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Prevalence, Severity and Impact of Renal Dysfunction in Acute Liver Failure on the U.S. Liver Transplant Waiting List

Nathalie H. Urrunaga, M.D., M.S.¹, Laurence S. Magder, Ph.D., M.P.H.², Matthew R. Weir, M.D.³, Don C. Rockey, M.D.⁴, and Ayse L. Mindikoglu, M.D., M.P.H.¹

¹Department of Medicine, Division of Gastroenterology and Hepatology, University of Maryland School of Medicine

²Department of Epidemiology and Public Health, Division of Biostatistics and Bioinformatics, University of Maryland School of Medicine

³Department of Medicine, Division of Nephrology, University of Maryland School of Medicine

⁴Department of Medicine, Medical University of South Carolina

Abstract

Background & Aims—Although renal dysfunction is a known complication of acute liver failure (ALF), its frequency, severity and impact among patients with ALF on the US liver transplant list are not well defined.

Methods—Organ Procurement and Transplantation data for ALF patients listed as status 1/1A from 2002–2012 were analyzed. The frequency and severity of renal dysfunction at the time of listing [the latter was categorized in 5 stages using estimated GFR (eGFR) according to Chronic Kidney Disease Epidemiology Collaboration creatinine 2009 equation) were determined and the association between renal dysfunction and waiting list mortality was assessed using Cox proportional hazard regression analysis.

Results—There were a total of 2,280 adult patients with ALF, including 56% with renal dysfunction (defined as eGFR <60 ml/min/1.73m²) at listing. The highest proportion of patients with renal dysfunction was among those with ALF caused by hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, fatty liver disease of pregnancy, heat stroke/hyperthermia-,

CORRESPONDENCE: Ayse L. Mindikoglu, M.D., M.P.H., Associate Professor of Medicine, Division of Gastroenterology and Hepatology, University of Maryland School of Medicine, 22 S. Greene Street, N3W50, Baltimore, Maryland 21201, Phone: 410-328-1358, Fax: 410-328-1897, amindiko@medicine.umaryland.edu.

AUTHORSHIP:

Nathalie H. Urrunaga M.D., M.S. designed and performed the study, analyzed the data, and wrote the paper.

Laurence S. Magder Ph.D., M.P.H. analyzed the data and contributed with important suggestions.

Matthew R. Weir, M.D. contributed with important suggestions.

Don C. Rockey, M.D. wrote the paper and contributed with important suggestions.

Ayse L. Mindikoglu M.D., M.P.H. designed and performed the study, analyzed the data, and wrote the paper.

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CONFLICT OF INTEREST

None to declare.

hepatitis A virus, drug-induced liver injury due to acetaminophen (APAP), phenytoin, trimethoprim-sulfamethoxazole and macrolides. Despite the fact that 69% (468/674) of patients with APAP-induced ALF listed as status 1/1A had renal dysfunction, only 0.9% underwent simultaneous liver-kidney transplantation. Six-week survival probabilities in patients with ALF on the liver transplant waiting list were 71%, 59%, 56%, 59% and 42% with renal dysfunction stages of 1, 2, 3, 4, and 5, respectively. Multivariate analysis showed that after controlling for age, etiology of ALF, INR, total bilirubin and region, the relative risk of death increased progressively as eGFR declined ($P<0.0001$).

Conclusions—Among patients with ALF on the liver transplant waiting list, renal dysfunction was common (overall prevalence of 56%). Most importantly, severe renal dysfunction was associated with significantly increased mortality.

Keywords

Renal dysfunction; acute liver failure; liver transplantation; CKD-EPI; OPTN

BACKGROUND

Acute liver failure (ALF) is defined as rapid loss of hepatic synthetic function with an international normalized ratio (INR) ≥ 1.5 and altered mental status in the setting of abnormal serum aminotransferases in a patient without known liver disease^{1, 2}. With the exception of few scenarios where the use of antidotes and targeted treatment is indicated^{3–6}, the current management of ALF is supportive and includes liver transplantation in highly selected patients². Improvement in intensive care unit monitoring and supportive care have increased survival; however the mortality still remains high⁷.

Early identification of factors that affect survival is a key to improving outcomes in ALF. Renal dysfunction in the setting of ALF has been associated with decreased survival⁸. Accurate assessment of the severity of renal dysfunction is crucial as it correlates with increased morbidity and mortality in patients with acute and chronic liver disease^{8–10}. The stage and severity of acute kidney injury is an independent predictor of mortality in patients with chronic liver disease⁹.

Although renal dysfunction may complicate ALF, little is known regarding its frequency, severity and impact in patients with ALF on the liver transplant waiting list in US. The objectives of the present study were to fill these gaps in knowledge.

METHODS

Study Population

The analysis was performed based on Organ Procurement and Transplantation Network (OPTN) from February 27, 2002 through September 30, 2012 (OPTN data as of December 14, 2012). Patients 18 years or older with ALF with status 1 or 1A listing were included in the analysis.

Study Variables

The diagnosis of ALF was based on diagnosis variables of “acute hepatic necrosis” and “status 1 or status 1A” at the time of United Network for Organ Sharing (UNOS) registration. Serum creatinine and estimated glomerular filtration rate (eGFR) were used to define renal dysfunction at listing. EGFR was calculated at the time of listing using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine (Cr) 2009 equation¹¹ and categorized according to eGFR stages: Stage 1 if eGFR ≥ 90 ml/min/1.73m², Stage 2 if eGFR 60 to <90 ml/min/1.73m², Stage 3 if eGFR 30 to <60 ml/min/1.73m², Stage 4 if eGFR 15 to <30 ml/min/1.73m², Stage 5 if eGFR < 15 ml/min/1.73m² or on dialysis¹². Renal dysfunction was defined as eGFR <60 ml/min/1.73m² at listing.

Statistical Analysis

All analyses were performed using SAS software, version 9.2 (Cary, NC, United States)¹³ and Minitab 16 statistical software (Minitab, Inc, State College, PA, United States)¹⁴. For categorical variables, the chi-square and Fisher exact tests were used to assess differences between patients with and without renal dysfunction. For continuous variables, the Wilcoxon rank-sum test was used to assess differences. We reported survival outcomes for two distinct time periods: 1) overall outcomes during entire time on the waiting list; and 2) all-cause mortality on the waiting list during 6 weeks after listing for ALF. A total of 91 patients were excluded from the survival analysis if their outcome on the waiting list was unknown (60), underwent living donor liver transplantation (10), transplanted at another center (multiple listing) (1), transferred to another center (1), refused liver transplant (2) or died during transplant procedure (17). To determine overall outcomes during entire time on the waiting list analysis, patients were followed from the time of listing until death, removal from the list due to improvement or deterioration, transplantation or until their last follow-up on the liver transplant waiting list. Patients were “right-censored” in the analysis if they were alive at the last follow-up on the waiting list, removed from the waiting list due to improvement or transplanted. For Cox multivariate regression analysis, patients were followed from the time of listing until the end of 6 weeks on the liver transplant waiting list and were “right-censored” in the analysis if they were alive at 6 weeks, removed from the waiting list due to improvement or transplanted. Patients who died or were removed due to deterioration during the 6 weeks post listing were considered as having died for purposes of the analysis. Survival curves were generated using Kaplan–Meier plots¹⁵ and compared using a log rank test. Cox multivariate regression analysis¹⁶ was performed to determine factors associated with mortality on the liver transplant waiting list during the 6 weeks after listing for ALF.

RESULTS

Patients Characteristics

We identified a total of 2280 patients with ALF listed as status 1 or 1A for liver transplantation during the study period, including 1271 (55.7%) with eGFR < 60 ml/min/1.73m² at listing (Table 1). The median number of days on the liver transplant waiting list was three days. Ninety-three percent of patients had a follow-up of 6 weeks or less and 7% had a follow-up of more than 6 weeks. The proportion of patients with renal dysfunction

was significantly greater among white patients, and those on life support at listing than patients without renal dysfunction (Table 1). On the other hand, sex and the presence of diabetes did not significantly impact the likelihood of renal dysfunction (Table 1). The highest proportion of patients with renal dysfunction was among those with ALF caused by hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, fatty liver disease of pregnancy, heat stroke/hyperthermia, hepatitis A virus, and drug-induced liver injury due to APAP, phenytoin, trimethoprim-sulfamethoxazole, and macrolides (Table 2). Compared to those without renal dysfunction, patients with ALF and renal dysfunction had significantly higher model for end-stage liver disease (MELD) scores (39 vs. 32, $P<0.0001$) compared to those without renal dysfunction (Table 1).

Severity of Renal Dysfunction at Listing Stratified by Etiology of ALF

The severity of renal dysfunction at the time of listing varied based on the etiology of ALF (Table 2). All patients with ALF due to heat stroke/hyperthermia, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, macrolide antibiotics, acute fatty liver disease of pregnancy (FLDP) had renal dysfunction (Table 2).

The highest median Cr and lowest median eGFR at listing was found in those with heat stroke-induced ALF (Cr=6.9 mg/dl, eGFR=9.1 ml/min/1.73m²), followed by FLDP (Cr=3.2 mg/dl, eGFR=18.2 ml/min/1.73m²), HELLP syndrome (Cr=3.2 mg/dl, eGFR=18.4 ml/min/1.73m²), trimethoprim-sulfamethoxazole (Cr=3.2 mg/dl, eGFR=25.8 ml/min/1.73m²), phenytoin (Cr=2.4 mg/dl, eGFR=29.8 ml/min/1.73m²), macrolide antibiotics (Cr=2.3 mg/dl, eGFR=22.7 ml/min/1.73m²), HAV (Cr=2.2, eGFR=34.2 ml/min/1.73m²) and APAP-induced ALF (Cr=2.1 mg/dl, eGFR=32.0 ml/min/1.73m²). The highest proportion of patients on dialysis at listing was among those who had HELLP syndrome (6 out of 10, 60%). Only 14.2% (96 out of 674) of patients with APAP-induced ALF were on dialysis at the time of listing.

Overall Survival Outcomes of Patients with ALF Stratified by eGFR

Table 3 shows overall outcomes on the liver transplant waiting list. Among patients with ALF and renal dysfunction, the proportion of patients who died (15.5% vs. 6.7%) or removed from the list due to deterioration (10.4% vs. 7.9%) was higher compared to those without renal dysfunction (Table 3). The proportion of patients with ALF who underwent simultaneous liver-kidney transplantation was significantly higher in those with renal dysfunction compared to those without renal dysfunction at the time of listing (1.5% vs. 0.2%, $P=0.001$). Only 0.9% of patients with APAP-induced ALF had simultaneous liver-kidney transplantation (Table 4).

Six-Week Survival Probabilities in Patients with ALF

The 6-week survival probabilities in patients with ALF were 71%, 59%, 56%, 59% and 42% with CKD stages of 1, 2, 3, 4, and 5, respectively ($P<0.0001$) (Figure 1). Interestingly, while the survival probability for patients with eGFR stages 1–4 tended to remain stable after being listed for about 12 days, the survival probability in those with eGFR stage 5 continued to decline over time while on the waiting list.

Mortality in Patients with ALF during the First Six Weeks on the Liver Transplant Waiting List

A multivariate Cox regression analysis was performed to identify independent predictors of mortality in patients with ALF during the first six weeks after listing for liver transplantation (Table 5). After controlling for age, etiology of ALF, INR, total bilirubin and region, the relative risk of death increased progressively as eGFR declined.

DISCUSSION

Here, we demonstrate that in 2,280 adult patients with ALF listed as status 1 or 1A for liver transplantation in the U.S. renal dysfunction was very common. Further, the data indicate that renal dysfunction complicating ALF predicts a significantly worse outcome, and that the risk of death increases as the degree of renal dysfunction worsens. Interestingly, despite that more than 2/3 of patients with APAP-induced ALF have renal dysfunction at the time of listing, less than 1% required simultaneous liver-kidney transplantation.

Our findings are consistent with other reports investigating the frequency of renal dysfunction in ALF^{17–21}. The prevalence of renal dysfunction in patients with ALF has been previously reported to be 38% to 79%^{17–21}. Differences in prevalence are likely due to variable definitions used to identify renal dysfunction and differences in the population studied. Prior studies have reported association of renal dysfunction with increased mortality in ALF patients^{17, 19, 20}, our data expand prior experience and emphasize that mortality in patients with renal dysfunction and ALF is high and that mortality increases with severity of renal dysfunction even after controlling for etiology of ALF, INR, total bilirubin and region. Our study evaluated the severity of renal dysfunction not only in APAP-induced ALF but also in several etiologies of ALF and its impact on mortality using a multivariate analysis.

We found that the prevalence of renal dysfunction, degree of severity and need for hemodialysis and SLKT varied depending on the etiology of acute liver failure. All patients with heat stroke/hyperthermia, HELLP syndrome, macrolide antibiotics, FLDP-induced ALF had renal dysfunction (Table 2) and patients with ALF secondary to APAP, phenytoin, HAV had a prevalence of renal dysfunction ranging from 63.6–69.4%; however only patients with ALF secondary to phenytoin, HAV and autoimmune hepatitis underwent simultaneous liver-kidney transplantation more frequently compared to those with ALF secondary to the other etiologies.

Why certain causes of ALF were associated with more renal dysfunction than others remains unclear. Acute liver injury is common in heat stroke and ALF has been reported as a complication, although ALF that requires liver transplantation in this setting is rare^{22, 23}. Renal dysfunction has been reported up to 50% of patients with heat stroke²⁴. Patients can recover from heat-stroke-induced renal dysfunction by early osmotic diuresis, alkalization of urine, correction of electrolyte abnormalities and hemodialysis²⁴.

HELLP Syndrome is a serious complication of pregnancy which can present with acute kidney injury in 8% of the cases²⁵. FLDP is an uncommon but potentially fatal liver disease that usually occurs during the second and third trimester. FLDP can be accompanied by

renal dysfunction and acute tubular necrosis in 56–100% patients^{26, 27}. Renal dysfunction in FLDP was attributed to inhibition of fatty acid beta-oxidation in the kidneys, hepatorenal syndrome as well as acute tubular necrosis²⁶. Renal dysfunction correlates with the severity of FLDP; with early initiation of supportive management usually resolves with delivery and rarely requires hemodialysis^{26, 27}.

Macrolide antibiotics can induce acute liver injury as well as acute and chronic kidney disease^{28–31}. Acute kidney injury from macrolides including erythromycin, azithromycin and telithromycin is usually secondary to acute interstitial nephritis that can be reversed by the administration of steroids^{28–30}.

Phenytoin has been associated with ALF³² and acute kidney injury secondary to prerenal azotemia³³, hypersensitivity syndrome³³, acute interstitial nephritis³⁴ or anti-neutrophil cytoplasmic antibody-associated vasculitis³⁵. Reports have documented resolution of renal dysfunction after supportive care and treatment with steroids and cyclophosphamide^{35, 36}. None required kidney transplantation^{35, 36}. In our study, phenytoin-induced ALF had the highest proportion of patients (15%) requiring simultaneous liver-kidney transplantation.

APAP hepatotoxicity, the most common etiology of ALF in the western world⁷ has been associated with renal failure secondary to multiple potential factors including release of endotoxins, hypovolemia, hepatorenal syndrome and acute tubular necrosis^{17, 20, 37–38}. The prevalence of acute kidney injury in ALF secondary to APAP has been reported between 53–76%^{17, 20}. In the majority of these patients, acute kidney injury was reversible³⁹. Consistent with these studies, we observed renal dysfunction in 69% of patients with ALF secondary to APAP (Table 2). Only 0.9% of patients with APAP-induced ALF required simultaneous liver-kidney transplantation.

Acute kidney injury can occur in patients with HAV infection with and without ALF^{40–42}. Mechanisms whereby renal dysfunction may occur during acute HAV infection include hypovolemia, tubular toxicity induced by hyperbilirubinemia and immune-complex mediated nephritis^{41–43}. The management is usually supportive although there have been reports of improvement of renal function after hemodialysis, plasmapheresis and corticosteroid use^{41, 43–46}. The majority of patients recover a normal renal function although permanent renal insufficiency has been reported^{40, 46}. We found that 3% of patients with HAV- induced ALF required simultaneous liver-kidney transplantation.

Among 118 of patients with ALF secondary to autoimmune hepatitis, 35% developed renal dysfunction and only 2.5% required simultaneous liver-kidney transplantation. Although the precise mechanism for renal dysfunction in autoimmune hepatitis is unclear; an association between autoimmune hepatitis and acute renal failure secondary to mixed cryoglobulinemic glomerulonephritis responsive to rituximab was reported⁴⁷.

Our study had several important strengths, including a large sample size and robust national data spanning 10 years with a mortality assessment. We also appreciate limitations. First; this was a retrospective analysis of prospectively collected data from different medical centers; therefore bias in data collection may be present. When we identified patients with ALF using the variables “acute hepatic necrosis” and “status 1 or 1A”, we observed that 7%

of patients (170 out of 2280) had a waiting time greater than 6 weeks. Our further analysis showed that these patients were listed initially with a diagnosis of ALF as status 1. However, 89% of them were temporarily inactive at the last follow-up on the waiting list and 10% were still active on the waiting list with a MELD score (non-status 1). Another limitation is that this dataset did not provide baseline serum creatinine before listing; thus we could not differentiate acute kidney injury from chronic kidney disease or acute kidney injury superimposed on chronic kidney disease⁴⁸. Current definitions for acute kidney injury include changes in serum creatinine and urinary output which are indirect markers of changes in GFR⁴⁸.

In summary, our data indicate that in those with ALF and listed for liver transplantation, renal dysfunction was very common and the prevalence and severity of renal dysfunction differed based on the etiology of ALF. Notably, our study indicates that renal dysfunction complicating ALF predicts a significantly worse outcome. Further investigation is clearly warranted to identify more accurate biomarkers for renal dysfunction in patients with ALF. This will be likely to facilitate earlier diagnosis, classification and treatment of renal dysfunction and hasten liver transplant allocation.

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ABBREVIATIONS

ALF	Acute Liver Failure
OPTN	Organ Procurement and Transplantation Network
UNOS	United Network for Organ Sharing
INR	International normalized ratio
MELD	Model for End-Stage Liver Disease

References

1. Lee WM, Stravitz RT, Larson AMCP. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology*. 2011; 55:965–7. [PubMed: 22213561]

2. Polson J, Lee WM. Disease AAftSoL. AASLD position paper: the management of acute liver failure. *Hepatology*. 2005; 41:1179–97. [PubMed: 15841455]
3. Czaja AJ, Freese DK. Disease AAftSoL. Diagnosis and treatment of autoimmune hepatitis. *Hepatology*. 2002; 36:479–97. [PubMed: 12143059]
4. Lee WC, Wu MJ, Cheng CH, et al. Lamivudine is effective for the treatment of reactivation of hepatitis B virus and fulminant hepatic failure in renal transplant recipients. *Am J Kidney Dis*. 2001; 38:1074–81. [PubMed: 11684562]
5. Peters DJ, Greene WH, Ruggiero F, et al. Herpes simplex-induced fulminant hepatitis in adults: a call for empiric therapy. *Dig Dis Sci*. 2000; 45:2399–404. [PubMed: 11258565]
6. Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med*. 1988; 319:1557–62. [PubMed: 3059186]
7. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002; 137:947–54. [PubMed: 12484709]
8. O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*. 1989; 97:439–45. [PubMed: 2490426]
9. Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology*. 2013; 57:753–62. [PubMed: 22454364]
10. Mindikoglu AL, Regev A, Seliger SL, et al. Gender disparity in liver transplant waiting-list mortality: the importance of kidney function. *Liver Transpl*. 2010; 16:1147–57. [PubMed: 20879013]
11. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150:604–12. [PubMed: 19414839]
12. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003; 139:137–47. [PubMed: 12859163]
13. SAS activity-based management 6.3: user's guide. Cary, N.C: SAS Institute, Inc; 2007.
14. Minitab 16 Statistical Software. Computer software. State College, PA: Minitab, Inc; 2010. www.minitab.com
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Amer Statist Assn*. 1958; 53:457–481.
16. Cox DR. Regression models and life-table. *J Royal Statist Soc B*. 1972; 34:187–220.
17. Wilkinson SP, Moodie H, Arroyo VA, et al. Frequency of renal impairment in paracetamol overdose compared with other causes of acute liver damage. *J Clin Pathol*. 1977; 30:141–3. [PubMed: 845262]
18. Wilkinson SP, Blendis LM, Williams R. Frequency and type of renal and electrolyte disorders in fulminant hepatic failure. *Br Med J*. 1974; 1:186–9. [PubMed: 4811848]
19. Tujios SR, Hynan LS, Vazquez MA, et al. Risk factors and outcomes of acute kidney injury in patients with acute liver failure. *Clin Gastroenterol Hepatol*. 2015; 13:352–9. [PubMed: 25019700]
20. Leithead JA, Ferguson JW, Bates CM, et al. The systemic inflammatory response syndrome is predictive of renal dysfunction in patients with non-paracetamol-induced acute liver failure. *Gut*. 2009; 58:443–9. [PubMed: 19001057]
21. Ring-Larsen H, Palazzo U. Renal failure in fulminant hepatic failure and terminal cirrhosis: a comparison between incidence, types, and prognosis. *Gut*. 1981; 22:585–91. [PubMed: 7262632]
22. Garcin JM, Bronstein JA, Cremades S, et al. Acute liver failure is frequent during heat stroke. *World J Gastroenterol*. 2008; 14:158–9. [PubMed: 18176983]
23. Jin Q, Chen E, Jiang J, et al. Acute hepatic failure as a leading manifestation in exertional heat stroke. *Case Rep Crit Care*. 2012; 2012:295867.
24. Yeo TP. Heat stroke: a comprehensive review. *AACN Clin Issues*. 2004; 15:280–93. [PubMed: 15461044]

25. Sibai BM, Ramadan MK, Usta I, et al. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol.* 1993; 169:1000–6. [PubMed: 8238109]
26. Castro MA, Fassett MJ, Reynolds TB, et al. Reversible peripartum liver failure: a new perspective on the diagnosis, treatment, and cause of acute fatty liver of pregnancy, based on 28 consecutive cases. *Am J Obstet Gynecol.* 1999; 181:389–95. [PubMed: 10454689]
27. Fesenmeier MF, Coppage KH, Lambers DS, et al. Acute fatty liver of pregnancy in 3 tertiary care centers. *Am J Obstet Gynecol.* 2005; 192:1416–9. [PubMed: 15902124]
28. Rosenfeld J, Gura V, Boner G, et al. Interstitial nephritis with acute renal failure after erythromycin. *Br Med J (Clin Res Ed).* 1983; 286:938–9.
29. Soni N, Harrington JW, Weiss R, et al. Recurrent acute interstitial nephritis induced by azithromycin. *Pediatr Infect Dis J.* 2004; 23:965–6. [PubMed: 15602202]
30. Tintillier M, Kirch L, Almpanis C, et al. Telithromycin-induced acute interstitial nephritis: a first case report. *Am J Kidney Dis.* 2004; 44:e25–27. [PubMed: 15264209]
31. Mansoor GA, Panner BJ, Ornt DB. Azithromycin-induced acute interstitial nephritis. *Ann Intern Med.* 1993; 119:636–7. [PubMed: 8395778]
32. Mindikoglu AL, Magder LS, Regev A. Outcome of liver transplantation for drug-induced acute liver failure in the United States: analysis of the United Network for Organ Sharing database. *Liver Transpl.* 2009; 15:719–29. [PubMed: 19562705]
33. Polman AJ, van der Werf TS, Tiebosch AT, et al. Early-onset phenytoin toxicity mimicking a renopulmonary syndrome. *Eur Respir J.* 1998; 11:501–3. [PubMed: 9551761]
34. Hyman LR, Ballow M, Knieser MR. Diphenylhydantoin interstitial nephritis. Roles of cellular and humoral immunologic injury. *J Pediatr.* 1978; 92:915–20. [PubMed: 660357]
35. Parry RG, Gordon P, Mason JC, et al. Phenytoin-associated vasculitis and ANCA positivity: a case report. *Nephrol Dial Transplant.* 1996; 11:357–9. [PubMed: 8671794]
36. Michael JR, Mitch WE. Reversible renal failure and myositis caused by phenytoin hypersensitivity. *JAMA.* 1976; 236:2773–5. [PubMed: 1036571]
37. Blakely P, McDonald BR. Acute renal failure due to acetaminophen ingestion: a case report and review of the literature. *J Am Soc Nephrol.* 1995; 6:48–53. [PubMed: 7579069]
38. O'Riordan A, Brummell Z, Sizer E, et al. Acute kidney injury in patients admitted to a liver intensive therapy unit with paracetamol-induced hepatotoxicity. *Nephrol Dial Transplant.* 2011; 26:3501–8. [PubMed: 21652548]
39. Lines SW, Wood A, Bellamy MC, et al. The outcomes of critically ill patients with combined severe acute liver and kidney injury secondary to paracetamol toxicity requiring renal replacement therapy. *Ren Fail.* 2011; 33:785–8. [PubMed: 21777171]
40. Fan PC, Chen YC, Tian YC, et al. Acute renal failure associated with acute non-fulminant hepatitis A: a case report and review of literature. *Ren Fail.* 2009; 31:756–64. [PubMed: 19814647]
41. Kim HW, Yu MH, Lee JH, et al. Experiences with acute kidney injury complicating non-fulminant hepatitis A. *Nephrology (Carlton).* 2008; 13:451–8. [PubMed: 18518930]
42. Pal RB, Saha P, Das I, et al. Fulminant hepatitis and glomerulonephritis—a rare presentation of hepatitis A virus infection. *Acta Paediatr.* 2011; 100:e132–4. [PubMed: 21342254]
43. McCann UG 2nd, Rabito F, Shah M, et al. Acute renal failure complicating nonfulminant hepatitis A. *West J Med.* 1996; 165:308–10. [PubMed: 8993209]
44. Jung YJ, Kim W, Jeong JB, et al. Clinical features of acute renal failure associated with hepatitis A virus infection. *J Viral Hepat.* 2010; 17:611–7. [PubMed: 19824944]
45. Watanabe S, Nomoto H, Matsuda M, et al. A case of acute renal failure associated with type A acute hepatitis responds dramatically to plasmapheresis. *Tokai J Exp Clin Med.* 1986; 11:1–4. [PubMed: 3810690]
46. Zikos D, Grewal KS, Craig K, et al. Nephrotic syndrome and acute renal failure associated with hepatitis A virus infection. *Am J Gastroenterol.* 1995; 90:295–8. [PubMed: 7847304]
47. Evans JT, Shepard MM, Oates JC, et al. Rituximab-responsive cryoglobulinemic glomerulonephritis in a patient with autoimmune hepatitis. *J Clin Gastroenterol.* 2008; 42:862–3. [PubMed: 18458643]

48. Section 2: AKI Definition. *Kidney Int Suppl.* 2011; 2:19–36. 2012.

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Figure 1. Survival probabilities in patients with ALF categorized according to severity of renal dysfunction. Survival curves were generated using Kaplan–Meier plots¹⁵ and compared using a log rank test.

Table 1
 Characteristics of Patients with ALF on the Liver Transplant Waiting List Stratified by eGFR at Listing

Characteristics	eGFR 60 ml/min/1.73m ²		eGFR <60 ml/min/1.73m ²		P Value
	N=1009	(Row %)	N=1271	(Row %)	
Sex					0.572
Male	297	43.4	388	56.6	
Female	712	44.6	883	55.4	
Race or Ethnicity					<0.0001
White	532	37.5	888	62.5	
Black	227	55.5	182	44.5	
Hispanic	128	54.7	106	45.3	
Asian	100	58.8	70	41.2	
Unknown	22	46.8	25	53.2	
Etiology of Acute Liver Failure					<0.0001
Acetaminophen	206	30.6	468	69.4	
Hepatitis B Virus	101	56.4	78	43.6	
Autoimmune Hepatitis	77	65.3	41	34.8	
Hepatitis A Virus	12	36.4	21	63.6	
Isoniazid	14	60.9	9	39.1	
Other*	599	47.8	654	52.2	
Life Support at Listing					<0.0001
Yes	443	35.6	802	64.4	
No	566	54.7	469	45.3	
Diabetes					0.488
Yes	55	41.4	78	58.7	
No	954	44.4	1193	55.6	
	Median	Range	Median	Range	P-value
Age (yr)	38	55	40	56	0.0002
Days on the Waiting List	3	2926	3	3671	0.0004
Serum Creatinine at Listing	0.8	1.6	2.6	19.0	<0.0001

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Characteristics	eGFR	60 ml/min/1.73m ²	eGFR <60 ml/min/1.73m ²	P Value	
	N=1009	(Row %)	N=1271	(Row %)	
Serum Total Bilirubin at Listing	16.3	59.9	7.3	98.6	<0.0001
INR at Listing	3.7	98.0	3.7	76.9	0.0571
MELD Score at Listing	32	63	39	53	<0.0001
Serum Sodium at Listing	139	43	139	50	0.0017

* Other: Wilson disease, mushroom/amanita, non-steroidal anti-inflammatory drugs, phenytoin, fatty liver disease of pregnancy, amoxicillin/amoxicillin-clavulanic acid, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, propylthiouracil, nitrofurantoin, heat stroke/hyperthermia, carbamazepine, infliximab, trimethoprim-sulfamethoxazole, disulfiram, Hepatitis E Virus, herbal supplements, macrolide antibiotics, Budd-Chiari syndrome, Epstein-Barr Virus, valproic acid

Table 2

Renal Dysfunction Stratified by Etiology of ALF on the Liver Transplant Waiting List

Etiology of ALF	eGFR ≥ 60		eGFR <60	
	ml/min/1.73m ²			
	N=1009	(Row %)	N=1271	(Row %)
Heat Stroke/Hyperthermia	0	0.0	3	100.0
Elevated liver enzymes, low platelet count (HELLP) Syndrome	0	0.0	10	100.0
Macrolide Antibiotics	0	0.0	4	100.0
Fatty Liver Disease of Pregnancy	0	0.0	9	100.0
Acetaminophen	206	30.6	468	69.4
Phenytoin	4	30.8	9	69.2
Hepatitis A Virus	12	36.4	21	63.6
Trimethoprim-sulfamethoxazole	3	37.5	5	62.5
Valproic Acid	2	40.0	3	60.0
Herbal Supplements	5	41.7	7	58.3
Mushroom/Amanita	5	45.5	6	54.6
Other	538	48.0	582	52.0
Epstein-Barr Virus	1	50.0	1	50.0
Carbamazepine	2	50.0	2	50.0
Hepatitis E Virus	1	50.0	1	50.0
Hepatitis B Virus	101	56.4	78	43.6
Non-steroidal anti-inflammatory drugs	6	60.0	4	40.0
Isoniazid	14	60.9	9	39.1
Amoxicillin/Amoxicillin-Clavulanic Acid	2	66.7	1	33.3
Autoimmune Hepatitis	77	65.3	41	34.8
Budd-Chiari Syndrome	2	66.7	1	33.3
Propylthiouracil	6	75.0	2	25.0
Wilson Disease	10	76.9	3	23.1
Infliximab	5	83.3	1	16.7
Disulfiram	4	100.0	0	0.0
Nitrofurantoin	3	100.0	0	0.0

Table 3

Overall Outcomes of Patients with ALF on the Liver Transplant Waiting List Stratified by eGFR at Listing

	eGFR		60 ml/min/1.73m ²		eGFR <60 ml/min/1.73m ²		P Value
	N=2189	%	N=973	(%=44.4)	N=1216	(%=55.6)	
Outcomes on the Liver Transplant Waiting List							
Alive	10	0.5	6	0.6	4	0.3	<0.0001
Death	254	11.6	65	6.7	189	15.5	
Liver Transplantation	1274	58.2	629	64.7	645	53.0	
Removed from the list as the condition improved	447	20.4	196	20.1	251	20.6	
Removed from the list as the condition deteriorated	204	9.3	77	7.9	127	10.4	
Simultaneous Liver-Kidney Transplantation							
Yes	21	1.0	2	0.2	19	1.5	0.001
No	2168	99.0	971	99.8	1197	98.4	

Table 4

Patients who underwent Simultaneous Liver-Kidney Transplantation Stratified by Etiology of ALF on the Liver Transplant Waiting List

	<u>Simultaneous Liver-Kidney Transplantation</u>			
	No		Yes	
	N	(Row %)	N	(Row %)
Phenytoin	11	84.6	2	15.4
Hepatitis A Virus	32	97.0	1	3.0
Autoimmune Hepatitis	115	97.5	3	2.5
Acetaminophen	668	99.1	6	0.9
Other/Unknown	1111	99.2	9	0.8

Table 5

Mortality in Patients with ALF during the First 6 Weeks on the Liver Transplant Waiting List*

Variable		Hazard Ratio	95% CI	P Value
eGFR at Listing (ml/min/1.73m ²)	eGFR 90	1.000		
	eGFR 60 to < 90	1.428	1.006–2.029	0.046
	eGFR 30 to < 60	1.866	1.366–2.549	<0.0001
	eGFR 15 to < 30	2.233	1.625–3.067	<0.0001
	eGFR < 15 or on Dialysis	2.770	2.071–3.705	<0.0001

* Controlled for etiology of ALF, INR, total bilirubin and region