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Incidence and outcomes of acute kidney injury including hepatorenal syndrome in hospitalized patients with cirrhosis in the US

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Abstract

Background and Aims: Acute kidney injury (AKI) in cirrhosis is morbid, but the incidence rates of different etiologies of AKI are not well described in United States patients. We compared incidence rates, practice patterns, and outcomes across etiologies of AKI in cirrhosis.

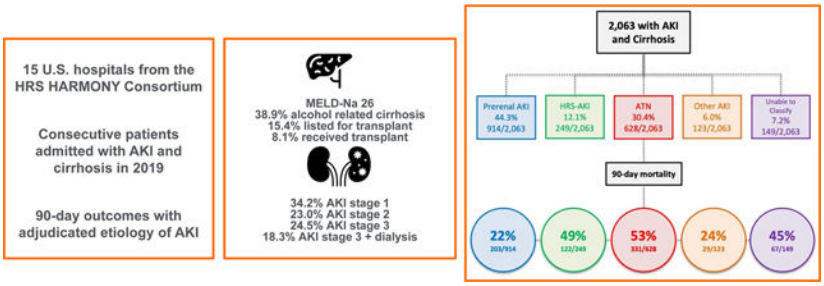
Methods: Retrospective cohort study of 11 hospital networks of consecutive adult patients admitted in 2019 with AKI and cirrhosis. Etiology of AKI was adjudicated based on pre-specified clinical definitions (prerenal/hypovolemic AKI, hepatorenal syndrome [HRS-AKI], acute tubular necrosis [ATN], other).

Results: 2,063 patients were included (median age 62 [IQR 54, 69] years, 38.3% female, median MELD-Na score 26 [19, 31]). The most common AKI etiology was prerenal AKI (44.3%), followed by ATN (30.4%) and HRS-AKI (12.1%); 6.0% had other AKI, and 7.2% were unable to classify. 8.1% patients received a liver transplant, 36.5% died by 90-days. Patients with prerenal AKI had the lowest rate of death (22.2%; $p < 0.001$) whereas patients with HRS-AKI and ATN were higher, but not significantly different from each other (49.0% vs. 52.7%; $p = 0.42$). Using

prerenal AKI as reference, the adjusted sHR for 90-day mortality was higher for HRS-AKI (sHR 2.78 [95% CI 2.18–3.54]; p <0.001) and ATN (sHR 2.83 [2.36–3.41]; p <0.001). In adjusted analysis, higher AKI stage and lack of complete response to treatment was associated with an increased risk of 90-day mortality (p <0.001 for all).

Conclusion: AKI is a severe complication of cirrhosis. HRS-AKI is uncommon and has similar outcomes to ATN. Etiology of AKI, AKI stage/severity, and non-response to treatment were associated with mortality. Further optimization of vasoconstrictors for HRS-AKI and supportive therapies for ATN are needed.

Graphical Abstract



Keywords

liver failure; acute on chronic liver failure; renal failure; liver transplant; vasoconstrictor

Introduction

Acute kidney injury (AKI) is a common complication of cirrhosis and acute-on-chronic liver failure (ACLF) and is associated with high morbidity and mortality.[1, 2] Treatment for AKI in cirrhosis is based on its etiology. Hypovolemic or pre-renal AKI is treated with volume resuscitation, hepatorenal syndrome (HRS-AKI) can be reversed with intravenous (IV) albumin infusion and splanchnic vasoconstrictors, and acute tubular necrosis (ATN) is generally managed supportively.[3] Earlier treatment of AKI is associated with greater chance of reversal of kidney injury and decreased mortality.[4, 5] Therefore, prompt and accurate identification of AKI severity (i.e., AKI stage based on relative change in serum creatinine [SCr]) and etiology is vital to optimize outcomes.

Current data on the incidence, outcomes, and practice patterns in United States (U.S.) patients with AKI and cirrhosis are limited to single center studies,[6, 7] which may be hard to generalize, or payer databases, which are larger but have incomplete clinical data.[8–10] As a result, application and analysis of the impact of current clinical guidelines are largely extrapolated from non-U.S. centers, where there are different standards of care and allocation systems for liver transplantation (LT) compared to the U.S. For example, terlipressin (a splanchnic-specific V1a-receptor agonist) is routinely used as the first-line vasoconstrictor for treatment of HRS-AKI in numerous countries but has only just been approved in the U.S. and is not yet in wide clinical use there.[3, 4, 11] A more comprehensive database of U.S. patients with AKI and cirrhosis is needed to characterize the

demographics and natural history of this population, and establish a baseline to determine how terlipressin's impending adoption into practice will affect outcomes.

In this manuscript, we provide a comprehensive and granular analysis of a large, consecutive series of patients across multiple academic centers to identify current practice patterns, define the incidence of AKI etiologies in cirrhosis at-large, and examine the scope of this problem as it affects U.S. patients.

Methods

Study Population and Setting

Consecutive adult patients age >18 years hospitalized with AKI and cirrhosis between January 1, 2019 and December 31, 2019 were eligible for this retrospective analysis. Patients from 11 different hospital network systems (11 LT centers, 15 total hospitals) were included (see Table S1 for a list of sites). 2019 was chosen as a complete calendar year to provide up-to-date secular trends while avoiding obfuscation by the coronavirus-19 pandemic.

Potential patients were identified via local centralized clinical data warehouse tools using a validated list of International Code of Disease version 10 (ICD-10) codes for cirrhosis (see Table S2).[12] Patients with at least one cirrhosis ICD-10 code and an inpatient SCr >1.5 mg/dL proceeded to a manual chart review to determine the accuracy of the diagnostic codes for cirrhosis and AKI (see Definitions). SCr >1.5 mg/dL was chosen as an AKI threshold given its previous validation as a significant determinant of prognosis and diagnostic relevance in this population.[13] Patients were excluded if they had liver disease without cirrhosis, did not meet criteria for AKI (*e.g.*, SCr >1.5 mg/dL due to chronic kidney disease), had a prior liver or kidney transplant, were on renal replacement therapy (RRT) at the time of admission, had AKI only after LT, or had incomplete clinical data. For patients with repeat admissions with AKI during the study period, only their first admission with AKI was included. Similarly, if a patient had recurrent episodes of AKI during the index hospitalization, only the first episode was considered. All data were obtained via review of electronic health records, United Network for Organ Sharing (UNOS) records, and if needed, by search of online obituaries and/or the Social-Security Death-Index.

Definitions

The etiology of cirrhosis was determined based on the clinical determination of the treating hepatologist and cirrhosis was confirmed by radiologic evidence, presence of complications related to cirrhosis, liver biopsy (if available) and/or endoscopic evidence of portal hypertension. Patients were classified as "listed" for LT if they were active on the UNOS waiting list during the index admission. AKI was defined using the 2015 International Club of Ascites (ICA)-AKI criteria, which uses relative change in SCr to define AKI stages.[3, 14, 15] Outpatient baseline SCr was recorded as the most recent outpatient value within 1-year of index admission. The relative difference between peak pre-transplant SCr, discharge SCr, and outpatient baseline SCr (where available) were used to stage AKI during admission.

Etiology of AKI was divided into 4 categories based on *a priori* definitions derived from previous literature[7, 16] and agreed upon by the principal investigators at each study site. AKI was considered (1) prerenal or hypovolemic if clinical history was consistent with volume depletion and there was improvement in AKI stage within 48-hours of volume resuscitation; (2) HRS-AKI if the patient met 2015 ICA HRS-AKI definition;[3] (3) ATN if clinical history was consistent with ischemic or nephrotoxic AKI and did not improve with volume resuscitation; and (4) other AKI, which included causes such as interstitial nephritis, glomerulonephritis, obstructive nephropathy, or abdominal compartment syndrome. Each patient had two independent adjudicators to agree on etiology of AKI, with a third adjudicator providing a tie-breaking diagnosis, if needed. Patients were deemed "unable to be classified" if there was disagreement between three adjudicators or there was insufficient clinical information available to determine etiology of AKI.

De-novo chronic kidney disease (CKD) was defined by Kidney Disease Improving Global Outcomes as the persistence of eGFR <60 ml/min per 1.73 m^2 for ≥3 months from the time of AKI event in patients who did not have pre-existing CKD prior to admission. [17] The Chronic Kidney Disease Epidemiology Collaboration equation was chosen to calculate eGFR. [18]

Data Collection and Management

Study data were collected and managed using REDCap electronic data capture tools hosted at each participating institution using a standard variable template across all sites.[19] Laboratory values were recorded at the time of admission unless otherwise noted. Model for End Stage Liver Disease-Sodium (MELD-Na) score and Chronic Liver Failure-Consortium (CLIF-C) ACLF score were calculated at the time of admission.[20–22] Patients were followed for 90 days from their date of admission for death, transplant, readmission, and the need for RRT. Vasoconstrictors were categorized into two categories: (1) those used for the treatment of HRS-AKI (i.e., midodrine and octreotide, norepinephrine) and (2) vasopressors used for shock (i.e., vasopressin, norepinephrine, epinephrine) in the intensive care unit (ICU).

Outcomes and Statistical Analysis

The primary outcome for this study was 90-day mortality. Secondary outcome was rate of AKI response at discharge (defined as per the ICA guidelines, where a complete response denoted an improvement in SCr to within 0.3 mg/dL of baseline, partial response denoted improvement in at least 1 AKI stage with SCr > 0.3 mg/dL above baseline, and overall response combines complete and partial response).[3] The main exposure of interest was etiology of AKI as a predictor of outcomes, with devoted 3-way modeling comparing prerenal AKI, HRS-AKI, and ATN. Survival curves for outcomes were estimated by AKI etiology, AKI stage, and response to therapy using Kaplan Meier method and compared using log-rank test. Patients who demonstrated improvement with volume resuscitation (and thus were classified as prerenal AKI) but later suffered worsening of SCr by discharge were captured as AKI nonresponders. Univariate data were compared using Chi-square, Fisher exact, Student's t-test, or Wilcoxon rank sum testing, as appropriate. Pre-specified multivariable regression models were used to evaluate the association between exposure

variables and outcomes using an empiric scientific selection process[23] adjusting for age, race, gender, transplant listing status, and MELD-Na score, using Fine and Gray analysis to account for competing risks of transplant.[24] Sensitivity analyses were performed using alternative models, including a previously derived model from the European literature, [7] multivariable model using variables from a proportional hazards stepwise selection algorithm ($p < 0.1$ for entry, $p < 0.05$ for final selection), stratified analysis by transplant listing status, and removal of patients with disagreement between adjudicators of etiology of AKI. All models were adjusted for study center as a categorical variable. All covariates used in multivariable models had <3.0% missing data, these values were imputed using single imputation methodology. Continuous data were presented as median (interquartile range). SAS version 9.4 (Cary, NC) was used for analysis and R studio version 1.4 (Vienna, Austria) was used to generate figures.

Ethics

This study was approved by each site's institutional review board. Each site abides by the guidelines set forth by the Declaration of Helsinki and Istanbul. The need for informed consent was waived.

Results

Of 6,596 patients screened, 2,063 met inclusion criteria and were included for analysis. (Figure S1). The median age was 62 [54, 69] years and the majority had ascites (77.9%). The median MELD-Na and CLIF-C ACLF scores were 26.0 [19.0, 31.0] and 48.8 [42.4, 55.7], respectively. Alcohol was the most common etiology of cirrhosis (38.9%); 14.7% met National Institute on Alcohol Abuse and Alcoholism criteria for alcohol-associated hepatitis. [25] 30.3% had documented CKD (eGFR <60 mL/min) at least 3 months prior to admission. 15.4% were listed for LT, 46.7% required ICU admission and the median inpatient length of stay was 9 [4, 16] days.

Patient Demographics and Clinical Characteristics

Comparison of patient demographics and clinical characteristics by etiology of AKI are presented in Table 1. 44.3% had prerenal AKI, 30.4% ATN, 12.1% HRS-AKI, 6.0% other AKI, and 7.2% were unable to be classified (Figure 1). 1844/2063 (89%) had full agreement between adjudicators. Among all patients, 34.2% had AKI stage I, 23.0% had AKI stage II, 24.5% had AKI stage III without RRT, and 18.3% had stage III requiring RRT. Comparisons of AKI etiology stratified by AKI stages can be found in Table S3. Patients with AKI stages 1 and 2 were more likely to have to prerenal AKI, 64.1% and 53.5%, respectively, whereas patients with stage 3 AKI were more likely to have ATN (47.5%) and HRS-AKI (17.5%). When stratified by ACLF grade, prerenal AKI was the most common etiology in ACLF grades 0, 1, and 2 (69.6%, 45.3%, and 47.1%, respectively), whereas ATN was the most common in ACLF grade 3 (41.5%, $p < 0.001$; Table S4). HRS-AKI was uncommon across all ACLF grades, but the proportion was highest in ACLF grade 3 (13.7%) compared to those with ACLF grade 0 (2.4%).

Overall, 66.5% patients were treated with IV albumin during their admission. Patients with HRS-AKI received more IV albumin (144 [100, 200] g) compared to prerenal AKI (101 [50, 175] g) and ATN (100 [63, 175] g; p <0.001). Vasoconstrictors for HRS were used most in HRS-AKI (77.1%) compared to prerenal AKI (21.5%) and ATN (49.0%; p <0.001). Vasopressors for shock were used most commonly in ATN (52.7%) compared to prerenal AKI (14.2%) and HRS-AKI (33.6%; p <0.001). For the latter, vasopressor use occurred after the diagnosis of HRS-AKI was made. RRT was most common in patients with ATN (62.6%), followed by HRS-AKI (17.4%), unclassifiable (11.3%), prerenal AKI (6.7%) and other AKI (1.9%; p <0.001).

Etiology of AKI and 90-Day Mortality

Patient characteristics and significant univariate predictors of 90-day mortality are displayed in Table 2. Patients who died had significantly higher MELD-Na (p <0.001) and CLIF-C (p <0.001) scores compared to patients who were alive. Correspondingly, patients who died also had higher rates of ICU admission, vasopressor use for shock, and mechanical ventilation (p <0.001 for all). In the entire cohort, in-hospital, 30, 60, and 90-day mortality were 19.3%, 24.7%, 32.5%, and 36.5%, respectively. Loss to follow-up rates were low at each time point: 0%, 7.7%, 9.8%, and 11.4%, respectively.

In unadjusted analysis, etiology of AKI was associated with 90-day mortality (Figure 2; p <0.001). Absolute rates of mortality at 30, 60, and 90-days by etiology of AKI are presented in Table 3. In pairwise analysis, patients with prerenal AKI had the lowest rate of mortality at 90 days (22.2%; p <0.001) whereas patients with HRS-AKI and ATN were not significantly different from each other (49.0% vs. 52.7%; p = 0.42). In multivariable regression analysis, using prerenal AKI as reference, the adjusted sHR for 90-day mortality was higher for HRS-AKI (sHR 2.78 [95% CI 2.18–3.54]; p <0.001) and ATN (sHR 2.83 [2.36–3.41]; p <0.001). Similar results were found in sensitivity analysis using alternative multivariable models, which can be found in Table S5.

Associations between AKI Stage, Response to Therapy, and 90-Day Mortality

Compared to stage I AKI, stage II and III AKI were associated with an increased risk of 90-day mortality in unadjusted (Figure 3; p <0.001) and adjusted analyses (stage II sHR 1.36 [1.08–1.71], p = 0.008; stage III without dialysis sHR 1.71 [1.38–2.13], p <0.001; stage III with dialysis sHR 3.63 [2.86–4.61], p <0.001); Table 3).

Factors associated with overall AKI response are presented in Table S6. 41.8% patients had complete response, 14.5% had partial response, and 42.8% had no response. Rates of overall response varied by etiology of AKI (76.1% prerenal AKI, 36.5% HRS-AKI, 39.8% ATN, 64.2% other AKI, 31.5% unable to classify, p <0.001). Patients who experienced complete response of their AKI had the lowest adjusted risk of 90-day mortality compared to those with partial response (sHR 2.04 [1.59–2.61], p <0.001) and those with no response (sHR 4.85 [4.03–5.84], p <0.001); Table 3 and Figure 4). Factors associated with overall AKI response among patients treated with vasoconstrictors (n = 788), are presented in Table S7.

Outcomes by Liver Transplant Status

8.1% of patients received a LT by 90 days (including 1.3% who received a simultaneous kidney transplant [SLKT]). Prerenal AKI was the most common etiology of AKI among patients who received a LT alone (39.2%) and SLKT (46.2%), followed by HRS-AKI (28.6% and 26.9%, respectively), then ATN (23.6% and 23.1% respectively). Patients not listed for transplant had a higher absolute risk of 90-day mortality compared to listed patients (40.1% vs. 16.7%, sHR 4.04 [3.00–5.45], p <0.001; Table 3). When examining etiology of AKI as a risk factor for death in stratified adjusted analysis, HRS-AKI and ATN had increased risk of 90-day mortality compared to prerenal AKI among 1,746 non-listed patients, but only ATN was associated with death among 317 listed patients (Table S5). When examining AKI response among the 167 patients who received a LT, complete response occurred in 35.9%, partial response in 10.8%, no response in 53.5% (including 20.3% who required RRT).

Other Outcomes

90-day survival probability by AKI etiology in patients without ascites and with ascites is visualized in Figure S2 and S3, respectively. We observed similar trends in mortality in both groups, with the ascites subgroup demonstrating higher absolute mortality relative to the group without ascites. 90-days after discharge, 58/157 (36.9%) patients who were at risk developed *de-novo* CKD after their index AKI episode. Rates of *de-novo* CKD were similar across etiologies of AKI (prerenal AKI 31.2%, HRS-AKI 52.6%, ATN 38.4%, other AKI 50.0%, unable to classify 42.9%; p = 0.34).

Discussion

In this study, we report the largest, and first consecutive, fully adjudicated cohort study of patients hospitalized with AKI and cirrhosis in a U.S. population, using the updated 2015 HRS-AKI criteria. We demonstrate distinguishing characteristics of the three main etiologies of AKI in this population – prerenal/hypovolemic AKI, HRS-AKI, and ATN. While etiology of AKI clearly influences practices patterns and outcomes, the overall short-term mortality between HRS-AKI and ATN was similar.

Our manuscript corroborates the incidence rates and mortality trends of HRS-AKI seen in other epidemiology studies. A recent analysis by Singal *et al.* of 2016–2019 National Inpatient Sample admissions demonstrated similar incidence of HRS (16.5% of admissions for AKI and cirrhosis using billing codes) to our study (12.1% fully adjudicated cases).[26] They also found nearly identical inhospital mortality rate to ours (24.5% vs. 25.8%). While billing data is not able to capture prerenal AKI or ATN reliably in this population, these findings suggest that the code for HRS provides a reasonable approximation for incidence of HRS-AKI. Singal's paper also notes a decrease in mortality over time in HRS. Our 90-day survival in HRS-AKI (51%) was better than historic 90-day survival rates from the European literature (15%), which likely reflects overall improvements in patient care as well as changes to HRS definitions across eras.[7]

One notable aspect of current practice patterns in our study was the variability in the use of IV albumin and HRS vasoconstrictors across different etiologies of AKI. Although guidelines recommend an IV albumin challenge on presentation for all AKI and cirrhosis, only 67% of all patients received it during their admission, with HRS-AKI at the highest rate (95%) and total volume (144 grams). It is difficult to determine why up to 1/3 of patients did not receive IV albumin. Some patients may have received it prior to admission (in the case of hospital transfer to a study center), some may have received other colloids like blood or crystalloids in its place, and some treating teams may have felt it not to be appropriate based on clinical examination. However, it is also likely that guidelines for treating AKI in cirrhosis have not been fully embraced across centers, suggesting a need for ongoing education on management of this population.[27] This opportunity may also extend to discontinuation of potential precipitant medications to prevent AKI, such as diuretics and beta blockers, which were prescribed at high rates across all patients. Similarly, while patients with HRS-AKI received HRS vasoconstrictors at the highest rate (77%), patients with pre-renal AKI (22%) and ATN (49%) received them regularly as well, despite not being subgroups where one would expect benefit nor where they are guideline-recommended. Interestingly, HRS vasoconstrictor use (which was predominantly midodrine and octreotide, as terlipressin was not yet available in the U.S. during this study period), was associated with worse survival, highlighting the ineffectiveness of off-label vasoconstrictors in current U.S. practice. We would caution against overinterpretation of this finding, as this is mere association, rather than a causal link. We did not record dose, time to initiation, or duration of these medications, thus providers may have been prescribing HRS vasoconstrictors as a “salvage therapy” after a patient’s kidney function had already declined beyond the point of reversal. Importantly, multiple guidelines recommend terlipressin as the first-line splanchnic vasoconstrictor for HRS-AKI,[3, 28–30] and given terlipressin’s recent FDA approval,[11] it is likely to become a prominent therapeutic option for HRS-AKI.[4] However, terlipressin must be used judiciously given its side effect profile (most notably, ischemia and respiratory failure).[31–33] It should only be prescribed in confirmed cases of HRS-AKI where its benefits outweigh its risks. Further study is needed to determine whether novel biomarkers may aid in establishing an HRS-AKI diagnosis and/or the likelihood of responding to vasoconstrictors.[16, 34–36]

We identified several risks factors for poor outcomes, many of which recapitulate findings in the literature and support that established clinical predictors of mortality remain excellent prognostic tools in AKI and cirrhosis. First, common prognostic models of liver disease (and their individual components), such as MELD-Na and CLIF-ACLF score, were strong predictors of survival.[20–22] Similarly, markers of critical illness and/or advanced liver disease (admission to the ICU, intubation, advanced encephalopathy, hepatocellular carcinoma), were also strongly associated with mortality.[7, 37–39] Peak AKI stage and response to treatment also correlate linearly with survival, emphasizing the importance of early identification and intervention to reverse AKI in this population.[4, 5, 32] Patients requiring RRT had the highest mortality (60%) compared to AKI without RRT (stage I 22%, stage II 32%, stage III 44%), though interestingly, 90-day mortality for those requiring RRT was lower than some previous studies (63–80%).[38, 40, 41] Given the growing body of literature of poor outcomes among non-LT candidates who require RRT, we may be seeing a

shift towards more conservative and/or palliative approaches, and a more selective approach to RRT in this group.[42]

The interplay between AKI and CKD in cirrhosis remains complicated. While 30.3% of the study population had pre-admission CKD, among the remaining patients at risk, 36.9% subsequently developed *de-novo* CKD 3 months after discharge, with similar rates across etiologies of AKI. This is consistent with prior literature outside of cirrhosis where any AKI event (regardless of it causing functional or parenchymal injury) predisposes a patient to future CKD, and warrants further study in patients with cirrhosis.[43] It is important to note that only eGFR at the time of transplant, not etiology of AKI/CKD, currently factors into allocation of SLKT, which may explain why prerenal AKI represented 46.2% of all SLKT. 5 of the 12 patients who underwent SLKT with prerenal AKI had pre-admission CKD, which suggests that their prerenal AKI during the index admission was one of a series of acute and chronic insults leading to a progressive decrease in eGFR, which for some, necessitated future SLKT. We may also hypothesize that listed patients with prerenal AKI were less likely to be deemed “status 7” or inactive due to illness, compared to those with HRS-AKI or ATN, adding to the high rate of SLKT in this subgroup.

The availability of LT continues to drive management decisions and influence outcomes in this population. We accounted for this competing risk in our mortality analyses. Additionally, in stratified analysis by transplant listing status, we saw similar results, though associations were weaker in the listed group due to a smaller sample size of 317 patients. Overall, we know that among listed patients, pattern/duration of kidney injury (*e.g.* acute or chronic) influences mortality.[44] Our analysis suggests that etiology of AKI should also be considered when modeling outcomes for this population.

These data should be interpreted in the context of their limitations. This study was retrospective, thus all findings should be viewed as associations without a causal link. While geographically diverse, nearly all sites were LT centers, which may influence referral patterns and overall demographics. Only the admission’s peak AKI episode was captured during the study period, which limits bias related to repeated measures, but does not capture recurrent episodes of AKI for each patient, which may contribute to the development of CKD and mortality during follow-up. The high mortality rates in this study could have been influenced by the exclusion of patients with less severe AKI (SCr <1.5 mg/dL), who have better prognosis compared to other stages of AKI.[45] Furthermore, given the lack of gold-standard kidney biopsy data in this population,[46, 47] etiology of AKI is defined by a clinical syndrome, though definitions were agreed upon by a multidisciplinary expert group, and sensitivity analyses excluding patients without adjudicator agreement showed consistent results with the primary models.

In conclusion, AKI is a severe complication of cirrhosis. HRS-AKI is uncommon and has similar outcomes to ATN. Etiology of AKI, AKI stage/severity, and non-response to treatment are associated with mortality. These data establish a baseline for U.S. patients as we anticipate optimization and implementation of newly available vasoconstrictors in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Listing of Abbreviations:

AKI	acute kidney injury
HRS-AKI	hepatorenal syndrome acute kidney injury
ATN	acute tubular necrosis
MELD-Na	Model for End Stage Liver Disease-Sodium
ACLF	acute on chronic liver failure
IV	intravenous
SCr	serum creatinine
LT	liver transplant
ICD-10	International Code of Disease version 10
RRT	renal replacement therapy
UNOS	United Network for Organ Sharing
ICA	International Club of Ascites
CLIF-C	Chronic Liver Failure-Consortium
ICU	intensive care unit

SLKT	simultaneous liver kidney transplant

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Highlights:

- Acute kidney injury is common and deadly in cirrhosis, but incidence and outcomes based on the etiology/cause are not well described in United States patients.
- Hypovolemic or prerenal acute kidney injury is the most common (44%), followed by acute tubular necrosis (30%) then hepatorenal syndrome (12%).
- Acute tubular necrosis and hepatorenal syndrome have similar outcomes (~50% mortality at 90 days).
- Acute kidney injury in cirrhosis is common, but hepatorenal syndrome is uncommon. New treatments for persistent and severe AKI in cirrhosis, such as further optimization of vasoconstrictors for hepatorenal syndrome and novel supportive therapies for acute tubular necrosis, are needed.

Impact and Implications:

Acute kidney injury (AKI) in cirrhosis carries high morbidity, and management is determined by etiology of the injury. However, a large and well-adjudicated multicenter database from U.S. centers that uses updated AKI definitions is lacking. Our findings demonstrate that acute tubular necrosis and hepatorenal syndrome have similar outcomes (~50% mortality at 90 days), though hepatorenal syndrome is uncommon (12% of all AKI cases). These findings represent practice patterns at U.S. transplant/tertiary centers and can be used as a baseline prior to the U.S. adoption of terlipressin.

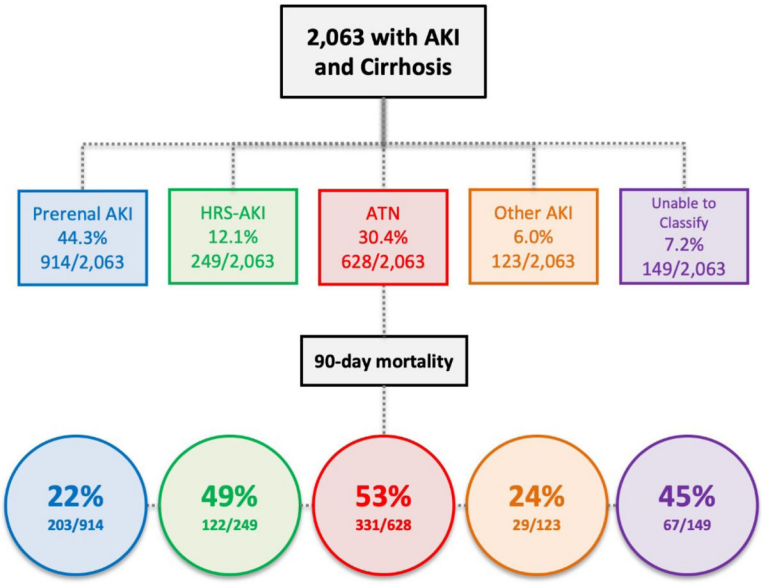

Figure 1: Distribution and outcomes of patients by etiology of acute kidney injury

Key: AKI (acute kidney injury), HRS (hepatorenal syndrome), ATN (acute tubular necrosis)

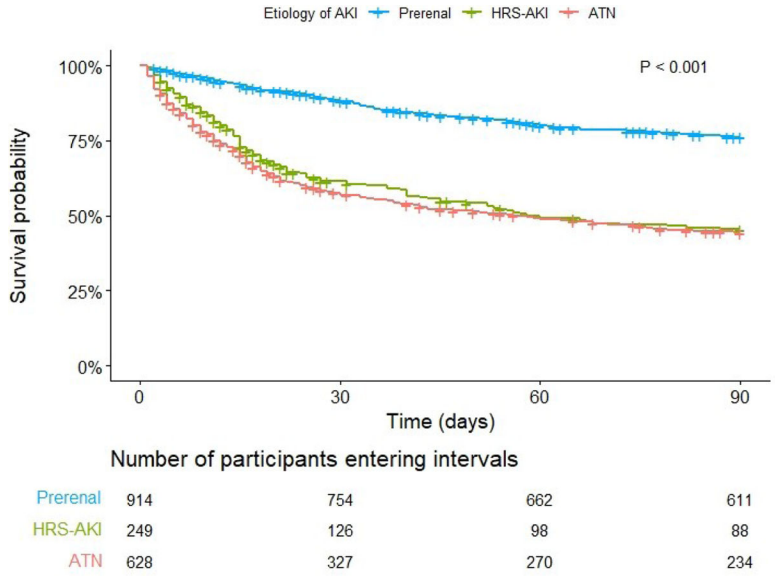

Figure 2: Ninety-day survival probability by etiology of acute kidney injury

Key: AKI (acute kidney injury, HRS (hepatorenal syndrome), ATN (acute tubular necrosis). P <0.001 (Log rank)

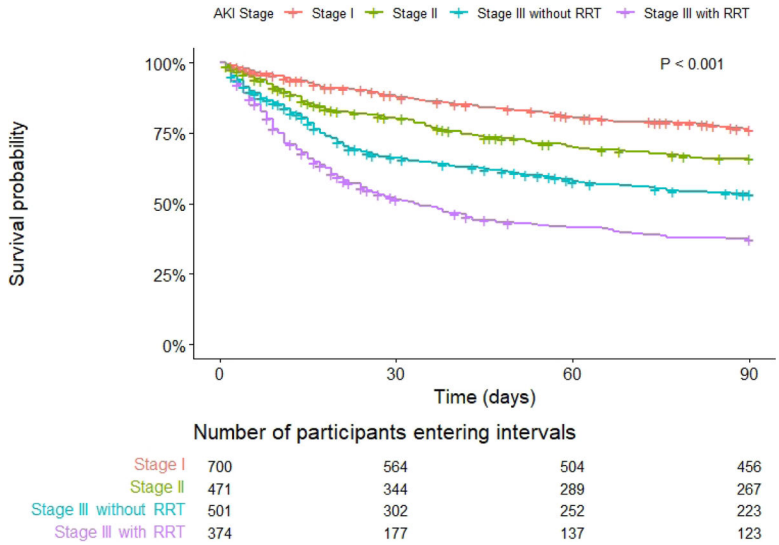

Figure 3: Ninety-day survival probability by acute kidney injury stage

Key: AKI (acute kidney injury), RRT (renal replacement therapy). P <0.001 (Log rank)

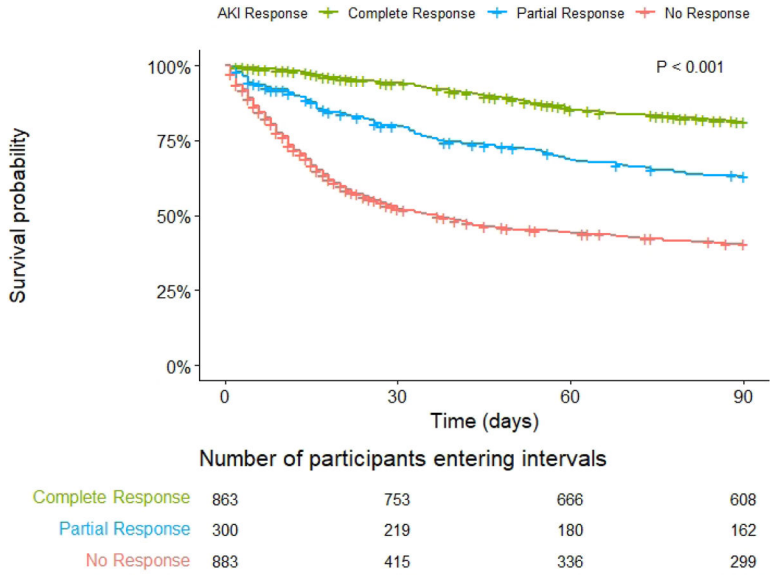

Figure 4: Ninety-day survival probability by acute kidney injury response

Key: AKI (acute kidney injury). P <0.001 (Log rank)

Complete response requires an improvement in SCr to within 0.3 mg/dL of baseline, partial response requires improvement in at least 1 AKI stage

Table 1:

Demographics and clinical characteristics by etiology of acute kidney injury

	All Patients (n = 2063)	Prerenal AKI (n = 914)	Hepatorenal Syndrome (n = 249)	Acute Tubular Necrosis (n = 628)	P Value	Other AKI (n = 123)	Unable to Classify (n = 149)
Age (years)	62 [54, 69]	62 [55, 70]	61 [53, 66]	61 [51, 68]	<0.001	65 [57, 71.5]	61 [52,68]
Female sex (%)	790 (38.3)	334 (36.6)	99 (39.8)	250 (39.8)	0.38	50 (40.7)	57 (38.3)
White race (%)	1676 (81.2)	761 (83.3)	212 (85.1)	494 (78.7)	0.03	96 (78.0)	113 (75.8)
Hispanic ethnicity (%)	180 (8.7)	90 (9.8)	24 (9.4)	38 (6.0)	0.05	9 (7.3)	19 (12.7)
Etiology of cirrhosis (%)					<0.001		
Alcohol	803 (38.9)	337 (36.9)	112 (45.0)	260 (41.4)		33 (26.8)	61 (40.9)
Hepatitis C	233 (11.3)	114 (12.5)	25 (10.0)	63 (10.0)		16 (13.0)	15 (10.1)
Non-alcoholic steatohepatitis	444 (21.5)	201 (22.0)	71 (28.5)	112 (17.8)		27 (22.0)	33 (22.1)
Multifactorial	191 (9.3)	94 (10.3)	14 (5.6)	61 (9.7)		13 (10.6)	9 (6.0)
Other	392 (19.0)	168 (18.4)	27 (10.8)	132 (21.0)		34 (27.6)	31 (20.8)
Complications of cirrhosis (%)							
Ascites	1607 (77.9)	643 (70.4)	242 (97.2) ***	512 (81.5)	<0.001	89 (72.4)	121 (81.2)
Encephalopathy	1212 (58.8)	497 (54.4)	174 (69.9)	405 (64.6)	<0.001	45 (36.6)	91 (61.1)
Gastrointestinal bleeding	712 (34.5)	303 (33.2)	80 (32.1)	253 (40.4)	0.007	33 (26.8)	43 (28.9)
Spontaneous bacterial peritonitis	289 (14.0)	111 (12.2)	50 (20.1)	102 (16.3)	0.003	10 (8.2)	16 (10.7)
Hepatocellular carcinoma	236 (11.4)	106 (11.6)	33 (13.3)	68 (10.8)	0.60	11 (8.9)	18 (12.1)
Characteristics of admission							
Admission mean arterial pressure (mmHg)	69.0 [60.7, 77.0]	70.0 [62.3, 78.0]	69.0 [61.3, 76.0]	64.8 [56.7, 74.0]	<0.001	73.3 [66.0, 82.3]	71.7 [64.3, 79.3]
Vasoconstrictors for HRS (%)	788 (38.2)	196 (21.5)	192 (77.1)	307 (49.0)	<0.001	25 (20.3)	68 (45.6)
Vasopressors for shock (%)	614 (29.8)	139 (15.2)	83 (33.6) ****	331 (52.7)	<0.001	23 (18.7)	38 (25.5)
Albumin given during admission (%)	1370 (66.5)	503 (55.1)	235 (94.8)	480 (76.7)	<0.001	54 (43.9)	98 (65.8)
Total albumin given during admission in g	122 [75, 175]	101 [50, 175]	144 [100, 200]	100 [63, 175]	<0.001	125 [75, 175]	100 [50, 184]
Intensive care admission (%)	963 (46.7)	267 (29.2)	132 (53.2)	464 (74.0)	<0.001	39 (31.7)	61 (40.9)
Mechanical ventilation (%)	551 (26.7)	130 (14.2)	68 (27.2)	304 (48.4)	<0.001	18 (14.6)	31 (20.9)
Renal replacement therapy (%)	374 (18.2)	25 (2.7)	65 (26.1)	234 (37.3)	<0.001	8 (6.5)	42 (28.4)
Medications prior to admission (%)							
Loop diuretic	1295 (62.8)	621 (68.0)	155 (62.2)	357 (56.9)	<0.001	74 (60.2)	88 (59.1)
Mineralocorticoid receptor antagonist	951 (46.2)	466 (51.2)	116 (46.6)	256 (40.8)	0.001	57 (46.3)	56 (37.6)

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	All Patients (n = 2063)	Prerenal AKI (n = 914)	Hepatorenal Syndrome (n = 249)	Acute Tubular Necrosis (n = 628)	P Value	Other AKI (n = 123)	Unable to Classify (n = 149)
Beta blockers	831 (40.3)	415 (45.4)	75 (30.1)	238 (37.9)	<0.001	55 (44.7)	48 (32.2)
MELD-Na score	26 [19, 31]	24 [18, 29]	30 [25, 34]	28 [21, 34]	<0.001	22 [17, 26]	26 [19, 34]
CLIF-C ACLF score	48.8 [42.4, 55.7]	45.3 [40.5, 51.2]	51.3 [45.0, 56.2]	54.0 [47.3, 60.9]	<0.001	47.2 [40.1, 51.7]	49.1 [41.2, 57.4]
Laboratory values							
Sodium (mEq/L)	134 [130, 138]	135 [131, 138]	131 [127, 136]	134 [130, 138]	<0.001	135 [131, 139]	135 [129, 139]
Outpatient baseline creatinine* (mg/dL)	1.10 [0.87, 1.37]	1.11 [0.90, 1.35]	1.10 [0.90, 1.45]	1.05 [0.79, 1.32]	0.01	1.24 [0.99, 1.49]	1.11 [0.86, 1.50]
Admission creatinine (mg/dL)	1.84 [1.50, 2.48]	1.84 [1.50, 2.48]	2.32 [1.67, 3.26]	2.02 [1.34, 3.27]	<0.001	1.86 [1.52, 2.64]	2.10 [1.37, 3.33]
Peak creatinine (mg/dL)	2.55 [1.93, 3.66]	2.08 [1.72, 2.70]	3.36 [2.42, 4.58]	3.24 [2.34, 4.71]	<0.001	2.43 [1.90, 3.30]	2.94 [2.12, 4.60]
White blood count (K/uL)	8.6 [6.0, 12.9]	8.0 [5.6, 11.6]	9.6 [6.1, 14.3]	9.8 [6.6, 14.7]	<0.001	7.3 [5.1, 10.2]	8.7 [6.1, 12.9]
Hematocrit (%)	29.6 [25.0, 34.9]	30.9 [25.7 36.3]	28.4 [23.9, 32.2]	28.9 [24.3, 33.7]	<0.001	31.0 [27.5, 35.7]	28.2 [24.6, 33.4]
Platelets (K/uL)	114 [73, 172]	116 [76, 177]	106 [70, 153]	112 [69, 168]	0.05	141 [85, 191]	122 [75, 164]
Albumin (g/dL)	2.90 [2.50, 3.60]	3.00 [2.60, 3.60]	2.80 [2.40, 3.20]	2.80 [2.30, 3.20]	<0.001	3.10 [2.70, 3.40]	2.90 [2.50, 3.40]
International normalized ratio (INR)	1.60 [1.30, 2.10]	1.50 [1.21, 1.90]	1.70 [1.40, 2.22]	1.80 [1.40, 2.50]	<0.001	1.40 [1.20, 1.88]	1.60 [1.30, 2.10]
Total bilirubin (mg/dL)	2.6 [1.1, 7.0]	2.0 [0.9, 4.4]	4.2 [1.8, 11.5]	3.5 [1.6, 11.0]	<0.001	1.4 [0.7, 2.5]	3.2 [1.2, 9.0]
Fractional excretion of sodium** (%)	0.35 [0.17, 0.91]	0.33 [0.13, 0.91]	0.25 [0.17, 0.53]	0.41 [0.17, 1.18]	0.001	0.60 [0.19, 1.99]	0.39 [0.14, 0.94]

Key: AKI (acute kidney injury), MELD-Na (Model for End Stage Liver Disease-Sodium), CLIF-C ACLF (CLIF Consortium Organ Failure Acute on Chronic Liver Failure Score). MELD and CLIF-C ACLF score were taken at hospital admission. All laboratory values were taken at admission unless otherwise noted.

Continuous variables given as median [interquartile range]. P values represent a three-way comparison between prerenal AKI, hepatorenal syndrome, and ATN, calculated by Chi square (categorical variables), Student's t test (parametric continuous variables) or Wilcoxon rank sum (non-parametric continuous variables).

*Available in 1700 patients.

**Available in 1149 patients.

***Presence of ascites is required for the diagnosis of HRS-AKI. Complications of cirrhosis were recorded at the time of admission, and thus, some patients were found to have ascites after admission, but before the diagnosis of HRS-AKI.

****Patients with HRS-AKI may have developed shock requiring vasopressors after the diagnosis of HRS-AKI was made.

Table 2:

Patient characteristics by vital status at 90 days

>	Alive (n = 1311)	Dead (n = 752)	P value
Age (years)	62 [54, 69]	62 [53, 69]	0.97
Female sex (%)	496 (37.9)	294 (39.1)	0.61
White race (%)	1071 (81.7)	605 (80.5)	0.52
Hispanic ethnicity (%)	132 (10.1)	46 (6.1)	0.003
Complications of cirrhosis (%)			
Ascites	962 (73.4)	645 (85.8)	<0.001
Encephalopathy	686 (52.4)	526 (69.9)	<0.001
Spontaneous bacterial peritonitis	168 (12.9)	121 (16.1)	0.05
Hepatocellular carcinoma	118 (9.0)	118 (15.7)	<0.001
Alcohol-associated hepatitis	177 (13.5)	126 (16.8)	0.05
Characteristics of admission			
Beta blocker prior to admission (%)	582 (44.4)	249 (33.1)	<0.001
Admission mean arterial pressure (mmHg)	70.0 [62.3, 78.0]	66.3 [57.7, 74.3]	<0.001
Vasoconstrictors for hepatorenal syndrome (%)	402 (30.7)	386 (51.3)	<0.001
Vasopressors for shock (%)	268 (20.5)	346 (46.0)	<0.001
Intensive care admission (%)	469 (35.8)	494 (65.8)	<0.001
Mechanical ventilation (%)	225 (17.2)	326 (43.5)	<0.001
Renal replacement therapy (%)	155 (11.5)	223 (29.7)	<0.001
Received liver transplant (%)	165 (12.6)	2 (0.3)	<0.001
MELD-Na score	24 [18, 30]	28 [23, 34]	<0.001
CLIF-C ACLF score	46.0 [40.5, 52.5]	53.4 [47.5, 59.6]	<0.001
Laboratory values			
Sodium (mEq/L)	135 [131, 138]	134 [129, 138]	0.001
Outpatient baseline creatinine * (mg/dL)	1.14 [0.90, 1.40]	1.00 [0.80, 1.30]	<0.001
Admission creatinine (mg/dL)	1.92 [1.51, 2.70]	2.00 [1.41, 3.03]	0.29
Peak creatinine (mg/dL)	2.33 [1.81, 3.34]	2.99 [2.22, 4.25]	<0.001
White blood count (K/uL)	8.1 [5.7, 12.1]	9.6 [6.6, 14.3]	<0.001
Hematocrit (%)	30.5 [25.3, 35.6]	28.7 [24.4, 33.4]	<0.001
Albumin (g/dL)	3.0 [2.6, 3.5]	2.7 [2.3, 3.2]	<0.001
International normalized ratio (INR)	1.50 [1.21, 2.00]	1.80 [1.50, 2.50]	<0.001
Total bilirubin (mg/dL)	2.0 [0.9, 4.8]	4.2 [1.9, 10.8]	<0.001
Fractional excretion of sodium ** (%)	0.38 [0.17, 1.13]	0.31 [0.16, 0.85]	0.03

Key: AKI (acute kidney injury), MELD-Na (Model for End Stage Liver Disease-Sodium), CLIF-C ACLF (CLIF Consortium Organ Failure Acute on Chronic Liver Failure Score). All laboratory values were taken at admission unless otherwise noted. Continuous variables given as median [interquartile range]. P values calculated by Chi square (categorical variables), Student's t test (parametric continuous variables) or Wilcoxon rank sum (non-parametric continuous variables).

* Available in 1713 patients.

** Available in 1149 patients.

Table 3:

Rates of mortality while in hospital and at 30, 60, and 90-days by etiology of acute kidney injury

	In Hospital	30-Day	60-Day	90-Day	Sub-Hazard Ratio (95% CI)	P value
Type of AKI						
Prerenal AKI	6.1%	10.9%	18.6%	22.2%	Reference	---
Hepatorenal syndrome	24.5%	36.1%	45.4%	49.0%	2.78 2.18–3.54)	<0.001
Acute tubular necrosis	37.6%	40.9%	48.4%	52.7%	2.83 (2.36–3.41)	<0.001
Other	6.5%	10.6%	20.3%	23.6%	1.04 (0.71–1.51)	0.85
Unable to classify	26.2%	33.6%	39.6%	45.0%	2.33 (1.75–3.09)	<0.001
AKI Stage						
Stage I	5.1%	11.0%	17.9%	21.7%	Reference	---
Stage II	11.3%	18.9%	28.0%	31.6%	1.36 (1.08–1.71)	0.008
Stage III without renal replacement therapy	22.6%	32.3%	39.3%	43.7%	1.71 (1.38–2.13)	<0.001
Stage III with renal replacement therapy	51.1%	46.5%	55.6%	59.6%	3.63 (2.86–4.61)	<0.001
AKI Response						
Complete response	2.2%	5.7%	13.1%	17.3%	Reference	---
Partial response	11.3%	19.3%	29.3%	34.3%	2.04 (1.59–2.61)	<0.001
No response	38.5%	44.7%	52.3%	55.6%	4.85 (4.03–5.84)	<0.001
Transplant Listing Status						
Listed for liver transplant	9.6%	8.5%	14.5%	16.7%	Reference	---
Not listed for liver transplant	21.2%	27.7%	35.8%	40.1%	4.04 (3.00–5.45)	<0.001

Key: AKI (acute kidney injury), HRS (hepatorenal syndrome), ATN (acute tubular necrosis). Absolute rates of death at in hospital, 30, 60, and 90 days represent unadjusted mortality rates at their respective intervals. Sub-Hazard ratios and P values are derived from multivariable models using Fine and Gray analysis for 90-day mortality, adjusted for age, race, gender, transplant listing status, center, and MELD-Na score.