF by Etiology

AKI group	APAP	Shock	Other	Total
Cr level 1.3	210 (28.5%)	8 (9.5%)	268 (34.2%)	486 (30.3%)
Intermediate	188 (25.5%)	34 (40.5%)	181 (23.1%)	403 (25.1%)
Stage 1	29 (3.9%)	3 (3.6%)	45 (5.7%)	77 (4.8%)
Stage 2	28 (3.8%)	2 (2.4%)	48 (6.1%)	78 (4.9%)
Stage 3	29 (3.9%)	0	41 (5.2%)	70 (4.4%)
RRT	254 (34.4%)	37 (44.0%)	200 (25.5%)	491 (30.6%)
Total	738	84	783	1605

NOTE. See text for explanation of stages.

Table 3

Presenting Features of AKI for APAP in ALF

Measures	No AKI	Intermediate	AKI stages 1 and 2	Stage 3 and RRT	<i>P</i> value ^a
Age, y	34.7 (17–78)	40.0 (17–81)	34.0 (21–72)	37.1 (18–78)	.006
Sex, female	168 (80.0%)	140 (74.5%)	42 (73.7%)	207 (71.2%)	.340
Race					
White	185 (88.1%)	162 (86.2%)	49 (86.0%)	241 (85.2%)	.655
Black	11 (5.2%)	17 (9.0%)	4 (7.0%)	27 (9.5%)	
Other	14 (6.7%)	9 (4.8%)	4 (7.0%)	15 (5.3%)	
HTN	24 (11.4%)	29 (15.4%)	5 (8.8%)	26 (9.2%)	.188
DM	29 (13.8%)	27 (14.4%)	5 (8.8%)	32 (11.3%)	.573
CKD	12 (5.7%)	14 (7.4%)	4 (7.0%)	15 (5.3%)	.789
EtOH	84 (40.2%)	109 (58.3%)	25 (43.9%)	150 (54.2%)	.001
Overdose (suicide vs others)	90 (43.5%)	63 (35.0%)	27 (47.4%)	107 (39.2%)	.233
Average dose of APAP, g (N = 229)	25.0 (0.175–594)	22.8 (0.01–900)	25.0 (0.09–250)	25.0 (0.05–750)	.957
ALT level, IU/L	3303 (153–23,700)	4021 (145–19,826)	5067 (60–26,600)	4042 (32–22,000)	.034
INR	2.5 (1.2–15.8)	2.9 (1.0–20.0)	3.3 (1.2–24.1)	3.1 (0.9–27.1)	<.001
Maximum Cr level, mg/dL	0.8 (0.4–1.3)	2.8 (1.4–10.0)	4.6 (1.4–12.5)	5.0 (0.7–15.4)	<.001
Coma grades III/IV	75 (35.7%)	106 (56.4%)	32 (56.1%)	176 (62.4%)	<.001
Maximum coma grades III/IV	88 (41.9%)	129 (68.6%)	37 (64.9%)	226 (80.1%)	<.001
MAP, minimum	78.5 (46–118)	75.0 (31–125)	77.0 (33–114)	73.0 (30–118)	.003
Use of vasopressors	24 (11.5%)	69 (36.9%)	14 (24.6%)	153 (54.4%)	<.001
Use of NAC	190 (91.3%)	168 (90.3%)	55 (96.5%)	252 (89.7%)	.429

NOTE. Results are shown as n (%) or median (low-high).

ALT, alanine aminotransferase; CKD, chronic kidney disease; DM, diabetes mellitus; EtOH, ethanol; HTN, hypertension; INR, international normalized ratio.

^aThe Kruskal–Wallis test was used for continuous measures, and the chi-square test was used for categoric measures.

Table 4

Presenting Features of AKI for Other Etiologies in ALF

Measures	No AKI	Intermediate	AKI stages 1 and 2	Stage 3 and RRT	<i>P</i> value ^a
Age, y	39 (17–73)	44 (16–87)	46 (18–86)	43 (16–84)	.018
Sex, female	183 (68.3%)	109 (60.2%)	54 (58.1%)	151 (62.7%)	.192
Race					
White	171 (63.8%)	131 (72.4%)	60 (64.5%)	163 (67.6%)	.440
Black	57 (21.3%)	31 (17.1%)	23 (24.7%)	44 (18.3%)	
Other	40 (14.9%)	19 (10.5%)	10 (10.8%)	34 (14.1%)	
HTN	42 (15.7%)	44 (24.3%)	23 (24.7%)	51 (21.2%)	.088
DM	41 (15.3%)	42 (23.2%)	19 (20.4%)	36 (14.9%)	.086
CKD	7 (2.6%)	11 (6.1%)	7 (7.5%)	19 (7.9%)	.055
ETOH	74 (27.8%)	47 (26.3%)	21 (23.6%)	72 (30.1%)	.651
ALT level, <i>IU/L</i>	837 (13–13,100)	571 (3–11,100)	811 (11–8960)	731 (7–10,660)	.072
INR	2.7 (1.2–18.0)	2.4 (1.0–20.1)	2.9 (1.2–12.3)	2.6 (1.1–26.1)	.158
Maximum Cr level, <i>mg/dL</i>	1.0 (0.5–1.3)	2.4 (1.4–10.0)	3.1 (1.4–8.4)	3.8 (0.5–17.9)	<.001
Coma grades III/IV	86 (32.2%)	85 (47.2%)	38 (40.9%)	124 (51.7%)	<.001
Maximum coma grades III/IV	124 (46.4%)	117 (64.6%)	63 (67.7%)	185 (77.1%)	<.001
MAP, minimum	78 (49–128)	73 (35–113)	69 (34–110)	67 (37–115)	<.001
Use of vasopressors	32 (12.0%)	49 (27.4%)	30 (32.3%)	134 (55.6%)	<.001
Use of NAC	61 (23.1%)	42 (23.3%)	24 (26.4%)	64 (26.8%)	.745

NOTE. Non-APAP and nonischemic etiologies were included. Results are shown as n (%) or median (low-high).

ALT, alanine aminotransferase; CKD, chronic kidney disease; DM, diabetes mellitus; EtOH, ethanol; HTN, hypertension; INR, international normalized ratio.

^aThe Kruskal–Wallis test was used for continuous measures, and the chi-square test was used for categoric measures.

Table 5

AKI and Outcome at Acute Hospital Phase (Alive, Transplanted, and Transplant-Free Survival) by Etiology

AKI group	APAP	Shock	Other	Total
Alive				
No AKI	201 (95.7%)	7 (87.5%)	242 (90.3%)	450 (92.6%)
Intermediate	129 (68.6%)	26 (76.5%)	115 (63.5%)	270 (67.0%)
Stages 1 and 2	37 (64.9%)	3 (60.0%)	44 (47.3%)	84 (54.2%)
Stage 3 and RRT	183 (64.7%)	22 (59.5%)	117 (48.5%)	322 (57.4%)
Total	550 (74.5%)	58 (69.0%)	518 (66.2%)	1126 (70.2%)
Transplanted				
No AKI	4 (1.9%)	1 (12.5%)	139 (51.9%)	144 (29.6%)
Intermediate	12 (6.4%)	0 (0.0%)	65 (35.9%)	77 (19.1%)
Stages 1 and 2	2 (3.5%)	0 (0.0%)	32 (34.4%)	34 (21.9%)
Stage 3 and RRT	47 (16.6%)	2 (5.4%)	84 (34.9%)	133 (23.7%)
Total	65 (8.5%)	3 (3.6%)	320 (40.9%)	388 (24.2%)
Transplant-free survival				
No AKI	197 (93.8%)	6 (75.0%)	108 (40.3%)	311 (64.0%)
Intermediate	120 (63.8%)	26 (76.5%)	56 (30.9%)	202 (50.1%)
Stages 1 and 2	35 (61.4%)	3 (60.0%)	16 (17.2%)	54 (34.8%)
Stage 3 and RRT	142 (50.2%)	21 (56.8%)	46 (19.1%)	209 (37.3%)
Total	494 (66.9%)	56 (66.7%)	226 (28.9%)	776 (48.3%)